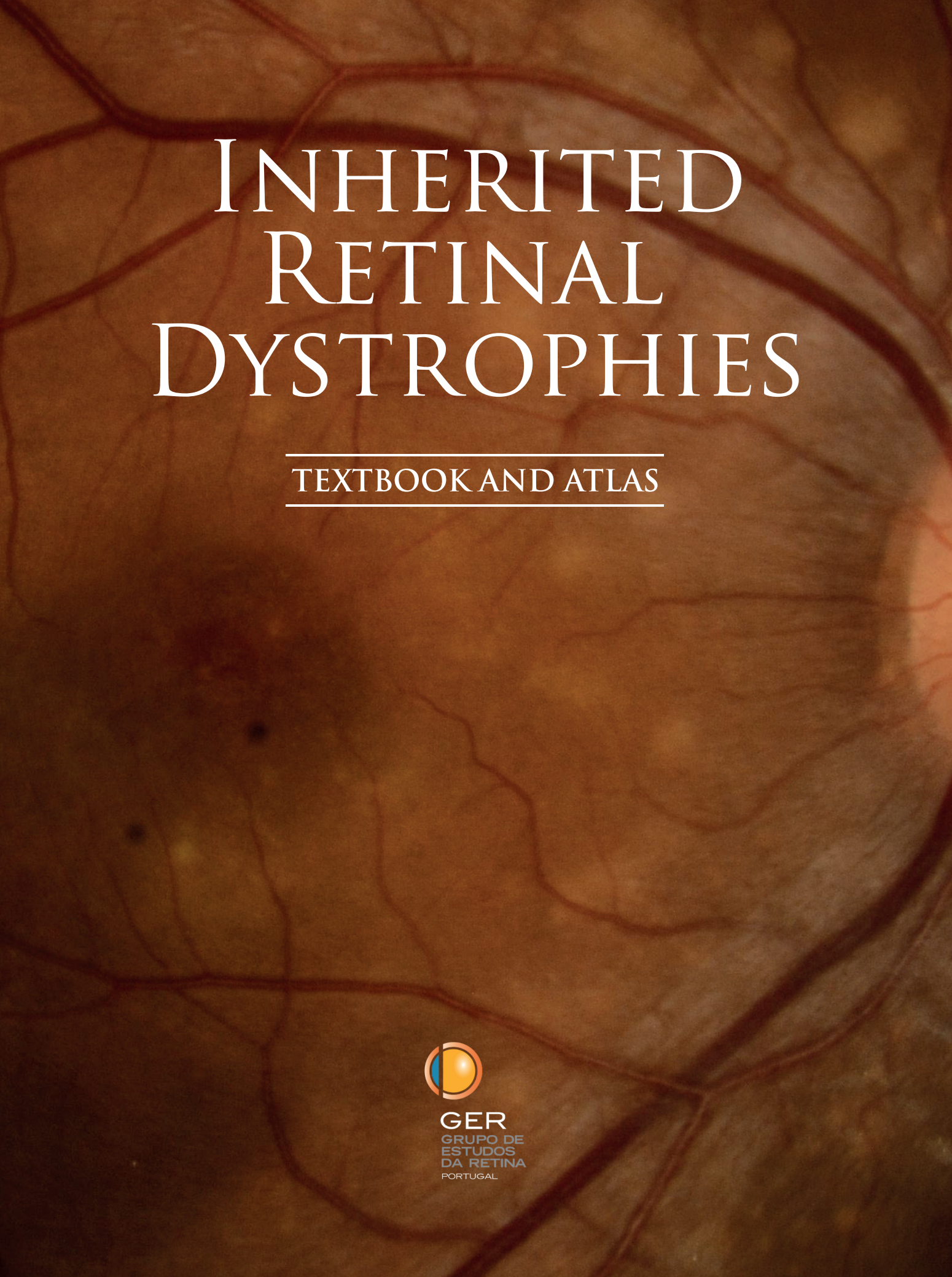

Inherited Retinal Dystrophies

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INHERITED RETINAL DYSTROPHIES

TEXTBOOK AND ATLAS

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INDEX

PREFACE

Inherited retinal dystrophies (IRDs) represent a genetically and phenotypically heterogenous group of eye diseases. Despite their low prevalence, the socioeconomic impact of rare eye diseases cannot be overstated, as these represent the leading cause of visual impairment and blindness among children and young adults in developed countries.

Over the last decades, major advances have been made in the field of IRDs. Improved genetic testing and better phenotyping have led to a better understanding of disease mechanisms and their natural history. Translational research opened new therapeutic avenues, culminating with the recent approval of the first gene therapy in Ophthalmology (and in Medicine). This important breakthrough will hopefully lay the groundwork for the development of gene therapies for other genes and conditions in a not too distant future. Two other dynamic and growing areas – regenerative medicine (stem cell therapy) and gene/genome editing (CRISPR) – may also become a reality, leading to a paradigm shift in the management of IRDs.

These fast changes in the field of IRDs place a major responsibility on ophthalmologists who need to be updated and capable of managing the expectations of their patients regarding molecular diagnosis and therapeutic prospects. It is the purpose of this book to compile the most current information in a single resource, conveying a thorough and comprehensive coverage of most common IRDs. It is also illustrated with paradigmatic cases of IRDs phenotypes, in the hope that it will act as a reference both for experienced ophthalmologists and residents.

Coordinating this publication and working hand in hand with national and international renowned colleagues was a great challenge but also a very valuable experience for me. This work proves that team effort results in great achievements. It is only by working together that progresses can be made, and this is particularly true in the field of orphan diseases. I can only hope that the reader will take full advantage of the contents herein, aiming to better assist patients with IRDs.

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MOLECULAR GENETICS AND GENETIC TESTING

Ana Luísa Carvalho

1. Introduction

Inherited retinal dystrophies (IRDs) are a clinical and genetic heterogeneous group of disorders that mainly affect the retina. Collectively they affect approximately 1 in 2000 to 1 in 3000 individuals, with *retinitis pigmentosa* being the most common subtype.

More than 250 genes have been described in association with syndromic and/or non-syndromic IRDs (https://sph.uth.edu/retnet/, accessed on 31 October 2018.). In the last years, new sequencing technology – next-generation (NGS) or massively parallel DNA sequencing –, has come to revolutionize molecular diagnosis in IRDs. These methods have contributed to an extreme reduction in time and costs for the molecular diagnosis of IRDs and helped turning genetic testing massively available. Nevertheless, the use of these technologies have limitations that the clinicians should know in order to choose the best investigation for each patient as well as for a correct interpretation of the results.

2. Basic Genetic Principles

The majority of IRDs follow one of the three mendelian inheritance patterns: autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL). Some of them, however, are transmitted atypically, with non mendelian inheritance pattern, like mitochondrial or digenic traits.

In order to establish a pattern of inheritance, it is crucial to obtain a medical history about the extended family in the form of a family tree (heredogram), which should have three-generation, or more if there is a suggestion of XL pattern. Since some IRDs causative genes are associated to a specific inheritance pattern, with this information in hand a targeted genetic analysis could be effective. Lastly, some IRDs have single inheritance trait so these information can allow to reinforce the diagnosis.

Table 1 - Characterization of inheritance patterns associated to IRDs (AD: autosomal dominant, AR: autosomal recessive, Mit: mitochondrial, XL: X-linked)

Inheritance pattern		Characterization
	AD	-Variants in genes on the autosomes -The condition is expressed in the heterozygous state -Variable expressivity, incomplete penetrance -Vertical pattern -Possible male-to-male transmission -Males and females are equally affected -Affected person has a 50% risk of transmitting to offspring
	AR	-Variants in genes on the autosomes -The condition is expressed in the homozygous or compound heterozygous state -Consanguinity -Horizontal pattern -Possible male-to-male transmission -Males and females equally affected -Usually, the parents and children of a patient are obligatory carriers (heterozygous) -25% risk of an affected child if both parents are carrier
	XL	-Variants in genes on the X chromosome -No male-to-male transmission -Males are affected in greater severity than females -Sometimes it is difficult to preview the phenotypic manifestations in carriers (heterozygous) females -Female carriers have a 50% chance of passing on the variant: risk of 25% of an affected child (50% to male sex) and 25% of a carrier child (50% to female sex) -All daughters of an affected male will be carriers (heterozygous)
Non Mendelian Inheritance	Mit	-Variants in genes on the mitochondrial DNA -Homoplasmy and heteroplasmy -Maternal transmission -No transmission occurs to descendants of males -Heteroplasmic female: risk under 100% for offspring

	Digenic*	-Involvement of two different genes -The condition is expressed when clinically relevant variants are present in two genes -Isolated case or pseudo-dominant pattern -25% risk of co-inheritance of both variants

**Concerning IRDs digenic inheritance is rare. The classic example is heterozygous ROM1 and PRPH2 variants in retinitis pigmentosa.*

3. Genetic Testing and molecular diagnosis of IRDs

Until recently, DNA sequencing was performed almost exclusively by conventional DNA sequencing (Sanger sequencing). This method is effective to analyze short fragments or small genes. However, for genetically heterogeneous diseases, strategies based on conventional DNA sequencing are very time-consuming, expensive, and generally unavailable. In the last years, several sequencing techniques have emerged like massively parallel DNA sequencing (next-generation sequencing - NGS). Such technology allows large-scale DNA sequencing with analysis of multiple fragments in one single reaction. With this technology it is possible to sequence whole genome (WGS), whole exome (WES, all the exons of all genes) or sequencing a gene targeted panel. NGS technologies have contributed to an exponential reduction in time and overall sequencing costs. As a consequence, they have strikingly increased the capacity to identify the underlying genetic cause of genetic diseases, particularly in genetically heterogeneous diseases like IRDs. However, a number of challenges have arisen with these new technologies, namely the interpretation of pathogenicity of the genetic variants identified.

3.1 Limitation and challenges in molecular diagnosis of IRDs

Molecular diagnosis is a challenge in IRDs:

-IRDs often display a phenotypic overlap;

-Variants in different genes may explain the same phenotype;

-Different variants in the same gene can cause a similar phenotype;

-Variants in a same gene can produce different retinal phenotypes (both in patients from the same family and from different families);

-Variants in a same gene can produce syndromic and non-syndromic phenotypes.

There are two major sequencing technologies for IRDs genetic testing: conventional DNA sequencing and NGS (table 2). Currently, NGS technology is the most widely used. For NGS technology there are three different approaches (targeted NGS, WES and WGS) (table 3).

Table 2: Sequencing technologies for IRDs

Conventional DNA sequencing	-Single gene disorders with a recognized phenotype -Disease or gene with a known mutational hot spot
NGS	-Disease with genetic heterogeneity (identical phenotypes being caused by variants in multiple genes)

Table 3: Comparison among different NGS sequencing approaches

	Gene panel (targeted NGS)	WES	WGS
Target regions	Subset of genes associated with a phenotype	All exons	All exons and introns
Costs	+	+/++	+++
New variants in novel genes	No	Yes	Yes
Deep intronic variants(1)	No*	No	No
CNVs (copy number variations)(2)	No/Yes	Yes	Yes
Secondary findings	No	Yes	Yes
Diagnostic yield (IRDs)	50-75%	20-30% uplift in diagnostic yield compared with gene panel	~30% uplift in diagnostic yield compared with gene panel or WES

**Can allow the discovery of deep intronic variants if the intronic region is included in the panel design. (1)Intronic variants: e.g. ~15% of the LCA patients has c.2991+1655A>G on CEP290 gene; (2)CNVs contribute to a molecular diagnosis of IRDs in 4,5% of cases. The genes most frequently identified with CNVs are EYS, USH2A and NPHP1.*

Table 4: Genetic tests approach according to phenotype and genetic etiology

One disease	Etiology	Genetic heterogeneity	Genetic test		Disease examples
			Conventional DNA sequencing	NGS	
Specific phenotype	One gene	Non or low	x		Best disease, choroideremia, X-linked retinoschisis
	Few genes	Mild	x	x	Achromatopsia, FEVR
	Many genes	High		x	RP, LCA
Non-specific phenotype	Many genes	High		x	

FEVR – familial exudative vitreoretinopathy; RP – retinitis pigmentosa; LCA – Leber Congenital Amaurosis

3.2 Importance of molecular diagnosis in IRDs

Identification of the genetic defect causing IRDs allows accurate diagnosis, prognosis and genetic counselling in affected individuals and their family.

To an affected individual, recognition of a genetic cause can allow:

-integration on gene therapy protocols or on clinical trials based on gene therapy;

-identification of syndromic forms of IRDs not clinically suspected. This is more relevant in pediatric patients because an IRDs can be the earliest manifestation of a syndromic entity;

-improvement on the medical management and prevention of complications;

-accurate prognosis of the clinical course of the disease;

-appropriate genetic counselling to patient and their family, with precise information for reproductive planning.

3.3 Genetic testing

In IRDs, genetic tests can be ordered in different settings like diagnosis testing, predictive or pre-symptomatic testing, carrier testing, prenatal testing and childhood testing.

In Portugal, ophthalmologists can and should order genetic tests and also provide the test results to an affected person (diagnosis testing). Concerning healthy relatives (predictive or pre-symptomatic testing, carrier testing, childhood testing) only medical geneticists can order and provide the test results and the appropriate genetic counselling.

- Diagnosis testing is performed on an affected individual. Should be offered to patients with clinical diagnosis or clinical findings suggestive of a genetic disorder whose causative gene(s) have been identified.
- Predictive or pre-symptomatic testing is performed on an asymptomatic at-risk individual. Such tests will give information regarding the predisposition or future prediction to develop the condition in the future.
- Carrier testing is performed on asymptomatic at-risk individual when an autosomal recessive or X-linked condition has been identified in the family. Usually, such tests will give information in order to reproductive planning.
- Prenatal testing can be an option for a couples in whom a molecular diagnosis is known in the family. Currently, there are two options: preimplantation genetic diagnosis and invasive test (chorionic villus sampling and amniocentesis).
- Childhood testing: it is now accepted that testing children may be appropriate on childhood-onset conditions where genetic test results will impact clinical management or support parenting/education. Childhood testing is not accepted in conditions where the symptoms would not begin until adulthood and there are no clinical reasons for genetic testing.

4. Diagnostic Evaluation

Clinical evaluation, including full ophthalmological and systemic examination, is essential in most IRDs. This information can be helpful before or after performing a genetic test, in order to select and interpret the analysis, respectively.

There is a wide range of syndromic forms of IRDs (table 5).

Table 5 - Syndromes with retinal dystrophies

	Systemic manifestations	Syndrome
Pediatric age	Neurologic symptoms	Mitochondrial disorders, Refsum disease, Batten disease, congenital disorders of glycosylation, Aicardi syndrome
	Molar tooth sign	Joubert syndrome
	Developmental delay	Bardet-Biedl syndrome, Refsum disease, Joubert syndrome
	Polydactyly	Bardet-Biedl syndrome
	Obesity	Alstrom syndrome, Bardet-Biedl syndrome, Cohen syndrome
	Diabetes mellitus	Alstrom syndrome, Bardet-Biedl syndrome
	Deafness	Usher syndrome, Refsum disease, Alstrom syndrome
	Vestibular dysfunction	Usher syndrome
	Malabsorption	Abetalipoproteinemia
	Renal disease	Bardet-Biedl syndrome, nephronophthisis
	Cardiomyopathy	Alstrom syndrome, mitochondrial disorders
Adult	Anosmia, neurological disturbance (peripheral polyneuropathy, ataxia), digital (foot) abnormalities, sensorineural hearing loss	Adult Refsum disease

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ELECTROPHYSIOLOGICAL TESTING

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1. Introduction

Electrophysiological testing of the visual pathway is based upon the recording of electrical potentials triggered by visual stimuli using electrodes on the surface of the eyes, the periorbital skin or the scalp. Standard techniques include the full-field flash electroretinogram (ffERG), the pattern electroretinogram (pattern ERG or PERG), the multifocal electroretinogram (mfERG), the electrooculogram (EOG) and the cortical-derived visual evoked potential (VEP) and each provides a non-invasive objective evaluation of function of a location (retina versus optic nerve, whole retina versus localized region) or cell type within the visual pathway. It can also be used to follow disease progression with repeated testing. Of note, electrophysiological testing is rarely, by itself, diagnostic, and must be coupled with a detailed clinical history, other ancillary exams and a bayesian differential diagnosis to attain the greatest clinical utility. The interest of electrophysiological testing is not limited to retinal dystrophies as it can provide useful information in cases of drug toxicity, vascular disease, and inflammatory or autoimmune conditions. Standardized testing is encouraged and specifications for each procedure are provided and regularly updated (usually every four years) by the International Society for Clinical Electrophysiology of Vision (ISCEV). In this introductory chapter, we will emphasize the fundamentals of ffERG, the technique of greatest importance in the context of retinal dystrophies, while also briefly covering the PERG, mfERG and EOG (as the VEP is of limited clinical utility in the context of retinal dystrophy it will not be discussed in this chapter). We recommend the readers to refer to the most recent ISCEV standards for further details on each technique [1–5].

2. Full-field ERG

The ff ERG records the summed response from the entire retina to a brief flash stimulus delivered in a full-field dome (a ganzfeld, "whole field" in german, stimulator). It measures the overall rod and cone retinal responses and is the only electrophysiologic test that directly evaluates rod function, which is of invaluable clinical utility in a number of diseases. Of note, the ff ERG provides no

topographical information. Indeed, an isolated macular lesion is unlikely to affect the ffERG to a significant extent. Macular disease is better evaluated using the PERG or the mfERG, with the latter providing a detailed topographical evaluation of the macula.

Testing is performed under maximum pupillary dilation, to ensure consistent stimulation of the whole retina. While a fixation point is presented in the dome, good or stable fixation is not required. Recording is made using electrode in contact with the cornea, conjunctiva or the lower eyelid skin. Reliable interpretation requires comparison to an electrode-dependent and age-matched normative database. Since the response of normal subjects is spread along a bell-shaped curve, it is important to know not only the mean of such response, but also the lower and upper limits of the distribution. Furthermore, in cases of unilateral or asymmetric disease, comparison with the fellow eye might be diagnostic since, for instance, interocular differences on the amplitude of the b-wave in normal subjects are small and usually under 10% [6].

The standard ISCEV ffERG include six protocols[2], named according to the state of adaptation (dark-adapted, DA, and light-adapted, LA) and stimulus flash strength (in candela-seconds per square meter, cd.s/m^2).

1. Dark-adapted 0.01 ERG (*weak* flash; rod-driven response; a-wave not recordable; b-wave: ON bipolar cells)
2. Dark-adapted 3.0 ERG (*strong* flash; combined, though rod dominated, rod-cone response; a-wave: photoreceptors and post-receptor ON pathways; b-wave: ON and OFF bipolar cells)
3. Dark-adapted 10 ERG (introduced in the 2015 ISCEV revision[2] it is similar to DA 3.0 ERG, has a larger a-wave, larger oscillatory potentials and allows better evaluation of negative waveforms)
4. Dark-adapted oscillatory potentials (evaluates middle retinal layers and vascular function; ON and OFF amacrine cells)
5. Light-adapted 3.0 ERG (cone-driven response, a-wave: cone photoreceptors and cone OFF bipolar cells; b-wave: ON and OFF bipolar cells)
6. Light-adapted 30 Hz flicker ERG (sensitive cone-driven response from post-receptoral ON and OFF pathways b-waves)

A minimum of 20 minutes of dark adaptation before recording rod responses and 10 minutes of light adaptation before recording cone responses is mandatory. DA ERGs are recorded sequentially without further dark-adaptation and thus only DA 0.01 ERG is a fully dark-adapted response. Electrophysiologic responses are evaluated not only by the qualitative morphology of the different waveform components, but also on the measurement of amplitude and implicit time of each component. The amplitude of the a-wave is measured from the baseline to the a-wave negative peak, and the amplitude of the b-wave is measured from the a-wave negative peak to the b-wave positive peak. The implicit time of each wave is the time from stimulus onset to its peak. A ffERG from a healthy subject can be appreciated in Figure 1.

Impairment of the DA 0.01 response is indicative of either rod photoreceptor dysfunction or selective dysfunction post-phototransduction or at the rod bipolar cell level. Abnormalities in the DA 3.0 can be divided in two major patterns, a-wave reduction with subsequent b-wave reduction (dysfunction mainly at the rod photoreceptor level) or preserved a-wave with selective b-wave reduction (post-phototransduction or inner retinal level). When this selective b-wave reduction occurs to the extent that the peak of the b-wave fails to reach the baseline (b-wave to a-wave amplitude ratio < 1), a *negative* ERG pattern emerges. A large number of conditions are associated with a *negative* ERG (the sensitivity of this finding varies from disease to disease) of which Schubert-Bornstein type congenital stationary night blindness, X-linked retinoschisis, central retinal artery occlusion, ischemic central retinal vein occlusion and melanoma-associated retinopathy are common examples. While oscillatory potentials (OPs) can be naturally appreciated in the rising limb of the DA 3.0 and 10.0 ERG b-waves, they can be isolated either through post-hoc processing or a specific protocol and are then designated in order of occurrence as OP1, OP2, OP3 and so on (the first OP, OP1, is usually discarded for averaging). Impairment of the OPs morphology and amplitude, thought to reflect impairment of amacrine signaling, occur in association with other ERG findings and thus have low clinical value.

Following light-adaptation, in order to minimize rod input, the LA 3.0 ERG can be obtained and is a measure of the general cone function. The LA 3.0 ERG is conceptually similar to the DA 3.0 ERG, with reduction of the a-wave and b-wave occurring at the cone photoreceptor or post-phototransduction/receptoral level, respectively. Finally, the LA 30 Hz flicker ERG is able to selectively suppress rod response at this frequency allowing for a sensitive measurement of cone-driven response from post-receptoral ON and OFF pathways. The amplitude of a flicker ERG is measured from trough to peak of a typical wave.

As mentioned in the introduction of this chapter, the ffERG (or visual electrophysiology in general) is rarely diagnostic by itself. Indeed, only three disorders are considered to have pathognomonic ERGs: cone dystrophy with supernormal rod ERG, enhanced S-cone syndrome, and bradyopsia[7]. In particular, bradyopsia requires a specialized testing protocol beyond the ISCEV standard ERG and can be missed or misdiagnosed if only the standardized ffERG protocol is used. Barring these three exceptions, the ffERG coupled with a thorough clinical history and ancillary examination the full-field ERG can be immensely helpful in the diagnosis of a wide range of conditions including retinal dystrophies (e.g. retinitis pigmentosa, cone-rod dystrophy, congenital stationary night blindness, fundus albipunctatus, X-linked retinoschisis), cases of infants with nystagmus or visual loss (e.g. Leber congenital amaurosis, achromatopsia), autoimmune retinopathy (paraneoplastic MAR/CAR, or non-paraneoplastic), drug toxicity (vigabatrin, quinine), vitamin A deficiency, retained metallic intraocular foreign bodies (to determine and monitor retinal toxicity) and as one more clue in cases of unexplained visual loss (looking for evidence of diffuse retinal dysfunction).

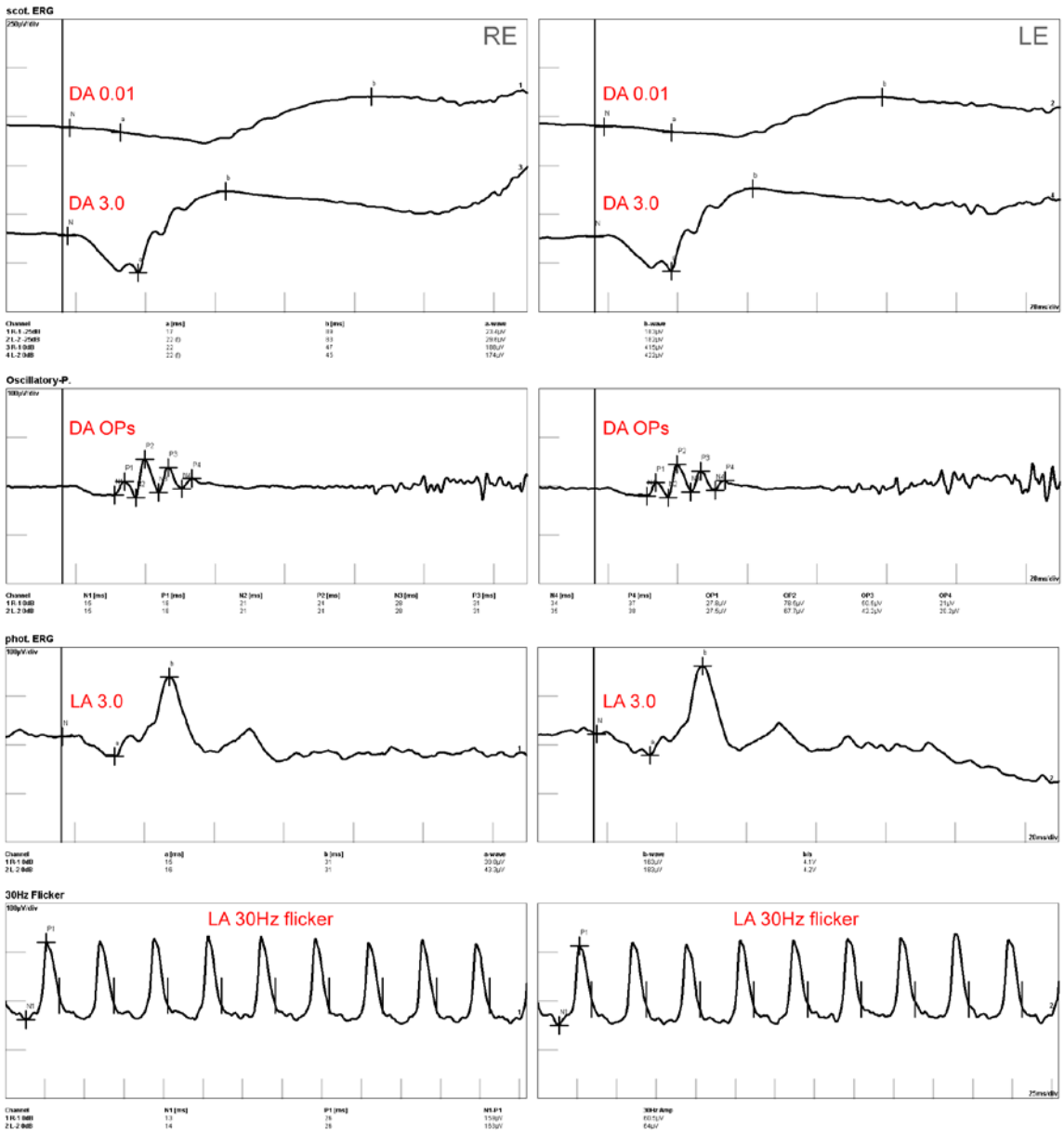

Figure 1 - Example of a normal ffERG, obtained in dark-adapted (DA) and light-adapted (LA) conditions. Amplitude and implicit time for each waveform component are quantified below each panel. The normal DA 0.01 (weak flash) is notable for the non-recordable a-wave (too small to be detected) and the prominent rod-driven b-wave. The normal DA 3.0 (strong flash) represents a combined, though rod dominated, rod-cone response; the a-wave and b-wave are clearly inscribed and oscillatory potentials (OPs) can be appreciated in the upper-limb of the b-wave. The OPs can be isolated using a DA OPs protocol, in which OP1 to OP4 are clearly distinguished. The LA 3.0 ERG demonstrates the cone-driven a- and b-wave. The LA 30Hz flicker is composed of multiple "b-waves" and represents a cone-driven response from post-receptoral pathways.

3. Pattern ERG

The PERG is a response generated through a checkerboard stimulus (alternating black and white squares in a regular phase frequency) and is mainly a measure of retinal ganglion cell function with contributions from other cellular elements. It is a macula-biased exam due to the high density of retinal ganglion cell projections in this area. It is important to note that while the PERG localizes the disease process to the macular area (or its projections through the optic nerve), it gives no topographical information in the context of localized macular dysfunction. Indeed, for characterizing macular function, the PERG has been somewhat superseded by the topographically informative mfERG.

The transient pattern ERG waveform is composed of negative (N) and positive (P) components, identified by the approximate latency in milliseconds from stimulus onset: the N35 (not always visible), P50 and N95. The P50 receives input from cells other than retinal ganglion cells while the N95 is dominated by retinal ganglion cell activity. In macular disease, reduction of the P50 is the primary alteration, with subsequent reduction of the N95 (such that the N95:P50 ratio is preserved or even increased). In the presence of an abnormal P50 wavelet, a ffERG will then differentiate between a generalized (and peripheral) retinal dystrophy or an isolated macular dystrophy (normal ffERG). Meanwhile, in optic nerve disorders, a relatively preserved P50 with a selective N95 reduction is found (decreased N95:P50 ratio). Some authors suggest that the PERG might be an important first exam when approaching any visual pathway dysfunction by using the P50 wavelet and the N95:P50 ratio as a way to differentiate between retinal/macular disease and optic nerve dysfunction[8,9]. However, in current clinical practice, the PERG is not used as frequently for this purpose since clinical history and examination, pupillary reflexes (namely a significant relative afferent pupillary defect in asymmetric optic neuropathies), visual field testing, optic disc evaluation (also with RNFL/GCC OCT) and brain imaging are usually sufficient to reliably identify (or exclude) primary optic nerve dysfunction.

4. Multifocal ERG

The mfERG as per the ISCEV standard measures cone function over 61 or 103 discrete hexagonal retinal areas within the central 40-50º of the posterior pole, centered on fixation (fovea). These hexagonal stimuli elements reverse rapidly between black and white frames in a pseudorandom sequence, in overall isoluminance conditions. The hexagonal pattern is scaled towards the periphery (increased hexagon size with increasing eccentricity) to produce comparable response amplitudes. The mfERG may be difficult (or impossible) to obtain and analyze in a patient with very poor visual acuity and/or nystagmus, due to inadequate fixation. The known pseudorandom sequence allows for cross-correlation and deconvolution of a waveform for each hexagonal element. The first-order response (first order kernel) of an hexagon is obtained by adding all the ERG recordings following a white frame and then subtracting all ERG recordings following a black frame. This produces a biphasic response consisting of an early negative component, N1, followed by a positive component,

P1. Each component may be characterized in terms of implicit time (time from stimulus onset to N1 trough/P1 peak) and amplitude (N1: from baseline to N1 trough; P1: from the N1 trough to P1 peak). The origins of the N1 and P1 components in this mathematically derived waveform remain unclear but are thought to include contributions from the same cells that compose the a-wave and b-wave of the light-adapted ffERG response, respectively. The spatial resolution of the mfERG allows for identification of discrete lesion areas (hemifield, annular, paracentral, ...) and when radial symmetry is present, averaging waveforms in concentric hexagon rings is an useful analysis strategy.

While the ffERG is not sensitive enough for the detection of macular damage and the PERG is not able to show topographical information, the mfERG does both. In a way, the mfERG is reasonably similar to a 24-2 visual field obtained by standard automated perimetry, though specific for cone-based macular function and without the need for subject collaboration aside from steady fixation. It provides no rod responses. It is particularly useful for the topographical evaluation of macular dystrophies (with or without generalized retinal involvement, as assessed by the ffERG) or, in more general terms, to demonstrate organic maculopathy (at any age if able to fixate) when the fundus is ambiguous or ancillary testing is inconclusive (e.g. early Stargardt or early hydroxychloroquine toxicity with inconsistent findings in visual field testing and OCT).

5. Electrooculogram (EOG)

The EOG is best described as a measure of retinal pigment epithelium (RPE) function. An electrical potential difference between the apical and basal surface of the RPE can be found, maintained by the integrity of both the RPE and the RPE - photoreceptors outer segments interaction. This potential difference creates a dipole between the cornea (positive) and the posterior eye (negative) and can be recorded using skin electrodes placed on both the medial and lateral canthus during 30º horizontal saccades. Fixation targets (15º to the right and the left) can be found in the ffERG ganzfeld dome and are alternately lit to direct fixation. The saccadic change of eye position allows for the indirect measurement of the resting potential of the RPE. The clinical EOG recording is initiated by a period of 15 minutes of dark adaptation, during which the recorded potential reaches a minimum (dark trough, DT), followed by a 15 minutes period of light adaptation, with an increase of the standing potential resulting in a light peak (LP). The LP/DT ratio is called the Arden ratio (usually between 1.7 and 4.3 in physiological conditions) and is a surrogate for RPE/photoreceptor function.

Importantly, severe rod dysfunction (as seen in the ffERG) will secondarily impair the EOG leading do a diminished Arden ratio, a non-specific finding with very limited clinical utility. Thus, the EOG is most useful when the rod-mediated ffERG is normal or mildly altered. In such scenario a decreased Arden ratio is indicative of primary RPE disease, such as Best disease (caused by mutations in bestrophin, a protein responsible for controlling a basal chloride channel in the RPE). Even so, while specific for Best disease in a suggestive clinical context, easy access to genetic testing has somewhat limited the clinical utility of the EOG in the present day.

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STARGARDT DISEASE

Juliana Sallum, Joao Pedro Marques, Rodrigo Brant

1. Synonyms

Fundus flavimaculatus, Stargardt 1, Juvenile Macular Degeneration

2. Epidemiology

Stargardt Disease (STGD) is an autosomal recessive maculopathy of early onset (childhood, early adulthood). It affects primarily the retinal photoreceptors and retinal pigment epithelium (RPE). The condition was first identified by Stargardt in 1909, who described 7 patients with a recessive inherited retinal dystrophy characterized by progressive macular atrophy surrounded by deep yellow retinal lesions.[1] Later, Franceschetti coined the term Fundus Flavimaculatus (FFM), describing a disease characterized by "fishlike" (pisciform) yellow-white lesions, now described as " flecks".[2] STGD is the most common hereditary macular dystrophy, affecting 1 in 8000 to 1 in 10000 patients in the USA.[3,4,5] A recent study in the United Kingdom established an annual incidence between 0,110 and 0,128 per 100000 individuals in that country.[6]

A later age at onset (>50 years) has been reported in a small number of patients. Late-onset STGD shows clinical overlap with juvenile-onset STGD, except for the later age at onset, slower disease progression, and better visual acuity. This milder phenotype is probably related to more residual ABCA4 function.

3. Genetics

OMIM number: # 248200
Inheritance: Autosomal Recessive
Gene/Locus: *ABCA4* / 1p22.1
Gene Locus MIM number: 601691
Other gene mutations involved: *ELOVL4*, *BEST1*, *PRPH2*

4. Signs and Symptoms

STGD is one of the most frequent causes of macular degeneration in childhood. The usual presentation is bilateral loss of central vision, which typically occurs between 7 and 20 years old. Visual deterioration is more rapid in the childhood onset form and most cases have a BCVA of 20/200 or less within two to three years of onset of disease. Deterioration thereafter is usually slow. Although central visual acuity is severely reduced, peripheral visual fields remain normal in most cases during the life spam of the individual.

In the early stages, no distinct macular or retinal changes are observed in the ophthalmological exam. The first ophthalmological sign is the disappearance of the foveolar reflex. In the original paper by Stargardt, the author described the occurrence of multiple yellow spots evenly distributed in the retinal fundus (flecks), located beneath the vessels, situated at the level of the RPE and sparing the peripapillary area (Figure 1). In more advanced stages, an oval area of RPE atrophy is seen, typically with a "beaten bronze" appearance. As the central atrophic zone increases in diameter, the advent of new flecks can be observed. However, in end stage STGD, the flecks may disappear with the increasing atrophy of the RPE. At this point, the underlying choroidal vascular net becomes visible (Figure 2).

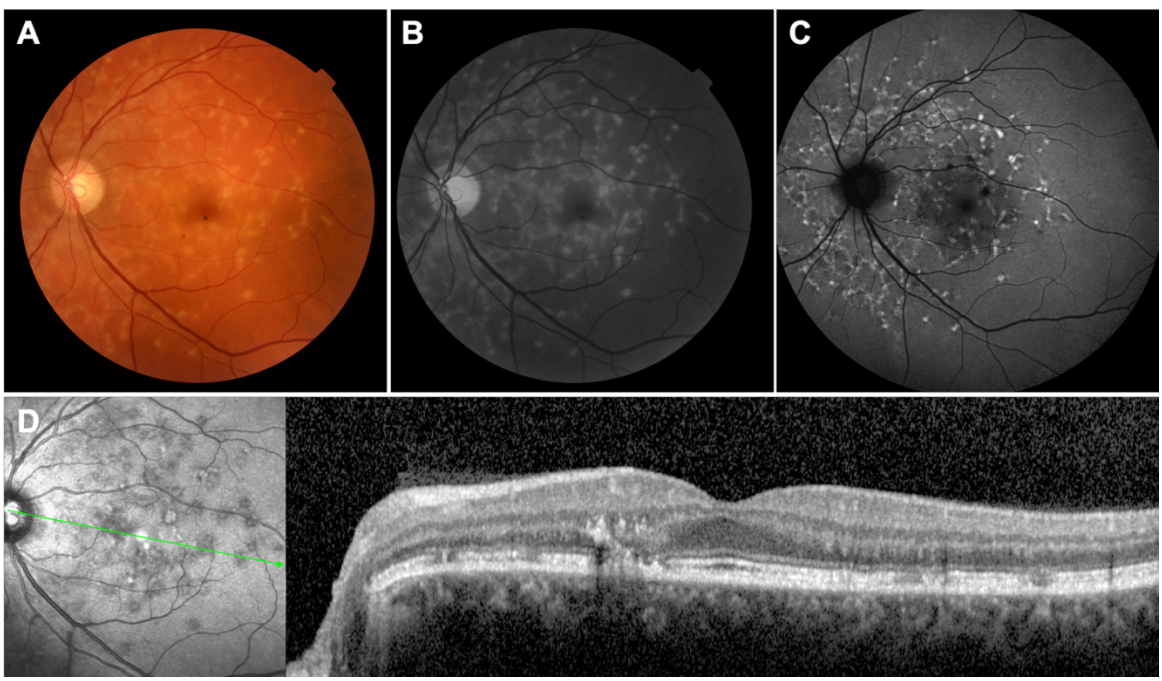

Figure 1. Multimodal retinal imaging in a case of early STGD. (A) Color Fundus Photography depicting multiple yellowish spots with a pisciform configuration (flecks) evenly distributed in the retinal fundus but sparing the peripapillary area. (B) The flecks appear white on Red free imaging. (C) On Fundus Autofluorescence (FAF), the atrophic flecks are hypoautofluorescent. The more recently developed flecks are hyperautofluorescent and represent lipofuscin accumulation in areas at risk of becoming atrophic. (D) Spectral-domain optical coherence tomography (SD-OCT) depicts areas of outer retinal atrophy along with the hyperreflective flecks.

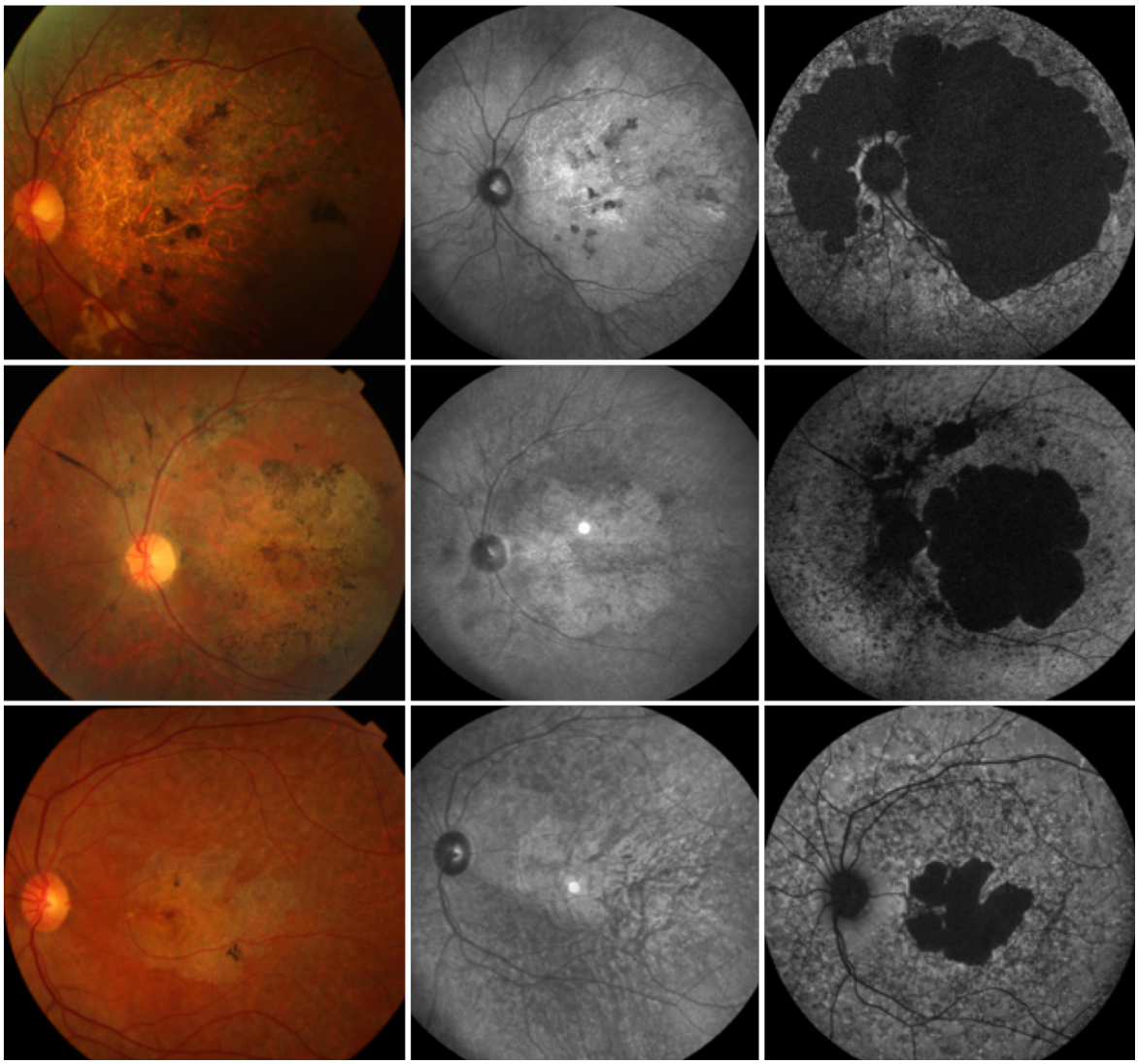

Figure 2 Three cases of end-stage STGD imaged with color fundus photography (CFP), near infra-red (NIR) and fundus autofluorescence (FAF). In advanced STGD the flecks disappear with the increasing atrophy of the RPE and pigment clumping can be seen. At this point, the underlying choroidal vascular net becomes visible and large areas of atrophy are identified as hypoautofluorescent coalescent zones on FAF.

5. Diagnosis and Imaging

Fluorescein angiography (FA) and Fundus Autofluorescence (FAF) can show a central defect in the RPE, with a normal periphery. Characteristically, FA depicts choroidal silence ("Dark Choroid") because of the increased filtering action of the RPE (Figure 3). In a study comparing macular cone structure, FAF and visual function in 12 patients with STGD and 27 age-matched individuals, the authors concluded that the disease progression correlates with lipofuscin accumulation leading to homogenous increased FAF with cone spacing abnormalities, followed by heterogeneously increased FAF with cone loss, and reduced FAF with cone and RPE cell death.[7] Due to its non-invasive

nature and ease of acquisition, FAF is extremely useful to document the progression of macular atrophy in STGD (Figure 4).

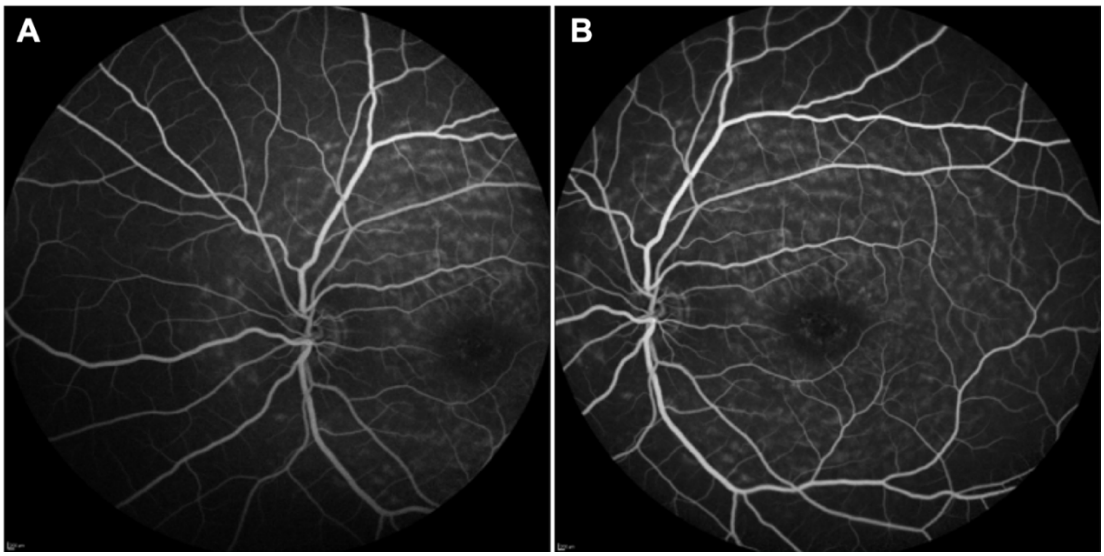

Figure 3 Field 1 (A) and field 2 (B) fluorescein angiography (FA) in a patient with STGD, highlighting the characteristic choroidal silence (dark choroid), macular flecks and peripapillary sparing.

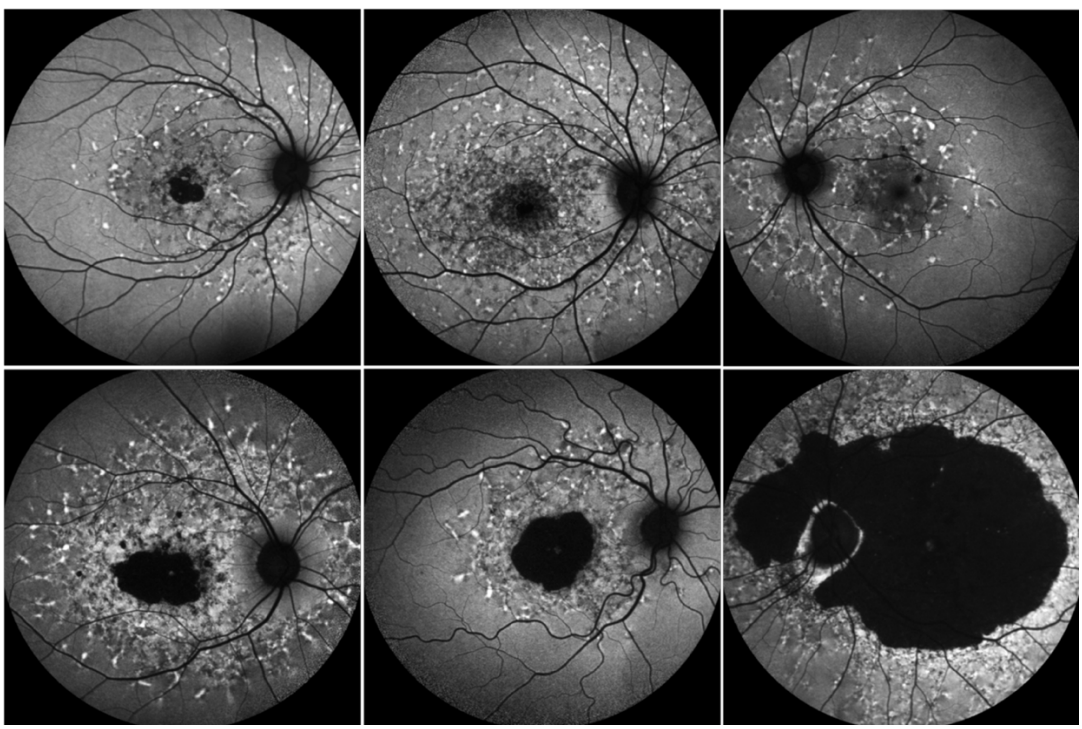

Figure 4 Fundus Autofluorescence (FAF) in STGD. Different patterns across different stages of SGTD are represented. Note the presence of flecks, atrophy and peripapillary sparing.

Spectral domain optical coherence tomography (SD-OCT) can show areas of disruption or complete loss of both inner and outer photoreceptors segment layers (Figure 1D), sometimes combined with thinning of other overlying retinal layers (Figure 6G). With the advent of OCT angiography (OCTA), the retinal and choroidal capillary networks could be studied, with new insights about the disease progression. In the early stages there is a severe loss of the choriocapillaris centrally and a transition zone of reduced choriocapillaris surrounding the central area of atrophy (Figure 5).[8] In advanced cases, OCTA images show increased intercapillary space and remodeling of the foveal avascular zone both at the superficial and deep retinal plexus (Figure 6D and 6E). Photoreceptor loss and RPE atrophy contribute to a notable central retinal thinning (Figure 6G).[9]

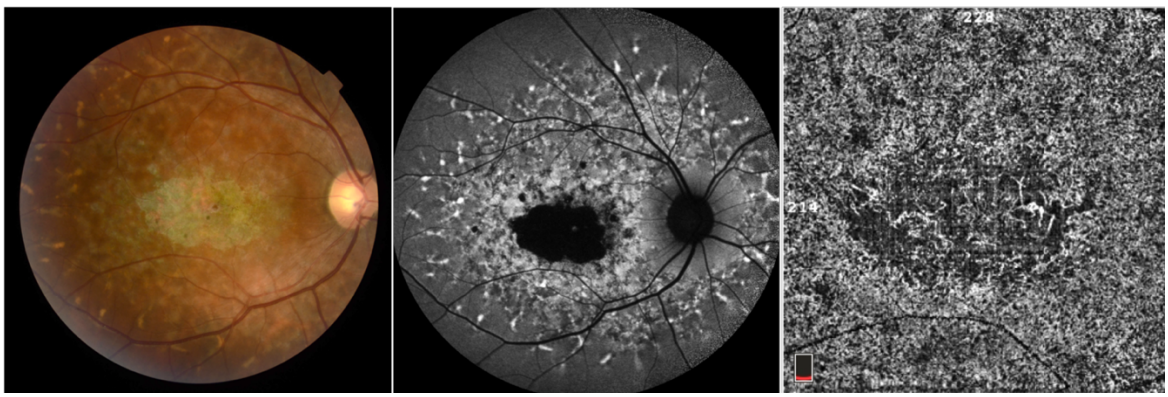

Figure 5 Central atrophy in STGD imaged from left to right with color fundus photography (CFP), fundus autofluoresecence (FAF) and optical coherence tomography angiography (OCTA). The choriocapillaris slab of OCTA depicts a central area of absence of choriocapillaris where the larger choroidal vessels are seen.

Fishman developed a 4 stage classification for STGD[10] that can be used clinically:

Stage 1 (Figure 7A)

- Pigmentary changes in macula (ranging from faint/irregular pigment mottling to beaten-bronze appearance to atrophy)
- Pisciform ring of flecks within 1 disc diameter on all sides of the fovea
- Normal Electroretinogram (ERG) and Electrooculogram (EOG)

Stage 2 (Figure 7B)

- Pisciform flecks present beyond 1 disc diameter from the margin of the fovea, often extending beyond the arcades and nasal to the optic disc
- ERG and EOG normal, but cone/rod response may be subnormal
- Prolonged period for dark adaptation

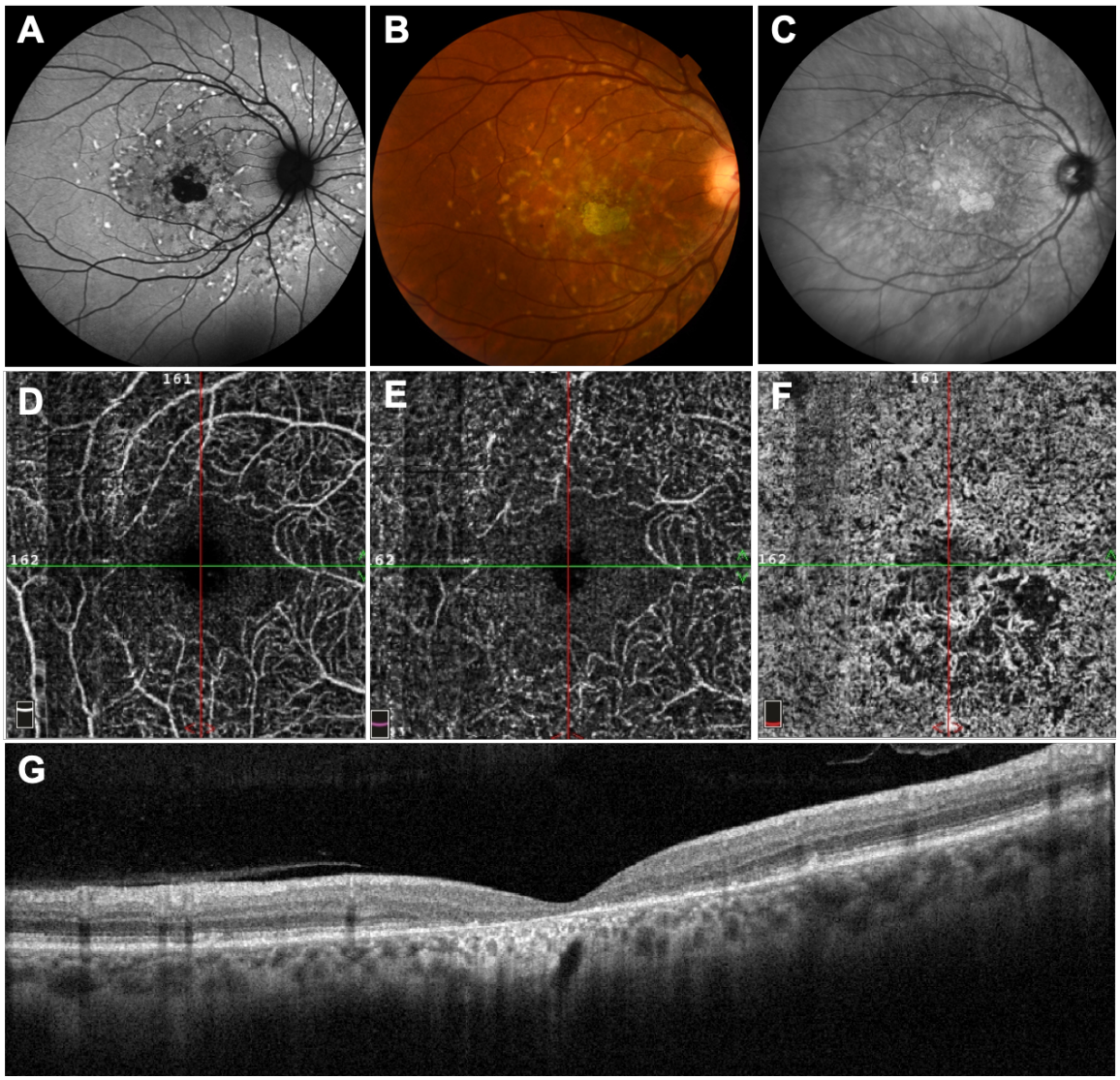

Figure 6 Fundus autofluorescence (A), color fundus photography (B) and near infrared imaging (C) highlight the flecks along with a central area of atrophy. Peripapillary sparing is of note. Images (D), (E) and (F) correspond to the optical coherence tomography angiography scan of the superficial capillary plexus, the deep capillary plexus and the choriocapillaris, respectively. Note the enlargement of the foveal avascular zone on D and E and the absence of choriocapillaris in the area of atophy. Spectral domain optical coherence tomography (G) depicts central retinal thinning with atrophy of the outer retinal layers.

Stage 3 (Figure 7C)

- Fundus exam shows diffusely resorbed flecks and choriocapillaris atrophy in the macula
- EOG testing reveals subnormal ratios
- ERG shows subnormal cone or cone and rod amplitudes
- Central field defects as well as peripheral/mid-peripheral field impairment can be seen

Stage 4 (Figure 7D)

- Fundus exam shows diffusely resorbed flecks and extensive choriocapillaris/RPE atrophy throughout entire fundus
- ERG testing shows reduced cone and rod amplitudes
- Peripheral fields show moderate to extensive restriction

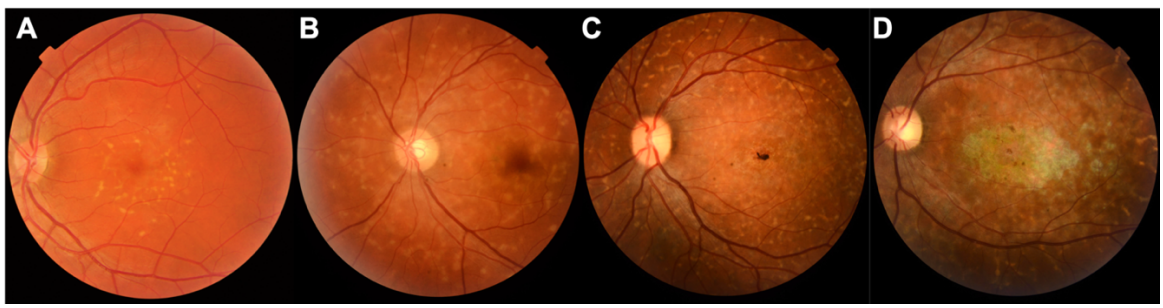

Figure 7 Different stages of STGD according to the Fishman Classification. (A) Stage 1 – few pisciform flecks are seen surrounding the fovea. (B) Stage 2 – flecks are more numerous and extend beyond the arcades and nasal to the optic disc. (C) Sage 3 – macular atrophy is now seen. (D) Stage 4 – extensive macular atrophy.

6. Treatment

Presently, no treatment options are available for SGTD, except for low vision rehabilitation.

Patients should be encouraged to maintain good sun protection and avoid high doses of vitamin A, which may lead to lipofuscin accumulation. Some patients report diminished vision when smoking, so smoking cessation should be encouraged.

Nevertheless, studies focusing on gene therapy, stem cell therapy and drugs that prevent the buildup of toxic metabolic waste products in the subretinal space are ongoing and will hopefully redefine the management of STGD in the years to come.

7. Prognosis

The visual prognosis is poor, leading to a final BCVA of 0,1 or worse in the end stages.

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BESTROPHINOPATHIES

Isabel Pires, Grimalde Trindade

1. Synonyms

Bestrophinopathies are inherited macular dystrophies caused by mutations in *BEST1* gene with heterogeneous phenotypes. To date, at least 5 distinct diseases have been associated with more than 200 mutations in *BEST1*: Best vitelliform macular dystrophy (BVMD), also known as Best disease, early-onset vitelliform macular dystrophy or juvenile-onset vitelliform macular dystrophy[1]; adult-onset vitelliform macular dystrophy (AVMD)[2]; autosomal recessive bestrophinopathy (ARB)[3]; autosomal dominant vitreoretinochoroidopathy (ADVIRC)[4] and retinitis pigmentosa (RP)[5].

2. Epidemiology

BVMD is the most common bestrophinopathy[6]. The incidence of BVMD has been reported to be 2/10.000 in Sweden[7], 1.5/100.000 in Denmark[8] and between 1/16500-1/21000 in Minnesota[9], underestimated due to absence of genetic testing[6]. AVMD (due to *BEST1* mutation), ARB, ADVIRC and RP are rare[6].

3. Genetics

The human *BEST1* gene (former *VMD2*) was identified in 1998, located on chromosome 11q12.3[1,10]. After that, 3 homologues were recognized: *BEST2*, *BEST3* and *BEST4* (former *VMD2LI*, *VMD2L2* and *VMD2L3*, respectively), not associated with human disease[11]. Bestrophin1 (Best1), the gene product of *BEST1*, is a transmembrane protein located at the basolateral plasma membrane of the RPE[12]. Within the RPE, Best1 functions as an anion channel and a regulator of intracellular calcium signaling [13, 14].

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Table 1. Genotype-Phenotype correlations among Bestrophinopathies

Gene *BEST1* chromosome	Disease Phenotype	Phenotype OMIM number	Inheritance pattern
11q12.3	BVMD	# 153700	AD
	AVMD	N/A	AD
	ARB	# 611809	AR
	ADVIRC	# 193220	AD
	RP	# 613194	AD

BVMD – Best vitelliform macular dystrophy; AVMD – adult-onset vitelliform macular dystrophy; ARB – autossomic recessive bestrophinopathy; ADVIRC - autosomal dominant vitreoretinochoroidopathy; RP – retinitis pigmentosa; MIM – Online Mendelian Inheritance in Man (www.omim.org); AD – autosomal dominant; AR – autosomal recessive.; N/A – not applicable

4. Signs and Symptoms

BVMD - variable age of onset –1st to 6th decade, mean 4th, and initial visual acuity (VA) - 20/200-20/20; usually bilateral and restricted to macula. Multiple macular lesions (multifocal Best disease), shallow anterior chamber or a macular hole may arise. Five stages have been proposed:

- Stage 1 (carrier/previtelliform): normal VA, RPE defects;
- Stage 2 (vitelliform): mild VA decrease, solitary 2-3mm central yellow subretinal vitelliform lesion (egg yolk) as depicted in Figure 1;
- Stage 3 (pseudohypopyon): the yolk settles and scrambles due to partial resorption of fluid;
- Stage 4 (vitelliruptive): VA loss; initial RPE atrophy (Figure 2)
- Stage 5 (atrophic/cicatricial): in this stage, choroidal neovascularization (CNV) may occur[15, 16].

AVMD - associated with mutations in *BEST1* and *PRPH2*, but the majority of the cases are idiopathic[6]. AVMD and BVMD overlap clinically, nevertheless AVMD has later onset – 5th decade, smaller lesion, slow progression and no or mild EOG decrease.

ARB - Rare; diagnosed in the first 2 decades of life with VA loss (around 20/40). Clinical findings include central serous detachment with subretinal scar, small vitelliform lesions scattered in the macular and extramacular area, usually sparing the peripapillary region (Figure 3). Hyperopia is a common finding among these patients[17].

ADVIRC – Rare, diagnosed in the 2nd decade or later. Characterized by peripheral pigmentary changes and white deposits, vitreous condensations; also hyperopia, shallow anterior chamber/narrow angle, early onset cataract, cystoid macular edema and retinal neovascularization[4,18]. Microcornea is usually present.

RP - Davidson *et al.* described the association of RP with *BEST1* mutation in five families, with variable age of onset[5]. Clinical findings included retinal gliosis, vascular attenuation, macular

edema, pale optic disk, flecks in the midperiphery, pigmentary changes in the periphery[17]. RP due to *BEST1* mutation may be multi-genic[6].

5. Diagnosis and Imaging

BVMD - EOG and Arden ratio are markedly abnormal (the later <1.55)[19]; genetic testing confirms BVMD. On Fundus autofluorescence (FAF), vitelliform material has increased FAF signal (lipofuscin accumulation) while RPE atrophy and scars have decreased. Fluorescein angiography (FA) reveals blocked fluorescence from vitelliform material in early frames, and late staining; as the yolk scrambles, window defects appear (RPE atrophy). OCT reveals hyperreflective material (vitelliform) between the photoreceptors and the RPE, RPE atrophy or CNV development. *AVMD* - EOG normal or slightly subnormal. *ARB* - EOG is decreased; FAF show mild increased FAF in the area of serous detachment and increased FAF in small vitelliform lesions; OCT and FA highlights serous detachment, vitelliform lesions and CNV. *ADVIRC* - EOG is abnormal.

6. Treatment

At the present moment there is no specific therapy for any of the bestrophinopathies[6]. Induced pluripotent stem cell derived RPE (iPSC-RPE) transplantation is appealing for bestrophinopathies – replacing damaged RPE with healthy RPE could cure patients with BVMD, AVMD; ARB, ADVIRC and RP. After genetic modification, healthy, patient derived iPSC-RPE could be transplanted and replace unhealthy RPE[6]. CNV may recover spontaneously or with intravitreal anti-VEGF therapy[20].

7. Prognosis

In BVMD legal blindness is rare, although an advanced disease stage is associated with VA loss[21]. AVMD is benign, with slow progression. ARB has mild VA loss, unless CNV develop[17]. ADVIRC is slowly progressive, with good visual prognosis[21]. RP is progressive, with central VA loss and constriction of the visual field[5].

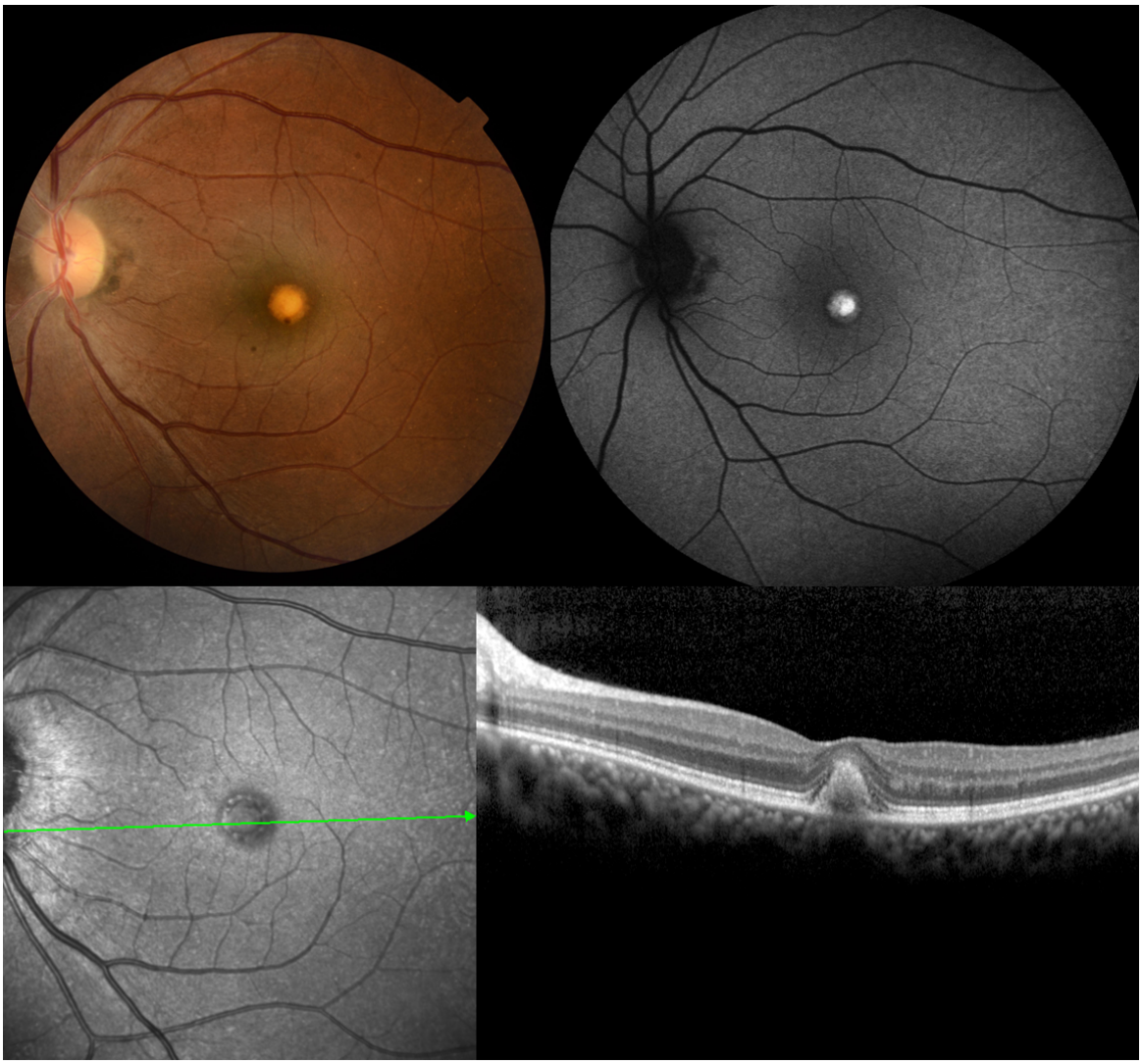

Figure 1. *Best vitelliform macular dystrophy, vitelliform stage. Note the solitary central yellow lesion (egg yolk) on color fundus photography* ***(top left)****. On fundus autofluorescence, the lesion appears hyperautofluorescent due to lipofuscin accumulation* ***(top right)****. Spectral-domain optical coherence tomography depicts hyperreflective material (vitelliform) between the photoreceptors and the RPE. (Courtesy of João Pedro Marques, MD)*

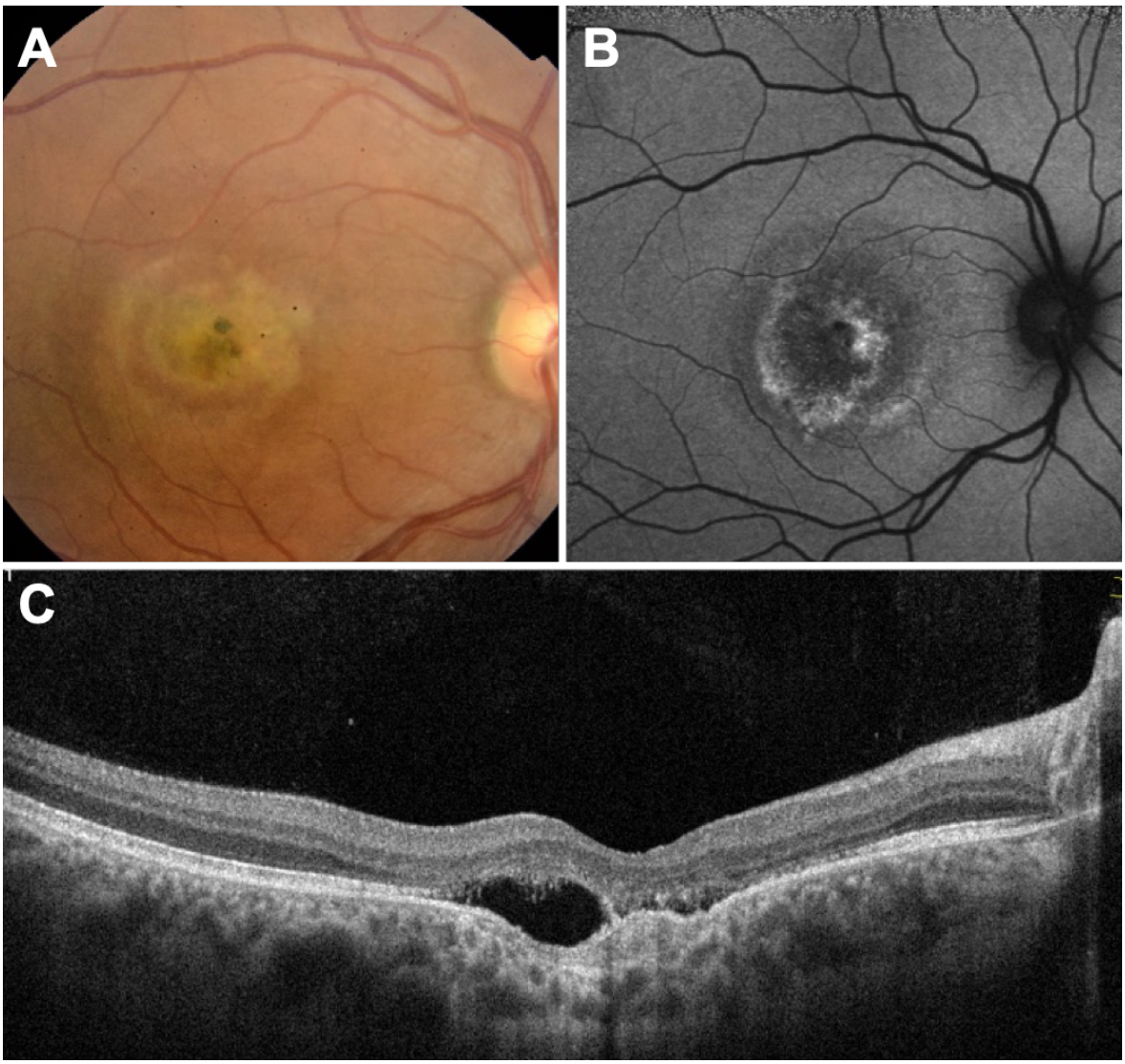

*Figure 2. Best vitelliform macular dystrophy, vitelliruptive stage. Multimodal imaging of the macula: **(A)** color fundus photography; **(B)** fundus autofluorescence; **(C)** OCT scan. (Courtesy of João Pedro Marques, MD)*

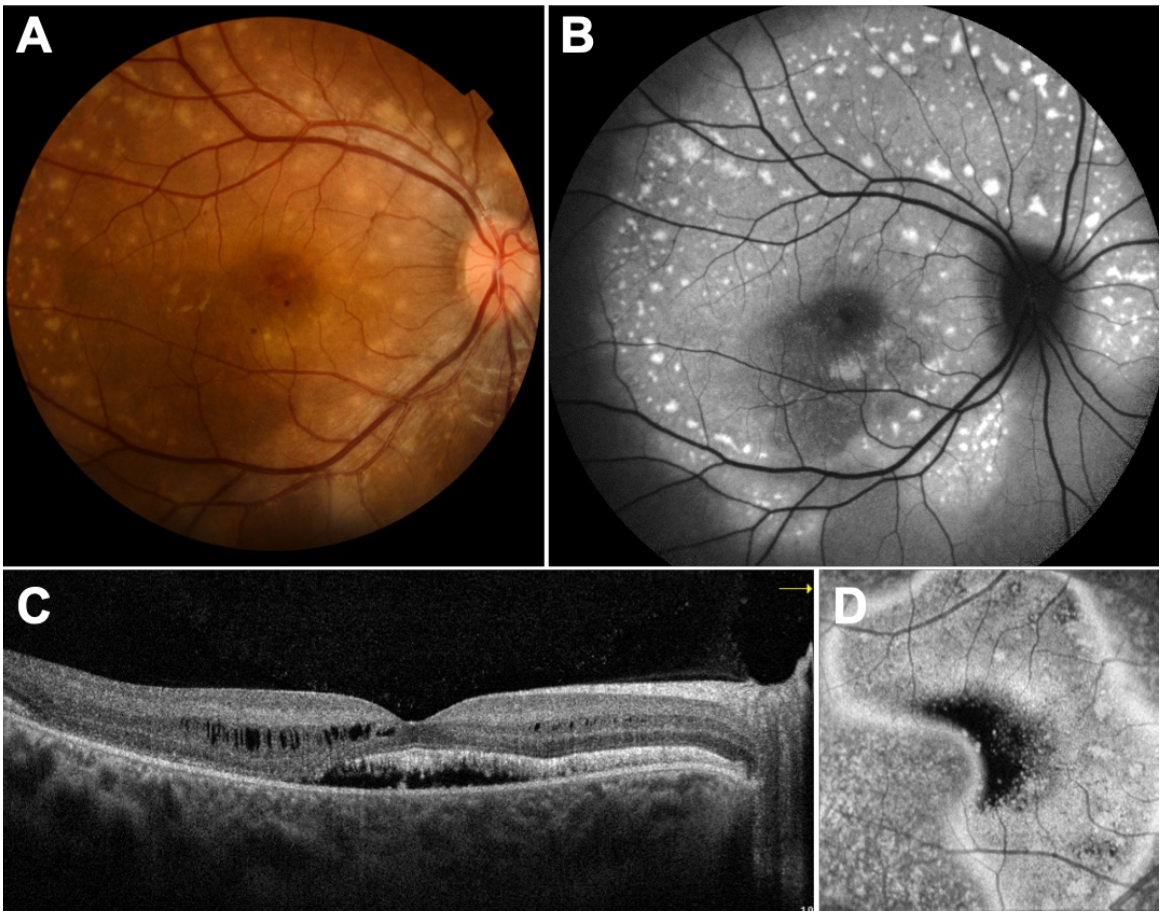

*Figure 3. Color fundus photography **(A)** and fundus autofluorescence **(B)** of a 22 year old hyperopic female with autosomal recessive bestrophinopathy show widespread yellowish flecks. Structural optical coherence tomography (OCT) shows intraretinal and subretinal fluid **(C)**. However, the best imaging method to document the extension of the subretinal fluid accumulation is the enface OCT **(D)**. (Courtesy of João Pedro Marques, MD)*

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LATE-ONSET RETINAL DEGENERATION

José F. Costa, Joana Pires

1. Synonyms

LORD; L-ORD; Late Onset Retinal Dystrophy; Autosomal Dominant Haemorrhagic Macular Dystrophy.

2. Epidemiology

Late-onset retinal degeneration (LORD) is a rare disease and its prevalence is currently unknown. Both genders are affected equally, with symptoms usually starting on the 5th to 6th decades[1].

3. Genetics

LORD (OMIM #605670) is an autosomal dominant rod-cone dystrophy primarily caused by mutations in the *C1QTNF5* (C1q and Tumour Necrosis Factor Related Protein 5) gene located at 11q23.3[2]. The function of this protein, which is expressed in retinal pigment epithelium (RPE) cells[3], is unknown. Mutations in the *C1QTNF5* gene might destabilize its product and lead to the formation of high molecular weight protein aggregates that accumulate in the endoplasmic reticulum, which impair RPE function[4]. This, in turn, leads to a deficient degradation of extracellular components, which accumulate beneath the RPE[5].

4. Signs and Symptoms

Patients with LORD are usually asymptomatic until their 40s. At this stage, the only ocular findings are long and anteriorly inserted zonules associated with atrophy of the iris border (Figure 1A and 1B)[1]. This might result in secondary open angle glaucoma, similar to what occurs in pigment dispersion syndrome[6].

The first symptoms are usually nyctalopia and delayed dark adaptation, which might precede fundoscopic changes[7]. These entail yellow-white macular punctate deposits and unspecific

pigmentary abnormalities in the midperiphery (Figure 1E). As they progress over several years, these areas comprised of sub-RPE deposits result in well-demarcated regions of chorioretinal atrophy that begin in the temporal retina and slowly progress to the fovea[8]. It is at this stage, usually after the 6th decade, that patients complain of worsening visual acuity. Ultimately, retinal atrophy affects both the posterior pole and the periphery, resembling late *retinitis pigmentosa*.

Sudden decreases in visual acuity are usually secondary to choroidal neovascularization (CNV), a common occurrence in late LORD. These lesions rapidly regress, resulting in subretinal fibrosis and atrophy[1].

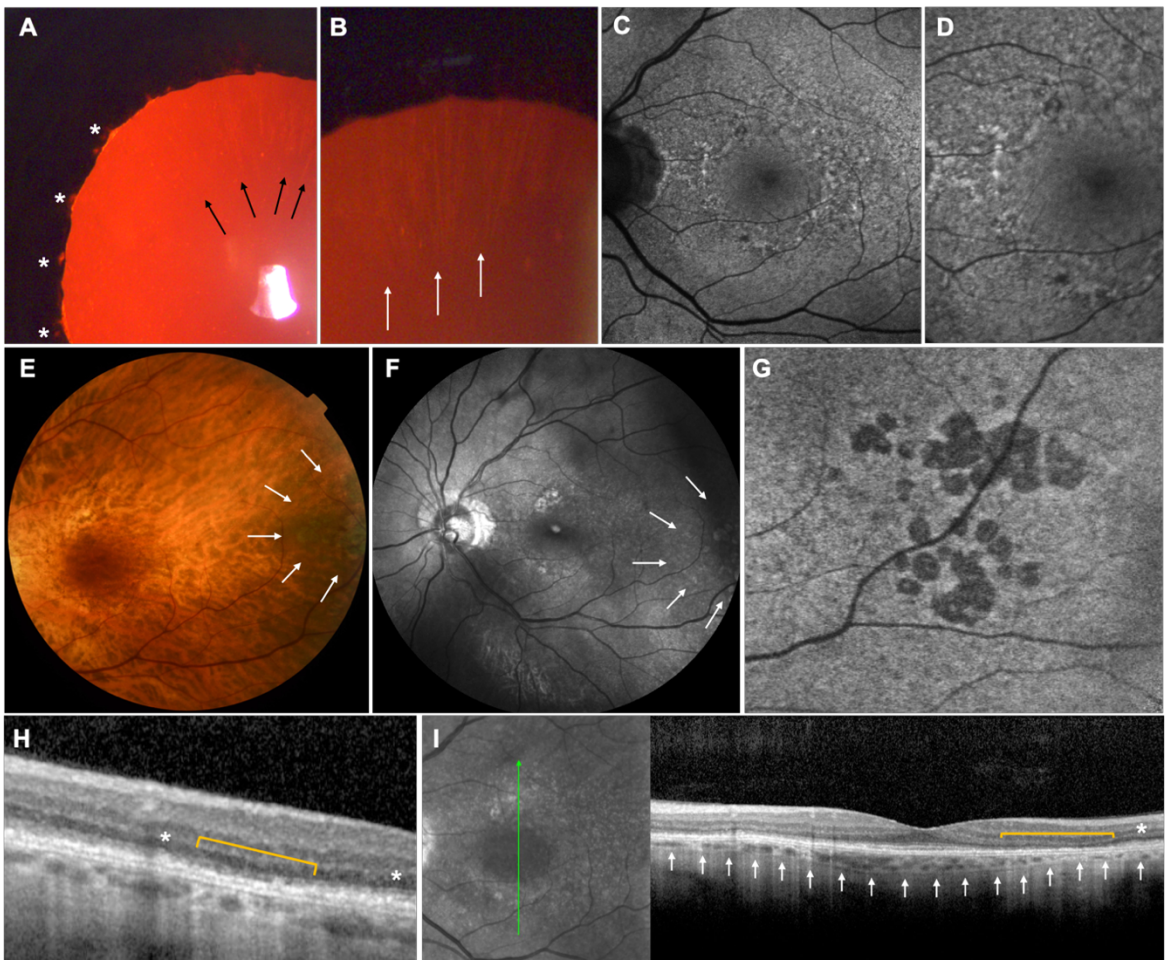

Figure 1 *Multimodal retinal imaging of a 67-year old male patient with LORD. The patient started complaining of delayed dark adaptation on his 50s.* ***(A)*** *and* ***(B)*** *Slit-lamp biomicroscopy showing anteriorly inserted zonules (arrows) and iris border atrophy (asterisks).* ***(C)*** *and* ***(D)*** *Fundus autofluorescence (FAF) reveales speckled hyper- and hypoautofluorescence surrounding the fovea.* ***(E)****, and* ***(F)*** *chorioretinal atrophy on the temporal macula (arrows) imaged with colour fundus photography and near infrared imaging.* ***(G)*** *A close up view of the same are imaged with FAF reveals the typical scalloped hypoautofluorecent patches associated with LORD.* ***(H)*** *and* ***(I)*** *SD-OCT B-scans detailing the subretinal deposits and thickening of the RPE/Bruch complex (asterisks), areas of outer retinal atrophy (brackets) and a thinned choroid (arrows). (Courtesy of João Pedro Marques, MD)*

5. Diagnosis and Imaging

Multimodal imaging is paramount in LORD diagnosis. SD-OCT in early LORD shows sub-RPE deposits of medium internal reflectivity, occasionally with a saw-toothed pattern mimicking retinal pseudodrusen (Figure 1H and 1I). As the disease progresses, overlying outer retinal disruption becomes evident. Additional findings include intraretinal hyperreflective deposits and choroidal thinning (Figure 1I)[8, 9]. Fundus autofluorescence shows scalloped areas of hypofluorescence that correspond to chorioretinal atrophy (Figure 1G). These are surrounded by speckled hyper- and hypofluorescence, implying lipofuscin accumulation (Figure 1C and 1D)[9]. Their location and extent mirrors the different stages of the disease. Full-field ERG has a pattern of rod-cone dysfunction but pattern ERG shows a greater degree of macular involvement than what is commonly seen in rod-cone dystrophies[10].

The main differential of early LORD is Age-related Macular Degeneration (AMD). Both entities present with delayed dark adaptation and sub-RPE deposits that progress to choroidal atrophy and CNV[1]. Early age of symptoms onset, peripheral involvement and family history aid in the diagnosis of LORD. Similarly, LORD might be mistaken for Sorsby Fundus Dystrophy, but these patients usually present with nyctalopia earlier, during their 30s, and the peripheral retina is relatively spared[10]. Advanced cases of LORD have less defining features and might be confused with several other diseases, including Choroideraemia, Gyrate Atrophy and Retinitis Pigmentosa[1]. At this stage, the anterior insertion of the zonules is helpful in making a correct diagnosis, as it is a unique feature of LORD.

6. Treatment

Vitamin A supplementation (up to 50,000 IU/day) might have a role in improving dark adaptation in early LORD[11, 12] (evidence level IV). Jacobson *et al* suggested that this is due to the sub-RPE deposits that limit the normal transport of nutrients to the retina and lead local chronic vitamin A deficiency[11]. If CNV develops, intravitreal anti-VEGF might be administered (evidence level V), but few cases have been reported and the results were not encouraging[13].

Additional causes of vision loss, such as secondary glaucoma and cataract, should be monitored. Cataract surgery can be safely performed in patients with LORD (evidence level IV), but special care must be taken during capsulorrhexis, as these patients might present a central zonule-free area as small as 3 mm[14].

7. Prognosis

LORD is an invariably progressive disease and most patients become legally blind in their 60s[14]. Therefore, early referral to a low vision specialist and prescription of visual aids is essential in allowing patients to continue to function safely and efficiently as they age.

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AUTOSOMAL DOMINANT DRUSEN (MALATTIA LEVENTINESE)

Lilianne Duarte, Ana Rita Laiginhas, Jennifer Jesus, Rafael Staudt Geraldes

1. Synonyms

Autosomal Dominant Drusen (ADD)/ Dominant Radial Drusen (DRD)/ Doyne Honeycomb Retinal Dystrophy (DHRD)/ Malattia Leventinese (MLVT).

2. Epidemiology

The term autosomal dominant drusen (ADD) describes a group of visual disorders that share phenotypic similarities with age-related macular degeneration (AMD), in which radiating drusen and macular degeneration occur in younger patients [1–3]. Two specific conditions were initially described as separate entities. First, Robert Walter Doyne coined the term Doyne honeycomb retinal dystrophy (DHRD) in 1899[4]; and a few years later, in 1925, a similar condition found in family members from the Leventine Valley of southern Switzerland was named Malattia Leventinese (MLVT) [5]. Only more than half a century later, in 1999 it was suggested that both disorders were no more than phenotypic variations of a defect in the same gene encoding the fibulin3 protein [1].

ADD normally manifests at younger ages comparing to the clear majority of cases of AMD. Affected patients typically exhibit drusen in the second and third decades, with the earliest reported age at 15 years old [6], although in several cases the condition remains asymptomatic until the fourth or fifth decade of life [1,7]. The prevalence of this rare condition remains unknown.

3. Genetics

OMIM (Online Mendelian Inheritance in Man; www.omim.org) ID:
Phenotype MIM number: # 126600
Phenotype: Doyne Honeycomb Retinal Degeneration
Location: 2p16.1

Inheritance: Totally Autosomal Dominant
Phenotype mapping key: 3
Gene/Locus: *EFEMP1*
Gene/Locus MIM number: 601548

Inherited in an autosomal dominant manner, a single non-conservative mutation from an arginine to a tryptophan in amino acid 345 (R345W) was identified in the epidermal growth factor (EGF)-containing fibulin-like extracellular matrix protein 1 gene (EFEMP1), located on chromosome 2, that encodes the protein Fibulin-3 [1,3,8–11].

4. Signs and Symptoms

The phenotype is extremely variable, with evidence of interocular, intrafamilial, and interfamilial variability[12,13].

The mild forms, usually found up to the age of thirty, characteristically present few small and innocuous hard drusen confined to the macula with preserved visual acuity (VA). [14,15]. The moderate form, mostly found after the 5th decade of life, is characterized by soft large drusen located at the posterior pole and peripapillary region. Drusen progressively increase in size and become confluent resulting in a honeycomb appearance[16]. At this stage, the patient can start a variety of symptoms, including reduced VA, paracentral scotomas, photophobia and metamorphopsia[14]. In advanced stage, vision loss may occur due to atrophic changes, sub-retinal pigmented epithelium (RPE) deposition of drusenoid material, and secondary choroidal neovascularization. If the disease continues to progress, additional central visual loss occurs, absolute scotoma become evident and patients usually blind by the age of 70 years [14] [17]. Differential diagnosis of ADD includes: cuticular/basal laminar drusen, AMD, Sorsby Macular Dystrophy, Stargardt Disease/Fundus Flavimaculatus , Pattern Dystrophies, Zermatt Macular Dystrophy, later stages of Best Disease .

5. Diagnosis and Imaging

On fluorescein angiography, drusen show two different patterns of staining: small drusen are hyperfluorescent in the early phases and become less hyperfluorescent during the late phases, while large drusen are hyperfluorescent in the early phases and then increase the hyperfluorescence, in the late phases[13]. On indocyanine green angiography, small radial drusen are mostly hyperfluorescent in the early phases with decreased fluorescence in the late phases of the sequence, whilst large drusen present hypofluorescence in the early phases and hyperfluorescent spots surrounded by a small halo of hypofluorescence in the late phases[18].

In fundus autofluorescence, a wide spectrum of focal hyperautofluorescence is observed in large drusen, while small drusen have less fluorescence intensity. A normal background autofluorescence has been reported.[19,13,20]

Some histopathologic reports have been published, illustrating deposits external to the basement membrane of the RPE that occupy the entire thickness of Bruch's membrane[21]. These features can be observed with Optical Coherence Tomography (OCT).

On spectral domain OCT (SD-OCT), small drusen appear as irregular thickening of the RPE/Bruch's membrane complex or as sawtooth RPE elevations. Large drusen are identified as focal or diffuse deposition of hyperreflective material between the retinal RPE and Bruch's membrane within the macula, determining focal dome-shaped or diffuse RPE elevation, respectively (Figure 1)[16].

Patients with ADD have also been studied using OCT angiography (OCTA-A)[22,23]. The authors concluded that OCT-A could be used in the early detection of CNV, thus precluding the need of Fluorescein Angiography.

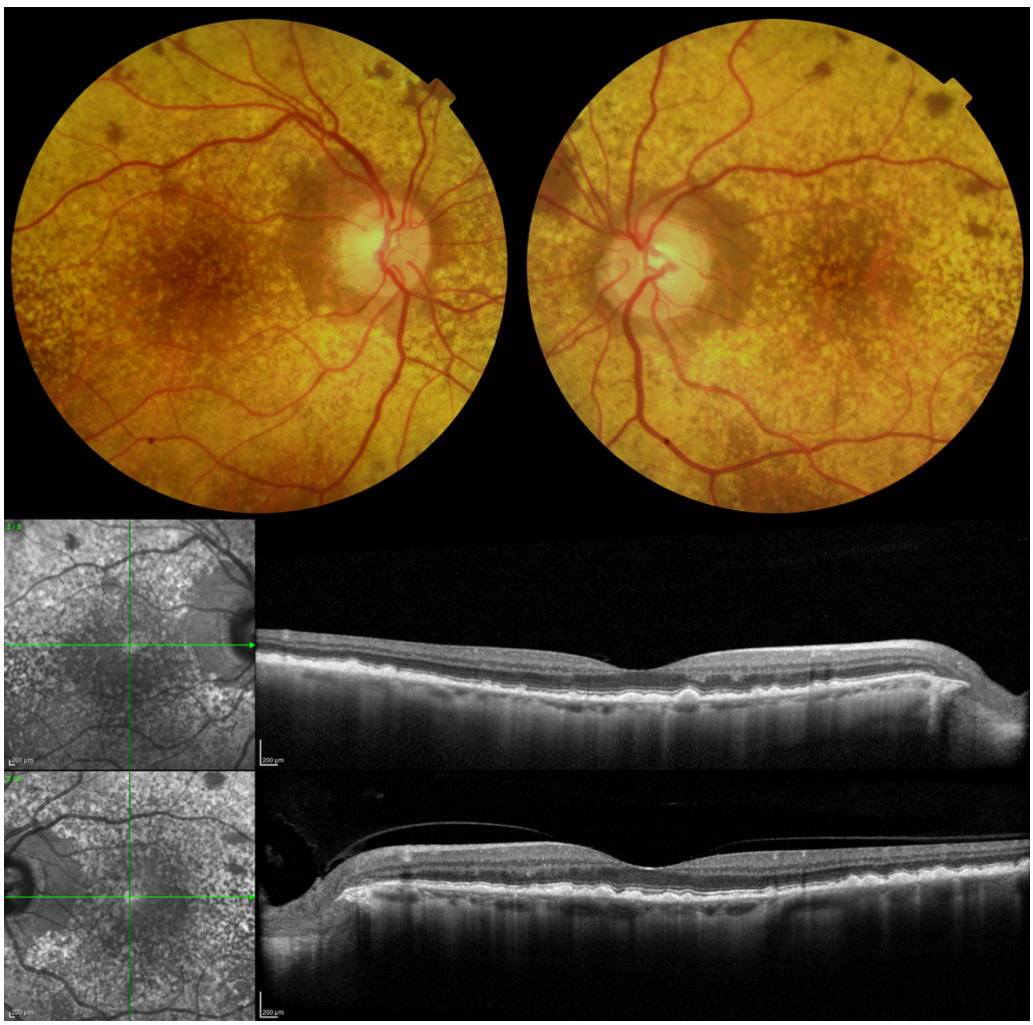

*Figure 1 A case of a middle-age woman, with best corrected visual acuity of 20/20 OU. Fundus image **(top)** showing scattered small and large drusen, appearing bright white on near-infrared images **(left bottom)**. On OCT **(right bottom)** small drusen appear as irregular thickening of the RPE/Bruch's membrane complex or as sawtooth RPE elevations. Large coalescent drusen form drusenoid deposits of the RPE.*

6. Treatment

As for many inherited retinal diseases, no medical or surgical specific treatment has been shown to treat, slow or prevent ADD [9]. Regular follow up is advised and patients should be instructed to report decreases in VA or *de novo* metamorphopsia, since the advent of CNV should prompt anti-VEGF treatment. Since ADD shares many phenotypic similarities with AMD (beside pathophysiologic differences), ADD-related CNV treatment should follow the guidelines for AMD-related CNV [2,11,24]. Before the anti-VEGF era, laser photocoagulation and photodynamic therapy were used to treat ADD-related CNV. Laser photocoagulation of the CNV has shown to lead to drusen reabsorption, significant improvement in VA, an increase in retinal sensitivity, a reduction in drusen thickness and was used as a prophylactic treatment for proliferative CNV [25,26,9]. It was suggested that laser treatment could accelerate the natural process of clearing the deposits of drusen material by retinal and choroidal phagocytic cells [27,28,29,30]. Photodynamic therapy was described in a few cases leading to VA improvement with long term visual and angiographic stability [31].

Intravitreal anti-VEGF therapy is now the gold-standard for CNV of any ethology, including ADD. Treatment of ADD-related CNV with Anti-VEGF (ranibizumab, bevacizumab, and aflibercept) demonstrated VA improvement, decrease in retinal edema and recovery of the retinal architecture (including foveal contour) on OCT, despite some RPE changes [32,33]. As in AMD, some lesions could be unresponsive to anti-VEGF therapy. Anecdotal reports of treatment with intravitreal triamcinolone have shown good results, suggesting that some lesions may represent a stage of degeneration similar to those observed in other dystrophic disorders such as best vitelliform macular dystrophy [34,35].

Although unusual, patients with ADD may occasionally present with submacular haemorrhage. Various treatment options, including observation, intravitreal gas, macular translocation, anti-VEGF, photodynamic therapy and pars plana vitrectomy are accepted.

7. Prognosis

Due to the rarity of the condition, specific treatment guidelines for the complications of ADD are not available. Further studies, with long-term follow-up, are needed to confirm the real benefits of the above-mentioned treatments and to determine the appropriate stage of disease to administer each intervention.

Despite ADD could seem innocuous during a long time, poor visual prognosis may develop in progressive forms managed conservatively. Patient education is very important to promptly diagnose CNV and begin treatment in order to enhance the patient's chances of a successful recovery.

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CUTICULAR DRUSEN

Sandra Barrão

1. Synomyms

Basal laminar drusen; drusen of Bruch membrane; early adult-onset grouped drusen

2. Epidemiology

Age-related macular degeneration (AMD) is the most common cause of visual impairment and blindness among older adults across the developed world. Cuticular drusen (CD) represent a distinct retinal drusen phenotype, although genetically related to AMD. CD were first described by Gass in 1977 as 'a distinctly different pattern of innumerable, uniformly small discretely round drusen, usually 25-75 mm in size, slightly raised, yellow subretinal nodules, that occurs in early and mild adulthood, and which may give the entire macular and paramacular area an orange peel appearance'. Clinically, he characterized cuticular drusen by a starry-sky fluorescence pattern (a 'stars-in-the-sky' or a 'milky way') most evident during the arteriovenous phase of fluorescein angiography (FA), as depicted in Figures 1 and 2.

CD have been found to present in twice as many women than men. A positive family history of drusen is frequently observed sharing an association with the Y402H haplotype of the *CFH* gene.

3. Genetics

Phenotype MIM number: # 126700
Phenotype: Basal Laminar Drusen
Location: 1q31.3
Inheritance: Autosomal Dominant
Phenotype mapping key: 3
Gene/Locus: *CFH*
Gene/Locus MIM number: 134370

Other genetic variants in the *ARMS2*, *CFB/C2*, *C3*, and *APOE* genes have been described. Genetic testing, including for the *CFH* Y402H risk allele, may become an useful diagnostic adjunct to imaging. This is particularly important given the relationship between CD and systemic diseases, such as renal insufficiency (dense deposit disease, also known as membranoproliferative glomerulonephritis type II with end-stage renal disease).

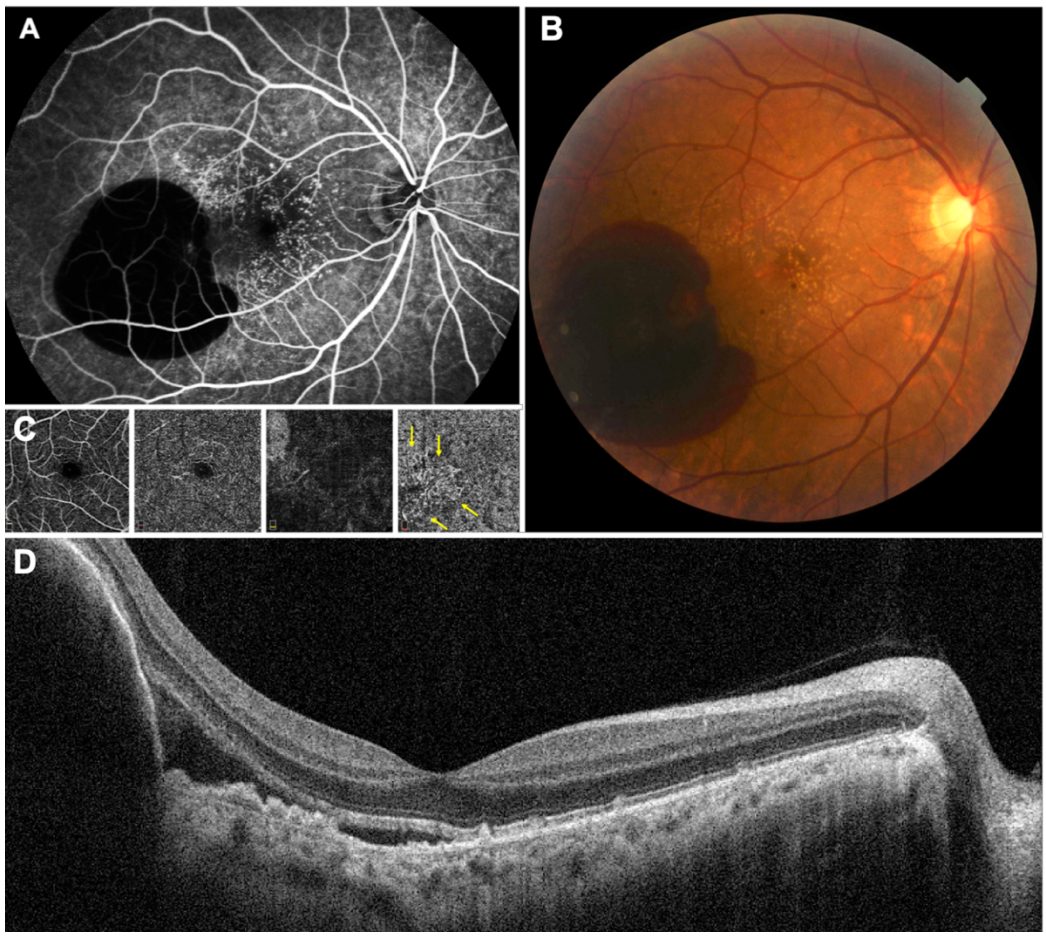

Figure 1 *Multimodal retinal imaging of a 32 year old male patient with cuticular drusen complicated by choroidal neovascularization (CNV).* ***(A)*** *Fluorescein angiography depicts the characteristic starry-sky fluorescence pattern along with a large subretinal hemorrhage. The hemorrhage and the cuticular drusen can also be seen on color fundus photography* ***(B)****. On Optical coherence tomography (OCT) angiography* ***(C)****, the choroidal neovascular membrane can be visualized easily on the choriocapillaris slab (yellow arrows). The horizontal structural OCT scan* ***(D)*** *demonstrates the precise location of the hemorrhage (sub-RPE), the presence of RPE undulation and double layer sign at the site of the type 1 CNV, subretinal fluid accumulation that involves the subfoveal area and the presence of cuticular drusen. (Courtesy of João Pedro Marques, MD)*

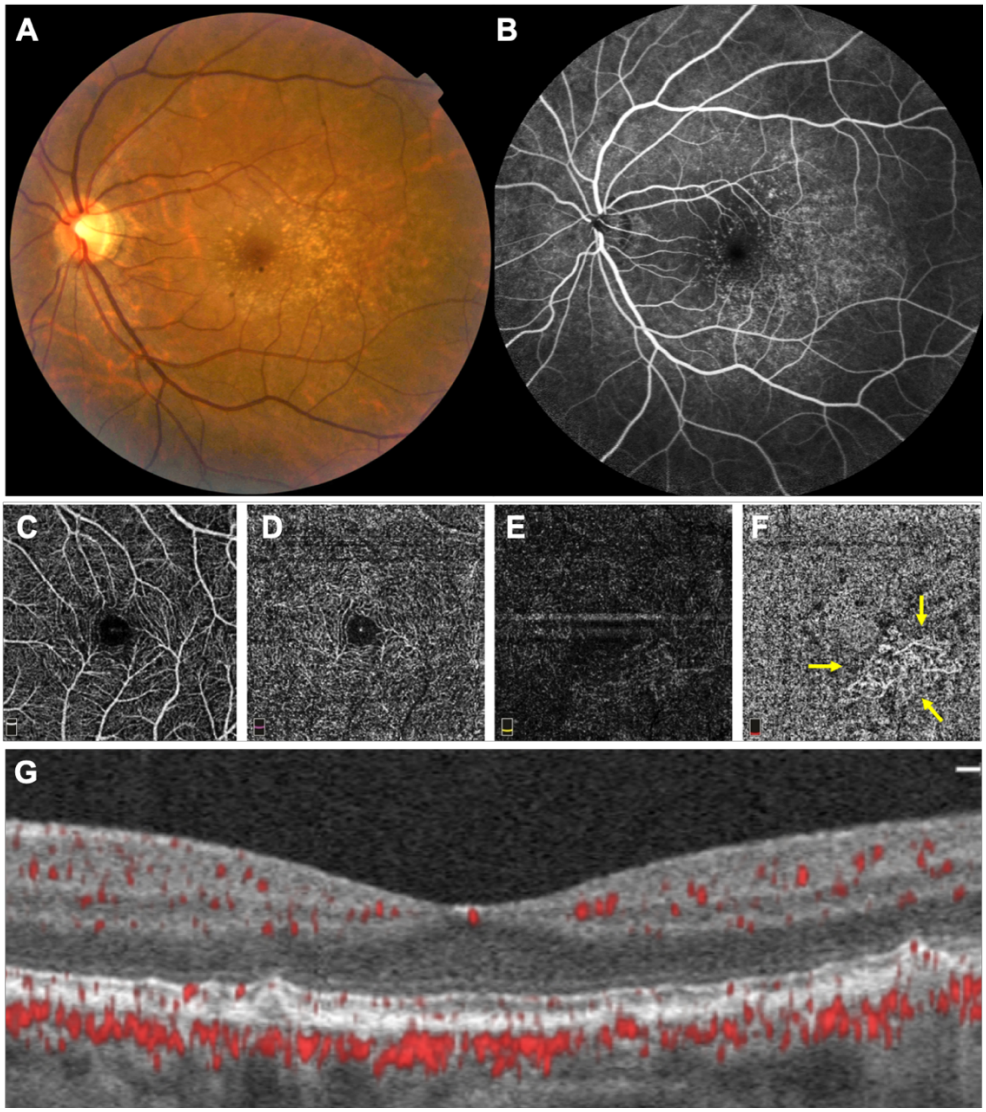

*Figure 2 Multimodal retinal imaging of the fellow eye of the patient imaged on Figure 1. **(A)** Color fundus photography depicts the cuticular drusen. Again, on fluorescein angiography **(B)**, the characteristic starry-sky fluorescence pattern is seen but no evidence of choroidal neovascularization. However, on optical coherence tomography (OCT) angiography **(C-F)**, a choroidal neovascular membrane can be visualized on the choriocapillaris slab **(F)**, highlighted with the yellow arrows. The horizontal structural OCT scan **(G)** seems unremarkable except for the presence of cuticular drusen. (Courtesy of João Pedro Marques, MD)*

4. Signs and Symptoms

Cuticular drusen typically become visible on fundoscopy in early adulthood, presenting as small (25-75 mm in diameter), yellowish, round, slightly raised subretinal deposits. In the early stages, generally asymptomatic, cuticular drusen are scattered randomly throughout the fundus, although a predilection towards the macular area is usually seen.

With advancing disease, these drusen often become more numerous, with clustered groups of drusen scattered throughout the retina. In time, these small basal laminar drusen may expand and ultimately merge to form a large vitelliform lesion, consisting on the subretinal accumulation of a semi-translucent to canary-yellow material. The affected vitelliform area may enlarge over time and contribute to a deterioration in visual acuity.

Other causes of vision loss are the advent of choroidal neovascularization (CNV) – usually developing at a younger age than typical AMD – or geographic atrophy (GA). CNV has been reported in 4-56% cases and GA can complicate the cuticular drusen phenotype in up to 1/3, with or without pre-existing CNV. Cuticular drusen are dynamic and exhibit characteristics of coalescence, resorption, and RPE disturbances. CD that enlarge undergo biochemical alterations, resulting in continuous deposits that constitute a substantial biophysical diffusion and transport barrier between the RPE and choriocapillaris and a nidus for inflammation, increasing the risk of complications.

5. Diagnosis and Imaging

Our understanding of CD phenotypes and life cycle is arguably less than it is for other drusen subtypes. CD appear to be histologically identical to typical small hard distinct drusen associated with AMD, but may have less overlying retinal pigment epithelium, creating that strikingly hyperfluorescent appearance on FA. Similar to hard and soft drusen, CD are localized between the basal lamina of the retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch's membrane, that is, the sub-RPE basal laminar compartment. The term cuticular drusen could be more accurate to define the condition because the cuticular layer comprises the basal lamina of the RPE and the inner collagenous layer of Bruch membrane. Aside from this unifying feature, there are several important distinctions in the morphologic characteristics, spatial density, and ultrastructure of sub-RPE drusen. These distinctions may signify separate pathways for CD biogenesis and may confer unique risks for the development of sight-threatening complications (resulting from GA and CNV). Precise drusen phenotyping serves an important purpose for stratifying the risk of complications in AMD as well as defining patient subsets that will benefit from specific therapies. This reiterates the importance of multimodal imaging evaluation for precise drusen phenotyping. The diagnosis of cuticular drusen may be erroneous if made in the absence of multimodal imaging.

5.1. Color and Red-free fundus photographs

On color photographs, cuticular drusen appear as clusters of multiple yellow or pale spots, with a diameter ranging from 25-75 mm. Size and spatial density of CD as seen in color and red-free photographs are comparable (Figure 3)

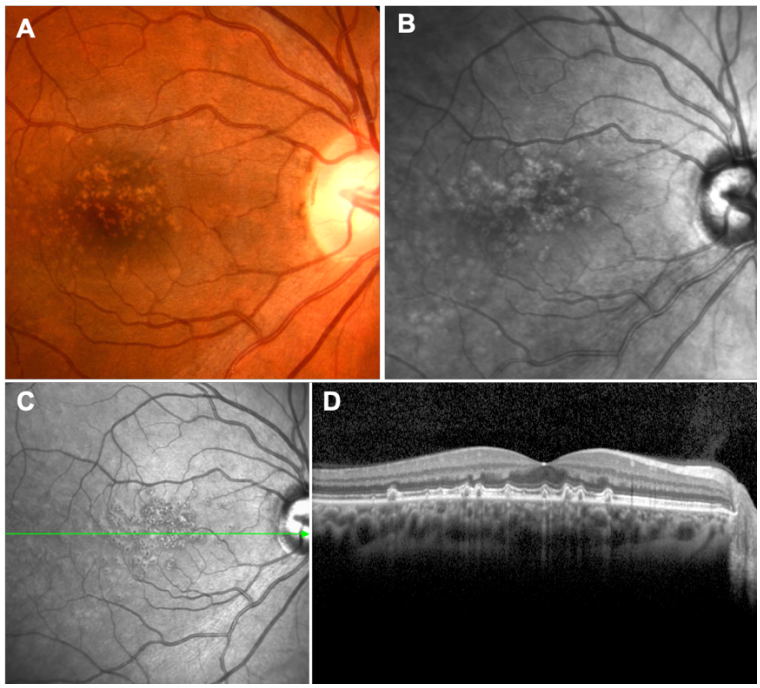

*Figure 3 Multimodal retinal imaging of a 41 year old female with a cuticular drusen phenotype. Note the multiple yellowish spots scattered in the macular area, whose size and spatial density are similar in color fundus photography **(A)**, redfree imaging **(B)** and near infrared imaging **(C)**. On spectral domain optical coherence tomography (SD-OCT), the characteristic "sawtooth" RPE elevations are seen **(D)**. (Courtesy of João Pedro Marques, MD)*

5.2. Fluorescein Angiography (FA)

On FA, cuticular drusen exhibit discrete dotlike hyperfluorescence during the early arteriovenous transit (conferring a starry-sky appearance) with reduced fluorescence intensity in the recirculation phase. During the FA study, the area of hyperfluorescence colocalized to each drusen does not appear to change.

5.3. Fundus autofluorescence (FAF)

On FAF, cuticular drusen are characterized by a hypoautofluorescent center with a hyperautofluorescent margin. The number and spatial density of cuticular drusen on FA and FAF imaging are considerably greater than on color or red-free photography. However, individual drusen appear larger on color photographs compared with FA and FAF. FA and FAF are highly concordant referring to CD size. The area of central hyperfluorescence on FA closely resembles the area of central hypoautofluorescence on FAF (Figure 4).

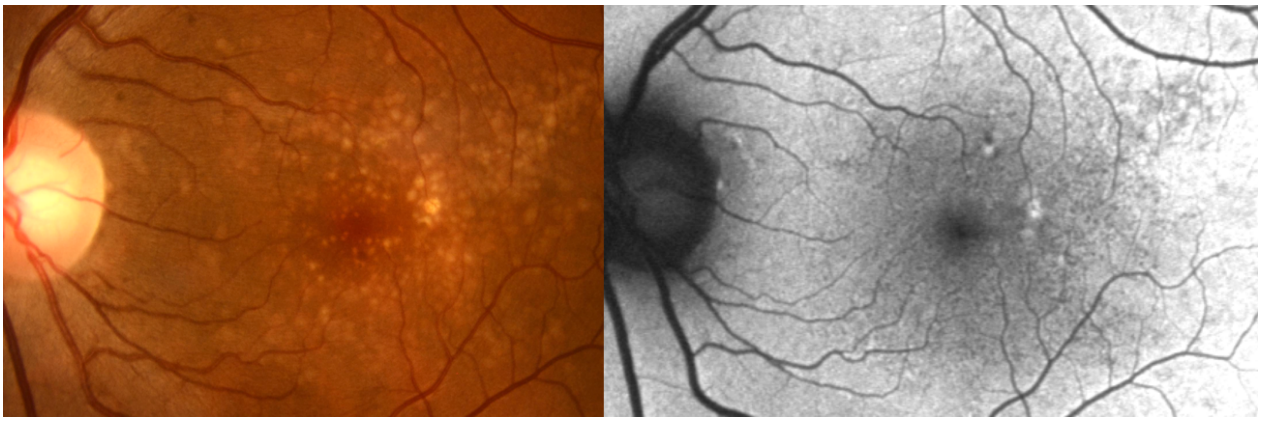

*Figure 4 Color fundus photography **(left)** and fundus autofluorescence (FAF) of a patient with cuticular drusen. Multiple small lesions with a hypofluorescent center are seen on FAF, the size of which is significantly smaller than on color fundus photography. (Courtesy of João Pedro Marques, MD)*

5.4. Optical Coherence Tomography (OCT)

OCT confirms the sub-RPE location of CD and reveals the characteristic "sawtooth" RPE elevations (Figure 5).

Three morphologic patterns of CD (Figure 5) are evident on OCT, despite consistent FA and FAF features:

- **type 1** (broadly 1/3 of eyes) as shallow elevations of the RPE basal laminar band, with drusen internal contents difficult to discern;
- **type 2** (almost half of eyes) as drusen of triangular morphologic characteristics resulting in a saw-tooth appearance;
- **type 3** (the less frequent) as broad, mound-shaped elevations of the RPE basal laminar band.

The reflectivity of cuticular drusen interiors on OCT is highly variable, with isoreflective, hyporeflective, and hyperreflective signatures evident even within the same eye (Figure 5).

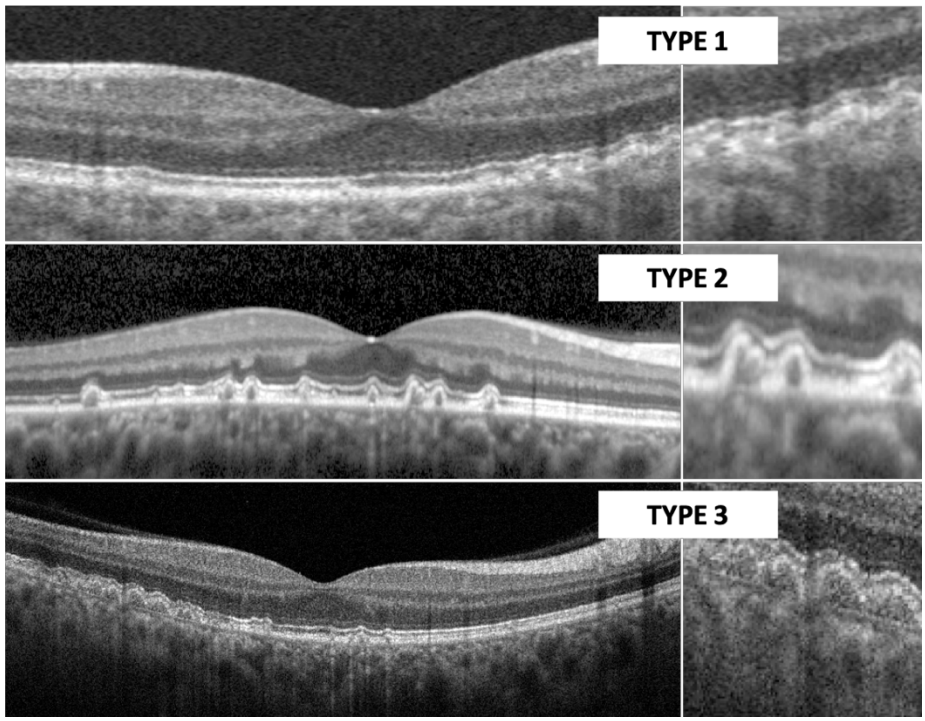

Figure 5 Morphologic patterns of cuticular drusen on spectral domain (SD) OCT. Type 1 pattern is characterized by shallow elevations of the RPE. In type 2 pattern, triangular morphologic features (saw-tooth appearance) can be seen. Finally, type 3 pattern is characterized by broad, mound-like elevations of the RPE band. (Courtesy of João Pedro Marques, MD)

5.5. Near infrared (NIR)

The NIR of CD shows hyporeflective centers with a surrounding hyperreflective margin in half cases (Figure 3B). Diffuse hyperreflectivity, heterogeneous reflectivity and a combination of these patterns are less common presentations. In comparison to FA, fewer CD are seen on NIR imaging.

5.6. Indocyanine green angiography (ICGA)

On ICGA, CD can be identified in 50% of cases. A discrete hyperfluorescence typically occurs in the early arteriovenous frames and persist throughout the late frames of the angiogram. They appear smaller and less numerous on ICGA when compared with FA. Despite being evident on images obtained with other methods, CD are not evident on ICGA in the remaining 50% of eyes (Figure 6).

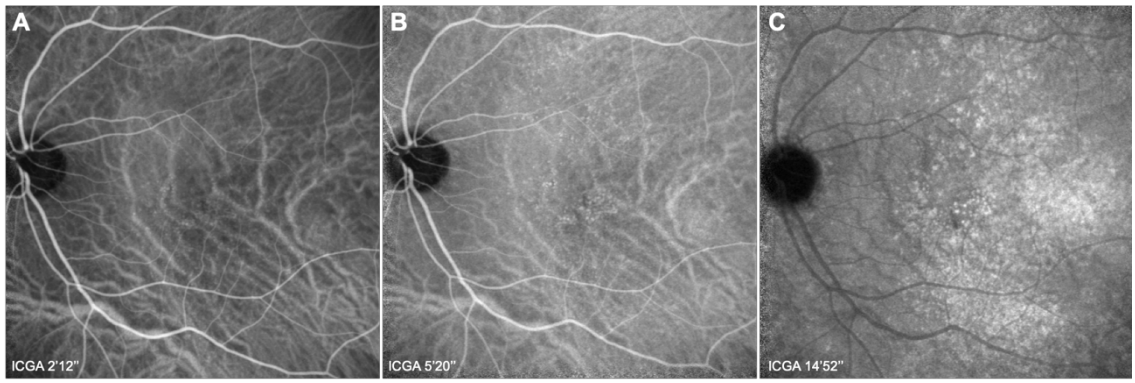

Figure 6 Indocyanine-green angiography (ICGA) findings in a patient with cuticular drusen (A-C). A discrete hyperfluorescence typically occurs in the early arteriovenous frames and persists throughout the late frames of the angiogram. (Courtesy of João Pedro Marques, MD)

6. Treatment and Prognosis

Whether the treatment and/or prognosis of CNV associated with cuticular drusen is different from CNV in AMD in general is currently unknown. Both photodynamic therapy (PDT) and intravitreal anti-VEGF drugs have been shown to improve the visual outcomes of CD-associated CNV.

Early screening for renal dysfunction in dense deposit disease patients may enable the early detection and treatment of this disorder, possibly increasing the likelihood of remission, and slowing or even preventing the progression to end-stage renal failure.

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SORSBY FUNDUS DYSTROPHY

Sara Vaz-Pereira, Helena Proença

1. Synonyms

Sorsby fundus dystrophy (SFD), Sorsby macular dystrophy, Sorsby pseudoinflammatory fundus dystrophy

2. Epidemiology

SFD is a rare inherited macular dystrophy. Although first described in 1949 by the distinct polish ophthalmologist Arnold Sorsby (1900-1980) in five families, it is still poorly understood.[1] Sorsby fundus dystrophy's prevalence is unknown with some authors suggesting an estimated prevalence of 1 in 220,000.[2] The onset of the disease is around the 4th to 6th decade of life with no gender predidection.[2]

3. Genetics

Identified in the OMIM database as disease #136900, SFD has an autosomal dominant inheritance pattern and is caused by a heterozygous mutation in the tissue inhibitor of metalloproteinases-3 (TIMP3) gene (#188826) on chromosome 22q12.[3] Most *TIMP3* mutations are in exon 5 and lead to a loss or gain of a cysteine residue, resulting in polymerization of the protein.[2] This leads to Bruch's membrane thickening and accumulation of lipid and proteinaceous material between the Bruch's membrane and RPE, observed as drusen-like deposits.[2]

4. Signs and Symptoms

Some of the earliest and often unnoticed symptoms of SFD are night-blindness and dyschromatopsia which can occur as early as the second decade of life.[2,4,5] At this stage, the fundus presents macular yellow to gray material at the level of Bruch´s membrane, which can coalesce in a uniform sheet or individualize to a drusen-like appearance (Figure 1A).[3,5] Reticular pseudodrusen

and RPE and choriocapillaris atrophy may also be a feature of SFD.[6] However, the patient commonly seeks medical attention during the fourth or fifth decade[4] because of sudden visual loss related to the development of choroidal neovascularization (CNV) (Figure 1.B and Figure 2) or macular geographic atrophy. Polypoidal choroidopathy can also complicate SFD.[4] Unlike age-related macular degeneration (AMD), SFD can extend beyond the temporal arcades to the periphery. Around the 4th to 6th decade, there is invariably severe vision loss down to hand motion.[3,5]

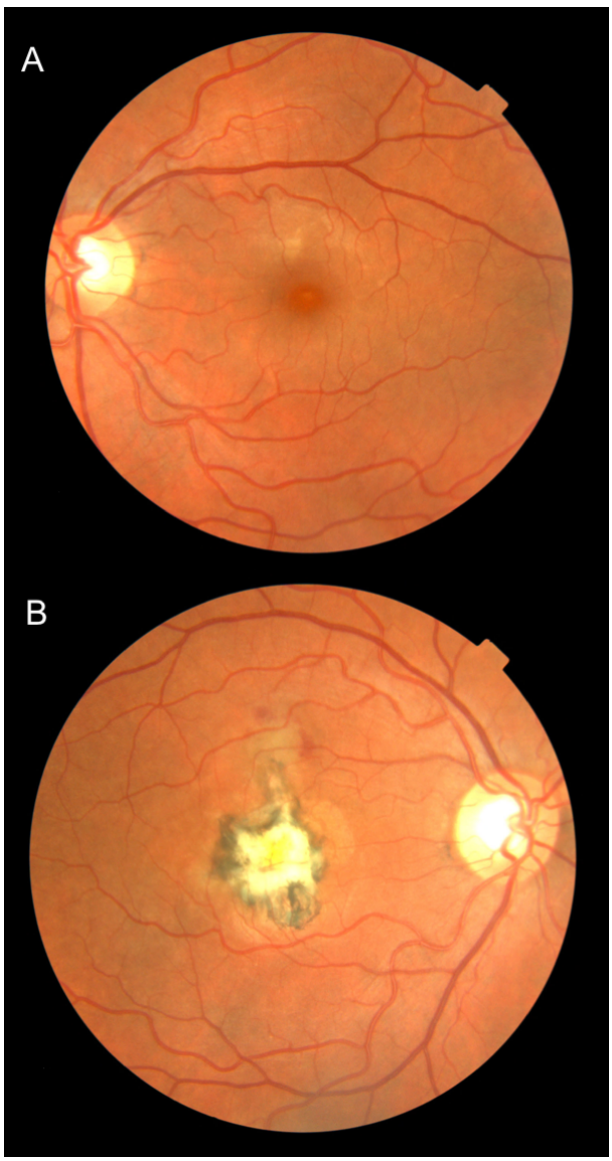

*Figure 1. Color fundus photographs of a patient with Sorsby fundus dystrophy, respectively early **(A)** and late-stage disease **(B)**. Note the macular yellow to gray material at the level of Bruch´s membrane in the left eye **(A)** and the presence of choroidal neovascularization with subretinal hemorrhage in the right eye **(B)**. (Courtesy of Gabriella De Salvo, MD).*

5. Diagnosis and Imaging

The evaluation for SFD should include a detailed medical and family history as well as clinical examination and ancillary testing. Multimodal retinal imaging with color fundus photographs, both conventional (Figures 1 and 2A and 2B) or ultra-widefield, fundus autofluorescence (Figure 2C and 2D), optical coherence tomography (OCT) (Figure 2E and 2F), fluorescein angiography (Figure 2G and 2H), indocyanin green angiography (ICGA) along with electrodiagnostics are generally useful.[4] OCT can detect signs of active CNV, such as intraretinal ou subretinal fluid and a fusiform thickening of the RPE (type 2 CNV).[7,8] Late stage CNV results in disciform scars (Figure 2E and 2F). Fluorescein angiography reveals mainly a predominantly classic CNV and the nonclassic component usually consists of hemorrhage.[7] The modern OCT-angiography has the advantage of being non-invasive while including the information of the structural OCT and visualizing the abnormal vascular network.[8] ICGA can be of benefit as it reveals a characteristically reduced fluorescence on late-phase images, even in asymptomatic carriers without fundoscopic changes.[4] Definite diagnosis is made by genetic testing with the identification of a *TIMP3* mutation.

Differential diagnosis should be made with AMD by contrasting clinical manifestations and findings. Features such as the earlier age of onset, nyctalopia and restriction of the visual field are unique to SFD.[9] They also differ in the type of yellow deposits though in the same sub-RPE location. In both entities, the natural course of the disease is towards neovascularization or geographic atrophy although the progression to the retinal periphery is not a feature of AMD.[9] Finally, they have different epidemiological characteristics (SFD is rare while AMD is a public health issue) and genetics (AMD has a complex etiology involving multiple alleles while SFD is explained by single gene mutations).[9] Other differentials include familial dominant drusen (*EFEMP1*), pattern dystrophies (*PRPH2*), late stage Best disease (*BEST1*) and central serous chorioretinopathy.[5] SFD end stages may be misinterpreted as late-stage-retinitis pigmentosa or cone-rod dystrophies.[4]

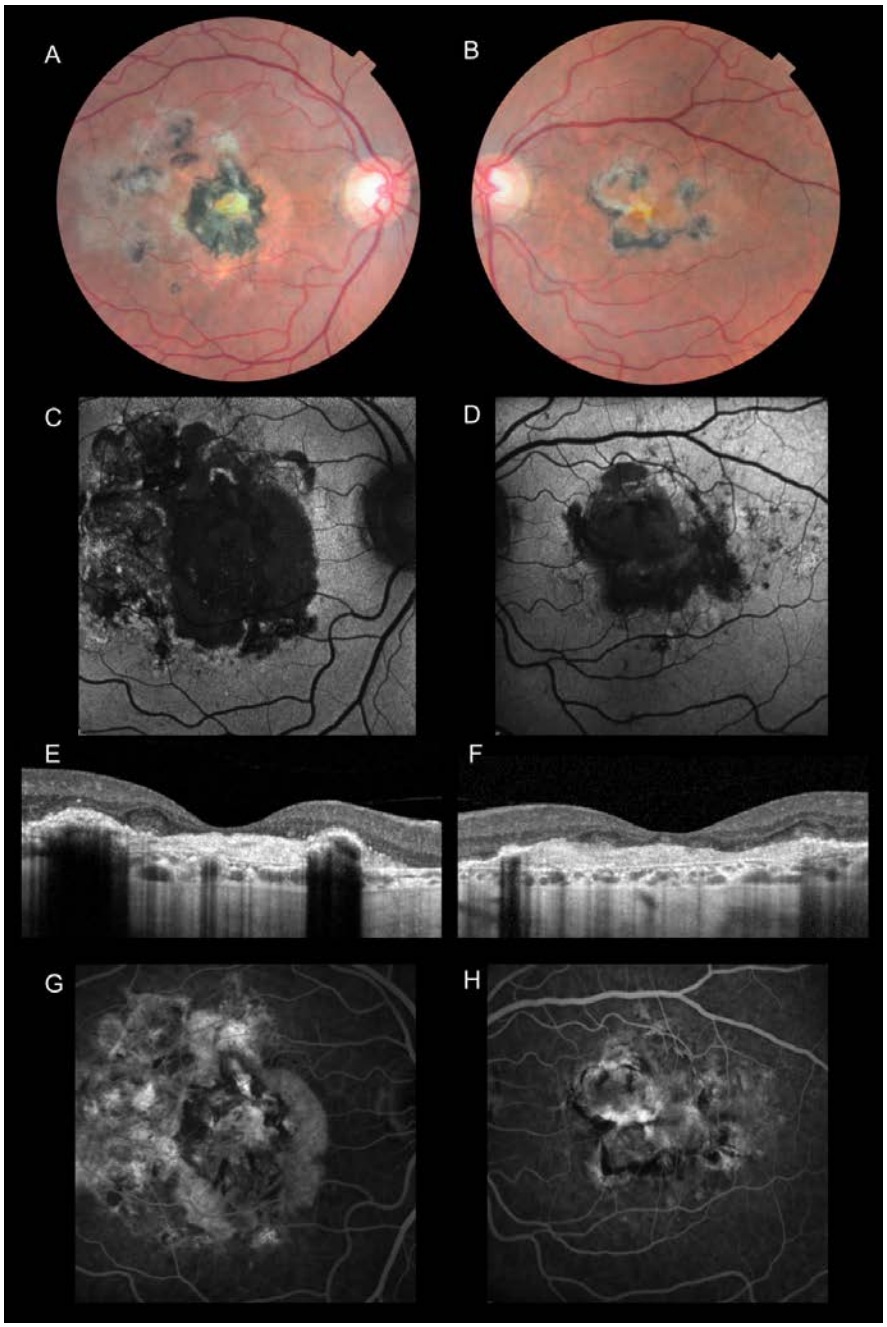

Figure 2. Multimodal imaging of the same patient depicted in Figure 1 showing bilateral macular disciform scars from end-stage choroidal neovascularization. Color fundus photographs, respectively from right (A) and left (B) eye. Fundus autofluorescence shows extensive macular hypoautofluorescence from the scarring, right (C) and left (D). Note some paramacular hyperautofluorescent areas in the left eye (D) suggestive of drusen-like deposits. OCT from both eyes (E) and (F) shows central retinal atrophy with subfoveal fibrosis, outer retinal disorganization and outer retinal tubulations in accordance with disciform scar. Late-phase fluorescein angiography reveals tissue impregnation and leakage, respectively right (G) and left (H). (Courtesy of Gabriella De Salvo, MD).

6. Treatment

There is no definite treatment for SFD. Early treatments involved improving the night-blindness in early-stage disease using high dose Vitamin A. Initial results were promising but the toxicity associated with higher doses and the lack of efficacy in lower doses led to its disinterest.[4,5] The current available treatment is directed at the control of complications, mainly the presence of subfoveal and juxtafoveal CNV. In the past, laser photocoagulation,[10] photodynamic therapy and intravitreal steroids have been used,[2,11,12] although with limited efficacy as in other causes of CNV.[2,7] In modern times, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies are the mainstay of treatment to control the presence of CNV and delay severe vision loss.[2,7,13-16] Low vision rehabilitation and low vision aids are recommended in end-stage disease.

7. Prognosis

The natural history of SFD usually leads to severe visual impairment, either by the presence of CNV or less frequently, because of RPE atrophy, as in dry AMD.[2] The latter group of patients develop chorioretinal atrophy without any signs of CNV. Enlargement of the atrophic area is expected with worsening visual acuity at faster growth rates ($7mm^2/y$) than AMD or Stargardt disease.[4] In a cohort of patients, CNV development was documented to occur at a mean age of 46.1 years in the first eye and 50.3 years in the second eye.[7] The median age at which vision was reduced to ≤20/200 was 48 years (first eye) and 54 years (second eye).[7]

Since the advent of antiangiogenic therapy, regression of CNV or polypoidal vasculopathy is possible, delaying or preventing visual function loss, especially if early treatment is provided. To achieve early CNV diagnosis and treatment, family screening of affected individuals and regular follow-up of SFD patients is recommended. Providing information to asymptomatic patients about CNV initial symptoms leads to early detection and improves prognosis.

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NORTH CAROLINA MACULAR DYSTROPHY

João Esteves Leandro, Sérgio Estrela Silva

1. Synonyms

Macular Dystrophy, Retinal, 1, North Carolina Type, MCDR1;
Central Areolar Pigment Epithelial Dystrophy (CAPED);
Retinal Pigment Epithelial Dystrophy, Central

2. Epidemiology

North Carolina macular dystrophy (NCMD) is a rare, autosomal dominant, highly penetrant congenital disorder, with widely variable expressivity. The macular defects are present on birth and generally considered nonprogressive (Figure 1). The prevalence is estimated to be lower than 1/1.000.000.

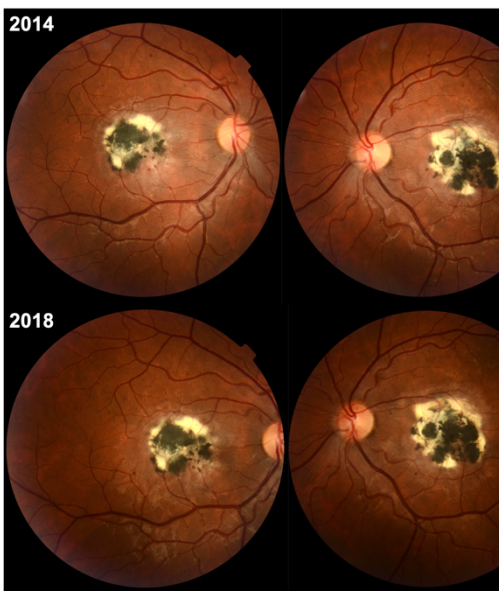

Figure 1 A bilateral central crater-like lesion of well-delineated chorioretinal degeneration in a 23 year old male patient with North Carolina Macular Dystrophy and a BCVA of 20/80 OU. Note that despite 4 years have passed between the top and bottom colour fundus photos, the lesion looks exactly the same, demonstrating the characteristic non progressive feature of the disease. (Courtesy of João Pedro Marques, MD)

3. Genetics

OMIM - #136550 6q16.2, AD, MCDR1 locus

This disorder is caused by heterozygous mutations in a DNase I hypersensitivity site, that is upstream of a gene encoding a retinal transcription factor, *PRDM13*. This gene is a member of a large family of "helix-loop-helix" DNA-binding proteins that play important roles during the development by controlling gene expression. It is believed that mutations on the regulatory regions of this gene, such as those occurring in NMCD affected families, may lead to various abnormalities in the developing macula. However, the precise mechanisms that cause these defects are yet to be revealed.

4. Signs and Symptoms

The clinical presentation of NCMD resembles that of age-related macular degeneration although at a much younger age. It includes abnormal accumulation of drusen, atrophy of the retinal pigmental epithelium (RPE) and photoreceptor cells and, ultimately, choroidal neovascularization (CNV).

The condition is present at birth with relatively good visual acuity, ranging from 20/20 to 20/400 (median 20/60), and normal colour vision. The ophthalmoscopic findings are usually more pronounced that one would predict from the visual acuity and are classified in 3 grades according to Gass:

- grade 1 - fine, small yellow drusen on the macula with mild RPE disturbances. Visual acuity is usually better than 20/30.
- grade 2 – larger, elevated and confluent yellow drusen with possible RPE atrophy or disciform scars with pigment clumping from CNV. Typical visual acuity ranges from 20/25 to 20/60, although it can drop to 20/100-20/400 secondary to CNV formation.
- grade 3 –a coloboma-like central lesion with chorioretinal atrophy and excavation, sometimes referred to as "macular caldera". Visual acuity ranges from 20/40 to 20/200.

Often, patients exhibit drusen-like deposits in the periphery, sometimes in a radial pattern.

5. Diagnosis and Imaging

The diagnosis of NCMD cannot be made based on the clinical examination of a single isolated individual as fundus findings, such as bilateral drusen in young patients, can overlap with conditions such as Doyne's honeycomb retinal dystrophy/malattia leventinese or cuticular drusen. Therefore, the diagnosis must rely on the examination of the entire family of affected individuals, often exhibiting an autosomal dominant trait, with complete penetrance and congenital/infantile onset. In addition, because of the wide phenotypic variability of NCMD, genotype analysis of the *MCDR1* locus is useful in establishing the precise diagnosis in a certain family.

Acillary imaging methods can be helpful in characterizing the clinical manifestations of the disease (Figure 2). Fundus autofluorescence, for example, can show mottled hypo-autofluorescence in areas of RPE disturbance and can delimitate the areas of atrophy.

Optical coherence tomography is able to identify the drusen, areas of retinal atrophy and subretinal fibrotic scars. In patients with grade 3 NCMD, there is complete loss of RPE and choriocapillaris inside the caldera's lesions. Fluorescein angiography is useful to reveal areas of active neovascularization.

The full-field electroretinogram (ffERG) is usually normal, although pattern electroretinogram (pERG) can be reduced in patients with grade III lesions. This translates the normal overall function of the retina, with defects restricted to the central macula.

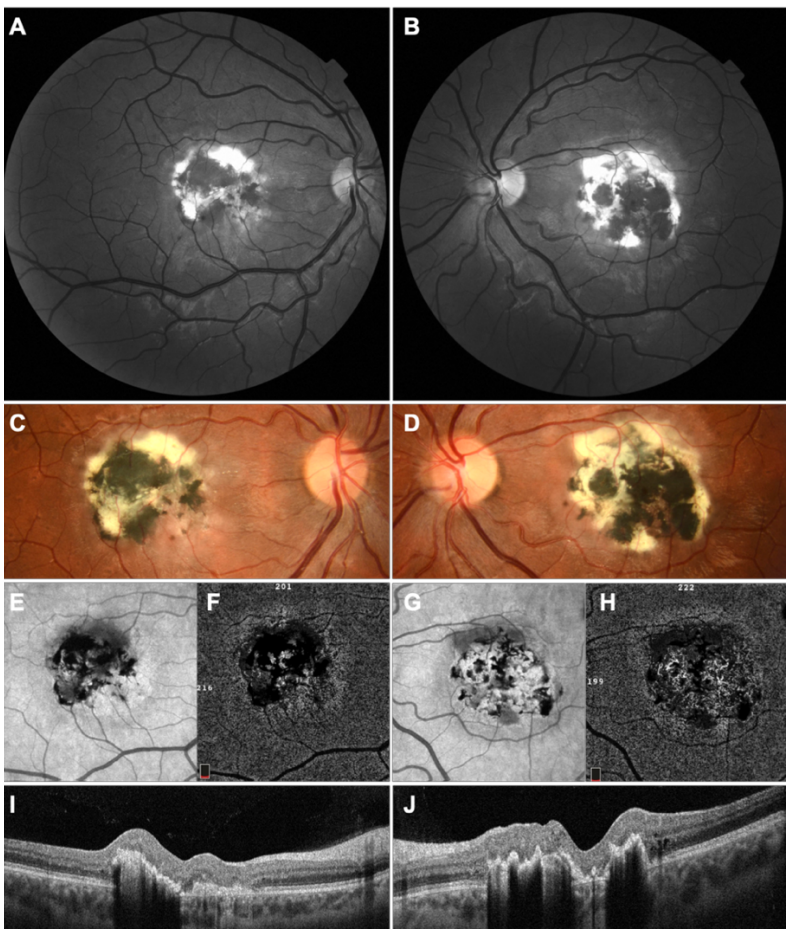

Figure 2 Multimodal retinal imaging of the same patient imaged in Figure 1. Red free imaging ***(A)*** *and* ***(B)****, depicting the central macular lesion. RPE pigment clumps appear darker, while the yellowish components of the lesion appear white. The correlation with color fundus photos can be seen on* ***(C)*** *and* ***(D)****. The enface OCT at the level of the choriocapillaris is shown on figures E and G, for the right and left eyes, respectively. The choriocapillaris slab of OCTA shows central choriocapillaris loss* ***(F)*** *and* ***(H)****. Finally, SD-OCT* ***(I)*** *and* ***(J)*** *highlights the disorganization of the normal macular architecture along with subretinal fibrotic scars. (Courtesy of João Pedro Marques, MD)*

6. Treatment

There is no known treatment for NCMD, although, low vision aids, such as glasses with high powered lens, can be useful when visual acuity is severely reduced.

For patients with choroidal neovascularization, which can occur rarely in grade II disease, standard treatment with anti-VEGF injections can be used.

7. Prognosis

As mentioned, NCMD is typically considered stationary. Visual acuity usually remains stable through life, unless choroidal neovascularization develops.

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PATTERN DYSTROPHIES

João Filipe Bernardes, Maria Luz Cachulo, Ângela Carneiro

1. Introduction

Pattern Dystrophies of the macula are a genetically and phenotypically heterogeneous group of diseases characterized by the deposition of yellow, grey, orange or black pigment in the macula, mainly affecting the photoreceptor-retinal pigment epithelium (RPE) complex, producing singular macular patterns [1,2]. Based on these patterns, Gass *et al.* proposed five distinct subgroups: Adult Onset Foveomacular Vitelliform Dystrophy, Butterfly-shaped Pigment Dystrophy, Reticular Dystrophy of the RPE, Multifocal Pattern Dystrophy Simulating Fundus Flavimaculatus, and Fundus Pulverulentus[3]. They are commonly autosomal dominant, but both penetration and phenotypic expression are variable[4,5]. For instance, family members with the same mutation can express different macular phenotypes. In fact, even a singular patient can exhibit different types of pattern dystrophy in each eye. Furthermore, it is also known that a specific pattern can develop into another in the same eye[3,6-10]. Unfortunately, there are no studies on the prevalence of pattern dystrophies. The age at onset is highly variable. Nonetheless, the majority of patients tend to suffer mild visual acuity loss and/or metamorphopsia after the fifth decade, while others remain asymptomatic[11]. In this chapter, we present a separate description for each of the 5 pattern dystrophies.

1.1. Adult Onset Foveomacular Vitelliform Dystrophy

1.1.1. Synonyms

Adult vitelliform macular dystrophy; Adult-onset vitelliform macular dystrophy; Adult-onset vitelliform dystrophy; Adult-onset foveomacular dystrophy; Adult-onset foveomacular pigment epithelial dystrophy; Adult vitelliform degeneration; Adult vitelliform macular degeneration; Adult-type foveomacular vitelliform degeneration; Gass disease; Pseudo-Best disease; Pseudo-vitelliform macular dystrophy.

1.1.2. Genetics

OMIM: #153840; #608161; #616151; #616152

Inheritance: autosomal dominant; unknown.

Genes: *BEST1* (chromosome 11q12.3); *PRPH2* (chromosome 6p21); *IMPG1* (chromosome 6q14); IMPG2 (chromosome 3q12). Sporadic AOFVD has been associated with a *HTRA1* single nucleotide polymorphism also found in age-related macular degeneration patients (AMD)[11-15].

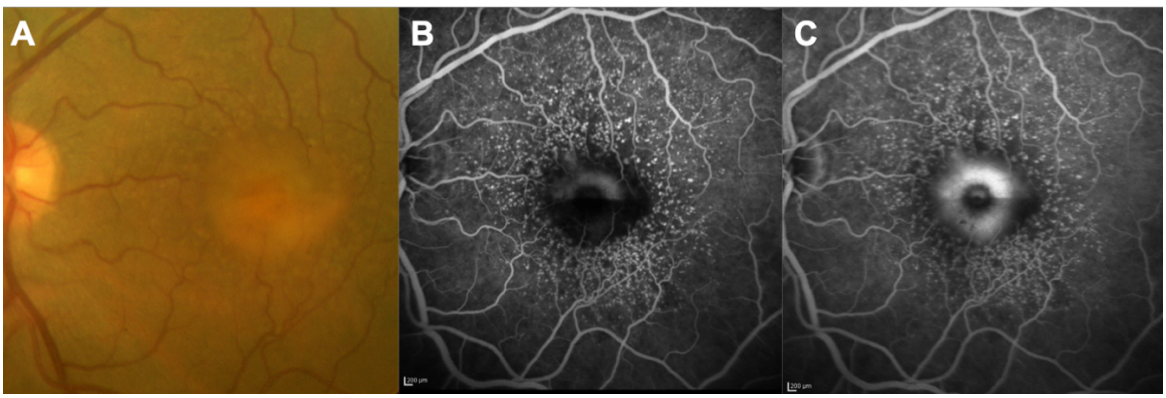

Figure 1 *Adult vitelliform macular dystrophy with cuticular drusen.* ***(A)*** *Color Fundus Photography showing a round, yellowish subfoveal lesion.* ***(B)*** *and* ***(C)*** *Fluorescein Angiography reveals central hypofluorescence surrounded by a hyperfluorescence halo.*

1.1.3. Signs

On fundus examination, a bilateral, central, symmetric, round/oval, yellowish subfoveal lesion is found (Figure 1A). Usually the lesion is one-third to one-half disc area; however, larger lesions have been observed. The vitelliform lesion can progress through the following stages: previtelliform, vitelliform, pseudohypopyon, vitelliruptive, atrophic and choroidal neovascularization (CNV)[3,11,16,17].

1.1.4. Diagnosis and Imaging

Diagnosis is essentially clinical. Nonetheless, fluorescein angiography typically reveals central hypofluorescence surrounded by a hyperfluorescence halo (Figure 1B and 1C). In fundus autofluorescence (FAF), due to lipofuscin-like accumulation, the lesion shows increased autofluorescence (Figure 2A). However, with time, progressive hypoautofluorescence, due to atrophy development, is seen[18-20]. Macular optical coherence tomography (OCT) reveals a singular, dome-shaped lesion localized between RPE and Ellipsoid Zone (EZ) and a frequent disruption of the EZ (Figure 2B). Optical coherence tomography angiography (OCTA) generally shows decreased vessel and flow density. An increased parafoveal vessel density in the deep capillary plexus is also seen. Full-field electroretinogram (ffERG) and electrooculogram (EOG) are usually normal, differentiating it from Best retinal dystrophy[6,17,21-25].

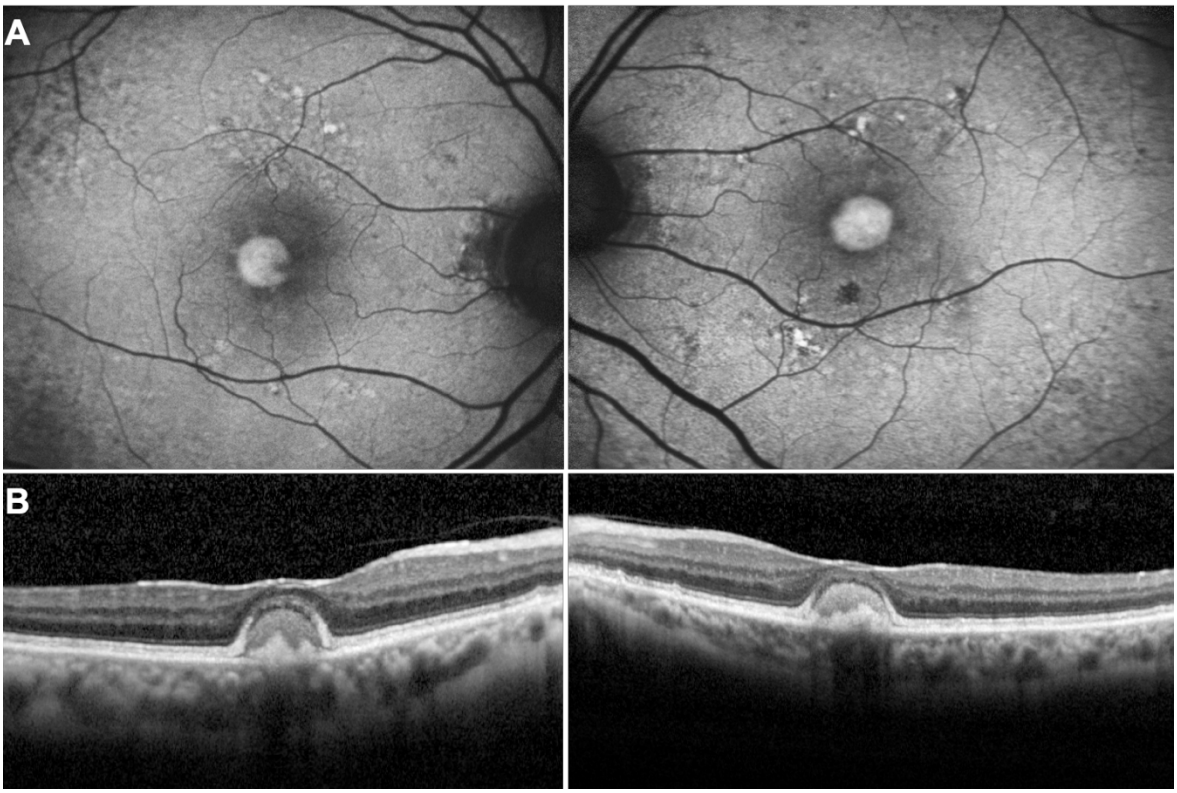

*Figure 2 Adult vitelliform macular dystrophy. **(A)** Fundus autofluorescence imaging of the right and left eyes showing hyperautofluorescence of the vitelliform lesion. **(B)** Optical Coherence Tomography of the macula reveals a dome-shaped lesion localized between the retinal pigment epithelium and the ellipsoid zone.*

1.2. Butterfly-shaped Pigment Dystrophy

1.2.1. Synonyms

Butterfly-shaped Pattern Dystrophy; Butterfly-shaped Macular Dystrophy

1.2.2. Genetics

OMIM: #169150; #608970

Inheritance: Autosomal dominant.

Genes: *PRPH2* (chromosome 6p21); *CTNNA1* (chromosome 5q31)[26-28].

1.2.3. Signs

A spoke-like pigment pattern is observed in the macula, forming 3 to 5 "arms" or "wings", which resemble the wings of a butterfly[29]. This is better appreciated in near infrared (NIR) imaging or FAF than on color fundus photography (Figure 3).

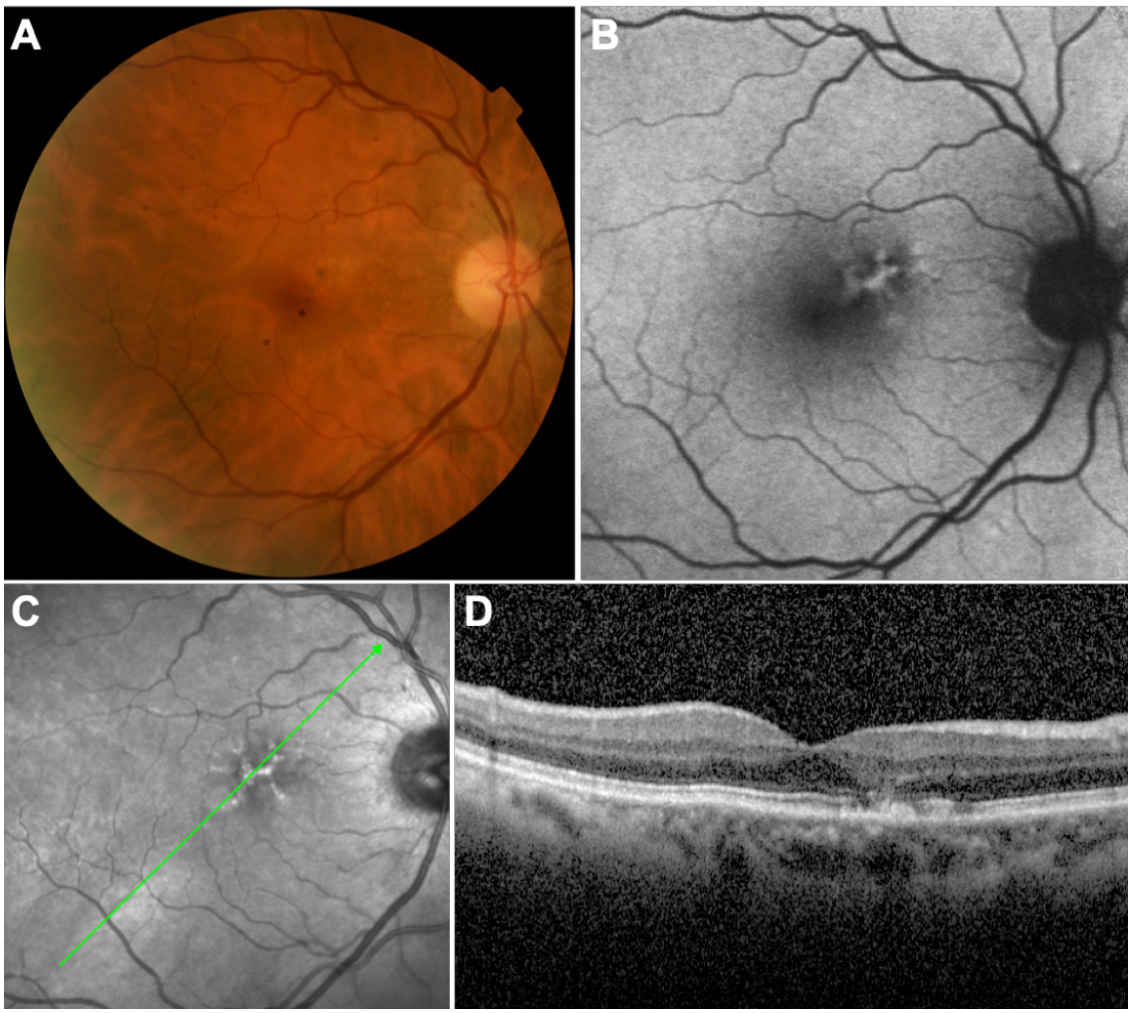

*Figure 3 Butterfly-shaped Pigment Dystrophy. **(A)** Color Fundus Photography of the right eye showing mild pigmentary changes in the macula. **(B)** Fundus autofluorescence shows a typical butterfly-shaped hyperautofluorescence distribution in the macula, also evident in the Near Infrared (NIR) Image **(C)**. Optical Coherence Tomography of the macula **(D)** shows juxtafoveal atrophy of the RPE and photoreceptors. (Courtesy of João Pedro Marques, MD)*

1.2.4. Diagnosis and Imaging

Fluorescein angiography highlights the characteristic butterfly shaped pattern, revealing hypofluorescent lesions surrounded by increased fluorescence. FAF yields a variable fluorescence pattern (Figure 3B). Macular OCT shows multiple lesions at the photoreceptor-RPE complex (Figure 3C) . Full-field ERG and EOG are usually normal or slightly abnormal[4,6,11,19,30-33].

1.3. Reticular Dystrophy of the Retinal Pigment Epithelium

1.3.1. Synonyms

None

1.3.2. Genetics

OMIM: #179840; #276800; #617175

Inheritance: Autosomal recessive; autosomal dominant; unknown.

Genes: *RCBTB1* (chromosome 13q14)[34].

1.3.3. Signs

Macular pigment deposition resembles a chicken wire or a fish net. A network of dark pigment lines extending to the periphery of the macula, with more densely pigmented areas, like knots, at their intersection is observed[3].

1.3.4. Diagnosis and Imaging

Fundus autofluorescence shows hyperautofluorescent lines that highlight the *fish net* pattern previously described. Macular OCT reveals a mainly hyperreflective material at the sub-RPE level. Full-field ERG and EOG are usually normal[35,36].

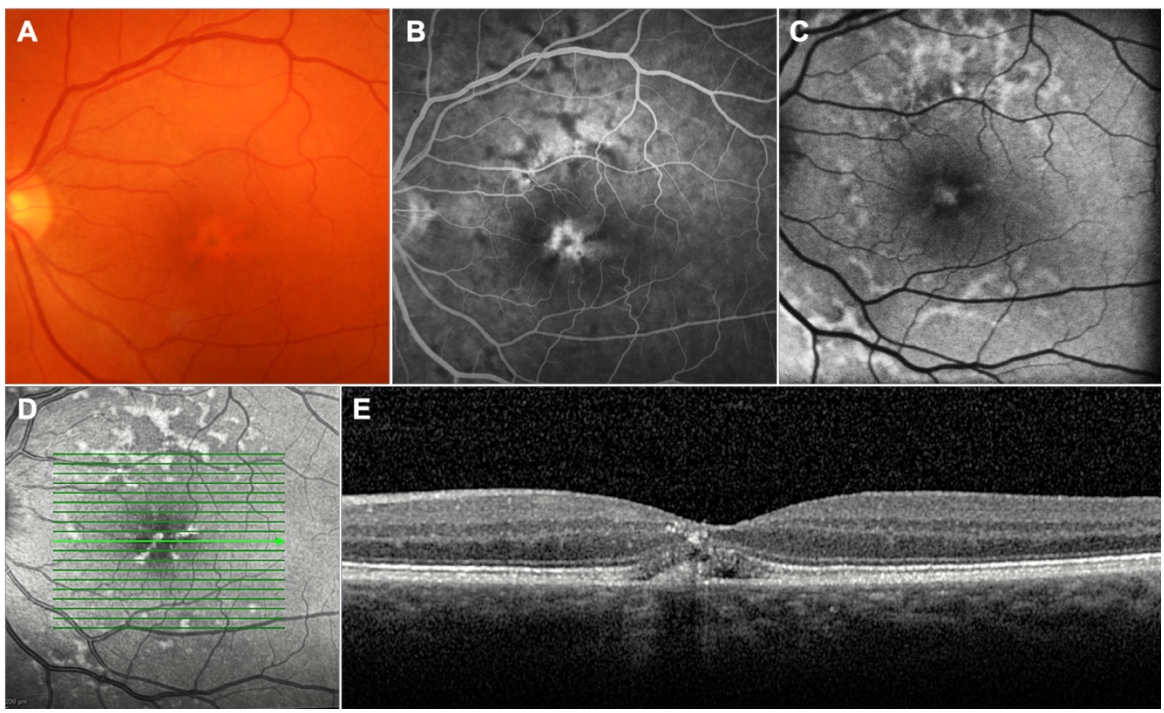

*Figure 4 Reticular Dystrophy of the Retinal Pigment Epithelium. **(A)** Color Fundus Photography of the left eye showing mild pigmentary changes in the macula. **(B)** Fluorescein Angiography depicts a leopard spot pattern in the superior macula and central leakage. **(C)** Fundus autofluorescence shows hyperautofluorescent lines that highlight the fish net pattern. This is also clearly seen on near-infrared (NIR) imaging **(D)**. On OCT **(E)**, subfoveal neurosensory retinal detachment with subretinal hyperreflective material is seen. (Courtesy of Maria João Furtado, MD)*

1.4. Multifocal Pattern Dystrophy Simulating Fundus Flavimaculatus

1.4.1. Synonyms

Multifocal Pattern Dystrophy simulating Stargardt Disease

1.4.2.Genetics

OMIM: #169150

Inheritance: Autosomal dominant; unknown.

Genes: *PRPH2* (chromosome 6p21)[5,37].

1.4.3. Signs

Presence of white/yellow flecks scattered around the temporal retinal vascular arcades and around the optic disc (Figure 5) resembling the flecks encountered in Stargardt disease[37]. Patches of atrophy that coalesce over time are usually seen as well.

1.4.4.Diagnosis and Imaging

In FAF, the flecks show an increased autofluorescence. Late in the course of the disease, the flecks may merge, resulting in an oval hyperautofluorescent zone. Hypoautofluorescent spots inside the oval band might develop, reflecting the beginning of macular atrophy (Figure 5C). These lesions will progressively expand both to the fovea and beyond the posterior pole. Fluorescein angiography shows the flecks as hyperfluorescent spots in the early and late phases (Figure 5D). Furthermore, the "dark choroid" sign, typical of Stargardt disease is not observed. On OCT, the flecks appear as reflectivity changes at the photoreceptor-RPE level (Figure 5E). Full-field ERG can be initially normal or slightly abnormal. However, as the disease progresses, a severely abnormal exam is usually found, demonstrating the panretinal character of this type of pattern dystrophy. A severe visual field constriction may ensue[11,37]. In contrast to typical Stargardt disease, this type of pattern dystrophy has a late appearance, around the fifth decade, a more benign course, and no choroidal silence in fluorescein angiography[4].

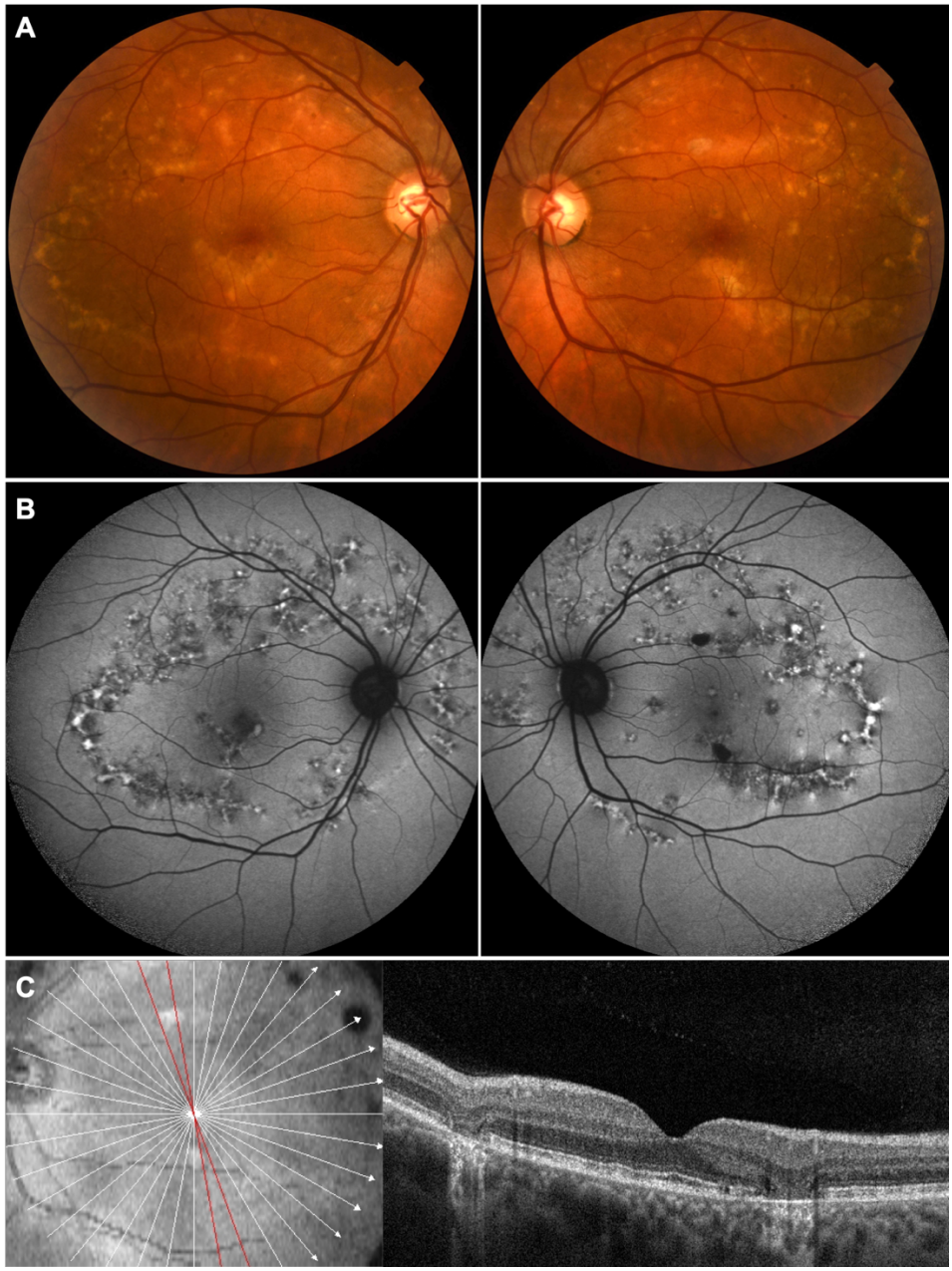

Figure 5 Multifocal Pattern Dystrophy Simulating Fundus Flavimaculatus in a 55 year old male with 20/20 vision OU. (A) Color Fundus Photography (right and left eye, respectively) shows the yellow-whitish flecks scattered around the temporal retinal vascular arcades and the optic disc. (B) Fundus autofluorescence image (right and left eye, respectively) depicting an increased autofluorescence associated with the flecks along with hypoautofluorescent areas that correspond to atrophic areas. (C) Spectral domain OCT of the left eye showing RPE and outer retinal atrophy in the areas where there is blockage of autofluorescence. The foveal architecture is preserved. (Courtesy of João Pedro Marques, MD)

1.5. Fundus Pulverulentus

1.5.1. Synonyms

None.

1.5.2. Genetics

OMIM: #169150

Inheritance: Autosomal dominant; unknown.

Genes: *PRPH2* (chromosome 6p21)

1.5.3. Signs

This rare form of pattern dystrophy is characterized by a granular appearance in the macula, with coarse mottling of RPE cells[3].

1.5.4. Diagnosis and Imaging

Fluorescein angiography reveals hypofluorescent spots in the macula. OCT shows hyperreflective humps at the level of the RPE. Full field ERG and EOG are usually normal to slightly abnormal[38,39].

2. Systemic associations

Pattern dystrophies have been associated with numerous systemic diseases, including Pseudoxanthoma elasticum (mainly Fundus Pulverulentus), Myotonic dystrophy, McArdle disease, Maternally inherited Diabetes and Deafness and Crohn disease[6,40-44].

3. Treatment

Unfortunately, no treatment prevents disease progression or restores visual acuity in patients with severe macular atrophy. CNV development is uncommon, yet its treatment with anti-vascular endothelial growth factor proved to be effective[45-49].

4. Prognosis

Pattern dystrophies are usually associated with a benign course. Nonetheless, a significant number of individuals may ultimately develop severe visual acuity loss, mainly due to macular atrophy or, more rarely, CNV[11,50-52].

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HYPOTRICHOSIS WITH JUVENILE MACULAR DYSTROPHY

Joana Pires, Rui Freitas, José F. Costa

1. Synonyms

Hypotrichosis with Cone-Rod Dystrophy.

2. Epidemiology

Hypotrichosis with juvenile macular dystrophy (HJMD) is a rare disorder, which has been described mostly in Arab Muslim, Israeli, Turkish and Pakistani families.[1-3] Its prevalence is unknown, and it has only been identified in approximately 50 patients since the first case was described in 1935.[5]

3. Genetics

HJMD (OMIM #601553) is a rare congenital autosomal recessive disorder, caused by a mutation in the *CDH3* gene (OMIM #114021), on chromosome 16q22. *CDH3* consists of 16 exons, spanning ~55 kilobases of genomic DNA, and encodes the molecule P-cadherin, a member of the cadherin transmembrane protein family, and a key component of adherens junctions. It is expressed in a wide variety of tissues, including the human retinal pigment epithelium (RPE) and the hair matrix, and is the only classic cadherin expressed at certain stages of development of these tissues.[6-8] The function of P-cadherin is not restricted to the formation of adherens junctions, as it is also involved in cell recognition, cell signaling, morphogenesis, and tumor development.[9] P-cadherin is not expressed in the neuroretina. The abnormal *CDH3* expression is thus postulated to affect the RPE monolayer, causing progressive macular degeneration.

Biallelic mutations in the *CDH3* gene can also cause Ectodermal dysplasia, ectrodactyly, and macular dystrophy syndrome (EEMS, OMIM #225280). The phenotype for EEMS includes macular dystrophy, ectodermal involvement (hypotrichosis, nail dysplasia and partial anodontia) and limb defects such as syndactyly, camptodactyly or ectrodactyly. HJMD and EEMS are overlapping

syndromes with shared features, such as hypotrichosis and macular dystrophy, and it has been suggested that these represent a continuous phenotypic spectrum related to mutations in the *CDH3*, rather than different syndromes. The classification as *CDH3*-related syndromes has been proposed, in which all patients have hypotrichosis and macular dystrophy, with variable additional limb and ectodermal anomalies.[10] Moreover, patients with the same genotype may have substantial hair, skin and retinal phenotypic variation.[11] Thus, HJMD and EEMS may represent phenotypic heterogeneity within the same syndrome, and the fact that the same mutation in different patients gives rise to both phenotypes suggests that the allelic mutation may not be the only factor determining the clinical status, and raises the possibility of modifier genes influencing disease expressivity. As so, no phenotype-genotype correlation has been established for hair and retinal changes between the type of mutation and its location along the *CDH3* gene.

4. Signs and Symptoms

HJMD is characterized by sparse scalp hair since birth, with limited growth throughout life, in association with a progressive visual impairment that begins in childhood, with or without limb and ectodermal anomalies. Sparse scalp hair (Figure 1) is the result of impaired regeneration, caused by defects in hair cycling and anchoring.[12] This is present from at least early childhood, with normal hair elsewhere, including eyebrows and eyelashes. Degeneration of the central retina causes bilateral and progressive visual deterioration. Patients may also have additional limb abnormalities.

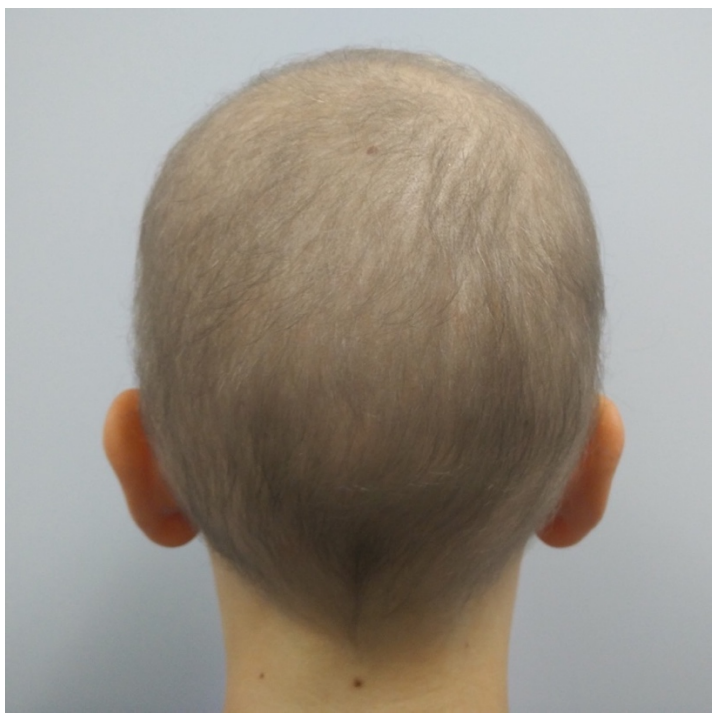

Figure 1 *Sparse and short hair in a child with Hypotrichosis with Juvenile Macular Dystrophy (HJMD).*

5. Diagnosis and Imaging

Fundus examination reveals bilateral and variable degrees of ring-shaped atrophy of the retina, RPE, and choroid, predominantly restricted to the posterior pole, with patchy intra-retinal pigment clumping (Figure 2). An earlier onset of these alterations is more likely than the *juvenile* nomenclature suggests, and there may be a broader involvement of the retina (extending beyond the macular region).[11, 13-15]

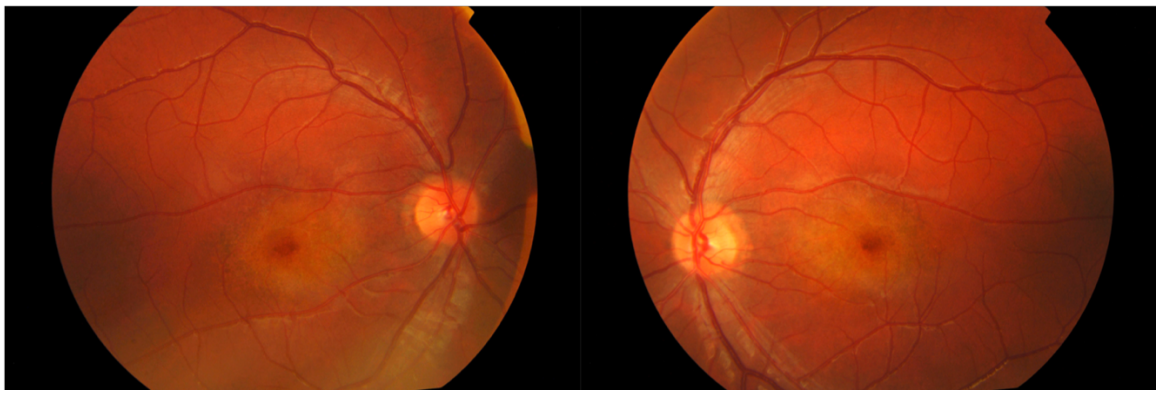

Figure 2 Bilateral hypopigmented ring-shaped areas of central retino-choroidal atrophy, with associated small foveal pigment clumps and coarse granular pigmentation.

Fundus autofluorescence shows confluent wedge-shaped hypoautofluorescent areas, corresponding to the RPE atrophy (Figure 3). A rim of relatively increased autofluorescence can surround this region.

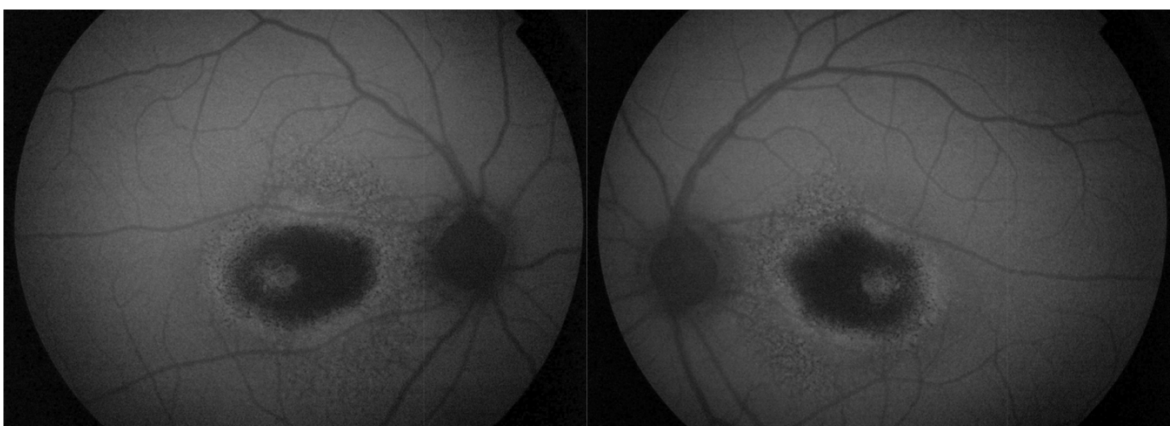

Figure 3 Fundus autofluorescence showing reduced central autofluorescence, with surrounding rim of relatively increased autofluorescence.

Optical coherence tomography (OCT) demonstrates variable degrees of disruption of the outer retina and RPE, with photoreceptor loss, inner segment/outer segment disruption (Figure 4A) and frequent outer retinal tubulations (Figure 4B). The overall size of the atrophic region does not appear to increase with time. However, the retinal thickness within the atrophic region decreases.[16]

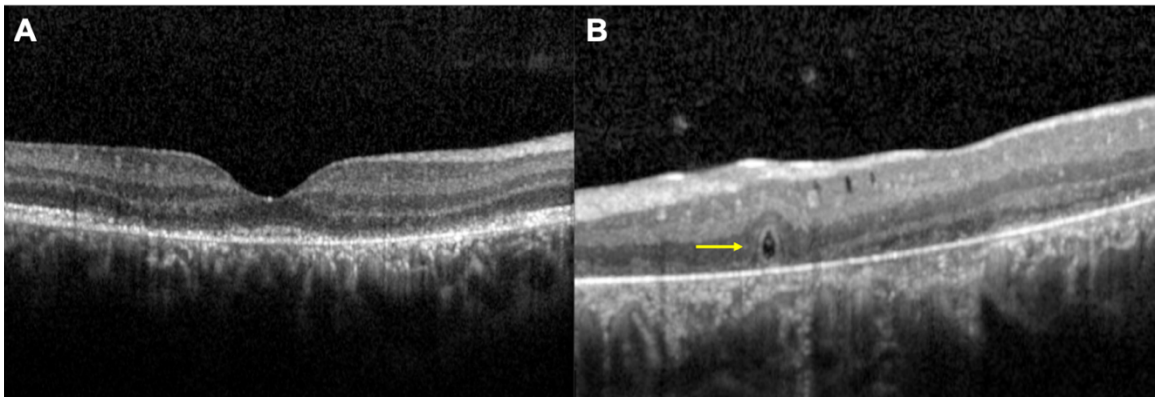

Figure 4 (A) Spectral domain optical coherence tomography (SD-OCT) showing preserved foveal center thickness with photoreceptor loss outside the foveal center. (B) Spectral domain optical coherence tomography (SD-OCT) showing an outer retinal tubulation over an area of localized photoreceptor degeneration.

Electrophysiological evaluation is consistent with macular dysfunction. The pattern ERG (P-ERG) usually shows a reduction in amplitude of the P50 wave — as this component mirrors macular photoreceptor and retinal ganglion cell function, this is a sensitive indicator of macular dysfunction. As the full-field electroretinogram (ffERG) is the electrical mass response of the entire retina to a light stimulus, a dysfunction confined to the macular region is usually not expressed by a reduced full-field flash ERG. As so, the full-field ERG responses (light- and dark-adapted) show normal amplitude. Nevertheless, there are reported cases of generalized dysfunction in some HJMD patients.[16] These full-field ERG abnormalities do not seem to progress with time, but the P-ERG deteriorates. The electrooculogram (EOG) is within normal limits, suggesting that HJMD is not a disorder of primary RPE dysfunction.[13] The pattern-reversal visual evoked potential (VEP) is usually subnormal, reflecting reduced macular function.

Despite the usefulness of multimodal imaging, a definite diagnosis can only be made by the identification of biallelic mutations via molecular genetic testing.

6. Treatment

There is currently no known treatment. Gene therapy for retinal degeneration has been evaluated in several clinical trials.[17-20] Recent successes in stem cell and genetic therapies for ocular diseases suggest that the retinal aspects of this disorder may potentially be treatable. The generally slowly progressive photoreceptor degeneration, the relative preservation of central foveal thickness,

and the absence of scar formation permits a time window for treatment.[15] As HJMD is caused by the loss of function of cadherin-3 in RPE cells, gene augmentation therapy, by targeting vectors bearing the therapeutic DNA to the remaining RPE cells, may be successful in preventing or retarding progressive visual loss.

7. Prognosis

The childhood-onset central macular dystrophy leads to progressive and severe deterioration of visual function. Visual acuity ranges from 20/30 to hand movements and deteriorates over time.[16] The extent of vision loss varies and its difficult to predict, and visual acuity usually declines to 10/32 or worse.[14, 16, 21] Vision loss is usually symmetrical, but asymmetric involvement has been reported.[14, 21, 22]

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CONE AND CONE-ROD DYSTROPHIES

João Branco

1. Synonyms

Cone dystrophy (CD or COD; OMIM #602093) and Cone-rod dystrophy (CRD or CORD; OMIM #120970) have historically been called inverse or central Retinitis Pigmentosa.

2. Epidemiology

The estimated prevalence of Cone dystrophy and Cone-rod dystrophy is 1/30000 to 1/40000 worldwide.

The onset of CD and CRD is usually in childhood or adolescence, with most patients reaching legal blindness between 35-50 years.

3. Genetics

The majority of CD/CRD are monogenic and follow a Mendelian inheritance pattern, i.e., autosomal dominant, autosomal recessive or X-linked. Although mainly non-syndromic (eye manifestations only), some syndromic forms exist (where other non-ocular tissues are concomitantly affected). To date, more than 30 genes (Table 1) have been reported in association with CD/CRD in the RetNet database (http://www.sph.uth.tmc.edu/retnet/).

4. Signs and Symptoms

CD and CRD are a rare, phenotypically and genetically heterogeneous group of disorders, characterized by progressive dysfunction of cones with normal rod function until late-stage disease (CD), or progressive loss of cone function that is early followed by loss of rod function (CRD).

Patients with CD present with decreased visual acuity, colour vision disturbances, photophobia and sometimes nystagmus. On fundus examination, the macula ranges from a normal appearance to a bull's eye maculopathy, and the optic disc may show temporal pallor.

Patients with CRD present with the same symptoms of CD, with additional progressive loss of peripheral vision and nyctalopia (due to rod dysfunction). In addition to the macular features observed in CD, patients with CRD develop retinal vascular attenuation and peripheral RPE changes (bone spicule hyperpigmentation).

Table 1. Genes associated with Cone/Cone-rod dystrophies

Gene	OMIM	Inheritance Pattern	Chromosome
AIPLI	#604392	AD	17p13.2
CRX	#602225	AD	19q13.3
GUCA1A	#600364	AD	6p21.1
GUCY2D	#600179	AD/AR	17p13.1
PITPNM3	#608921	AD	17p13.2-p13.1
PROM1	#604365	AD	4p15.32
PRPH2	#179605	AD	6p21.1
RIMS1	#606629	AD	6q13
SEMA4A	#607292	AD/AR	1q22
UNC119	#604011	AD	17q11.2
ABCA4	#601691	AR	1p22.1
ADAM 9	#602713	AR	8p11.22
ATF6	#605537	AR	1q23.3
C21ORF2	#603191	AR	21q22.3
C8ORF37	#614477	AR	8q22.1
CACNA2D4	#608171	AR	12p13.33
CDHR1	#609502	AR	10q23.1
CERKL	#608381	AR	2q31.3
CNGA3	#600053	AR	2q11.2
CNGB3	#605080	AR	8q21.3
CNNM4	#607805	AR	2q11.2

GNAT2	#139340	AR	1p13.3
IFT81	#605489	AR	12q24.11
KCNV2	#607604	AR	9p24.2
PDE6C	#600827	AR	10q23.33
PDE6H	#601190	AD/AR	12p12.3
POC1B	614784	AR	12q21.3
RAB28	612994	AR	4p15.33
RAX2	610362	AD/AR	19p13.3
RDH5	601617	AR	12q13.2
RPGRIP1	605446	AR	14q11.2
TTLL5	612268	AR	14q24.3
RPGR	312610	XL	Xp11.4
CACNA1F	300110	XL	Xp11.23

5. Diagnosis and Imaging

Following the recommendations on Clinical Assessment of patients with Inherited Retinal Dystrophies (IRD) by the American Academy of Ophthalmology (AAO), the diagnosis of CD/CRD should comprise:

- Multimodal Retinal Imaging: Color fundus photography, Fundus autofluorescence (FAF) and Optical Coherence Tomography (OCT)
- Visual Field testing (VF)
- Full-field electroretinogram (ffERG)
- Molecular genetics (genetic testing)

In FAF, patients with CD present a variable pattern of central hypoautofluorescence with surrounding hyperautofluorescence (Figure 1A and 2B). In the OCT, perifoveal atrophy of the outer retina is seen in mild cases (Figure 2C), while a full thickness atrophy of the retina is seen in advanced stages (Figure 1E). VF illustrate a central scotoma and in the ffERG, reduced cone amplitude responses, with normal rod responses for ≥ 5 years are required for a diagnosis of CD.

Patients with CRD, present a central area of hypoautofluorescence in the macula with peripheral areas of punctate hyper- and hypoautofluorescence in FAF. In the OCT, central atrophy of the outer retina is present and in the VF a central scotoma with variable peripheral involvement in seen. In the ffERG reduced cone and rod responses, with cones more affected.

The ffERG is the gold standard for differentiating CD from CRD. Diminished cone amplitudes are mandatory.

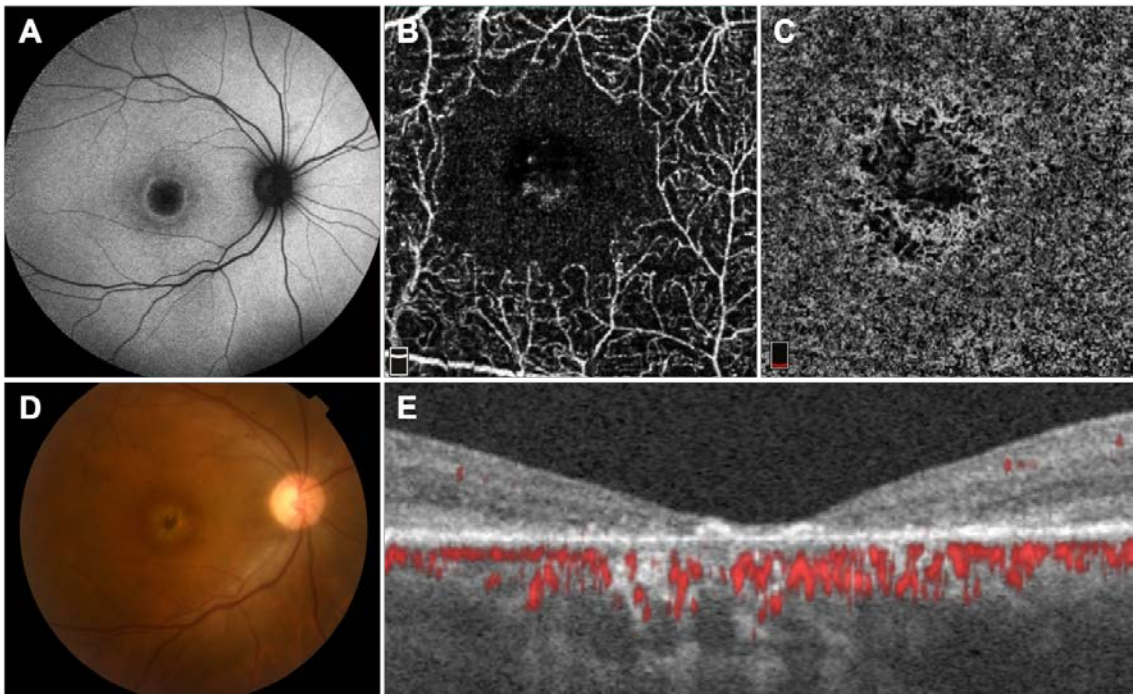

*Figure 1 Cone dystrophy in a 52 year old female. Note the central hypoautofluorescence with a hyperautofluorescent halo in FAF **(A)**. OCT-angiography of the superficial plexus **(B)** shows an enlarged FAZ, while the choriocapillaris slab **(C)** shows a well delimitated area of significant choriocapillaris atrophy. On color fundus photography **(D)**, bull's eye maculopathy is evident. The vessels have normal caliber and optic nerve head has a normal appearance. On OCT **(E)**, central atrophy is observed. (Courtesy of João Pedro Marques, MD)*

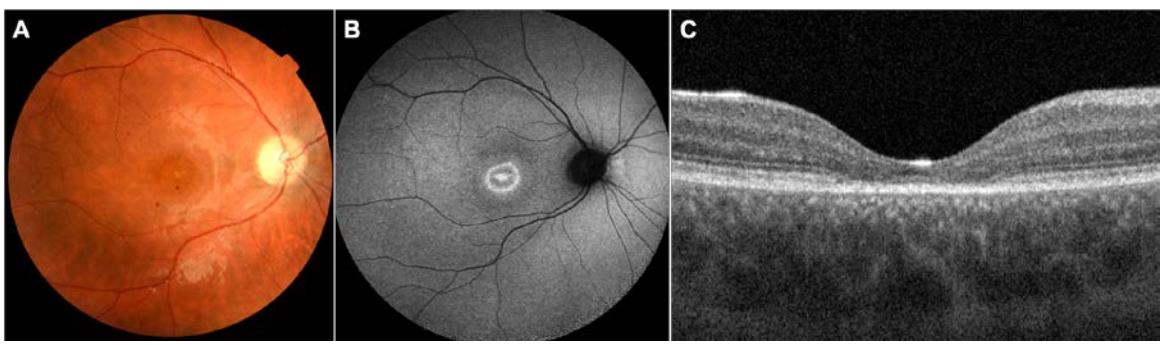

*Figure 2 Mild cone dystrophy in a 23 year old male. **(A)** Color fundus photography depicts only very discrete hypopigmentary changes in the macula. **(B)** A beautiful representation of a bull's eye is seen on FAF. **(C)** OCT is remarkable for the presence of perifoveal atrophy of the outer retina with preserved RPE. (Courtesy of João Pedro Marques, MD)*

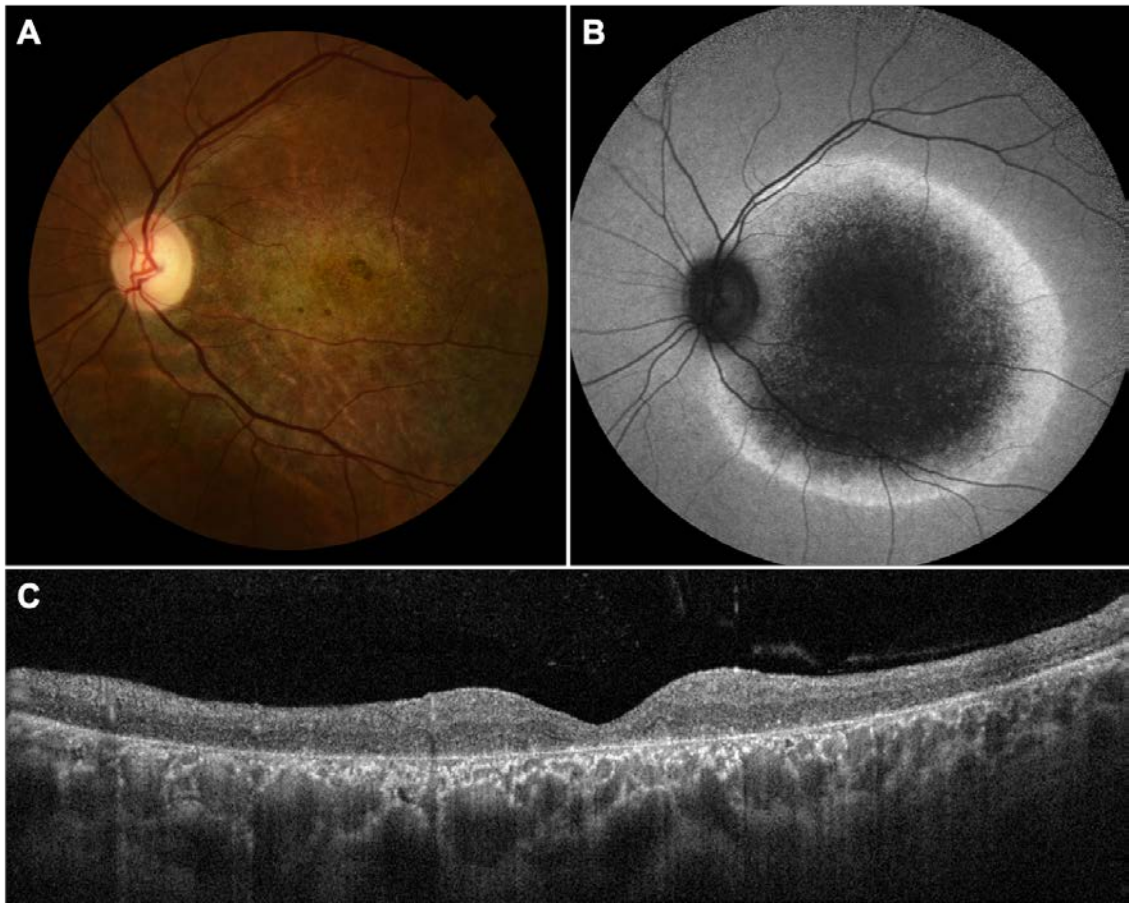

Figure 3 *Cone-rod dystrophy in a 42 year old male.* ***(A)*** *Color fundus photography depicts generalized atrophy of the RPE in the macula with some pigment clumping. Temporal pallor of the optic nerve head is seen.* ***(B)*** *Central hypoautofluorescence with a hyperautofluorescent halo is observed in FAF.* ***(C)*** *OCT depicts generalized atrophy of the outer retina and RPE. (Courtesy of João Pedro Marques, MD)*

6. Treatment

No therapy that restores visual function or halts disease progression is currently available. Studies in animal models of IRD, and some ongoing human trials, bring a hope for future treatment strategies involving gene therapy (replacement or editing), stem cell based therapies, and retinal implant technology or retinal transplantation.

7. Prognosis

CD and CRD are progressive cone disorders with an early onset that usually progress to legal blindness in middle age. CD has a slightly more favorable course. Early onset of the disease and mutations in the *ABCA4* gene have been reported as independent prognostic parameters of visual loss.

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BIETTI CRYSTALLINE CORNEORETINAL DYSTROPHY

Nuno Silva, Fábio Trindade

1. Synonyms

Bietti Crystalline Dystrophy, Bietti Crystalline Retinopathy, Bietti Tapetoretinal Degeneration with Marginal Corneal Dystrophy

2. Epidemiology

Bietti Crystalline Corneoretinal Dystrophy (BCCD) occurs with an estimated frequency of 1 in 67.000 people [1]. It affects both genders equally and is more common in people from East Asia (ie. people with Chinese and Japanese ancestry). BCCD typically manifests after the second decade of life, with an average age at onset of 29.3 years [2]. Although rare, BCCD may be underdiagnosed. Pediatric cases have been reported [3, 4].

3. Genetics

BCCD (OMIM #210370) is an autosomal recessive retinal dystrophy caused by homozygous or compound heterozygous mutations in the *CYP4V2* gene on chromosome 4q35.1-q35.2 [5, 6, 7, 8]. *CYP4V2* relates to the cytochrome P450 family of enzymes, which are involved in the formation and breakdown of various intracellular components. Although not fully understood, *CYP4V2* mutations are thought to lead to abnormal lipid breakdown[5]. It is unknown how this translates into the specific signs and symptoms of BCCD.

Despite common features, the clinical picture of BCCD differs widely between patients, even among relatives with the same CYP4V2 allelic variant [7, 9, 10]. This suggests that disease-modifying factors may be at play. Uncommon regional forms of BCCD may represent degeneration associated with allelic variants that allow for residual functional gene product or other modifying factors[11].

4. Signs and Symptoms

The hallmark of BCCD is a chorioretinal degeneration characterized by the presence of yellow-white crystals and/or complex lipid deposition in the retina (see Figures 1 and 2). Progressive RPE and choroidal atrophy ensue, and patients manifest with symptoms similar to those of other forms of chorioretinal degeneration: reduced visual acuity, nyctalopia, abnormal electroretinogram (ERG), visual field loss and impaired color vision. Marked interocular asymmetry is common but with time BCCD results in bilaterally severe visual impairment and legal blindness in largely all patients around the fifth or sixth decade. Visual field loss is progressive and usually presents as scotomata that enlarge with disease progression; central, paracentral and ring scotomata are most common. Choroidal neovascularization is possible but uncommon in BCCD [12, 13].

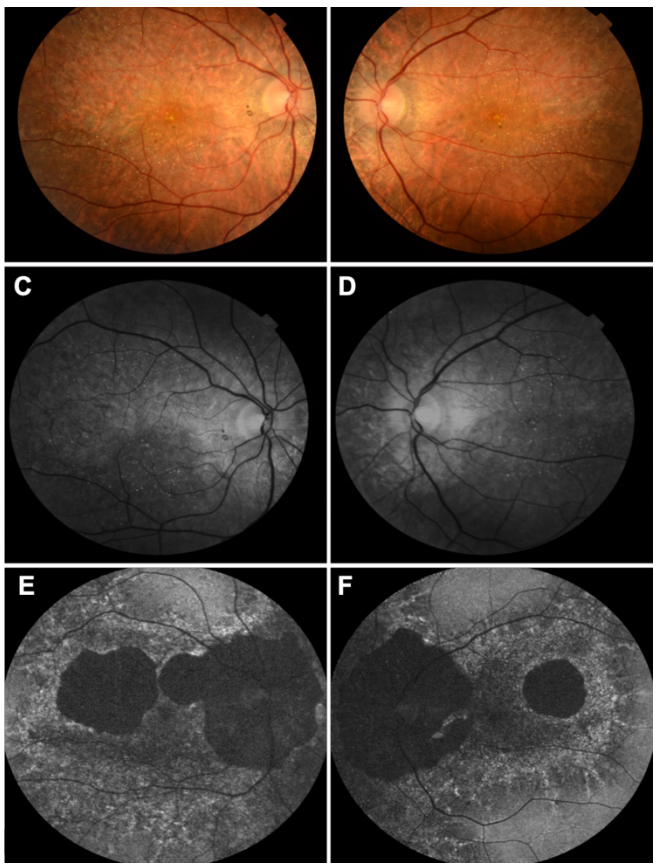

Figure 1: Color fundus photography of the right and left eye (A and B) of a patient with BCCD; typical features include infinite small yellow-white crystalline deposits and variable degrees of chorioretinal atrophy. Red-free photographs (C and D) demonstrate a greater number of crystals due to higher contrast. Blue-light fundus autofluorescence (E and F) shows well-defined areas of hypoautofluorescence involving the peripapillary region asd encroaching on the fovea; the granular hyperautofluorescence outside these areas indicate distressed retinal pigment epithelial cells. (Courtesy of João Pedro Marques, MD).

5. Diagnosis and Imaging

BCCD is one of the few ocular conditions that can be reliably diagnosed through careful examination alone, given its pathognomonic clinical picture. Fundoscopy typically reveals infinite small yellow-white crystalline deposits scattered throughout the posterior pole that sometimes extend into the midperiphery (Figures 1 and 2). These coexist with variable degrees of RPE and

choriocapillaris atrophy, pigment clumping and choroidal vessel sclerosis. Deposits diminish and disappear progressively in areas of severe chorioretinal atrophy [10] so that areas where crystals remain observable may actually signal areas where retinal degeneration has not yet severely developed [14]. Crystalline deposits at the corneal limbus can be identified in up to one third of BCCD patients [15]. They are thought to be more common in European patients and not always readily identifiable with slit-lamp biopmiscroscopy[16].

Standard red-free fundus photography can provide improved contrast allowing for the discrimination of a greater number of crystals than fundoscopy might suggest (Figures 1 and 2). Fundus autofluorescence can indicate areas of RPE atrophy as patches of hypoautofluorescence (Figure 1). Outside these areas, granular hyperautofluorescence is usual [17].

Optical coherence tomography (OCT), especially spectral domain OCT (SD-OCT), can be of value in both the diagnosis and management of BCCD. Degeneration in BCCD initiates at the outer retinal layers, followed by retinal and choroidal thinning (see Figures 2, 3 and 4). Crystalline deposits are usually identified as hyperreflective dots located at the RPE/choriocapillaris level [14, 18, 19]. In areas of RPE atrophy, outer retinal tubulations can also be observed as spherical hyperreflective structures in the outer nuclear layer[14].

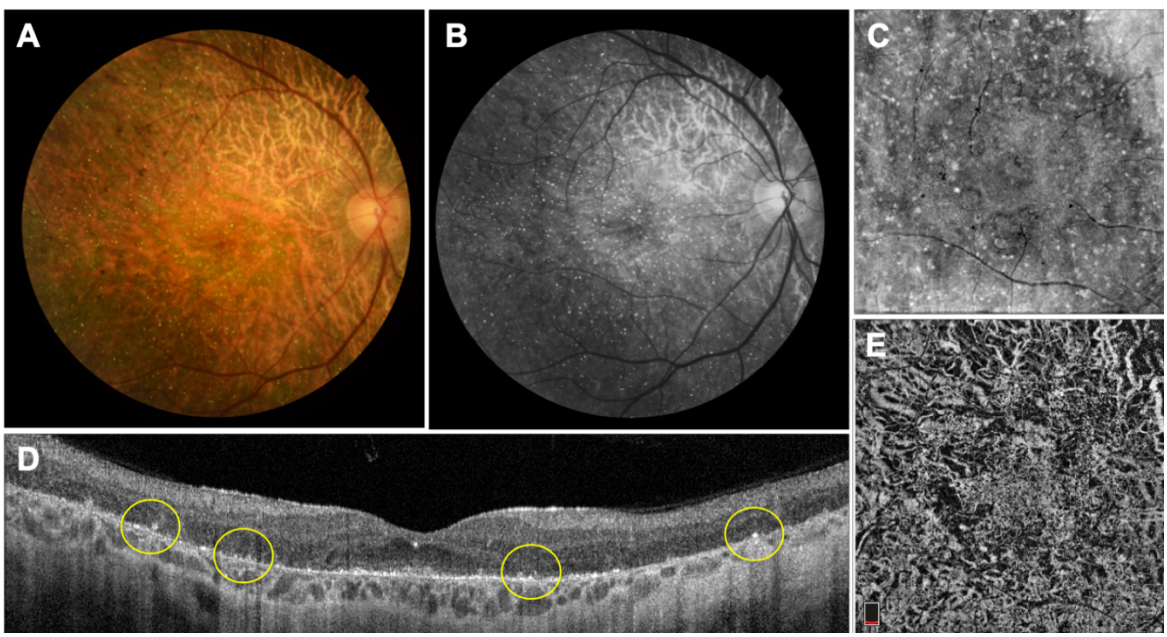

*Figure 2 Bietti crystalline corneoretinal dystrophy. The presence of crystals containing lipids and cholesterol esters and accumulating in the cornea, the retina and choroid are the hallmark of this rare disease. CFP **(A)** and redfree **(B)** demonstrate the crystals along with RPE atrophy. **(C)** Enface OCT of the outer retina with a large number of crystals. **(D)** SD-OCT shows severe atrophy of the outer retina and RPE along with multiple crystals (yellow circles). **(E)** Severe atrophy of the choriocapillaris is seen on the choriocapilaris slab of OCTA. (Courtesy of João Pedro Marques, MD)*

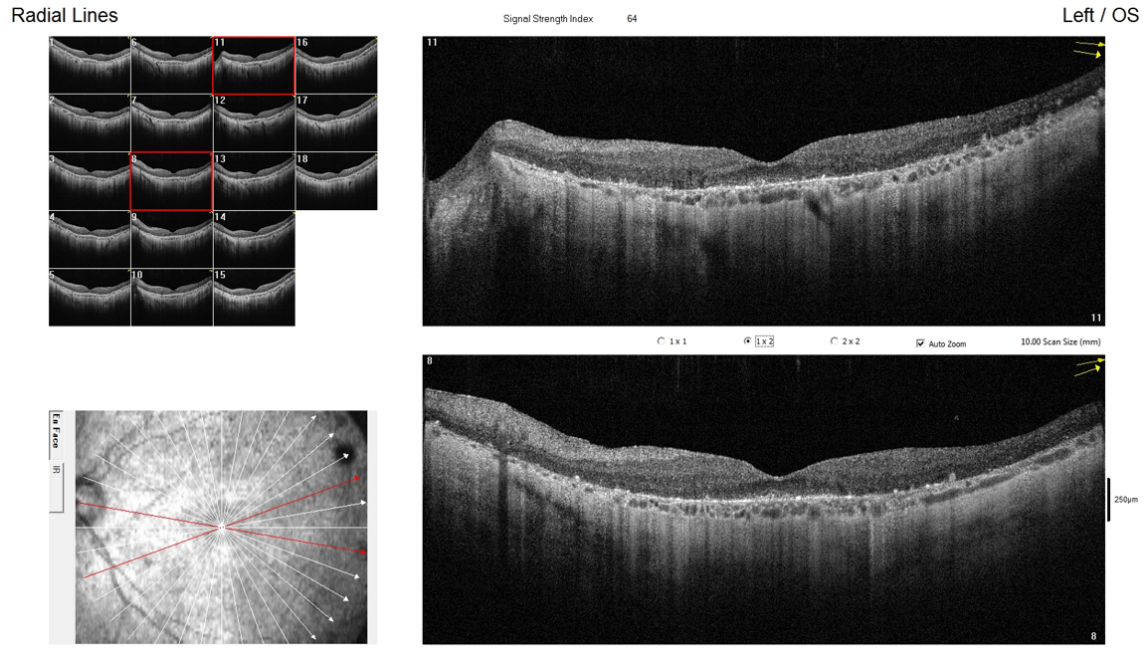

Figure 3: SD-OCT sections of the left eye of the same patient featured in Figure 1. Crystalline deposits in BCCD are seen as hyperreflective dots located at the RPE/choriocapillaris level. There is severe outer retinal disruption. (Courtesy of João Pedro Marques, MD)

Electrophysiology is not necessary for the diagnosis of BCCD but can be utterly useful for its management, establishing the magnitude and extent of retinal degeneration. In BCCD, full-field ERG (ffERG) can demonstrate varying degrees of cone and rod dysfunction, ranging from normal through severely diminished up to undetectable scotopic and photopic responses[20]. Although test results usually correlate well with the stage of disease progression[9, 20, 21], this is not always the case. Normal ffERG responses in BCCD patients with severe chorioretinal atrophy can suggest residual neural retina viability despite disruption to retinal lamination [11]. On the other hand, regional forms of BCCD (ie. forms that predominantly affect the posterior pole) can present with normal ffERG [11, 22, 23]; in these cases, multi-focal ERG (mfERG) can better detect abnormal retinal function.

OCT-angiography is a novel technique that can be of value in monitoring BCCD progression. *En face* selective visualization of the outer retinal layers and choriocapillaris can provide accurate mapping of areas where degeneration has ensued (see Figures 2 and 4).

Molecular testing (sequence analysis) of *CYP4V2* confirms the clinical diagnosis in most cases.

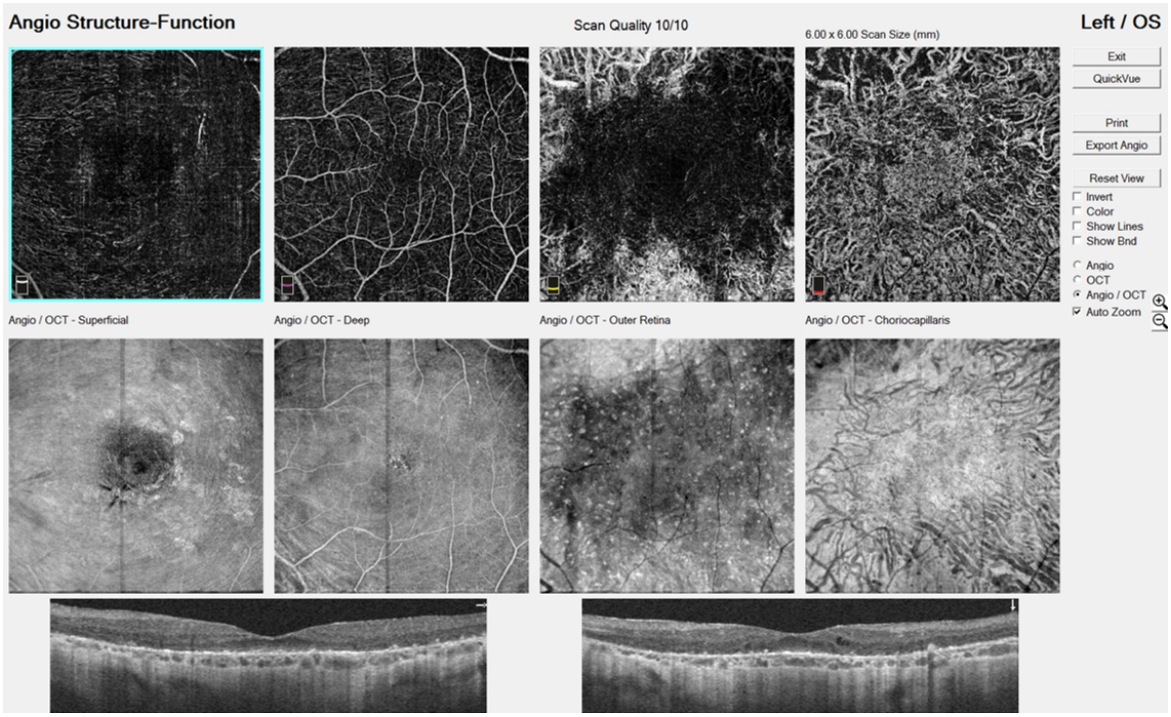

Figure 4: OCT-angiography shows that degeneration in BCCD localizes to the outer retinal layers and choriocapillaris and provides an accurate mapping of affected retinal areas. The enface image of the outer retina clearly depicts the crystalline deposits. On the choriocapillaris slap of the OCTA, severe choriocapillaris atrophy is seen. (Courtesy of João Pedro Marques, MD)

6. Treatment

BCCD has no definite treatment. The extent of disease for each individual patient should be determined at baseline through fundoscopic examination, perimetry, OCT and ERG, where available. Regular ophthalmological examination every one or two years is recommended to monitor disease progression. As necessary, affected individuals should be referred to low vision specialists, state services or organizations/professionals providing help for the visual impaired. Affected individuals and their siblings can and should be provided with genetic counselling.

7. Prognosis

Despite some clinical variability, BCCD is a progressive and severe retinal degeneration, culminating in severe chorioretinal atrophy and seriously affected visual function in largely all patients. By the fifth or sixth decade, the majority of patients become legally blind.

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ACHROMATOPSIA AND OTHER COLOR VISION DISTURBANCES

Sónia Torres-Costa, Amândio Rocha Sousa

1. Synonyms

Rod monochromacy

2. Epidemiology

Achromatopsia is an inherited autosomal recessive retinal disease that affects the cone cell function[1]. It is present in about 1:30,000 to 1:50,000 births[1, 2]. Curiously, this disease is already known by many people for its discussion in the book *The Island of the Colorblind* written by the neurologist Oliver Sacks. In his book, Sacks discussed the high frequency of achromatopsia in the small Micronesian population of Pingelap, an atoll in the Pacific Ocean. After a typhoon hit the island in 1775, one of 20 survivors was heterozygous for achromatopsia[1]. Due to consanguinity, nowadays almost 5% of the population presents achromatopsia and 30% are carriers[1].

3. Genetics

Six genes have been associated with achromatopsia, five of which are related to components of the cone-specific phototransduction cascade and one of which is related to the endoplasmic reticulum function[2]. The most commonly affected genes are *CNGB3* (cyclic nucleotide gated channel beta 3), mutated in ~40–50% of affected individual, and *CNGA3* (cyclic nucleotide- gated channel alpha 3) mutated in approximately 25% of affected patients[1]. These genes encode for the α and ß subunits of the cGMP-gated cation channel, respectively[2]. Other involved genes are *GNAT2* (guanine nucleotide binding G protein, alpha transducing activity polypeptide 2) mutated in less than 2%, *PDE6C* (phosphodiesterase 6C, cGMP-specific) also mutated in less than 2%, and *PDE6H* (phosphodiesterase 6H, cGMP-specific) responsible for nearly 0.3%[1]. Lately, a novel achromatopsia disease gene designated *ATF6* was identified in patients with achromatopsia and normal cone

phototransduction genes. The *ATF6* gene is associated with the endoplasmic reticulum function, and consequently, the unfolded protein response[2]. It has also been noted that there is no association between genotype and phenotype regarding retinal structure and function[3].

Table 1 Genetic characterization of patients with achromatopsia (information obtained in Online Mendelian Inheritance in Man® https://www.omim.org/).

Location	Phenotype	Phenotype MIM number	Inheritance	Gene/Locus	Gene/Locus MIM number
2q11.2	Achromatopsia 2	#216900	AR	*CNGA3*	#600053
8q21.3	Achromatopsia 3	#262300	AR	*CNGB3*	#605080
10q34	Achromatopsia 5*	#613093	AR	*PDE6C*	#600827
1p13.3	Achromatopsia 4	#613856	AR	*GNAT2*	#139340
12p12.3	Achromatopsia 6	#610024	AR, AD	*PDE6H*	#601190
1q23.3	Achromatopsia 7	#616517	AR	*ATF6*	#605537

** There is evidence that cone dystrophy-4 (COD4) and achromatopsia-5 (ACHM5) can be caused by homozygous or compound heterozygous mutation in the PDE6C gene (600827) on chromosome 10q34.*

4. Signs and Symptoms

Achromatopsia main symptoms are color blindness, photophobia, nystagmus, central scotomas or eccentric fixation and decreased visual acuity, often less than 20/200[1, 4]. These symptoms usually start at birth or early infancy and their severity varies depending on genetic and phenotypic variability. Signs and symptoms vary as cases range clinically from complete (typical) to incomplete (atypical) achromatopsia, depending on the number and type of functioning cone cells[1]. In typical complete achromatopsia, patients present usually as soon as 6 months of age with photophobia, pendular nystagmus and poor visual acuity[1]. Although the nystagmus may become less perceptible overtime, visual acuity is usually stable (around 20/200 or less). This is in contrast to other cone dystrophies in which visual acuity progressively worsens[1]. Photophobia persists and may remain a debilitating symptom[1]. In incomplete achromatopsia, also known as atypical achromatopsia, this triad of symptoms may be less pronounced[2]; in visual acuity can reach 20/80[1]. In these cases, one or more cone types may be partially functioning along with the rods[2].

5. Diagnosis and Imaging

To establish the correct diagnosis of achromatopsia a complete clinical and family history along with a thorough ophthalmological evaluation is needed. Additional exams should include visual

field testing, electrophysiology, optical coherence tomography (OCT), fundus autofluorescence (FAF), color testing. Only genetic testing can confirm the diagnosis.

Fundoscopic examination: usually normal, although there may be narrowing of blood vessels, retinal pigment epithelium disturbances or alteration of the foveal reflex[1].

OCT: The most common findings on OCT are the loss of the photoreceptor layer in the foveal region, foveal hypoplasia and ellipsoid layer disruption [1-3, 6].

FAF: Patients with achromatopsia demonstrate age-dependent changes in FAF, which appear to be progressive and to correlate with foveal atrophy and cavitation on OCT[7]. In fact, younger patients have been shown to have foveal hyperautofluorescence, whereas older patients have a punched-out foveal hypoautofluorescence with discrete borders and sometimes with variable degrees of surrounding hyperautofluorescence[7].

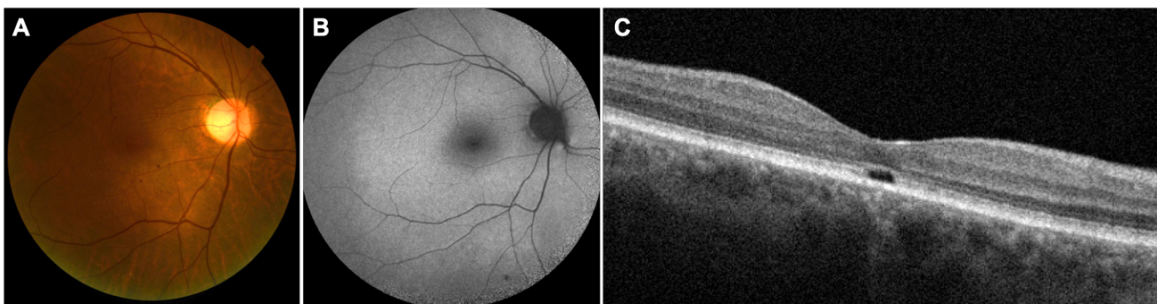

Figure 1 Multimodal retinal imaging of a 55 year old female patient with Achromatopsia. Note the absence of fundoscopic (A) or fundus autofluorescence (B) changes. Optical coherence tomography (C) shows the characteristic loss of the photoreceptors layer in the foveal region. (Courtesy of João Pedro Marques, MD)

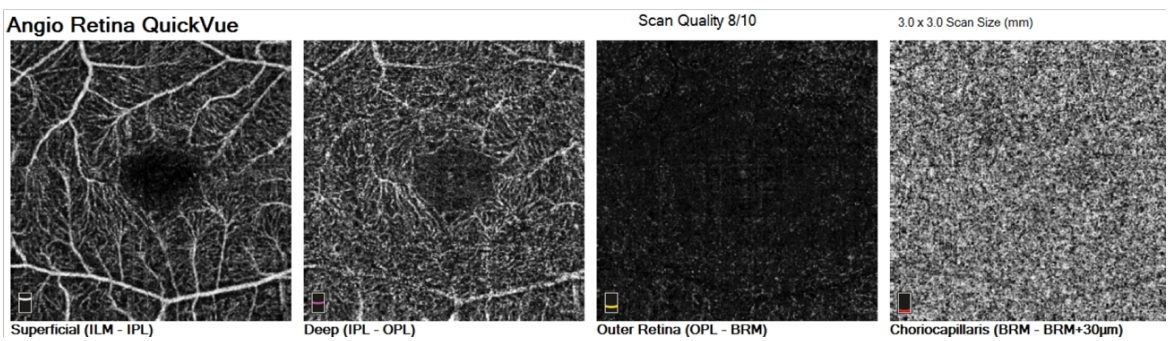

Figure 2 Optical coherence tomography angiography (OCTA) of the same patient in Figure 1. Both the superficial and deep capillary plexus appear normal, as well as the outer retina and the choriocapillaris slabs. (Courtesy of João Pedro Marques, MD)

Visual field testing: Frequently demonstrates a relative central scotoma[1].

Electrophysiology testing: Typical full-field electroretinogram (ffERG) in achromatopsia shows an absence of cone response[2]. Nevertheless, it has been reported that 75% of patients with

achromatopsia had normal responses in ff ERG[5]. The exam often fails to demonstrate pathologic changes due to the limited number of photoreceptors within the fovea compared with the entire retina[1]. Multifocal ERG (mfERG) simultaneously records signals from different retinal locations, allowing the detection of localized abnormalities in the macular, paramacular, or mid-peripheral retina not obvious on examination[2]. The diagnosis of achromatopsia is supported when there is an absent response from a 30- or 15-Hz stimulus in the cone driven pathway. However, it should be noticed that mfERG cannot differentiate between complete and incomplete achromatopsia[1, 2].

Color testing: Patients with achromatopsia demonstrate abnormalities in all three axes of color vision[2]. Testing modalities include the Rayleigh anomaloscope, the Farnsworth Munsell 100-Hue test and Panel D-15 tests[1]. It is important to notice that color vision tests may sometimes be unreliable as patients may distinguish colors based on differences in brightness using their undamaged rod photoreceptors or by association in object–color relationships[2].

Molecular genetic testing: Can be useful for securing the diagnosis, risk assessment in relatives, prenatal diagnosis, identifying carriers and new affected genes and also for prognosis[2]. The sensitivity and specificity of genetic tests are 100% and >95%, respectively, when all the following genes *CNGB3*, *CNGA3*, *GNAT2*, and *PDE6C* are tested[1]. Since achromatopsia is a disease with a complete penetrance, prenatal testing confirms clinical expression at birth[6].

5.1. Differential diagnosis

In the differential diagnosis of achromatopsia, we should consider blue cone monochromacy, red-green color blindness, cone dystrophies, Alström syndrome and cerebral achromatopsia.

Blue cone monochromacy, also known as S cone monochromacy or X-linked incomplete achromatopsia, is an X-linked recessive condition caused by disruption of the red and green pigment gene cluster at Xq28[1]. In this disease, long and medium wavelength- sensitive cones are absent, while short cones are preserved; unlike achromats who lack all cones. Patients typically present poor color discrimination, nystagmus, eccentric fixation, and absence of fundus abnormalities[1]. The Berson color plates, which have varying degrees of blue/purple chroma arrows, are one useful way of differentiating X-linked incomplete achromatopsia (able to distinguish the blue/purple arrows on test plates) from autosomal recessive achromats (who fail to distinguish any of the plates)[1].

Red–green color blindness, including variations (protanopia, deuteranopia, protanomaly, and deuteranomaly) are the most common forms of color blindness and affect nearly 8% of males[1]. These are associated with X-linked mutations affecting medium or long cones, resulting in varying degrees of red and green misperception. Two genes associated with red–green defects are *OPN1LW* (long red cones) and *OPN1MW* (medium green cones)[1].

Cone dystrophies are characterized by the presence and function of cone cells at birth, with progressive deterioration over time. The inheritance of cone dystrophies can be autosomal dominant, autosomal recessive or X-linked. Overtime, patients start to present symptoms such as photophobia, glare sensitivity and decreased visual acuity. A bull's eye maculopathy may be seen on fundoscopic exam[1].

Alström syndrome is an autosomal recessive disorder characterized by cone–rod dystrophy with systemic findings such as obesity, hearing loss, glucose intolerance, and dilated cardiomyopathy[1].

Cerebral achromatopsia is an acquired disorder, following traumatic injury or cerebral infection and inflammation[1].

6. Treatment

Currently, there is no cure for achromatopsia. Filtered glasses and contact lenses, color recognizing devices, and other technological aids are usually focused on improving quality of life[2]. New perspectives of treatment such as gene therapy, the use of neuroprotective compounds such as the ciliary neurotrophic factor, which has been shown to inhibit progressive degeneration of rod and cone photoreceptors and also stem cell–based therapy are being studied[2].

7. Prognosis

On OCT, progressive longitudinal changes in retinal morphology have been observed in patients with achromatopsia[8]. For instance, cone loss observed in OCT occurred in 42% of affected individuals who were younger than 30 years and up to 95% in patients older than 30 years[9]. According to this, achromatopsia may be a progressive disorder and the implementation of gene therapy during the early stages of the disease may provide the best prognosis[8, 9].

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NON-SYNDROMIC RETINITIS PIGMENTOSA

Teresa Dinah Bragança

1. Synonyms

Pigmentary degeneration; Tapetoretinal degeneration; peripheral hereditary retinal dystrophy; rod-cone dystrophy.

2. Epidemiology

The term retinitis pigmentosa (OMIM #268000) describes a heterogeneous group of noninflammatory peripheral retinal dystrophies which are genetically determined and affect the photoreceptors and the retinal pigment epithelium[1,2]. RP has a global prevalence of 1:4000, making it the most common inherited retinal dystrophy (IRD) and an important cause of visual disability and blindness across the world.[3]. The disease may appear early in life or later on; be generalized or more localized, with variable pigmentation and severity. Approximately 70-80% of the affected individuals have non-syndromic retinitis pigmentosa (NSRP), while the remaining 20-30% have syndromic forms, associated with extraocular manifestations.

3. Genetics

In 1990, the rhodopsin (*RHO*) gene, identified by RP Dryja, was the first gene associated with autosomal dominant RP (adRP)[4]. To date, >3000 mutations in > 80 genes have been linked to NSRP[5], thus illustrating the wide heterogeneity among affected individuals.[6] Even among family members, harboring the same mutation, different clinical findings and distinct disease evolution can be found. This may indicate the presence of unidentified genetic or environmental factors that can have influence in the outcome of the NSPR. A thorough family history is very important in any patient with suspected RP and drawing a pedigree for each proband is an easy and effective way of assessing the mode of inheritance. Autosomal recessive RP (arRP) is the most frequent form (50-60% cases), followed by adRP (30-40%) and X-linked RP (5-15%). Mutations in *RHO*, *USH2A*, and

RPGR are found in about 30% of cases of NSRP. The *RHO* gene is responsible for about 20-30% of adRP cases, the *USH2A* gene is presumed to cover about 10-15% of arRP and the *RPGR* and *RP1* genes account for most cases of X-linked RP. Moreover, the severity of the disease is correlated with the disease's Mendelian pattern of inheritance: X-linked RP has a more severe disease course compared to patients with arRP and adRP. The best long-term prognosis with respect to retaining central vision is adRP. Common clinical characteristics of the genetic subtypes of NSRP are presented in Table 1.

Table 1 Common clinical characteristics of the genetic subtypes of non-syndromic RP

Clinical Feature	Associated genes
Age of onset < 5 years old	*BBS1, C2orf71, C8orf37, CRB1, CNGA1, DHX38, FSCN2, IDH3A, IFT140, LRAT, MERTK, NR2E3, NRL, OFD1, PDE6G, PRPF3, PRPF31, RBP3, RDH12, RP2, RP32 locus, RPE65, RPGR, RPGRIP1, SNRNP200, SPATA7, TTC8, TULP1*
Age of onset < 10 years old	*ABCA4, AGBL5, BBS2, BEST1, CLN3, CNGB1, CWC27, HGSNAT, IFT172, IMPDH1, IMGP2, PDE6A, PDE6B, POMGNT1, PRCD, PROM1, PRPF8, REEP6, RHO, RLBP1, RP9, SLC7A14, ZNF513, RP6 locus, RP22 locus, RP24 locus*
Age of onset > 50 years old	*CRX, RBP3, HGSNAT*
Early macular atrophy	*C2orf71, C8orf37, CDHR1, CERKL, CRX, DHX38, FSCN2, GUCA1B, HK1, IDH3A, IFT140, IMPG2, MERTK, PROM1, PRPF6, RDH12, RP2, RPGR, RPGRIP1, SAG, SPATA7, TTC8, ZNF513*
Bull's eye maculopathy	*BBS2, CDHR1, CRB1, IMPG2, HK1, MERTK, NRL, PRCD, PROM1, RP2, RP32 locus*
Dense pigment migration	*BEST1, CDHR1, CRB1, EYS, IFTA140, PDE6A, PDE6B, PRPF8, RDH12, SNRNP200*
Absence/Scarcity of retinal hyperpigmentation	*CDHR1, CLN3, FAM161A, HGSNAT, LRAT, NRL, OFD1, RLBP1, RP1, RPE65, RPGRIP1, TTC8, USH2A*
Pericentral pigmentary retinopathy	*CERKL, CNGA1, CNGB1, CRX, DHDDS, HGSNAT, HK1, NR2E3, PDE6B, PRPF31, PROM1, PRPH2, RHO, TOPORS, TULP1, USH2A*

Adapted from Verbakel SK et al. Progress in Retinal and Eye Research (2018)

4. Signs and Symptoms

In the early stages of RP, fundus examination may appear normal, as bone spicule-shaped pigment deposits are either absent or sparse, vascular attenuation is minimal, and the optic disc is normal. These signs are known as the ophthalmic triad of RP (Figure 1)[6]. Although the anatomical involvement of the central retina can appear early on (RP genotypes with early macular atrophy), usually central macular function remains relatively preserved until the final stages of the disease. The symptoms arise from the initial rod photoreceptor degeneration and in a late stage from the

cone photoreceptor and retinal pigment epithelium decline. As the rod photoreceptor cells are the first to be affected, the initial symptoms of RP are usually decreased night vision (nyctalopia) and difficulties with dark adaptation. Visual field constriction ensues and in later stages, when deterioration of the cones cells develops, central visual acuity declines and color vision becomes compromised[7]. Photophobia and photopsia often manifest during later stages[8]. The progression of the disease symptoms occurs in a symmetrical and similar way.[9] Although the age at onset can be varied, difficulties with dark adaptation begin in the adolescence, and visual loss in the mid-peripheral field arise in young adulthood.

Other ocular complications that can be associated with NSRP include:

- posterior subcapsular cataract (up to 45% of cases)
- cystoid macular edema (up to 50% of cases)
- vitreoretinal interface disorders: epiretinal membrane formation (up to 35% of cases) or macular hole
- optic nerve head drusen (up to 10% of cases). These are particularly common in CRB1 related RP, where optic nerve head drusen are seen in 1/3 of the affected individuals.

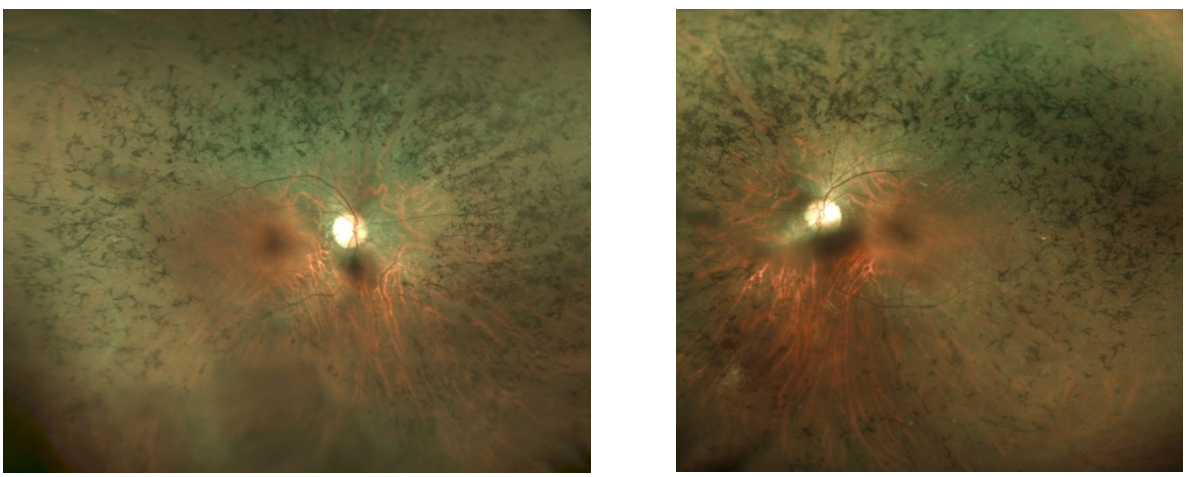

Figure 1 Ophthalmic triad in RP: bone spicule hyperpigmentation, waxy look of the optic nerve head and narrowing of blood vessels in the retina.

5. Diagnosis and Imaging

Difficulties with dark adaptation, nyctalopia, loss of the mid-peripheral visual field and signs of the ophthalmic triad, without extra ocular manifestations, should immediately raise the possibility of NSRP. Electrophysiological testing will confirm the clinical diagnosis of NSRP. The electroretinogram (ERG) shows a very compromised, or even null, function of the photoreceptor cells that occurs early, even there are still no fundus abnormalities or night blindness symptoms[10]. The rod dysfunction precedes the cone dysfunction, so under scotopic conditions the response decreases earlier than in photopic conditions[11]. Color vision testing can reveal, in advanced stages,

a blue-yellow dyschromatopsia[12]. The perimetry shows a progressive bilateral and symmetric loss of the visual field.

Fundus autofluorescence (FAF) exposes a characteristic pattern of lipofuscin distribution creating, in 50–60% of RP patients, an abnormal parafoveal ring or curvilinear arc of increased autofluorescence (Figure 2), not visible on ophthalmoscopy[13]. Nevertheless, several other autofluorescence patterns can be found (Figure 3).

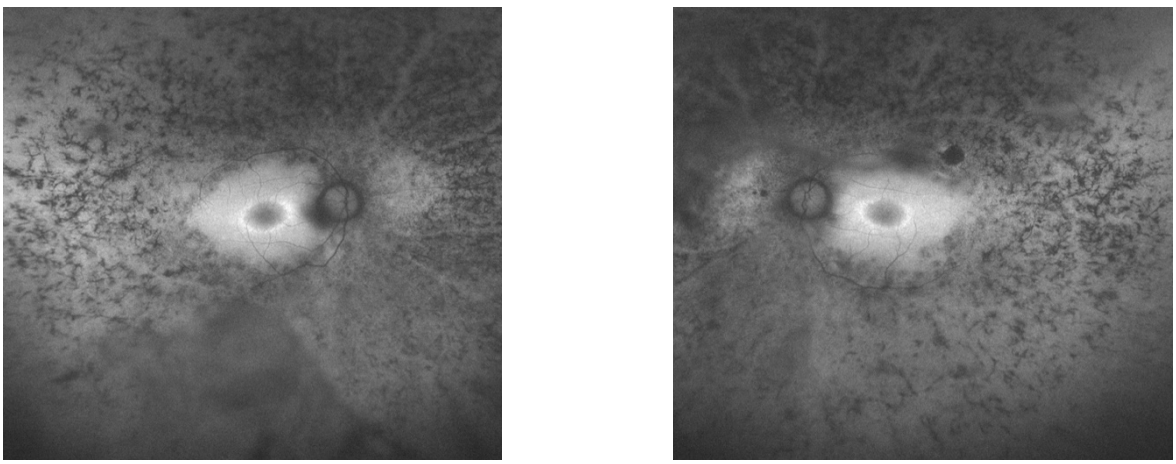

Figure 2 Fundus autofluorescence (FAF) exposes a characteristic pattern of lipofuscin distribution creating a parafoveal ring of hyoperautofluorescence.

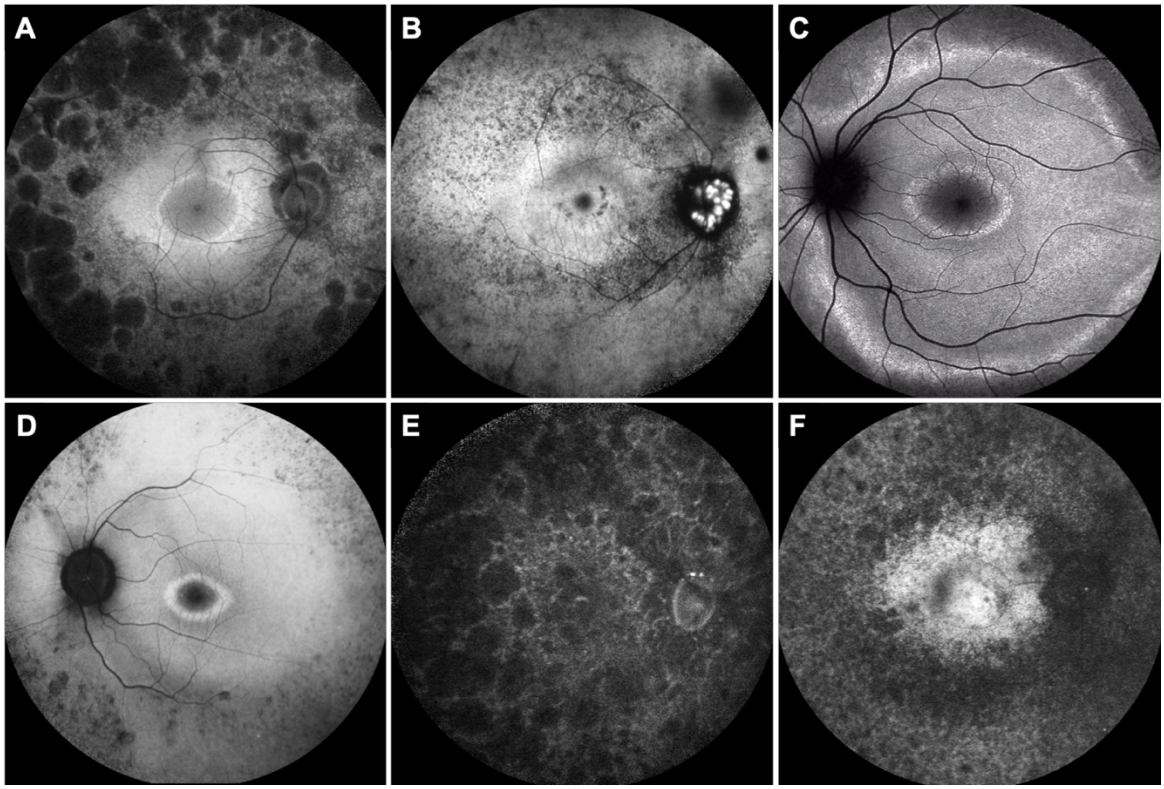

Figure 3 Different fundus autofluorescence (FAF) patterns in RP. ***(A)*** *Typical features of RP with a parafoveal ring of hyperautofluorescence, vessel thinning and RPE atrophy in a patient with autosomal dominant RP.* ***(B)*** *A case of CRB1 related RP evidencing optic nerve head drusen.* ***(C)*** *A young female with NR2E3 related RP depicts the typical double concentric hyperautofluorescent ring (this feature is pathognomonic of NR2E3).* ***(D)*** *An early fom of autosomal recessive RP in a male patient. Vessel thinning, a parafoveal ring of hyperautofluorescence and foci of hypoautofluorescence compatible with outer retinal atrophy and bone spicule hyperpigmentation.* ***(E)*** *Late-stage RP with no autofluorescence left.* ***(F)*** *A case with advanced RP where an abnormal pattern of increased autofluorescence may is observed at the central macula and is associated with central visual impairment. (Courtesy of João Pedro Marques, MD)*

The Fluorescein Angiography (FA) can reveal diffuse blocked fluorescence due to the presence of bone spicule hyperpigmentation, narrow vessels, hipoperfusion of the optic disc and chorioretinal atrophy (first at the periphery and later at the posterior pole) (Figure 4). Late leakage due to cystoid macular edema is sometimes seen.

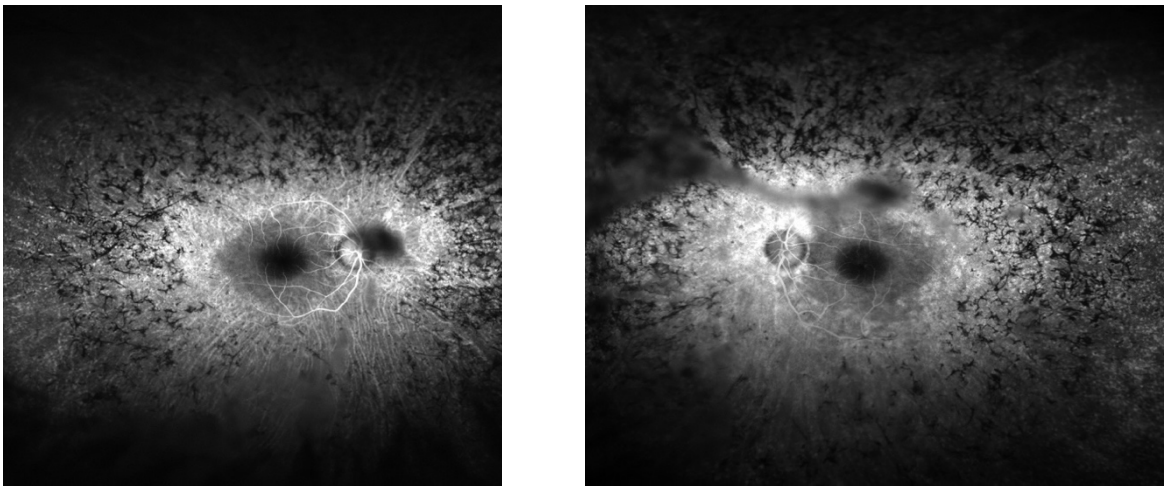

Figure 4 Fluorescein Angiography (FA) - diffuse blocked fluorescence that corresponds to the bone spicule hyperpigmentation, narrow retinal vessels, hipoperfusion of the optic disc and chorioretinal

The shortening of the photoreceptor outer segments begins in the interdigitation zone, then in the ellipsoid zone, and after in the external limiting membrane. This finding, evidenced in Optical Coherence Tomography (OCT), is responsible for the progressive decrease in thickness and disorganization of the outer retinal layers. After the outer nuclear layer becomes thinner and in an advanced state of the disease, there may be a complete loss of both the outer segment and the outer nuclear layer, although the inner retinal layers usually remain preserved.[14, 15] The typical OCT findings in RP are depicted in Figure 5.

Given the latest developments in gene therapy, molecular diagnosis (genetic testing) should be offered to every patient and both the probands and their families should have the access to genetic counseling.

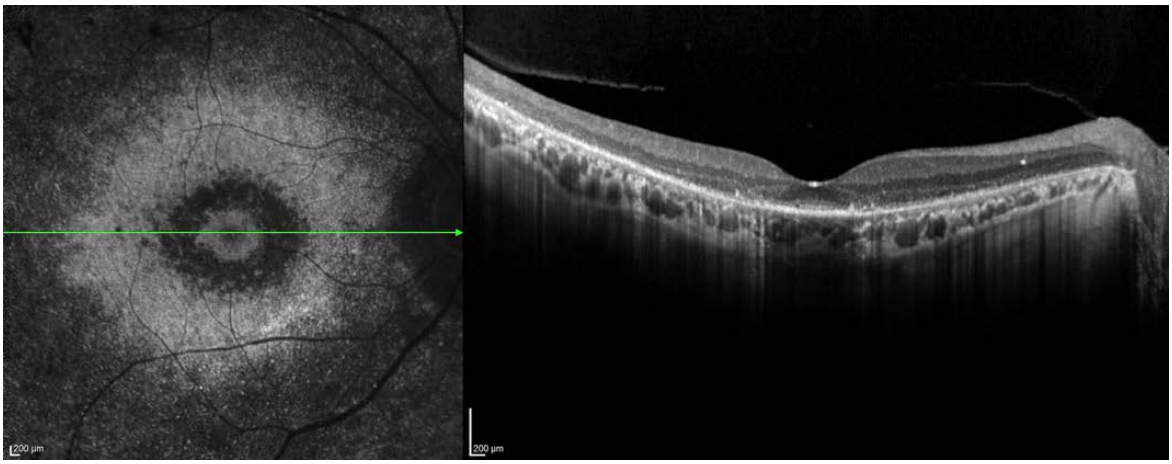

Figure 4 *Horizontal scan of spectral-domain optical coherence tomography (SD-OCT) depicting generalized loss of photoreceptor outer segments and ellipsoid zone except for a small preserved area in the central millimeter. This area of anatomically and functionally intact retina has a good correlation with the visual field and fundus autofluorescence*

6. Treatment

After the landmark publication in the Lancet of the 3-year results of efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy, the Food and Drug Administration (FDA) approved voretigene neparvovec (Luxturna®, Spark Therapeutics Inc.) for the treatment of arRP/Leber congenital amaurosis (LCA) patients with confirmed biallelic RPE65 mutations and sufficient viable retinal cells. In November 2018, the product was granted drug marketing authorization approval from the European Medicines Agency (EMA) and will be commercialized in Europe by Novartis. This is the first gene therapy product to become approved in Ophthalmology and other genes are expected to be targeted in the near future. Retinal implant technology can be an option for some patients with RP. Cell-based therapies and retinal transplantation should be possible in a few years. It is important to treat the associated ocular problems, such as cataracts, vascular abnormalities or cystoid macular edema. Patients with severe visual impairment or blindness should be referred to a low vision clinic.

7. Prognosis

It is important to classify the patients according to their clinical manifestations and molecular diagnosis to establish a predictive outcome of the rate of progression of the disease. Patients with adRP have a better prognosis than patients with arRP. Patients with an X-linked subtype have the worst outcome. Although the evolution of the NSRP is variable even in the same family, normally the nyctalopia appears in adolescence, and the loss of visual field in young adulthood. Patients who develop early symptoms have a faster and more severe evolution.

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USHER SYNDROME

João Carlos Ribeiro, João Pedro Marques

1. Synonyms

Hallgren syndrome, Usher-Hallgren syndrome, RP-dysacusis syndrome, and dystrophia retinae dysacusis syndrome. [1, 2, 3]

2. Epidemiology

Usher syndrome (USH) is an autosomal recessive disorder characterized by the association of sensorineural hearing loss (SNHL), visual loss due to retinitis pigmentosa (RP) and, in some cases, vestibular dysfunction[3]. The prevalence of syndromic forms of RP is less well documented than isolated RP. The general prevalence of Usher syndrome (all forms) is estimated to be from 3.0 (Sweden)[4] to 8.0 per 100 000 habitants (in Denmark)[5]. Most groups believe this estimation is understated. Preliminary data from our group estimates the prevalence at 9.8 per 100 000 habitants (36% USH1, 62% USH2) in the Portuguese population.

3. Genetics

Until now, 10 causative genes (*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *USH1G* and *CIB2* in USH1; *USH2A*, *GPR98* and *WHRN* in USH2; and *CLRN1* in USH3) and three additional loci have been identified. In addition, four other genes have been associated with USH: *PDZD7* (10q24.31), *HARS* (USH 3; 5q31.3), *CEP250* and *ARSG* (17q24.2). A significant genetic heterogeneity is also found.

Table 2. Usher Syndrome clinical classification in 3 types USH1: Usher syndrome type I; USH2: Usher syndrome type II; USH3: Usher syndrome type III.

Symptom	USH1	USH2	USH3
Hearing Loss	Congenital profound SNHL	Congenital sloping SNHL moderate- severe SNHL in low frequencies to severe-profound loss in high frequencies	Born with normal hearing or mild HL which gets worse over a decade or more. Resembles USH2 in teenagers and young adults; looks like USH1 in older people
Vestibular function	Areflexia	Normal	Variable
Night vision loss	Before puberty	At puberty	Variable
Visual fields loss	Before puberty	Second to third decade of life	Variable

Table 3. Usher Syndrome clinical classification in 3 types[3]. Cytogenetic locations are included for all USH genes.

USH subtype	Cytogenetic location	Gene	Protein	Non-syndromic forms
USH1B	*11q13.5*	*MYO7A*	*Myosin VIIa*	*DFNA11, DFNB2, non-syndromic RP, USH atypic*
USH1C	*11p15.1*	*USH1C*	*Harmonin*	*DFNB18*
USH1D	*10q22.1*	*CDH23*	*Cadherin 23*	*DFNB12*
USH1E	*21q21*	*unknown*		
USH1F	*10q21.1*	*PCDH15*	*Protocadherin 15*	*DFNB23*
USH1G	*17q25.1*	*USH1G*	*SANS*	*DFNA20/26*
USH1H	*15q22-23*	*unknown*		
USH1J	*15q23-25.1*	*CIB2*	*Calcium integrin binding protein 2*	*DFNB48*
USH1K	*10p11.21-q21.1*	*unknown*		*DFNB33*
USH2A	*1q41*	*USH2A*	*Usherin*	*RP15, RP39*
USH2C	*5q14.1*	*GPR98*	*G protein-coupled receptor 98*	*Febrile-seizure*
USH2D	*9q32-34*	*WHRN*	*Whirlin*	*DFNB31*
USH3A	*3q25.1-2*	*CLRN1*	*Clarin 1*	*RP61*
USH3B	*5q31.3*	*HARS*	*HARS*	*Charcot-Marie- Tooth type 2W*

USH 1: Usher syndrome type 1; USH2: Usher syndrome type 2; USH3: Usher syndrome type 3

4. Signs and symptoms

USH is divided into three subtypes according to the clinical disease severity and progression. Type I (USH1, OMIM #276900), type II (USH2, OMIM #276901) and type III (USH3, OMIM #276902). USH1 is characterized by profound congenital SNHL, prepuberal onset of RP, and vestibular dysfunction. USH2 is characterized by moderate to profound (sloping pattern) congenital SNHL, later onset of RP and normal vestibular function. USH3 displays post lingual, progressive SNHL, variable vestibular dysfunction, and variable onset of RP. A certain degree of overlapping and atypical cases can be seen.

5. Diagnosis and Imaging

Diagnosis and phenotyping can be a very challenging task. There are no established sensitive biomarkers for early diagnostics and/or disease progression of USH. Clinical evaluation encompasses a complete questionnaire and medical interview with specific questions regarding the onset and progression of HL, visual impairment, gross motor developmental milestones and syndromic manifestations in the proband or family members. Subsequent physical examination includes a general physical examination, examination of the eye, ear, nose, throat and otoneurological examination[6]. Tonal audiometry (Figure 1) and click-evoked auditory brainstem exam, videonystagmography with caloric stimulation and rotatory testing are common clinical otoneurological exams used to help diagnose USH patients.

Ophthalmologic examination includes best-corrected visual acuity, ocular mobility assessment, slit-lamp examination (posterior subcapsular cataracts are common as in other forms of RP) and fundus examination. This should be complemented by visual field testing (Figure 2A) along with multimodal retinal imaging: digital color fundus photography (Fig 3A), optical coherence tomography (OCT) (Figures 2B, 3C and 4) and fundus autofluorescence (FAF) (Figure 3B). As in other forms of RP, electrophysiology testing (Figure 3) is also commonly performed.

Genetic testing (molecular diagnosis) oriented by the ocular phenotype and the type and degree of hearing loss and vestibular dysfunction will confirm the diagnosis of USH. Olfaction testing may also help in subtyping diagnosis.[7]

Criteria for USH phenotypes included sensorineural hypoacusia of various degrees associated with nyctalopia, diffused retinal dystrophy on fundus examination, visual-field loss and abnormal ERG responses.

6. Treatment

There is currently no cure for USH. Hearing amplification by hearing aids, assistive listening devices and cochlear implants (CI) are well established. To be fully effective, a neonatal hearing diagnosis must be obtained so that neuroplasticity is present and USH 1 or older USH2 patients are treated with good hearing results. Low vision aids are usually provided. Retinal implants are currently being used for very advanced cases. Gene-based therapies (both by viral and nanoparticle

gene addition-replacement)[8] and stem cell therapies are currently under development and will hopefully be part of the treatment arsenal in the future.

7. Prognosis

Regarding the SNHL, an early diagnosis and intervention permits keeping social hearing levels. As in other forms of RP, USH patients will progressively lose visual field. The role of the ophthalmologist is to detect and treat manageable complications of the disease (cataract, cystoid macular edema, necessity of low vision aids, etc) to help the patient cope with his/her visual problems. A molecular diagnosis will allow for genetic counseling and prognosis. With the recent advances in gene therapy, the importance of establishing a molecular diagnosis cannot be overemphasized.

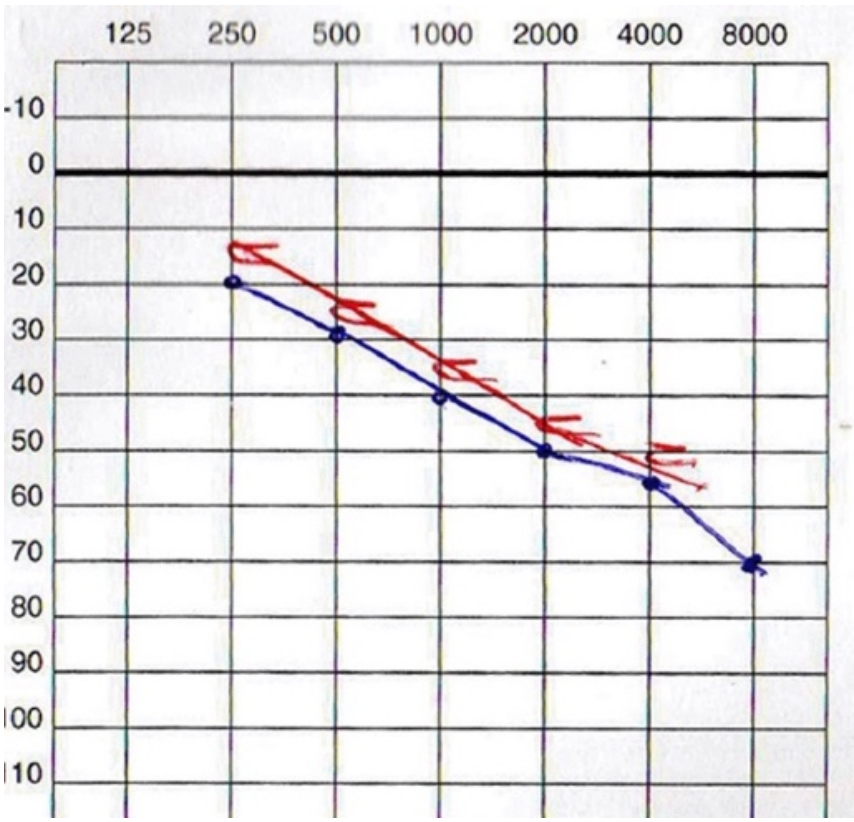
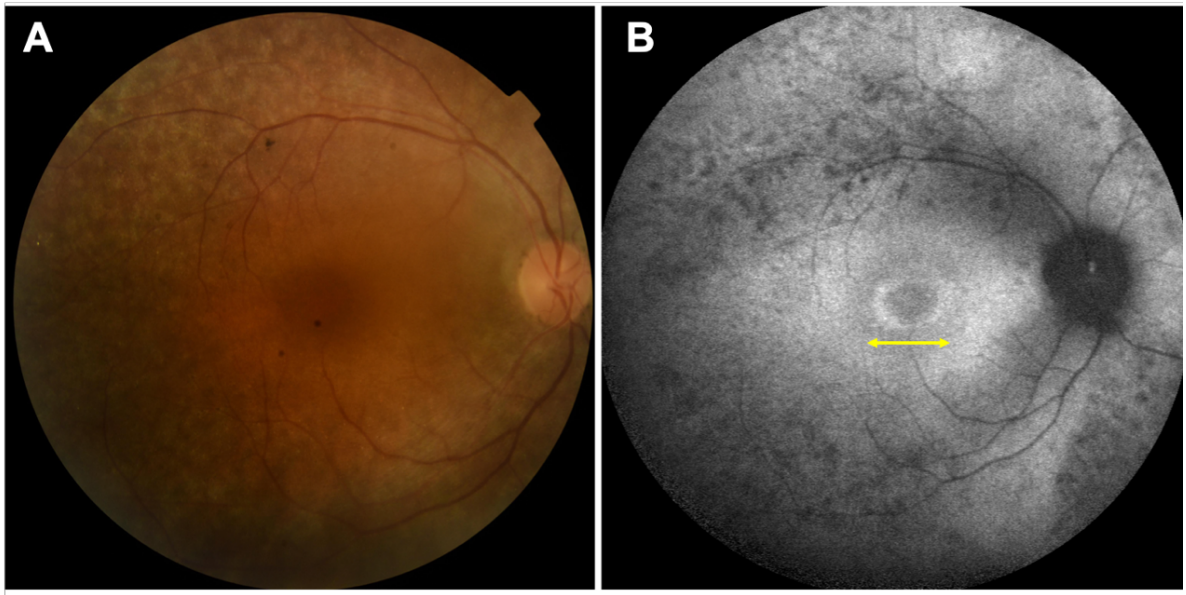


Figure 1. Tonal audiogram representative of a USH 2 patient.

Figure 2. ***(A)*** *Automated perimetry (10-2) of a 38-year old female patient with USH1. Note the bilateral constriction of the visual field, despite a good foveal response.* ***(B)*** *Optical coherence tomography of the same patient highlighting the area of anatomically intact retina (yellow). This area correlates well with the functionally intact retina that is illustrated in the visual fields.*



RETIscan Multifocal ERG

Name:	Date: 5/24/2017 3:12:49 PM	Device:	CRT Monitor	Electrodes:	Other	Operat. Mode:	ERG FOK
First Name:	Channel: OS	Resolution:	61 Segments	Ampl.Range:	±100µV	Test Type:	FOK
Date of Birth:	Result:	View Angle:	30deg	Cut Offs:	5Hz - 100Hz	Correlated:	83ms
ID:	Comment:	Distortion:	1 : 4	Artifact Level:	2%	Averages:	8
Sum Resp.(B):Sum P1-wave: 0.00	Operator: DSU	Fixation:	Seg 31/ Cross	Sampled:	1023Hz	Filter:	2*Smooth 50Hz
Diagnosis:						Result view:	Result view: Static perimetry

Ring	Amp.P1 [nV/deg²]	Amp.P1 [µV]	Amp.N1 [µV]	PeT.P1 [ms]	PeT.N1 [ms]
1	**17.5**	0.265	0.004	49.8	13.7
2	**6.85**	0.147	0.041	43.0	15.6
3	**3.39**	0.106	0.006	48.9	27.4
4	**0**	0.000	0.048	19.5	19.5
5	**0**	0.000	0.002	19.5	19.5

1µV
50ms
Amp.P1 [nV/deg²]

20° 10° 0° 10° 20°

19
nV/deg²
0

OS

Figure 3. Multimodal retinal imaging and multifocal electroretinography (mfERG) of a 40-year old female patient with USH2. (A) Color fundus photography illustrating characteristic features of retinitis pigmentosa. Note the presence of vessel thinning along with whitish flecks outside the vascular arcades that correspond to areas of outer retinal atrophy and precede the appearance of bone spicule hyperpigmentation. (B) Fundus autofluorescence (FAF) of the same eye displaying a typical hyperautofluorescence macular ring that encloses the area of functionally normal retina (yellow double arrow vector). Note the mid peripheral hypoautofluorescence flecks that correspond to the areas of outer retinal atrophy seen of CFP). (C) Optical coherence tomography depicts a normal foveal depression and integrity of the internal layers. However, the external retinal layers, are absent outside the central millimeter. The area of anatomically intact retinal (shown in yellow) correlates with the hyperfluorescent ring seen on FAF. The mfERG shows a marked and generalized reduction in the amplitudes of response; mfERG can be used for staging and evaluation of the rate of progression.

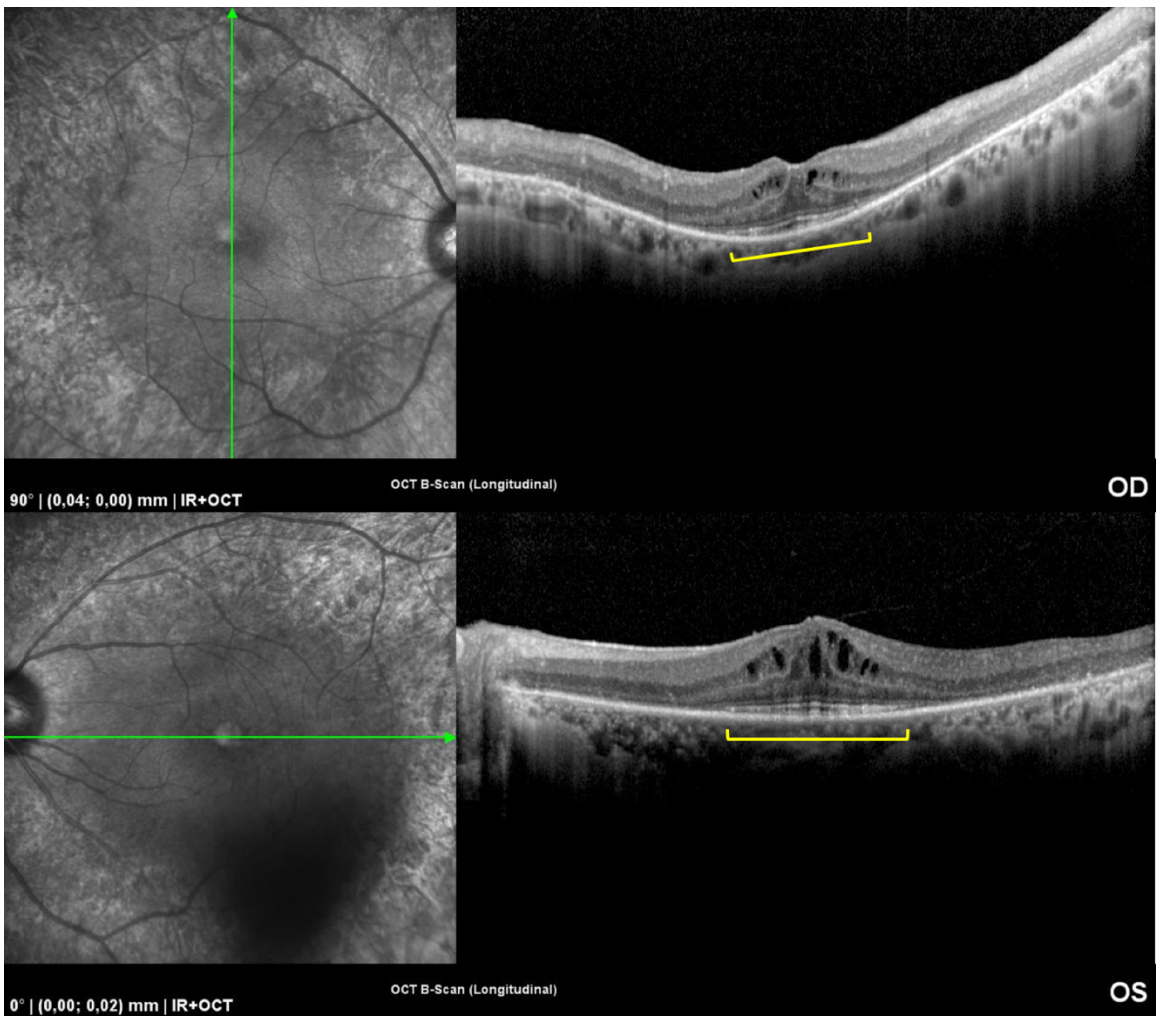


Figure 4. Right (top) and left (bottom) near infra-red imaging and optical coherence tomography of a 73 year old male with USH2. Here, both tomographic scans show a common complication of retinitis pigmentosa – cystoid macular edema. Still, the area of anatomically intact outer retina (yellow) is quite good given the advanced age of the patient.

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BARDET-BIEDL SYNDROME

Filomena Pinto, José Henriques

1. Synonyms

Biedl-Bardet Syndrome; Laurence–Moon–Bardet-Biedl syndrome[1]

2. Epidemiology

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive, clinically and genetically heterogeneous pleiotropic ciliopathy [1,2]. It is caused by mutations in multiple genes that are involved in the function of the primary cilium and is highly prevalent in consanguineous populations[1,3]. BBS has a prevalence of ~1:100,000 in North America and Europe, but it is more common in certain isolated communities including Newfoundland (1:18,000)[4] and Kuwaiti Bedouins (1: 13,500)[1,5,6].

3. Genetics

BBS (OMIM #209900) is a rare autosomal recessive multisystem disorder caused by defects in genes encoding for proteins that localize to the primary cilium/basal body complex. Twenty-one disease-causing genes[1,7,8] have been identified to date (Table 1), which are responsible for 80% of cases with a clinical diagnosis of BBS[5]. Mutations in *BBS1* and *BBS10* account for the majority of cases (~51 and ~20%, respectively) in Northern Europe and North America[5].

BBS is one of the most well-studied conditions in the family of diseases caused by defective cilia, collectively known as ciliopathies[1]. The genes that cause BBS can also cause other ciliopathies, with the classic example being *CEP290*, which can cause Joubert syndrome, Leber congenital amaurosis, Meckel syndrome, and Senior-Loken syndrome besides BBS[1,9].

Table 1. Genes known to cause BBS

BBS type	Gene name
BBS1	*BBS1*
BBS2	*BBS2*
BBS3	*ARL6*
BBS4	*BBS4*
BBS5	*BBS5*
BBS6	*MKKS*
BBS7	*BBS7*
BBS8	*TTC8*
BBS9	*BBS9*
BBS10	*BBS10*
BBS11	*TRIM32*
BBS12	*BBS12*
BBS13	*MKS1*
BBS14	*CEP290*
BBS15	*WDPCP*
BBS16	*SDCCA8*
BBS17	*LZTFL1*
BBS18	*BBIP1*
BBS19	*IFT27*
BBS20	*IFT172*
BBS21	*C8orf37*

4. Signs and Symptoms

4.1. Primary Features

Rod-cone dystrophy[10,11] with early macular involvement is the initial ophthalmic presentation that usually prompts referral and investigation for BBS. It is present in more than 90% of the cases[5], impairs dark adaptation, peripheral vision (rod response) and central visual acuity (cone response). The first signs of retinal dysfunction may not be apparent until the age of seven to eight years, at

which time nyctalopia and decreased peripheral field begin to become manifest[3,12,13]. Between 20-30 years of age, the involvement of the macula is evident with severe visual impairment (20/200 or less) and legal blindness in 63.6% of the cases[14]. The electrophysiological evaluation with full-field ERG shows rod-cone or cone-rod patterns[11].

Postaxial polydactyly is evident in 68%-81% of cases[5] with involvement of the 4 limbs (21%) or just hands (9%) or feet (21%)[3,5]. Truncal obesity occurs in 72%-92% of affected individuals. Birth weight is usually normal, but significant weight gain begins in early childhood and worsens with ageing, being more prominent in trunk and proximal limbs[3,5]. Other typical features include (1) cognitive delay with learning disabilities and variable degrees of impairment (from severe intellectual disability to average intelligence)[3,5] and hypogonadism in men or genital abnormalities in women, with diminished fertility[3,5]. Renal anomalies are a major cause of morbidity and mortality, with renal failure present in 53%-82% of cases[3,5].

4.2. Secondary Features

Other features of BBS include: (1) speech disturbances (54-81%) due to probable incoordination of pharyngeal and/or laryngeal muscles[3,5]; (2) delayed development and behavioural changes (50-91%) with emotional immaturity, depression, disinhibition, and obsessive/compulsive behaviours[3,5]; (3) ophthalmic abnormalities beyond retinopathy, which include nystagmus, strabismus, high myopia, cataracts, and glaucoma[3,5]; (4) brachydactyly (46-100%) of the fingers and toes as well as syndactyly (8-95%) between the 2nd and 3rd toes[3,5]; (5) ataxia and imbalance (40-86%), with no evidence of cerebellar dysfunction[3,5]; (6) diabetes mellitus type 2 (6-48%), beginning in adolescence (may be related to obesity)[3,5] and (7) cardiovascular anomalies (7%) with valvular stenosis and aortic-ventricular septal defects[3,5]. Some patients may also have anosmia/hyposmia (60%), hypertension and hyperlipidemia, hepatic involvement, craniofacial dysmorphisms, Hirschsprung disease and orodental abnormalities (51%).[3,5]

5. Diagnosis and Imaging

The diagnosis of BBS is established by clinical findings such as rod-cone dystrophy, truncal obesity, polydactyly, cognitive delay, male hypogonadism/female genital malformations and renal abnormalities. The presence of 4 primary or 3 primary and 2 secondary features is sufficient for the diagnosis[3,5]. Fundus examination reveals the presence of typical retinitis pigmentosa features like disc pallor, arteriolar attenuation and bone spicule hyperpigmentation. Atrophic macular degeneration is common[11]. Optical coherence tomography (OCT) demonstrates paracentral retinal thinning with disruption of the outer layers. Other features include internal limiting membrane wrinkling and deposits adjacent to and anterior to Bruch's membrane[15].Full field electroretinogram (ffERG) shows decrease in rod and cone amplitudes as early as 2 years of life with scotopic ERG affected before the photopic response[12].

Molecular genetic testing can be used to confirm the diagnosis. As genotype-phenotype correlations are unclear, it is prudent as a first approach to sequence the genes that are most

commonly mutated (in persons of northern European origin these include *BBS1* and *BBS10*)[16]. When this workup is negative, next generation sequencing (NGS), whole exome sequencing (WES) or whole genome sequencing (WGS) can be used[21,22].

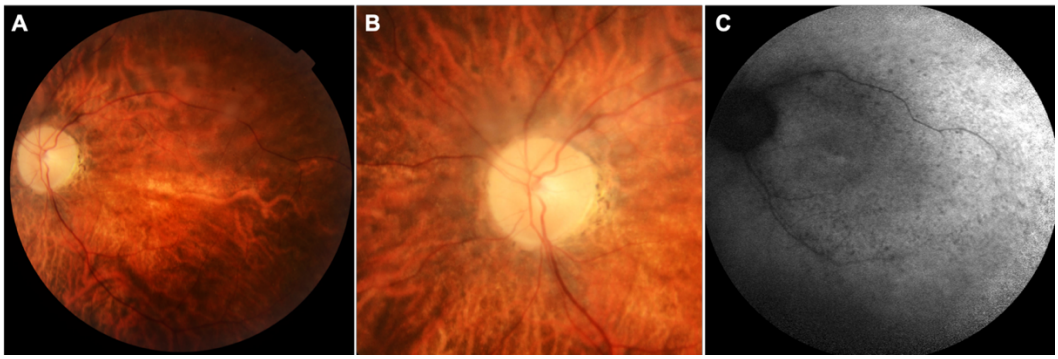

*Figure 1. Retinal imaging of a 20 year old female patient with genetically confirmed BBS (BBS10 mutation). Color fundus photography reveals diffuse atrophy of the retinal pigment epithelium (RPE) **(A)**, a pale optic nerve head and arteriolar attenuation **(B)**. Fundus autofluorescence is remarkable for the presence of pinpoint hypoautofluorescent spots (areas of outer retinal atrophy) and vessel thinning **(C)**. (Courtesy of João Pedro Marques, MD)*

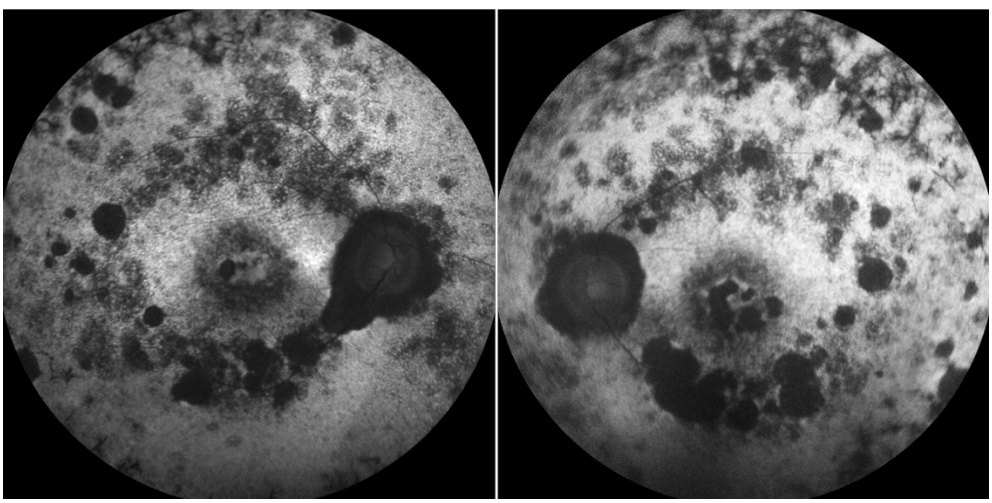

Figure 2 Fundus autofluorescence of a 44 year old male patient with genetically confirmed BBS (BBS2 mutation). Note the presence of bilateral macular atrophy, vessel thinning and foci of hypoautofluorescence (associated with areas of outer retina and RPE atrophy) inside and outside the vascular arcades. (Courtesy of João Pedro Marques, MD)

6. Treatment

Treatment of BBS is multidisciplinary, focusing on management of obesity, diabetes, hypertension and metabolic syndrome. Renal and cardiac anomalies, diabetes and hypertension are

treated as in the general population. Genital anomalies, polydactyly and other malformations may be surgically corrected. No therapy exists for the progressive visual loss, but early evaluation by a low-vision specialist facilitates introduction of low vision aids and mobility training. Educational planning should take the prospect of future blindness into consideration[16].

6.1. Current and Future Therapies

Patients with BBS and related ciliopathies have seen significant advances in the development of various therapeutic approaches, particularly, genetic therapies. Developing genetic therapies in BBS is a challenging task due to the large number of disease-causing genes and private mutations[23]. Some options include:

- Generation of induced pluripotent stem cells [24,25,26]
- Gene Therapy involving a viral vector carrying a wild-type gene that integrates the gene into the host genome[27]. In mice, electroretinogram function seems to be improved after subretinal injection of Viral AAV vectors containing the wild-type *Bbs1*[28]
- Readthrough Therapy allows normal RNA translation into a full-length protein to be produced[29], which may result in a less severe clinical phenotype[1]
- Exon Skipping Therapy operates at the level of RNA transcription allowing the transcriptional machinery to "skip" exons containing undesirable genetic sequences[30]. In BBS, this form of therapy could benefit up to 9% of patients[1]
- Genome Editing – CRISPR-Cas9 allows DNA to be deleted, replaced, or corrected[31,32]. Targeted endonucleases create double-stranded breaks at specific points in the genome allowing for DNA repair, which can restore the wild-type genotype[33]. Promising results have been achieved in cells from patients with the motile ciliopathy primary ciliary dyskinesia where ciliation was restored on replacement of the wild-type *DNAH11* sequence[34].

6.2. Genetic counselling

BBS is typically inherited in an autosomal recessive manner. It is thus prudent to use the following autosomal recessive risk figures when providing genetic counselling: at conception, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier and a 25% chance of being unaffected and not a carrier[16].

7. Prognosis

Rod-cone dystrophy often begins in childhood and is present in almost 90% of BBS patients. A visual acuity of 20/200 or worse by the second to third decade of life is expected, given the common macular involvement. Visual fields are usually abnormal by age ten and a central island of vision remains by age 17. Legal blindness will be expected by age 20 years in about 65% of BBS patients[16]. Regarding other organs/systems, the prognosis depends on the affected organ/system and on the degree of impairment.

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REFSUM SYNDROME

Bernardete Pessoa, Melo Beirão

1. Synonyms

Adult Refsum disease (ARD), Classic Refsum disease, Disorder of Cornification 11 (Phytanic Acid Type), DOC 11 (Phytanic Acid Type), Heredopathia Atactica Polyneuritiformis, Hypertrophic Neuropathy of Refsum, Phytanic Acid Storage Disease, Hereditary motor and sensory neuropathy type 4 (HMSN 4), Phytanic-CoA hydroxylase deficiency. [1,2]

2. Epidemiology

The prevalence of Refsum disease is believed to be very low. According to some authors, 4%–5% of retinitis pigmentosa patients may have Refsum disease[3]. Males and females are affected equally[2]. About 60 cases have been reported worldwide. Prevalence rates are not known but the disorder may be underdiagnosed. In the United Kingdom, prevalence has been estimated to be 1/1,000,000. The fact that most of the patients described in the publications have been identified in Norway and the United Kingdom, where the awareness of Refsum's disease is high, suggests that the actual prevalence of Refsum's disease may be much higher.

3. Genetics

Refsum syndrome has been associated with two rare, autosomal recessive, peroxisomal diseases. One, Infantile Refsum disease (IRD), is a disorder of peroxisomal biogenesis that presents during childhood. Abnormalities of general peroxisomal biogenesis and function, similar to that seen with Zellweger's syndrome and neonatal adrenoleukodystrophy, were identified in IRD, and it is now classified as a milder variant of Zellweger syndrome[4] (figure 1). The adult Refsum disease (ARD) presents as an adult-onset disease. The genes responsible for the failure in the metabolism of phytanic acid have been traced to the short arm of chromosome 10 (10pter-p11.2) and the long arms of chromossome 6 (6q22-q24), chromossome 7 (7q21.2) and chromossome 8 (8q21.13).

Genetic counselling. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if the *PEX7* (<10%) or *PHYH* (>90%) pathogenic variants have been identified in an affected family member. Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder[5,6].

4. Signs and Symptoms

This is a neurocutaneous syndrome related with the accumulation of phytanic acid in plasma and tissues[2]. Onset of symptoms in ARD ranges from age seven months to after age 50 years. Usually, first manifestations of ARD occur in children aged 2-7 years; however, diagnosis is usually delayed until early adulthood. Because the onset is insidious, it is difficult for many individuals to know exactly when symptoms first started[7-9]. ARD is characterized by early-onset retinitis pigmentosa (a universal finding) and anosmia (present in most, if not all, patients)[10]. Gibberd *et al* (11) found an abnormal smell test, tested experimentally, in all individuals. Other findings may occur in the following ten to 15 years in decreasing order of frequency: neuropathy, deafness, ataxia and ichthyosis [10,12]. Psychiatric disturbances have also been described[7].

The clinical picture of ARD is often that of a slowly developing, progressive peripheral neuropathy manifested by paraesthesia of arms and legs, sensory motor and reflex changes with severe motor weakness and muscle wasting, especially of the lower extremities[1,13]. Ichthyotic symptoms may include dryness, itchiness, and scaliness of the skin, (ranging from mild hyperkeratosis of the palms and soles to severe scaling of lamellar ichthyosis type observed on the trunk)[1,2]. Some investigators distinguish between acute ARD and chronic ARD. In acute ARD, polyneuropathy, weakness, ataxia, sudden visual deterioration, and often auditory deterioration are often accompanied by ichthyosis, cardiac arrhythmias, elevated liver transaminases and bilirubin. Triggers for acute presentations include weight loss, stress, trauma, and infections. In contrast, in chronic ARD, RP is present, but the other features of ARD are generally subtle[7].

Cardiac arrhythmia and heart failure caused by cardiomyopathy are potentially severe health problems which develop later in life[7]. Hepatic/renal symptoms are clinically silent despite fatty degeneration[2]. Skeletal defects (knees, elbows, and short tubular bones of the hands and feet) are not related directly to phytanic acid levels. The full constellation of signs and symptoms is rarely seen in an affected individual; most features develop with age[7].

4.1. Ophthalmologic findings

In general, individuals with retinitis pigmentosa (pigmentary retinal degeneration, tapeto-retinal degeneration) due to Refsum disease experience night blindness before the appearance of additional clinical symptoms, years before the progressive changes of constricted visual fields and decreased central visual acuity. Often the typical "bony spicule type" of pigmentary retinal degeneration is lacking (retinitis pigmentosa *sine pigmento*), and the pigmentation appears as fine granules or has a "salt and pepper" type of appearance (Figure 1). Visual failure in Refsum patients may also be aggravated by optic nerve atrophy, cataract and vitreous opacities. Nystagmus—usually of moderate

degree—has also been recorded in ~25% of patients. Miosis and poor reaction of the pupils to light may also contribute to the poor vision[13].

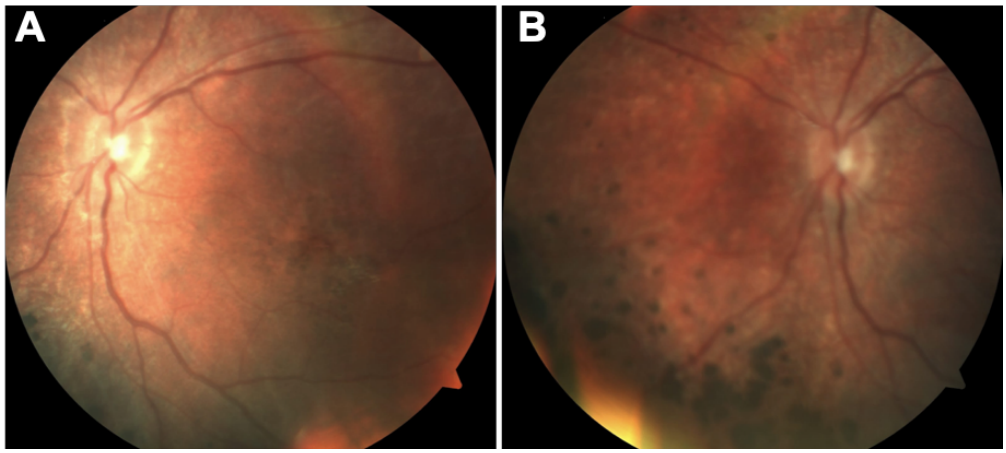

*Figure 1 Left eye color fundus images of a nine year old female, with Infantile Refsum Syndrome (now classified as a milder variant of Zellweger syndrome), diagnosed since age four. The typical aspect of retinitis pigmentosa in a Refsum Syndrome can be observed **(A and B)**, with fine hyperpigmentation granules or a "salt and pepper" appearance (Image Courtesy of Vasco Miranda, MD).*

5. Diagnosis and Imaging

5.1. Laboratory Studies

Plasma phytanic acid

An excellent marker for the disease with no reports in the literature of false negatives. A disturbed visual capacity, together with anosmia (the first clinical manifestations of the disease in most patients) should lead to prompt analysis of plasma phytanic acid levels in order to start therapy. (7,13) The normal range is ≤0.2 mg/dl. Levels in Refsum disease are ≥10-50 mg/dl[14].

Electroretinography (ERG)

ERG shows a reduction or complete absence of rod and cone responses. Night blindness can be difficult to ascertain, particularly in children. ERG can help support the diagnosis in early stages[7].

Visual field testing

Over the years, a concentric visual field constriction develops gradually. Finally only tubular vision remains.[13]

Other Laboratory studies

Cerebrospinal fluid (CSF) shows an albuminocytologic dissociation with a protein level of 100-600 mg/dl.; Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels are decreased[14].

Other Tests

Skeletal radiography is required to estimate bone changes. Phytanic oxidase activity estimation in skin fibroblast cultures is important[14]. Electrocardiogram (ECG) is helpful to rule out cardiac conduction defects[14]. Smell function test is useful[13].

Urine acylcarnitine analysis by nuclear magnetic resonance electrospray ionization-MS/MS seems to be a new tool for the diagnosis of peroxisomal biogenesis disorders [15].

Skin biopsy shows features of ichthyosis vulgaris. Nerve biopsy examination shows nerve demyelination with marked Schwann cell proliferation and onion bulb formation[14].

5.2. Differential diagnosis

Other causes of retinitis pigmentosa and sensorineural hearing loss should be considered in the differential diagnosis (Usher syndromes, types 1, 2, and 3; Alström syndrome; Kearns-Sayre syndrome; Sjögren-Larsson syndrome). Refsum disease should not be confused with infantile Refsum disease, a misnomer that belongs to the Zellweger syndrome spectrum (Figure 1).[2]

6. Treatment

6.1. Standard Therapies

There is no curative therapy for Refsum disease. The dietary restriction of phytanic acid (meat from ruminant animals like cow, sheep and goat; some seafoods and nuts) and avoidance of sudden weight loss (because there is mobilization of the phytates that are in the adipocytes) is advised[16,17]. Plasmapheresis or lipid apheresis can be used for arrhythmias, ataxia, sensory neuropathy and ichthyosis, particularly in acute presentations, because phytanic acid is in lipoproteins[18]. Some drugs should be avoided. That is the case of ibuprofen (because it interferes with the metabolism of phytanic acid) and amiodarone (due to the risk of hyperthyroidism, which causes an increase in the metabolism and mobilization of adipose tissue lipids). Other treatments are symptomatic and supportive. Regarding the ophthalmologic manifestations of Refsum syndrome, cataracts are treated with standard phacoemulsification. However, iris hooks are often required, since these patients frequently present changes in pupillary dilation. The zonular fibers are also fragile and the surgeon may need to use an iris-fixated or scleral-fixated intraocular lens. The efficacy of treatment in the progression of retinitis pigmentosa as well as anosmia and deafness has not been proven[19-21]. Some authors report that even with a strict diet, retinitis pigmentosa progresses (BP Leroy 2007, personal communication).

6.2 Investigational Therapies

Enzyme replacement therapy, as used in other lysosomal diseases, is currently being investigated. It is believed that in the future the treatment of choice will be gene therapy.

7. Prognosis

Prognosis in the absence of treatment is generally poor. Severe cases or late diagnosis may be life-threatening. The main cause of death is arrhythmia and heart failure.[2] In early diagnosed and treated cases, phytanic acid decreases slowly, followed by improvement of the skin scaling and, to a variable degree, reversal of recent neurological signs. Attenuation of neurologic, ophthalmologic, and cardiac symptoms requires constant adherence to a suitable diet along with plasmapheresis. (2). Early-onset disease is not necessarily associated with a poor prognosis for life span[7].

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ALSTRÖM SYNDROME

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1. Synonyms

ALMS, ALSS

2. Epidemiology

Alström syndrome is a very rare condition[1-6]. The prevalence is unknown but is thought to range between 1:500,000 and 1:1,000,000[1-3,5,6]. It has been more frequently described in French Acadian populations of Nova Scotia and Lousiana as well as in Saudi Arabia[1-5]. There are no differences in gender prevalence[1-3]. Clinical manifestations generally start in infancy although some findings develop later in life. Several clinical phenotypes can be identified in affected individuals and there is a very wide variability in clinical manifestations among families, making the diagnosis difficult[1-6].

3. Genetics

Alström syndrome (OMIM #203800) is an autosomal recessive monogenic condition caused by bi-allelic mutations in the *ALMS1* (2p13.1)[1-6] gene. Although its function is not completely known, it is thought to be related to ciliary signaling function, cell differentiation, intracellular trafficking and energy and metabolism homeostatis[6-8]. The resulting protein is expressed in several organs. Mutations in this gene result in a shorter and nonfunctional protein which is responsible for the multisystemic pathological changes observed in this syndrome[1-8].

4. Signs and Symptoms

The major phenotypes that are generally observed in children include infantile-onset cone–rod retinal dystrophy, sensorineural hearing loss, insulin resistance, obesity and acanthosis nigricans (Figure 1). During adolescence, affected individuals develop other major conditions observed in this condition such as type 2 diabetes mellitus, hypertriglyceridemia and adolescent-onset dilated cardiomiopathy[1-6]. Short stature, scoliosis, alopecia, and metabolic features such as male

hypogonadism and hyperandrogenism in female patients may be present in adulthood. Patients also frequently develop progressive pulmonary and hepatic disfunction with varying severity degrees. Renal disease in the form of progressive glomerulofibrosis is a prominent clinical feature in adult patients[1-6].

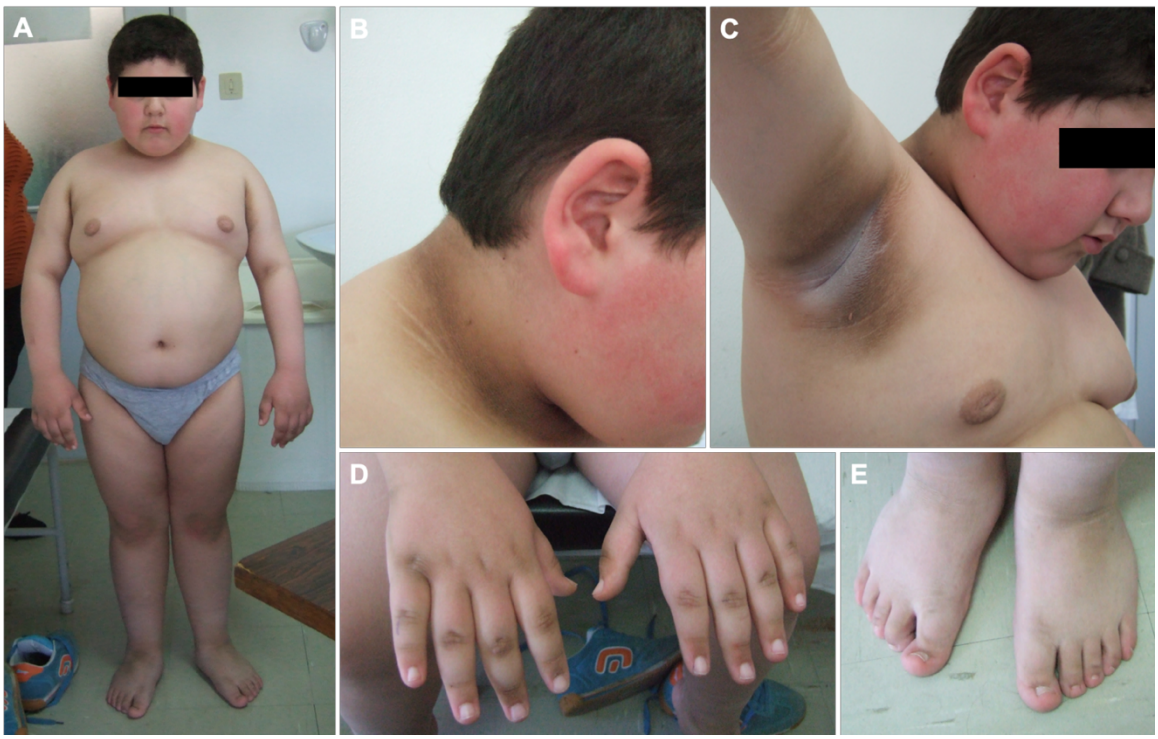

*Figure 1 A patient with Alström syndrome depicting some of the most frequent physical characteristics. **(A)** Obesity and short stature; **(B and C)** Acanthosis nigricans; **(D and E)** Normal digital morphology (fingers and toes) in Alström syndrome, contrasting with polydactyly usually found in Bardet-Biedl Syndrome. (Courtesy of Ana Luísa Carvalho, MD)*

4.1. Ocular findings

The hallmark ocular finding in Alström syndrome is cone-rod retinal dystrophy developing within the first few weeks of life. Nystagmus and photophobia are the first clinical manifestations[2-6], mostly presenting at 6-9 months of age[9]. Virtually all affected infants have low vision in the first year of life[1-6,9]. Cones are affected first in Alström syndrome and therefore the vision that young children experience comes primarily from rods. As the disease progresses, photophobia decreases, and visual acuity loss ensues[2-6,9]. Pathological studies show a reduction of cell layers in the posterior retina and depletion of peripheral cells, the outer nuclear layer, and photoreceptors[3]. Fundoscopy findings include optic disc pallor, attenuated retinal vessels and retinal pigment epithelium atrophy with pigmentary changes, exhibiting a retinitis pigmentosa-like pattern. There are no pathognomonic clinical findings[2-6,9]. Although retinal dystrophy is the most prominent ocular finding in this disease, cataract is also a common feature[2,3,6].

5. Diagnosis and Imaging

Diagnosis of Alström syndrome is mostly based on clinical findings. However, given the diagnostic challenges, Marshall *et al* developed major and minor clinical diagnostic criteria for Alström syndrome for different age groups (infants under 2 years, children 3-14 years, adolescents/adults) (Table 1) that must be revised as the child grows[3]. Genetic testing should be done whenever clinical diagnostic criteria are not entirely met but there are some suggestive clinical findings. In these cases, identification of one mutation in *ALMS1* gene is diagnostic. When two distinct mutations are found, confirmation that each mutation is inherited by a different parent should be undertaken[2,3].

Regarding ocular findings, there are no pathognomonic clinical findings. Electroretinography shows severe cone function impairment (diminished/absent a and b waves in the photopic single flash cone response and 30-Hz flicker) with mild or no rod involvement early in the disease. As the disease progresses, a more severe rod dysfunction is seen (diminished/absent a and b waves in the scotopic and dark-adapted bright flash). Fundus autofluorescence may be useful by enhancing retinal pigment atrophy changes[2,3]. Recent studies with spectral domain optical coherence tomography have shown progressive retinal thinning accompanied by loss of photoreceptors and retinal pigment epithelium that initially spares the fovea, as well as marked parafoveal outer nuclear layer (present even in early stages) and prominent choroidal vasculature[10]. Differential diagnosis in young children is challenging since some clinical findings only develop later in life and there are other genetic conditions that have clinical similarities with Alström syndrome[2-6]. Alström syndrome is frequently misdiagnosed in infancy as Leber congenital amaurosis or achromatopsia since they frequently present with photophobia and nystagmus in young infants[2,3,9]. Bardet-Biedl syndrome is also a relevant differential diagnosis since it also presents with obesity and type 2 Diabetes. However, it is generally excluded by the absence of hearing loss and abnormal digital morphology[2,3]. Clinical similarities can also be found with Biemond II Syndrome, Wolfram Syndrome, Cohen Syndrome, sporadic infantile dilated cardiomiopathy, and some mitochondrial disorders[3].

7. Treatment

There is no specific treatment for Alström syndrome. Clinical strategies are employed to diminish the impact of the clinical manifestations of this disease. Regarding ocular manifestations, vision can be aided in the first few years with dark/red-tinted glasses and referral to a Low Vision specialist. Cataract surgery may benefit the affected individuals[1-3].

8. Prognosis

Severe visual loss occurs in all patients with Alström syndrome, with 1/3 of patients being legally blind by 9 years of age, 50% by age 12 and 90% by age 16[1-3].

Table 1 – Adapted table of diagnostic criteria developed for Alström Syndrome, by Marshall *et al*[3]

	Under 2 years	3-14 years	15 years - Adulthood
Proof	2 ALMS1 mutations	2 ALMS1 mutations	2 ALMS1 mutations
Minimum diagnosis requires	2 major criteria or 1 major and 2 minor criteria	2 major criteria or 1 major and 3 minor criteria	2 major and 2 minor criteria or 1 major and 4 minor criteria
Major criteria	- *ALMS1* mutation in 1 allele and/or family history - Vision (nystagmus, photophobia)	- *ALMS1* mutation in 1 allele and/or family history - Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	- *ALMS1* mutation in 1 allele and/or family history - Vision (history of nystagmus in infancy/ childhood, legal blindness, cone and rod dystrophy by ERG)
Minor criteria	- Obesity - DCM/CHF	- Obesity and/or insulin resistance and/or T2DM - DCM/CHF (history of) - Hearing loss - Hepatic dysfunction - Renal failure - Advanced bone age	- Obesity and/or insulin resistance and/or T2DM - DCM/CHF (history of) - Hearing loss - Hepatic dysfunction - Renal failure - Short stature - Males: hypogonadism; Females: irregular menses and/or hyperandrogenism
Other variable supportive evidence	- Recurrent pulmonary infections - Normal digits - Delayed developmental milestones	- Recurrent pulmonary infections - Normal digits - Delayed developmental milestones - Hyperlipidemia - Scoliosis - Flat wide feet - Hypothyroidism - Hypertension - Recurrent UTI - Growth hormone deficiency	- Recurrent pulmonary infections - Normal digits - History of developmental delay - Hyperlipidemia - Scoliosis - Flat wide feet - Hypothyroidism - Hypertension - Recurrent UTI/urinary dysfunction - Growth hormone deficiency - Alopecia

Abbreviations: ERG, electroretinogram; T2DM, type 2 diabetes mellitus; DCM/CHF, dilated cardiomyopathy with congestive heart failure; UTI, urinary tract infections.

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FUNDUS ALBIPUNCTATUS AND RETINITIS PUNCTATA ALBESCENS

Tiago Fernandes, João Pedro Marques

1. Synonyms

Fundus Albipunctatus cum hemeralopia; Albipunctate Retinal Dystrophy; Lauber's Disease

2. Epidemiology

Fundus Albipunctatus (FA) and Retinitis PunctataAlbescens (RPA) belong to a heterogeneous group of so-called *flecked retina syndromes*. Despite the phenotypic overlap in the early stages, the first distinction between these two entities was made by Lauber in 1910.[1] While FA is in most cases a stationary form of night blindness, RPA refers to a severe subtype of retinitis pigmentosa (RP) with nyctalopia, progressive peripheral visual field constriction and ultimately central visual acuity loss due to macular atrophy. RPA might account for 0.5% of all RP cases or 1% of autosomal recessive and sporadic RP.[2] Assuming that the prevalence of RP in developed countries is ~1:4 000, RPA should have an approximate prevalence of 1: 800000.[3] FA is a rare disease and its prevalence is unknow.

3. Genetics

FA (OMIM #136880) shows an autosomal recessive inherence pattern, even though an autosomal dominant or pseudodominant inheritance has been suggested in one family with this disease.[4] FA is caused almost exclusively by mutations in the*RDH5* gene (12q13.2) encoding 11-cis retinol dehydrogenase 5, a key enzyme in the final restorative step of the retinoid cycle in the retinal pigment epithelium. However, mutations in two other genes, retinaldehyde binding protein 1 (*RLBP1*, 15q26.1) and RPE-specific protein (*RPE65*) are also known to be associated with FA.[5]

RPA (also OMIM #136880) is mostly inherited as a autosomal recessive condition, however, it has been described in association with autosomal dominant RP. RPA is most frequently associated with mutations in the *RLBP1* gene (15q26.1) and occasionally in *RHO* (3q22.1), *RDS* and *RDH5* genes.

4. Signs and Symptoms

Patients with FA usually complain of impaired night vision from an early age, that is characteristically stationary. They have delayed dark adaptation, meaning difficulties adapting from a bright light to dark conditions. It often takes hours for adaptation to occur, and some patients with FA may experience minimal changes even after hours of dark adaptation.[6] Visual acuity (VA) is usually well preserved. On the other hand, RPA is considered a rod-cone dystrophy type of RP that typically features early childhood-onset night blindness and progressive peripheral visual field loss.[3] Over the years, central VA is usually affected due to progressive macular atrophy.

5. Diagnosis and Imaging

A phenotypic overlap of the fundus appearance in patients with FA and RPA is well described. Therefore, electrophysiological studies combined with appropriate genetic testing stand as crucial tools in the differential diagnosis between the two. FA is characterized by the presence of numerous dull-white or pale-yellow punctate lesions, the diameter of which resemble the size of second-order arterioles, scattered in a regular radial pattern throughout the retina with greater density in the midperiphery and the posterior pole with exception of the fovea (Figures 1A and 1D).[7, 8] However, some studies have evidenced RPE changes that can affect the fovea in up to 30% of patients.[6, 9, 10] RPA patients often show similar fundus changes (Figures 2A, 2B and 2C) but manifest a severe and progressive hereditary retinal dystrophy. Pigment clumping with a bone-spicule-like configuration can be observed in patients with advanced RPA.[11] Macular involvement is relatively frequent, usually in the form of progressive macular atrophy (Figures 2A, 2C and 2E).

On electroretinography (ERG), individuals with FA usually experience markedly reduced scotopic responses, but ultimately tend to reveal an improvement in the dark-adapted ERG response due to the slow rate of regeneration of photopigment.[9] However, not all FA patients depict a full recovery of the scotopic ERG response and this improvement can also be observed in some cases of RPA. In FA, electronegative ERG along with cone dysfunction have also been reported in some series.[10]

On spectral domain optical coherence tomography (SD-OCT), FA is characterized by numerous hyperreflective lesions in the outer retina, varying in shape and size, located at the level of the RPE, and extending into the overlying ellipsoid zone of the photoreceptors as well as the outer nuclear layer (ONL) (Figure 1F).[11] SD-OCT findings in patients with RPA show that the retinal white spots are also located at the level of the RPE, most of them wide-based and with extension to the ellipsoid zone (Figure 2E). These lesions differ from those of FA, as the latter are more dome-shaped and extend not only to the ellipsoid zone but also into the ONL.[11]

In FA, OCT-Angiography (OCT-A) shows preservation of the superficial and deep capillary plexus (SCP and DCP, respectively) density and a regular foveal avascular zone (FAZ) (Figure 1B). On the other hand, in cases of RPA, OCT-A depicts an irregular FAZ (Figure 2D), along with focal atrophic changes at the level of the choriocapillaris (Figure 2G).

6. Treatment

Referral to a low vision clinic is important for every patient with severe visual impairment or blindness. Although there is no approved treatment for any of the conditions, recent studies in animal models and in patients suffering from FA, suggest that food supplements containing 9-cis-β-carotene from the alga Dunaliellabardawil may improve the cone and rod visual function in these patients. This potential and very promising therapy is readily available and is being evaluated in retinal dystrophies of similar mechanisms such as various types of RP. Combination therapy involving 9-cis-β-carotene and more radical therapeutic methods, including gene and stem cell therapies, might help some patients with RP,[12] as suggested for a mouse model of Leber congenital amaurosis[13]. Recent progresses provide hope that multiple inherited retinal dystrophies will soon be treated by pharmaceutical intervention.

7. Prognosis

While FA is characteristically a non-progressive form of night blindness, RPA is a progressive condition with a poor visual prognosis. Given the phenotypic similarities between the two, genetic testing is very important for prognosis. The ophthalmologist's role is to manage the patient's expectations regarding the natural history of the disease and to manage its treatable complications such as cataract and macular edema.

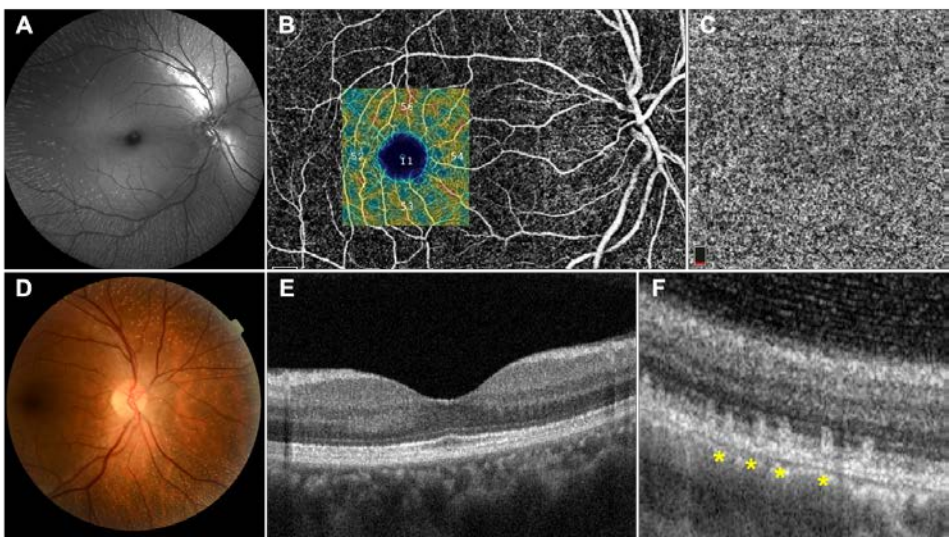

Figure 1 (A) Redfree image depicting the flecks scattered in a radial pattern in a patient with FA. (B) OCTA shows normal vessel density in the superficial capillary plexus, along with a regular FAZ. (C) The choriocapillaris layer in OCTA has a normal appearance. (D) Note the presence of the typical whitish-yellow flecks in the fundus, densely packed in the midperiphery retina and sparing the macula. (E) and (F) SD-OCT demonstrating integrity of the internal and external retinal layers subfoveally. No flecks are seen perifoveally. A close up segment of the OCT highlights the deposits (yellow asterisks). They are located deep in the retina and extend into the ellipsoid zone and outer nuclear layer.

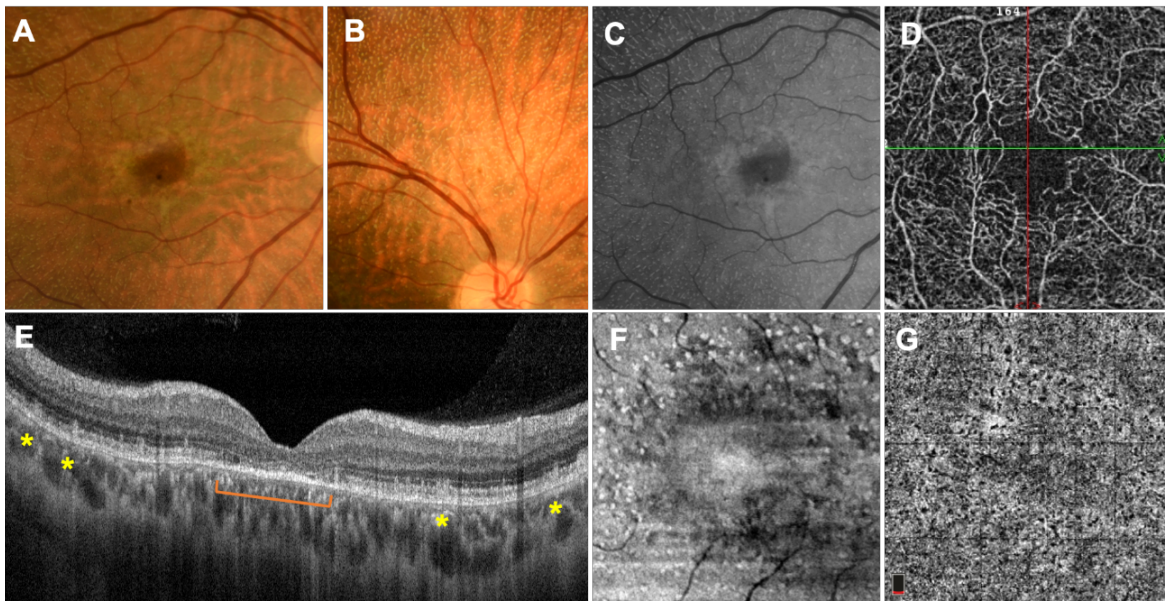

Figure 2 (A) Similar distribution of the flecks is observed in a patient with RPA, however, an increased number of flecks is seen inside the vascular arcades and macular pigmentary changes are also present. (B) A close-up of the flecks. (C) Redfree imaging of the same patient evidencing both the flecks and the macular atrophy. (D) The superficial capillary plexus imaged with OCTA shows an enlarged and disrupted foveal avascular zone. (E) On SD-OCT, the flecks (yellow asterisks) appear as wide-based lesions extending from the RPE into the ellipsoid zone. Foveal sparing is of note. However, atrophy of the outer retinal layers is observed subfoveally (orange). (F) Enface OCT at the level of the outer retina depicting the flecks. (G) OCTA of the choriocapillaris layer evidences focal areas of hypoperfusion and atrophy.

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CONGENITAL STATIONARY NIGHT BLINDNESS

Maria Luísa Colaço, Diana Silva

The term Congenital Stationary Night Blindness (CSNB) comprises a heterogenous group of non-progressive inherited retinal disorders that most frequently have a normal fundus and can be autosomal dominant, autosomal recessive, or X-linked. CSNB results from defects in visual signal transduction either within rod photoreceptors, or in rod and cone bipolar pathways[1]. In 1952 Schubert and Bornschein discovered that some patients with CSNB may have an abnormally interesting electroretinogram (ERG) in which the a-wave is larger than the b-wave, the so called electronegative ERG (b/a<1) or Schubert-Bornschein ERG. The disease spectrum has been traditionally divided into the Schubert-Bornschein form due to a signal transmission defect from the photoreceptors to the bipolar cells, and the Riggs form which represents a dysfunction of the rods. Later, Miyake and co-workers proposed a new classification further dividing the Schubert-Bornschein type of CSNB into the complete (c) and incomplete (ic) sub-types of CSNB. The complete form is characterized by selective ON bipolar cell dysfunction, and the incomplete form is due to a signaling defect involving both ON and OFF bipolar pathways.[2]

1. Synonyms

Congenital Stationary Night Blindness (CSNB); Schubert-Bornschein type; Riggs type; complete CSNB (cCSNB); incomplete CSNB (icCSNB). The terms CSNB 1A and 2A refer to the complete and incomplete variants of X-linked CSNB. The terms CSNBB1 and CSNBB2 are sometimes used as abbreviations for complete and incomplete CSNB irrespective of the mode of inheritance.

2. Epidemiology

The exact prevalence of CSNB or its different types is not known. Nevertheless, it seems that X-linked CSNB is more prevalent than the other forms of transmission. In a recent meta-analysis, X-linked CSNB accounted for 57,9% of cases, autosomal recessive and sporadic CSNB accounted for 40% and 2,1% of cases had autosomal dominant CSNB. Fundus abnormalities were found in 23,6% of cases.[2] Penetrance of CSNB1A and CSNB2A is probably 100% but expressivity is variable[3]. Clinically mild cases may be missed if electroretinography is not performed.

3. Genetics

There are currently 17 genes known to be mutated in CSNB, 12 autosomal recessive, 2 X-linked, and 3 autosomal dominant[4] with more than 360 identified mutations. In 1998, the first gene mutated in X-linked CSNB was discovered to be *CACNA1F*, and 2 years later, *NYX* was assigned to X-linked CSNB. They encode bipolar cell membrane proteins that are involved in signaling between photoreceptors and bipolar cells.[4] cCSNB is linked to mutations in *NYX* (X-linked), and in *GRM6*, *GPR179*, and *LRIT3*, the latter four being autosomal recessive. These genes encode proteins localized at the dendritic tips of ON-bipolar cells.[2] On the other hand, icCSNB is linked to mutations in *CACNA1F* (X-linked), in *CABP4* and *CACNA2D4*, the latter two autosomal recessive, coding for proteins localized to the photoreceptor synaptic terminal. [2]

Riggs-type CSNB is linked to mutations in genes involved in rod phototransduction that can be inherited in an autosomal dominant (*RHO*, *PDE6B*, and *GNAT1*); or autosomal recessive manner (*GNAT1* and *SLC24A1*). [2]

Prenatal testing and carrier testing for families in which the pathogenic variant has been identified is possible.

Table 1 – Description of the 17 genes known to cause CSNB

GENE	LOCATION	PHENOTYPE	MIM NUMBER	INHERITANCE
GNAT1	3p21.31	Riggs	#610444	AD; AR
PDE6B	4p16.3	Riggs	#163500	AD
RHO	3q22.1	Riggs	#610445	AD
SLC24A1	15q22.31	Riggs	#613830	AR
NYX	Xp11.4	cCSNB	#310500	X-linked
GRM6	5q35.3	cCSNB	#257270	AR
TRPM1	15q13.3	cCSNB	#613216	AR
GPR179	17q12	cCSNB	#614565	AR
LRIT3	4q25	cCSNB	#615058	AR
CACNA1F	Xp11.23	icCSNB	#300071	X-linked
CABP4	11q13.2	icCSNB	#608965	AR
CACNA2D4	12p13.33	icCSNB	#608171	AR
GNB3	12p13.31	CSNB1H*	#617024	AR
RDH5	12q13.2	FA	#136880	AR
RLBP1	15q26.1	FA	#136880	AR; AD
SAG	2q37.1	Ogushi	#258100	AR
GRK1	13q34	Oguchi	#613411	AR

** CSNB1H – ON bipolar cell dysfunction and reduced cone sensitivity*

Source: www.omim.org

4. Signs and symptoms

The phenotype of different forms of CSNB seems to be somewhat variable. Clinical manifestations include:

- Reduced Visual Acuity: vision is reduced in all affected males with X- linked inheritance in the range of 20/30 to 20/200. However, some variants may have normal or almost normal visual acuity;
- History of defective dark adaptation: Night blindness is a subjective finding. Patients with the complete form of the disease usually report severe nyctalopia, while those with the incomplete form do not uniformly report night blindness. Furthermore, this symptom may be present from early childhood and infants may grow used to this and fail to report it to the physician;
- Myopia: ranging from low to high (≥ -10,00 D); a few affected individuals have hyperopia;
- Nystagmus and strabismus;
- Normal color vision, even though some individuals with severe CSNB may show color vision deficits;
- Normal fundus examination: The ocular fundus in CSNB is characteristically normal except for persons with high myopia which may show myopic degeneration with tessellated fundus, tilted disc or a peripapillary temporal crescent (Figure 1);
- Characteristic findings on ERG (explained in detail below);
- Family history consistent with the mode of inheritance.

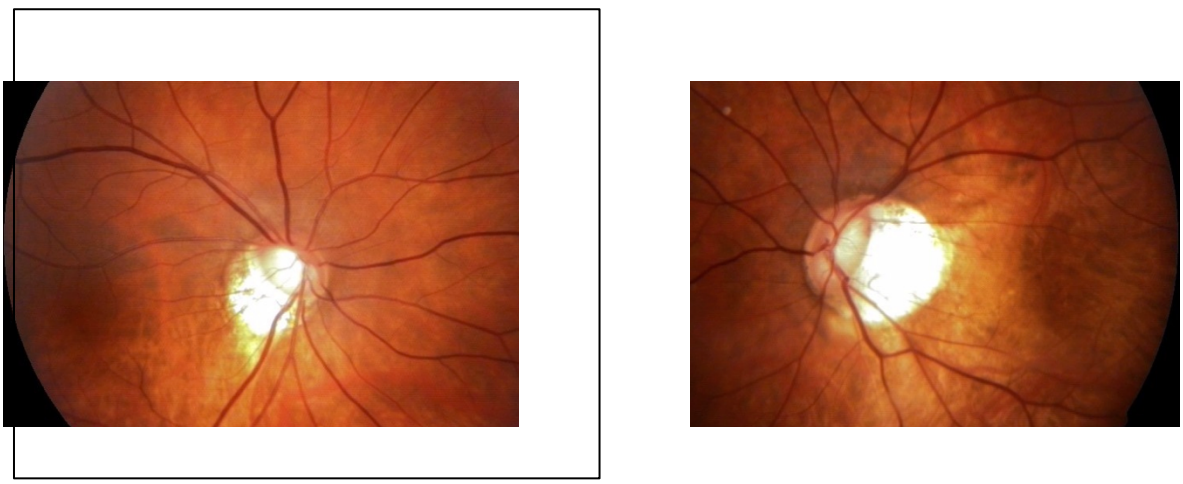

Figure 1 *Color fundus photography of a CSNB patient with myopic changes: tessellated fundus; peripapillary atrophy and disc pallor. (Courtesy of Miguel Raimundo, MD).*

Riggs-type CSNB was historically reported for the first time in the southern French Nougaret family. This sub-type of CSNB has a relatively mild phenotype that includes normal photopic visual acuity, normal visual fields, normal color vision and normal fundus appearance. Night blindness and elevated thresholds on dark adaptometry are usually the only findings. For these reasons, this form of CSNB may be overlooked.[1]

The clinical features of patients with complete CSNB are similar even when the causative gene is different[6]. cCSNB patients typically have a history of congenital night blindness, decreased visual acuity (with a median of 20/40)[10], moderate to high myopia, nystagmus and strabismus. The later should be recognized and managed to avoid additional amblyopia. Color vision, visual fields and fundus appearance are usually normal except for myopic changes.

The phenotype in icCSNB is somewhat more heterogenous than in cCSNB. Patients seldom complain of night blindness, they express light sensitivity, variable degrees of refractive errors that range from myopia to hyperopia, visual acuity is lower than in cCSNB (about 20/60), visual fields are normal but color vision may show variable defects. Hence, icCSNB patients may have more severe daylight symptoms than those with cCSNB, in keeping with involvement of both the cone ON and OFF-bipolar systems.

A precise ERG analysis can provide the correct differentiation between complete and incomplete types. Miyake et al state that complete and incomplete CSNB are two different clinical entities, with a good phenotype/genotype correlation since genes involved in icCSNB affect proteins at the presynaptic level, impacting both ON and OFF bipolar cells or their synapses in the rod and cone visual pathways[1,7]; while those in cCSNB affect postsynaptic ON-bipolar cell function leaving the OFF pathway intact.

Two diseases that are considered part of the spectrum of non-progressive CSNB but have a characteristic abnormal fundus appearance and autosomal recessive inheritance are Oguchi disease and Fundus Albipunctatus (FA). Oguchi disease is caused by pathogenic variants in either the gene encoding arrestin, *SAG*, or the gene encoding rhodopsin kinase, *GRK1*. The fundus has an abnormal golden sheen color, which becomes normal after prolonged dark adaptation (Mizuo-Nakamura phenomenon).

Fundus Albipunctatus is a form of CSNB caused by pathogenic variants in *RDH5*, the gene encoding retinol dehydrogenase. The fundus shows scattered white dots throughout the retina (Figure 2). The ERG is typically electronegative but normalizes with prolonged dark adaptation (>4 hours, or overnight patching).

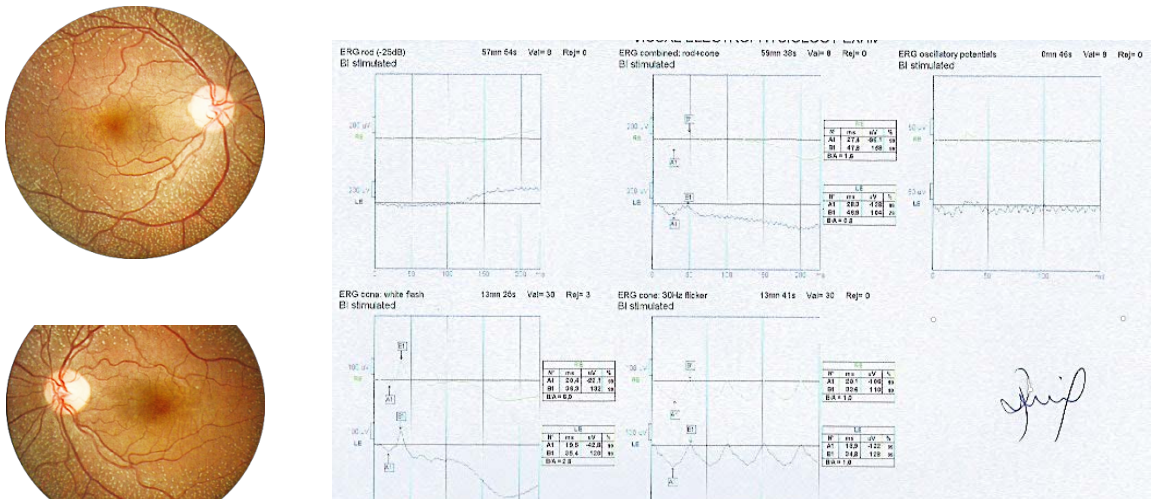

Figure 2 *Color fundus photography and electrophysiological findings in Fundus Albipunctatus. Rod response after 1 hour of dark adaptation is abolished; bright flash DA with a b-wave severely reduced and an electronegative ERG; oscilatory potencials severely reduced; cone response preserved.*

5. Diagnosis and Imaging

The full-field eletroretinogram (ffERG) is critical for functional phenotyping and precise diagnosis. Patients with CSNB associated with normal fundi may be sub-divided into Schubert-Bornschein and Riggs sub-types based on ffERG findings.

5.1. Schubert-Bornschein type of CSNB

The Schubert-Bornschein type of CSNB has the typical electronegative ERG in which scotopic a-wave amplitude is normal or minimally subnormal, but the b-wave is severely reduced. This ERG phenotype reflects dysfunction occurring post-phototransduction and affecting signal transmission between photoreceptors and bipolar cells, and is the most common type of ERG abnormality associated with CSNB.

The complete form of CSNB is characterized by specific ffERG anomalies that are related to with ON-bipolar dysfunction. Under scotopic conditions, there is no detectable ERG to a dim flash (0,01 cd.s.m^{-2}), thus the term "complete", and there is an electronegative scotopic bright flash ERG (3,0 or 10,0 cd.s.m^{-2}) with a normal a-wave and a severely reduced b-wave. Some mildly subnormal a-waves have been reported and may relate to myopia.[8] Under photopic conditions, the single flash response (3,0 cd.s.m^{-2}) frequently has a normal a-wave amplitude but with a broadened trough; the waveform has a sharply rising b-wave with no oscillatory potentials and a mildly reduced b/a ratio. These photopic ERG characteristics are typical of loss of function of the ON-pathway with preservation of the OFF-pathway This is confirmed by long duration stimulation (200 ms), which

reveals an electronegative ON response but a normal OFF response. The S-cone ERG b-wave is also markedly abnormal consistent with S-cones connecting only to ON-bipolar cells.[1] Interestingly, a similar ERG phenotype is encountered in melanoma-associated retinopathy (MAR) with antibodies against TRPM1 (one of the dysfunctional proteins in cCSNB).[9]

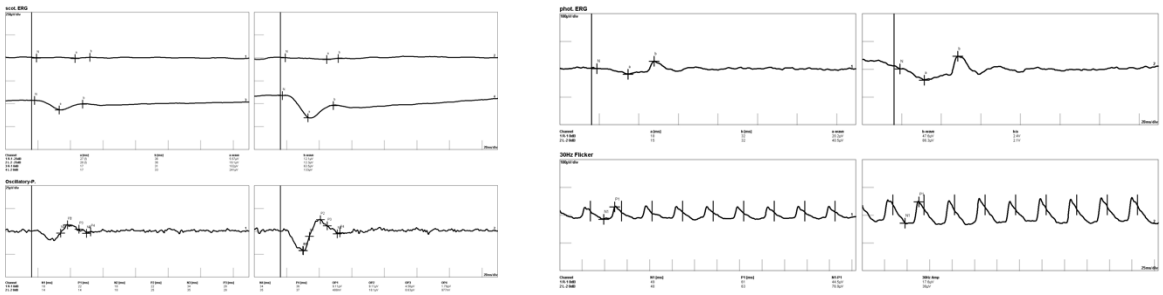

Figure 3 Electrophysiological findings in cCSNB. Scotopic response is abolished; combined response has an electronegative waveform; oscillatory potencials with altered morphology and reduced amplitude; photopic ERG relatively preserved although with slightly reduced amplitude. (Courtesy of Miguel Raimundo, MD)

In icCSNB, the scotopic dim flash ERG is present, thus the term "incomplete", but the amplitude is subnormal; there is a normal a-wave in the scotopic bright flash ERG, confirming normal rod phototransduction, but a reduced b-wave (electronegative waveform). Photopic responses are more severely affected than in the complete form; the light-adapted (LA) 30Hz ERG (L and M-cone response) is markedly subnormal and delayed with most having a distinctive bifid peak. The single flash cone ERG (LA 3,0) is also markedly subnormal with a profoundly reduced b/a ratio. Long duration stimulation (200ms) shows abnormalities in both ON and OFF-responses.

There is no distinction between the two Schubert-Bornschein types of CSNB and no clear distinction between other causes of nystagmus except for electrophysiology.

5.2. Riggs type of CSNB

The ERG findings in this rare type of CSNB are characterized by a decreased a-wave amplitude in response to a bright flash under dark adaptation (rod photoreceptor dysfunction), and possible additional reduction of b/a ratio giving an electronegative waveform. Photopic ERGs are preserved, consistent with normal cone system function.[1] In cases where an electronegative waveform is observed, it likely represents the contribution of the dark-adapted cone system to the bright flash ERG (since there is absence of rod function). The scotopic red flash ERG may be informative in this case by revealing preserved dark-adapted cone function and absent rod function.[1]

In conclusion, eletrophysiology is essential to the diagnosis and differentiation among the CSNB spectrum. Additional non-standard recordings useful to the ISCEV standard protocol include: prolonged dark adaptation, scotopic red flash ERG (Riggs type); short-wavelength stimulation and long duration stimulation (200ms) to better distinguish ON and OFF bipolar cone pathways.

The differential diagnosis for CSNB with normal fundus appearance and night blindness includes: (1) rod-cone dystrophies, (2) choroideremia, (3) enhanced S cone syndrome, (4) vitamin A deficiency and (5) MAR. The differential diagnosis of an electronegative ERG includes: (1) X-linked retinoschisis, (2) snowflake vitreoretinal degeneration, (3) a few rod-cone dystrophies, (4) Juvenile Batten disease, (4) Infantile Refsum disease, (5) Mucolipidosis IV, (6) Duchenne-Becker muscular dystrophy, (7) central retinal artery occlusion (CRAO) or ischemic central retinal vein occlusion (CRVO), (8) Birdshot chorioretinopathy; (9) Diffuse unilateral subacute neuroretinitis (DUSN), (10) MAR and (11) retinal toxicity (vigabatrin; quinine; methanol; ocular siderosis).

6. Treatment and Prognosis

CSNB is usually non-progressive. Visual acuity remains stable after infancy and is generally good (about 20/40-20/60). Visual fields are usually normal as well as color vision. In cases where color vision deficits are reported, these are usually mild. Apart from night blindness disturbances and photophobia, that can be more or less severe, prognosis is related to the severity of the refractive error, the presence strabismus and nystagmus. All these manifestations should be addressed early in order to prevent amblyopia. The use of glasses and filtered lenses may be helpful to treat the refractive error and photophobia. Strabismus surgery may correct ocular alignment, improve binocularity, and/or help to bring a null point to a better functional range and improve head posture.

There have been some reports of a few progressive forms of night blindness usually with some degree of cone dysfunction and there are pathogenic gene variants described that are in the barrier between CSNB and rod-cone dystrophies. The combination of ERG, fundus examination, and clinical findings allows comprehensive phenotyping and differential diagnosis that can help direct the genetic investigations.

To date, no gene therapy approaches for CSNB have been undertaken. Current gene therapy trials are targeting photoreceptor expression. Gene therapy in CSNB would require bipolar cell targeting, which is technically challenging.

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KEARNS–SAYRE SYNDROME AND MATERNALLY INHERITED DIABETES AND DEAFNESS

Catarina Almeida, João Luís Silva, Ricardo Faria

1. Kearns–Sayre Syndrome (KSS)

1.1. Synonyms

Ophthalmoplegia-plus syndrome; Ophthalmoplegia, progressive external, with ragged-red fibers; CPEO with ragged-red fibers.[1]

1.2. Epidemiology

The exact prevalence is unknown, but has been estimated at approximately 1 to 3 per 100,000 individuals.[2]

1.3. Genetics

In the majority of the cases, KSS (OMIM #530000) is due to a single mitochondrial DNA (mtDNA) deletion. However, there are a number of cases in which is due to mtDNA point mutations, such as m.3249G>A in the tRNA (Leu) gene, m.3255G>A in the tRNA (Leu) gene, or m.3243A>G in the tRNA (Leu) gene.[3] The mtDNA deletions causing KSS are sporadic in 96% of the cases, with negative family history. However, in 4% of the cases, maternal transmission has been reported. On the contrary, mtDNA point mutations are maternally transmitted in the majority of the cases, with marked intrafamilial phenotypic heterogeneity.[4]

1.4. Signs and Symptoms

KSS is classically characterized by the triad of chronic progressive external ophthalmoplegia (CPEO), retinitis pigmentosa and onset before age 20.[5] Cardiac conduction defects, elevated cerebrospinal fluid protein or cerebellar ataxia usually accompany the ophthalmological phenotype.[6] Other symptoms may include dysphagia, endocrine disorders (diabetes, short stature

due to growth hormone deficiency, hypoparathyroidism), proximal myopathy, dementia and elevated lactate levels.[6-8] CPEO is usually the presenting clinical abnormality[5], often with initial bilateral ptosis that is followed by limitation of ductions in all directions and marked delay of the ocular saccades. Downward gaze may be spared until late in the course of the disease. Curiously, despite ocular misalignment, these patients rarely complain of diplopia. Weakness of the orbicularis oculi and facial muscles is common.[9] Retinal findings may include a salt-and-pepper pigmentary retinopathy and nummular RPE atrophy limited to the macular region or even a retinitis pigmentosa-like peripheral retinopathy.[5]

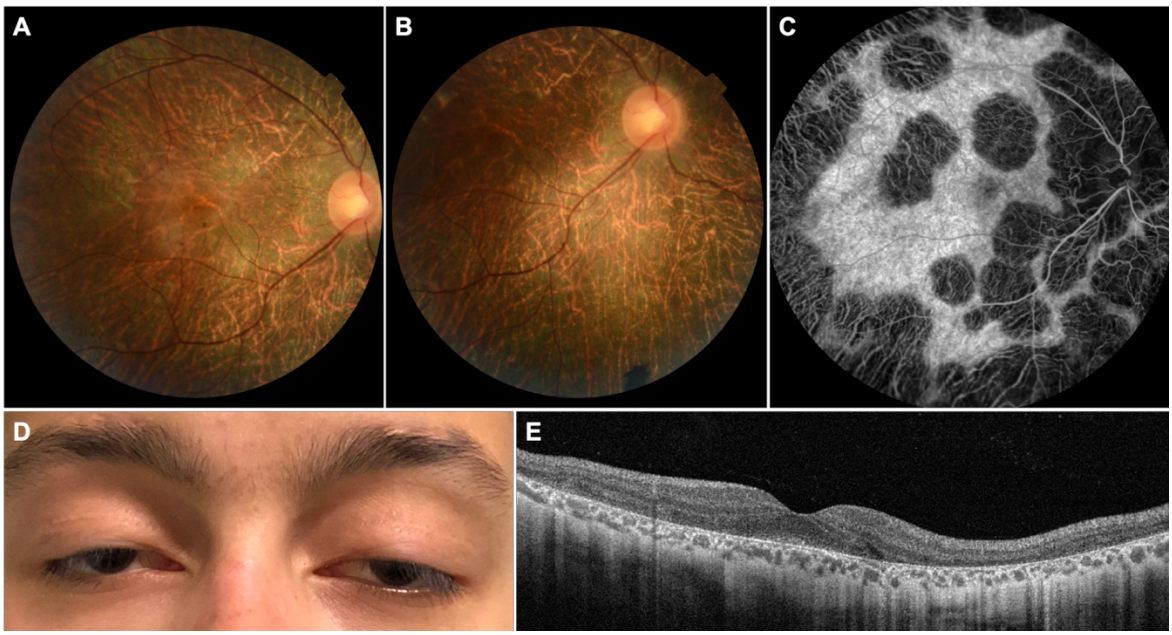

*Figure 1 Photos of a 19 year old patient with genetically confirmed KSS (a large single mtDNA deletion was identified in a muscle biopsy). Color fundus photography shows patchy areas of retinal pigment epithelium (RPE) atrophy that spare the fovea **(A)** and foci of RPE hyperplasia **(B)**. On fluorescein angiography, the patchy RPE atrophy is very well demarcated **(C)**. The patient has short stature, ophthalmoplegia and bilateral ptosis **(D)**. A vertical scan of spectral-domain optical coherence tomography (SD-OCT) displays severe outer retina and RPE atrophy with foveal sparing. (Courtesy of João Pedro Marques, MD)*

1.5. Diagnosis and Imaging

The diagnosis of KSS is established upon the phenotype (Berio's diagnostic criteria) if there is presence of all three cardinal features (CPEO, onset before the age of 20 years old, pigmentary retinopathy), and at least one of the additional features (hypoacusia, ataxia, peripheral nervous system involvement, short stature, growth hormone deficiency, lactic acidosis, dysmorphism, hypoparathyroidism, emesis, aortic insufficiency, subaortic septum hypertrophy, right bundle-branch block, double vision, or white matter lesions).[10] Diagnosis may be confirmed through muscle biopsy that shows "ragged red fibers" on trichrome stain.[5] Biochemical investigations of the muscle homogenate in KSS may show deficiency of respiratory chain complexes I, II, or IV, or combined

deficiency of complexes I and IV, complexes I, III, and IV, complexes I, IV, and V, or of complexes I, III, IV, and V.[11] Electrocardiography should be performed in all patients suspected of KSS to detect any life-threatening cardiac conduction abnormalities. Neuroimaging may help in the assessment for other causes of neurological deficits. In CPEO, magnetic resonance imaging (MRI) of the orbits demonstrates significant symmetrical extraocular muscle atrophy involving all four recti.[12] Genetic testing and counseling should be offered to all patients who have mitochondrial cytopathies.[9]

1.6. Treatment

There is currently no treatment for the underlying disease process of KSS. Therapies for mitochondrial disorders are very limited and, despite numerous anecdotal reports of success with various therapies, a recent Cochrane review of 678 abstracts and articles found no evidence supporting any intervention in the management of mitochondrial disease.[13] However, some trials have shown promising trends. Coenzyme Q10 (CoQ10), essential for normal mitochondrial function and deficient in a proportion of patients with KSS, has been associated with improved exercise tolerance, cardiac function, and ataxia.[14] CoQ10, along with creatine and lipoic acid, have shown promising results in improving surrogate markers of cellular energy dysfunction in patients with KSS.[15] Other treatments, such as thiamine, also aim to bypass or enhance oxidative phosphorylation but only occasionally have been shown to improve exercise tolerance, cardiac conduction or lactic acidosis. CoQ10 and these other treatments do not improve the ophthalmoplegia, retinopathy or ptosis in patients who have KSS. However, modified CoQ10 has led to second and third generation quinones, idebenone and EPI-743, that have shown promising results in Leber's hereditary optic neuropathy, providing new direction for possible therapy targeting mitochondrial disorders.[16-18] Complaints that arise from ptosis often are handled by ptosis crutches. Surgical attempts to treat the ptosis may result in exposure keratopathy and corneal ulceration because of weak orbicularis oculi muscles and a poor Bell's reflex. Symptomatic ocular deviations may be treated successfully with strabismus surgery.[9,19] Low vision aids benefit patients with severe vision loss from pigmentary retinopathy and maculopathy.[19] Periodic evaluation by a cardiologist is indicated in KSS. In some instances, placement of a pacemaker for prophylactic pacing or for treatment of symptomatic cardiac block is necessary to prevent sudden death. The systemic use of corticosteroids is contraindicated in KSS because of the possible precipitation of coma and death from hyperglycemic acidosis.[20]

1.7. Prognosis

Visual outcome depends on the severity of the retinopathy. CPEO leads to a slowly progressive loss of lid and extraocular motor function. The diplopia may or may not worsen because the symmetry of the ophthalmoplegia may prevent strabismus.[9] Mortality in KSS is often related to sudden cardiac death and it may not be heralded by symptoms such as syncope.[21]

2. Maternally Inherited Diabetes and Deafness (MIDD)

2.1. Synonyms

Ballinger-Wallace disease; Diabetes-deafness syndrome, maternally transmitted.[1]

2.2. Epidemiology

The prevalence is unknown but it is estimated that as many as 1% of patients with diabetes mellitus have MIDD.[22,23]

2.3. Genetics

In 85% of cases, MIDD (OMIM #520000) is caused by a point mutation *m.3243*A>G in the mitochondrial gene *MT-TL1*, encoding the mtRNA for leucine.[22-24] In rare cases it is caused by a point mutation on *MT-TE* and *MT-TK* genes, encoding the mtRNAs for glutamic acid, and lysine, respectively.[22]

2.4. Signs and Symptoms

As the name implies, MIDD is clinically characterized by deafness and diabetes resulting from poor insulin secretion.[5] Signs and symptoms of this disorder can appear in any age although usually during the second decade of life, following a period of normal development.[5,25] Bilateral sensorineural hearing loss is seen in 85–98% of MIDD cases,[23] and in the majority of cases, patients exhibit diabetes similar to type II.[25] However, it has been described that diabetic retinopathy is less frequent than in the classic form of diabetes.[26,27] In over 80% of cases, MIDD patients develop macular changes that simulate pattern dystrophy[23,25], the severity of which varies between patients. It is believed that this variability is due to the proportion of the mutated mtDNA in the retinal tissue.[26] The most frequent macular phenotype associated with the m.3243A>G mutation is a distinct macular dystrophy characterized by discrete circumferentially oriented patches of parafoveal atrophy that coalesce over time, but spare the fovea until late in the disease process.[5,25] Mottling of the RPE with pale pigment epithelial deposits and pigment clumping may also be noted.[5]

2.5. Diagnosis and Imaging

Full-field ERG (ffERG) is typically normal in MIDD, but with localized areas of reduced neuroretinal function on multifocal ERG (mfERG).[23,28,29] Fundus autofluorescence (FAF) findings associated to the m.3243A>G mutation are quite characteristic and can be differentiated from other dystrophies, such as in the Stargardt disease or geographic atrophy of age-related macular degeneration. The main characteristics that differentiate the MIDD syndrome are diffuse dotted hyperautofluorescence, particularly surrounding the atrophy areas, and the fact that the atrophy changes involve the macular and peripapillary area, generally without exceeding the vascular

arcades.[5,28] Another distinguishing feature from other macular dystrophies is that FAF imaging reveals much more widespread pigment epithelial abnormality than would be expected from the fundoscopic appearance.[5] Microperimetry, as well as mfERG, can be important in monitoring central retinal function.[29,30] Additionally, mitochondrial genome screening is indicated in order to diagnose this syndrome, as patients could benefit from genetic counseling.[25]

2.6. Treatment

Management is symptomatic. Oral antidiabetic agents and/or insulin therapy are used to treat diabetes. Hearing aids or cochlear implants are recommended for the hearing loss. Administration of CoQ10 supplements has been proposed for treatment of the mitochondrial defect. Treatment of MIDD should be initiated at an early stage, since complications may lead to renal disease or MELAS syndrome (myocardial complications, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes).[22]

2.7. Prognosis

As with all mitochondrial disorders, there is wide phenotypic variation in this disorder owing to heteroplasmy and mitotic segregation, with variable mutation load in different tissues and family members, some of whom might be asymptomatic with only retinal findings, making it difficult to give predictions on an individual's visual prognosis.[5,24] MIDD typically progresses slowly over several years and has a good visual prognosis when confined to the perifoveal region.[28,31] However, atrophic areas can progress toward the fovea with central vision loss mimicking geographic atrophy seen in Stargardt disease or age-related macular degeneration.[24]

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X-LINKED RETINOSCHISIS

Renato Santos-Silva, Rufino Silva

1. Synonyms

Juvenile retinoschisis, X-linked juvenile retinoschisis

2. Epidemiology

X-linked retinoschisis (XLRS) affects male patients with a prevalence ranging from 1:5,000 to 1:20,000. It is usually diagnosed in the first decade of life, with cases described as early as age 3 months.

3. Genetics

Mutations in *RS1* (retinoschisin) gene (MIM #00839) causes XLRS (OMIM #312700). *RS1* gene is located in the X chromosome (Xp22.13) and has a X-linked recessive inheritance pattern. *RS1* has 6 exons and encodes a 224 aminoacid protein. Penetrance is almost complete with variable clinical expression. *RS1* gene is expressed in photoreceptor and bipolar cells in the retina and in the pinealocytes of the pineal gland. Retinoschisin is anchored to retinal membranes and regulates intracellular MAP kinase signaling and photoreceptor degeneration. In most cases, abnormal retinal function is determined by the absence of retinoschisin on retinal membranes. However, in some mutations there still is synthesis and secretion of retinoschisin, although the protein is dysfunctional.

At the current time, 212 different pathogenic variants of the RS1 gene have been reported (https://databases.lovd.nl/shared/genes/RS1, accessed in October 31, 2018). About 60% of them are missense mutations.

4. Signs and symptoms

XLRS is an early onset retinal degenerative disease, affecting males usually during the first decade of life. It typically presents with reduced central vision, radial streaks in the fovea, splitting of inner retinal layers and reduced bipolar cell function producing a negative electroretinogram (ERG). Foveal schisis is present in all XLRS patients. Peripheral retinoschisis occurs in less than 50% of patients, with the temporal retina more frequently affected. Vitreous veils are commonly seen in retinoschisis, caused by the occurrence of large atrophic inner breaks in the thin inner schisis cavities.

On ophthalmoscopy, foveal schisis presents with a spoke-wheel pattern and peripheral schisis as a sharply delineated detachment of the inner retina. Peripheral retinoschisis does not usually affect de macula, although it may happen in a small proportion of patients. Rarely, retinoschisis may affect the entire retina. At about age 30 years, macular alterations may change from the traditional spoke-wheel pattern to unspecific mild pigment abnormalities.

Clinical expression is highly variable ranging from almost complete schisis of the retina at age 3 months to normal visual acuity with minor foveal pigmentary changes with an electronegative ERG. Clinical signs and symptoms are usually symmetric in both eyes. Visual acuity is reduced to about 20/100 in most patients although it can vary.

There are several clinical cases described before age 1 year. This fact in association with the absence of acute vision loss in cases of XLRS suggests that the onset of this disease is congenital, although the diagnosis is delayed because the moderate visual loss associated with it does not interfere with the daily tasks of small infants.

Female carriers are asymptomatic although minor changes in retinal function can be observed. Although full field ERG is usually normal in carriers, evaluation with multifocal ERG showed that abnormal macular function exists in a small subset of female carriers.

5. Diagnosis and imaging

In patients up to 30 years old the most frequent feature is the presence of a spoke-wheel pattern in macula that can be seen fundoscopically or in color fundus photography (Figure 1A). After age 30, this pattern tend to be replaced by unspecific retinal abnormalities. Peripheral retinoschisis (Figure 1C) may also be seen on ophthalmoscopy in about 50% of patients, more commonly in the temporal retina. Optical coherence tomography (OCT) has an important role in the diagnosis of XLRS by showing the presence of macular retinal splitting and pseudo-cystoid changes that can involve multiple retinal layers, from the retinal nerve fiber layer to the nuclear layer (Figures 1E, 1F and 2D). In older patients the retinoschisis may be absent, with retinal thinning and epiretinal membrane formation that can make the differential diagnosis with other macular dystrophies difficult. OCT angiography (OCT-A) may depict superficial and deep vascular plexus irregularities due to the schisis. On enface imaging at the level of the deep plexus, a petaloid pattern is usually evident (Figure 1D and 2C). In fundus autofluorescence (FAF), the spoke-wheel pattern is also seen with increased autofluorescence in the center of the macula, either irregularly shaped or with a radial structure that enlarges with increasing foveal schisis (Figure 2A). Fluorescein angiography

(FA) does not have a significant importance in the differential diagnosis of XLRS. On FA there is no leakage or hyperfluorescence associated with the cystic-like spaces or retinal splitting (Figure 2B). However, FA may show retinal pigment epithelium (RPE) changes in older adults.

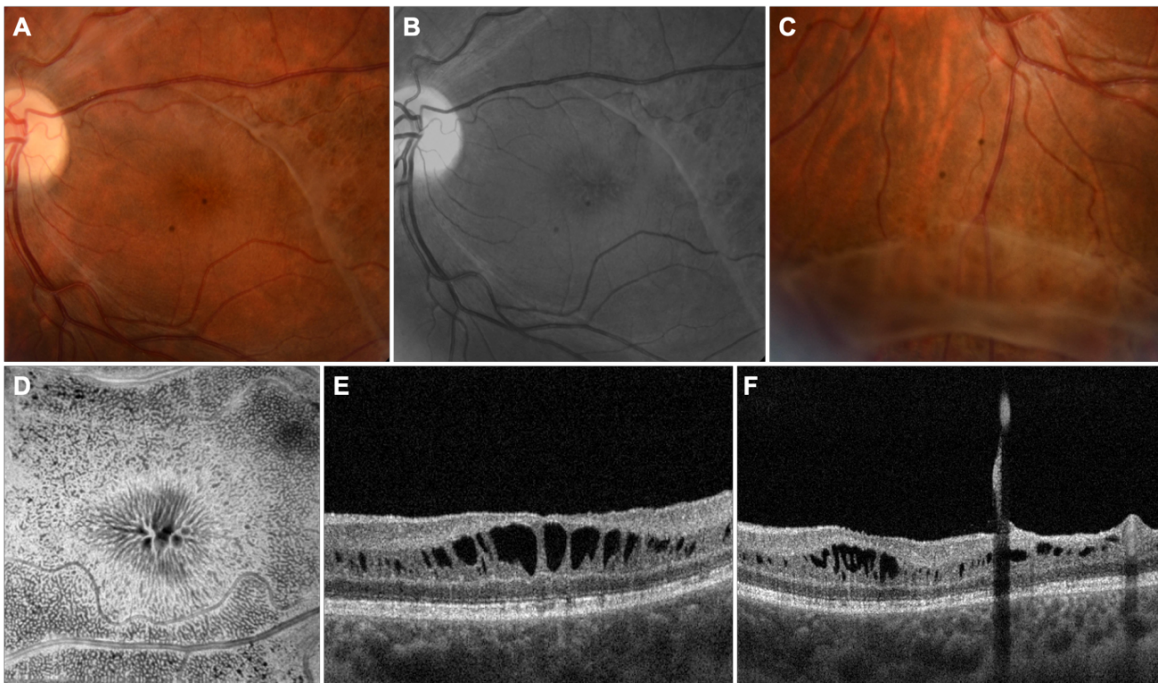

*Figure 1 Multimodal retinal imaging in a patient with XLRS. **(A)** Color fundus photography (CFP) showing macular irregularities with a spoke-wheel pattern, along with vitreous veils. **(B)** The spoke-wheel pattern is easily seen on red free imaging as well. **(C)** Peripheral schisis can be seen inferiorly. The enface optical coherence tomography (OCT) at the level of the deep retina **(D)** provides a beautiful view of the foveal and macular schisis. Images **(E)** and **(F)** show OCT scans of the macula, depicting the pseudo-cystic spaces and vitreomacular interface abnormalities, respectively. (Courtesy of João Pedro Marques, MD)*

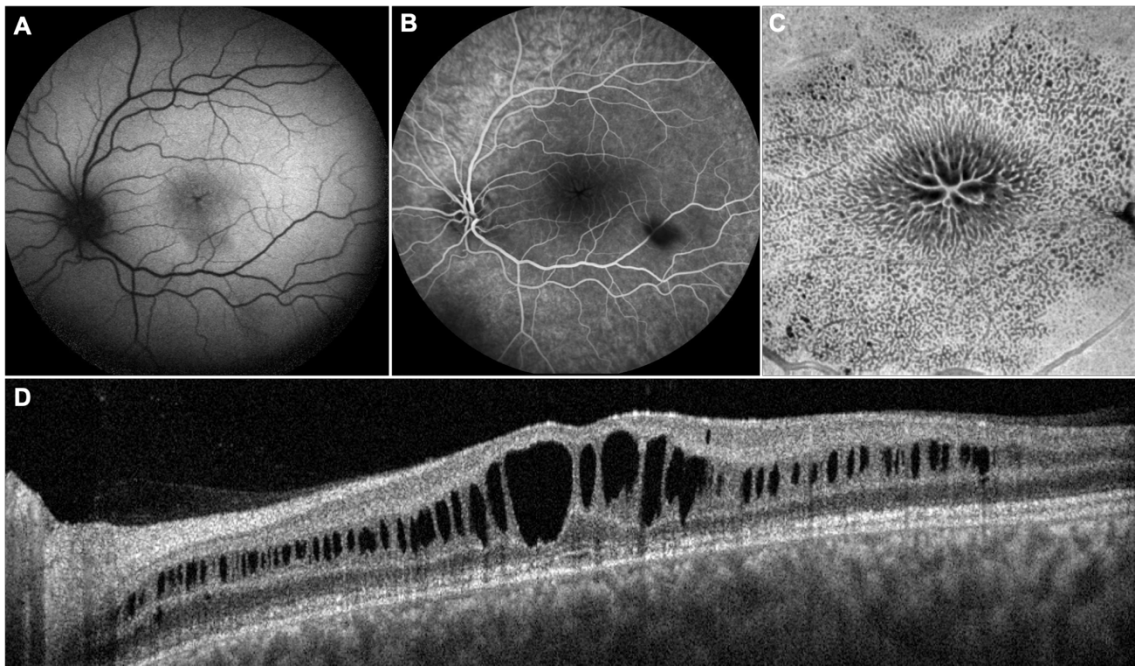

Figure 2 Another patient with XLRS. ***(A)*** *On fundus autofluorescence, the spoke-wheel pattern is seen.* ***(B)*** *Fluorescein angiography adds very little to the diagnosis. As observed here, there is no leakage or hyperfluorescence associated with the cystic-like spaces or retinal splitting.* ***(C)*** *Enface optical coherence tomography (OCT) conveys the best characterization and distribution of the schisis.* ***(D)*** *OCT with inner retinal splitting and pseudo-cystoid changes involving multiple retinal layers. (Courtesy of João Pedro Marques, MD)*

Electrophysiology has significant importance in the diagnosis of XLRS. Since the origin of the retinal dysfunction in XLRS is an abnormality in the ON- and OFF-pathways at the level of bipolar cells, the most characteristic change is the electronegative ERG in which the *b wave* is smaller than the *a wave* in the dark-adapted (DA) 3 and DA 10 ERG (Figure 3). However, only about 50% of patients present with an electronegative ERG with an *a wave* larger than the *b wave*. Many patients have a reduced *b/a* ratio, with a *b wave* slightly larger than the *a wave*. Importantly, a normal ERG does not exclude the diagnosis of XLRS. In young males the most important differential diagnosis of an electrionegative ERG is congenital stationary light blindness. Multifocal ERG and pattern ERG also show abnormalities in macular function of patients with XLRS.

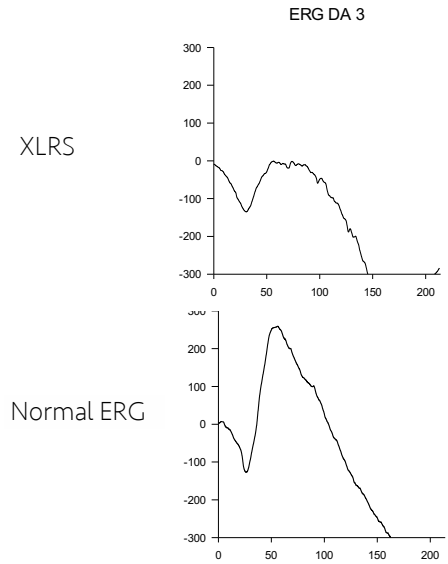

Figure 3 Electronegative dark adapted (DA) 3 ERG with a diminished b wave (normal exam bellow).

6. Treatment

Topical carbonic anhydrase inhibitors (CAI) may be used to reduce the schisis in the posterior pole, and in about half of the eyes there is a small improvement in visual acuity of about logMAR 0.1. In some patients this improvement is only seen after several months. If the retinoschisis worsens during treatment with dorzolamide or other CAI, suspension of the treatment and later retreatment might have an effect.

Gene therapy appears promising since restoration of the *b wave* on ERG and retinoschisin expression on all retinal layers were achieve after injection of adeno-associated viral vectors carrying functional *RS1* gene into Rs1 knock-out mouse models. There are currently 2 clinical trials in phase 1/2 underway (NCT02317887 by the National Eye Intitute and NCT02416622 by Applied Genetic Technologies Corp). Pars-plana vitrectomy is recommended when there is a retinal detachment or a vitreous hemorrhage that does not spontaneously disappear.

7. Prognosis

Usually visual acuity reduces gradually during the first and second decades of life and then remains stable until later in life. Some complications of this disease may produce a sudden reduction of vision such as retinal detachment or vitreous hemorrhage.

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ENHANCED S-CONE SYNDROME/GOLDMANN-FAVRE SYNDROME

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1. Synonyms

Retinoschisis with Early Nyctalopia/Hemeralopia; Favre Hyaloideoretinal Degeneration

2. Epidemiology

Enhanced S-cone Syndrome (ESCS)/Goldmann-Favre Syndrome (GFS) is a rare inherited retinal dystrophy, with a prevalence bellow 1/1000 000 and both genders equally affected.[1] Its first manifestations occur in childhood, usually during the first decade of life[2, 3] and has a wide clinical spectrum, of which GFS is considered the most severe form.

3. Genetics

ESCS/GFS (MIM #268100) is inherited in an autosomal recessive pattern and is associated with homozygous or compound heterozygous mutations in the *NR2E3* gene (MIM 604485), located on chromosome 15q22.32.[4,5] *NR2E3* is uniquely expressed in the outer nuclear layer of the retina, restricted to the photoreceptors, and it controls the differentiation of photoreceptors, by suppressing cone differentiation during embryogenesis, and regulating the expression of cone-specific genes found in rods.[3, 5, 6] Loss of NR2E3 results in abnormally differentiated rods (with cone features), decreased number of rods, and a significant increase in S-cones. [6, 7] Nearly 50 *NR2E3* gene variations and mutations have been reported in patients with various retinal degenerative disorders, the most commonly reported are p.R311Q and c.119-2A>C mutations, with no clear genotype–phenotype correlation.[5] ESCS and GFS have been far exclusively associated with mutations in *NR2E3*, but autosomal recessive mutations in other genes involved in the embryonic development of rod and S-cones, such as *NRL*, have been identified. [8,9]

4. Signs and symptoms

Classical symptoms of GFS are night blindness (and sometimes hemeralopia) since childhood and variable progressive loss of central and peripheral vision.[2,10,11]. Clinical features are usually bilateral and symmetrical, involving the vitreous, retina and lens. Vitreous changes are degenerative and include liquefaction and fibrillar strands. Fundus features include equatorial chorioretinal atrophy, pigment clumping along the retinal vascular arcades with peripheral pigmentary retinopathy, retinoschisis (peripheral, especially in the inferotemporal quadrant, and less commonly macular), cystoid macular edema and, in later stages, vascular abnormalities (opaque retinal vessels and diffuse leakage from retinal capillaries) with optic disc pallor. Posterior cortical lens opacities are common.[2, 10] Additional features of GFS include characteristic electrophysiologic abnormalities and abnormal dark adaptation and visual field, described below. [12]

ESCS was first described in patients with a characteristic electroretinogram hypersensitivity of short wavelength-sensitive cones, variable degree of night blindness and mild visual field loss, associated with foveal or peripheral schisis, and typical torpedo-like numular midperipheral pigmentary deposits with yellow dots.[13,6,14] A similar ERG pattern of retinal disfunction was later shown in GFS, proving that GFS and ESCS are two phenotypes in a clinical spectrum, with GFS being the most severe form.[15] A sequential timeline of changes was suggested, starting with normal fundus appearance, followed by RPE mottling along the arcades, development of white dots and finally deep nummular pigmentary deposition, with possible later resolution of schisis and normalization of macular thickness.[7 , 16 , 17]

5. Diagnosis and Imaging

GSF/ESCS diagnosis is based on characteristic fundus appearance and by the presence of pathognomonic abnormalities in electrophysiologic tests, and/or mutation analysis of the *NR2E3* gene. Differential diagnosis includes generalized photoreceptor dystrophies such as atypical retinitis pigmentosa, congenital stationary night blindness and Bietti crystalline corneoretinal dystrophy, as well as other hereditary vitreoretinopathies like juvenile X-linked retinoschisis, Stickler's syndrome and familial exudative vitreoretinopathy. [5, 6, 8]

ERG and Dark Adaptometry: Characteristic findings are enhanced short-wavelength (blue) sensitivity and virtually no change in wave form response to light and dark adaptation (indicating the hypersensitivity to blue light is mediated predominantly by s-cones and not rods), absent rod function and a disproportionately reduced 30-Hz cone flicker to the single-flash cone amplitude.[7] Dark-adaptation findings generally included monophasic curves with normal cone thresholds or biphasic curves with much raised rod final thresholds. [2, 10]

Visual fields: visual field defects may be central and peripheral according to fundus changes.[10] Depending on the severity of the disease, visual fields may range from nearly full to tunnel vision.[15]

Fluorescein Angiography: diffuse vascular leakage in the posterior pole and cystic macular edema may be found in some cases[2,12], while in others leakage may be absent, suggesting cystoid changes are likely secondary to schisis.[10,14]

Fundus Autofluorescence (FAF): reported abnormalities include decrease of autofluorescence peripheral to the arcades, a ring of relatively increased autofluorescence in the transitional zone, preservation of autofluorescence within the central macula with a spoke-like area of relatively increased autofluorescence centred on the fovea, and multiple foci of hyperautofluorescent spots around the disc and arcades.[7,14]

Microperimetry: studies report reduced foveal sensitivity and dense scotomas corresponding to areas of retinoschisis and cystoid changes on SD-OCT.[18] Patients with schisis may show a significant and permanent reduction in retinal sensitivity, that does not return to normal even after resolution of cystoid changes.[7]

Optical coherence tomography (OCT): findings include lamellar macular holes, retinoschisis, microcystic spaces, alterations of photoreceptor layers and deterioration of the laminar organization of the retina, epiretinal membrane with vitreomacular traction, enhanced foveal and retinal thickness, and elevated foveal contour.[18,19,3] The increase in thickness and deterioration of the anatomical structure may be due to the fact that S-cone cells, which are larger than rods, are situated where the rods should be.[3]

Two-color pupillometry: ESCS patients show generally well-preserved cone and melanopsin mediated pupillary light reflexes, indicating intact inner-retinal function, and greater sensitivity to short-wavelength light under higher-luminance conditions.[20]

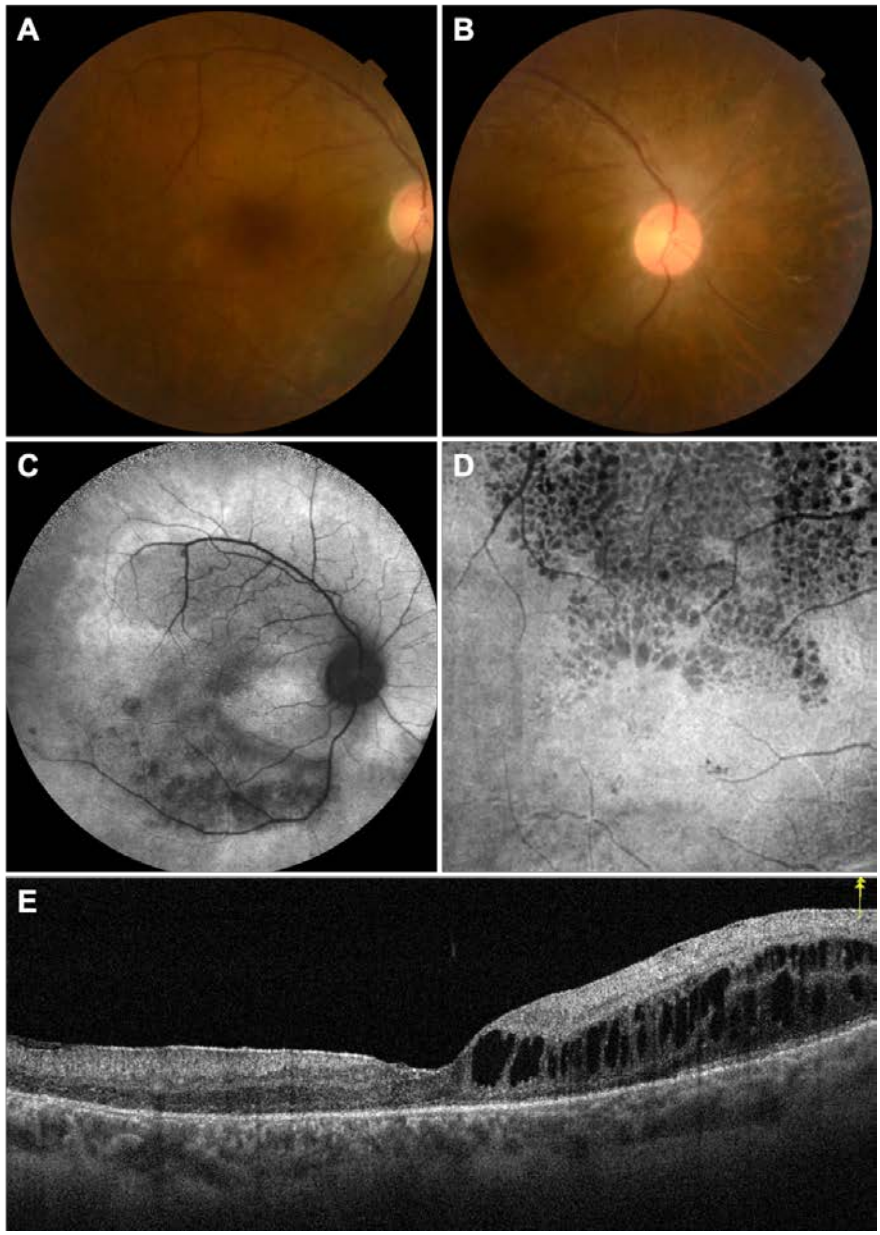

Figure 1 (A) and (B) Color fundus photographs showing pigmentary changes along the vascular arcades, thin and opaque peripheral vessels, and slight disc pallor. (C) Fundus Autofluorescence showing a mottled pattern of decreased autofluorescence inside the arcades and hyperautofluorescent spots outside the arcades, near the disc and close to the fovea. (D) En face OCT image at the level of the retinal deep plexus highlighting the location of the multiple macular pseudocysts. (E) OCT image revealing extensive pseudocystic changes with increased retinal thickness in the superior macula. (Courtesy of João Pedro Marques, MD)

Genetic testing: Screening for the NR2E3 mutation can be a valuable diagnostic aid in advanced stages of ESCS when electrophysiological tests cannot reveal the typical S-Cone responses and pigmentary changes may not be characteristic. With the recent developments in the field of gene therapy, genetic testing assumes a pivotal role and should be offered to every patient.

6. Treatment

There is no definite treatment for GFS/ESCS. Gene therapy may be a future option, as studies with *Nr1d1* delivery in mice models showed a possible disease-modifying effect.[21] Genetic counseling is recommended for both patients and potential carriers. Carbonic anhydrase inhibitors (CAI) may improve RPE metabolism, reducing intraretinal cysts, improving both retinal thickness and function, especially in those patients with early or mild cystoid formation[7,22,23]. Macular retinoschisis is a significant cause of visual morbidity, independently of photoreceptor degeneration. Retinoschisis may resolve spontaneously due to an accelerated posterior vitreous detachment, suggesting a possible therapeutic role of removing vitreous tractions in these patients. Laser photocoagulation was also reported for schisis resolution.[7]

7. Prognosis

Clinical features, functional impairment and disease progression vary among patients. Some experience visual loss from childhood while others maintain retinal functional into old age.[11] However, the prognosis for central and peripheral vision is poor in many patients, particularly by late middle age.[24]

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FAMILIAL EXUDATIVE VITREORETINOPATHY

Tatiana Queirós, Nuno Gomes, Borja Corcóstegui

1. Synonyms

Criswick-Schepens Syndrome

2. Epidemiology

Familial exudative vitreoretinopathy (FEVR) defines a group of inherited vitreoretinal diseases characterized by abnormal or incomplete vascularization of the peripheral retina and poor vascular differentiation, leading to variable clinical manifestations ranging from no effects or minor anomalies to retinal detachment and blindness. The inheritance patterns and expressivity show a heterogeneous course, as do the clinical features and prognosis of the disease. Epidemiological data on this rare disease are still unknown. Age of onset of FEVR is classically described as being at neonatal/infancy period, although patients can present at any age. Previous studies have shown that around 50% of patients are asymptomatic. Most symptomatic individuals with FEVR experience onset in early infancy, frequently manifesting retinal folds, tears, and retinal detachments in the first decade of life. The disease tends to become quiescent in the late teens or early twenties; however, later recurrences frequently occur with an unpredictable clinical course.

3. Genetics

The inheritance pattern of FEVR can be autosomal dominant (AD), autosomal recessive (AR) and X-linked recessive (XR), with the AD form being the most commonly observed. To date, six genes have been reported to be associated with FEVR. The frizzled-4 (*FZD4*; 11q14.2; MIM #133780), low density lipoprotein receptor like protein 5 (*LRP5*; 11q13.2; MIM #601813), and tetraspanin-12 (*TSPAN12*; 7q31.31; MIM #613310) genes have all been associated with AD or AR-FEVR. Mutations in the zinc finger protein-408 (*ZNF408*; 11p11.2; MIM #616468) and kinesin family member 11 (*KIF11*; 10q23.33; MIM #148760) genes have exclusively been reported to have an AD pattern of inheritance. In contrast, XL-FEVR can be caused by mutations in the Norrie disease pseudoglioma (*NDP*; Xp11.3;

MIM #305390) gene. Still, the genetic effect attributable to the above mentioned genes is about 50%, indicating that additional risk loci for FEVR remain to be identified.

4. Signs and Symptoms

The presentation and course of the disease show considerable variability, making the diagnosis and management challenging. The symptoms of FEVR vary widely among patients in the same family, and even between the two eyes of a given patient, with phenotypes ranging from the absence of visual symptoms to total blindness. The hallmark of FEVR is peripheral retinal avascularity, which often has a V-shaped pattern in the temporal periphery. In mild cases, these peripheral retinal changes do not cause any symptoms (Figure 1). In moderate to severe cases, pre-retinal neovascularization and fibrosis at the junction between vascular and avascular retina can occur that causes traction of the macula and retinal vessels (Figure 2). This can cause varying degrees of macular ectopia and visual dysfunction. In severe cases, the traction can lead to retinal detachment (RD) and retinal folds resulting in very poor vision (Figure 3). RDs are a common finding in FEVR and occur in 21–64% of affected individuals. They can be rhegmatogenous, tractional or serous in nature. Advanced tractional RDs can progress to form radial folds in the retina, sometimes described as 'falciform'. Less common findings are retinal exudation (Figure 4), secondary epiretinal membrane formation, peripheral retinoschisis, neovascularization, vitreous hemorrhage, secondary glaucoma (neovascular or phacomorphic), phacolytic uveitis, retinal capillary hemangioma, retained hyaloid vascular remnants and persistent fetal vasculature.

FEVR patients with *LRP5* mutations have reduced bone mass, and those with severe *NDP* mutations are more likely to have progressive deafness and mental retardation. Extra-ocular associations in FEVR are otherwise extremely rare.

5. Diagnosis and Imaging

Careful dilated fundus exam (generally under anesthesia) is important in these patients for accurate clinical staging and determining need for further management. The diagnosis of FEVR should be based on the following findings: lack of peripheral retinal vascular development in at least one eye; lack of history of prematurity or in a preterm born, a disease tempo not consistent with retinopathy of prematurity; variable degrees of vitreoretinal traction, subretinal exudation, or retinal neovascularization occurring at any age. A positive family history will assist in making the diagnosis. However, a negative family history would not exclude FEVR, as novel mutations can also occur. Currently, for accurate diagnosis, a thorough examination combined with wide field fluorescein angiography (FA) is essential. Also and because of the phenotypic heterogeneity, it is important to identify asymptomatic family members. FA with peripheral sweeps or wide-field angiography is indispensable in examining family members. Genetic testing can be offered for confirmation purposes and screening of family members if the genetic defect is known.

There have been different grading systems developed in an attempt to classify FEVR. The most recently update is shown in Table 1. Of note, the disease does not necessarily follow the stages sequentially and the eyes do not always present with symmetrical findings

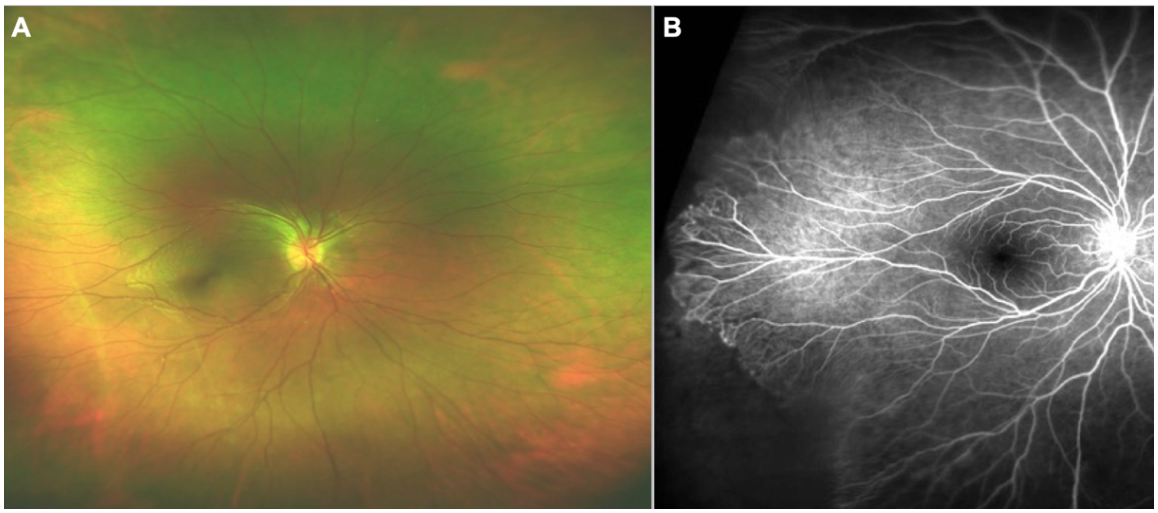

*Figure 1 Wide field imaging **(A)** of a mild case of FEVR depicting the hallmark of the disease - peripheral retinal avascularity, best appreciated on widefield fluorescein angiography **(B)**.*

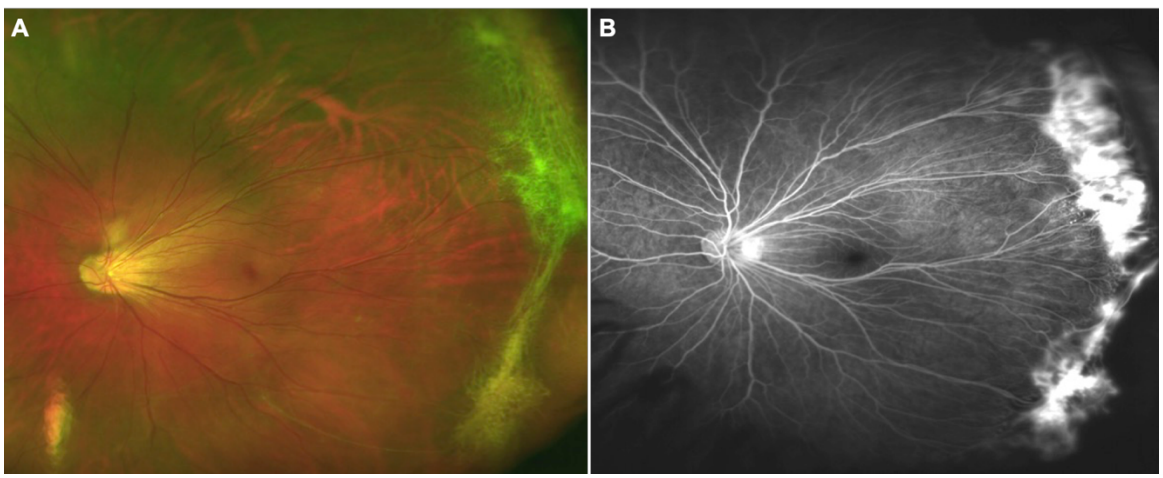

Figure 2 Pre-retinal neovascularization and fibrosis at the junction between vascular and avascular retina producing traction on the macula and retinal vessels (macular ectopia).

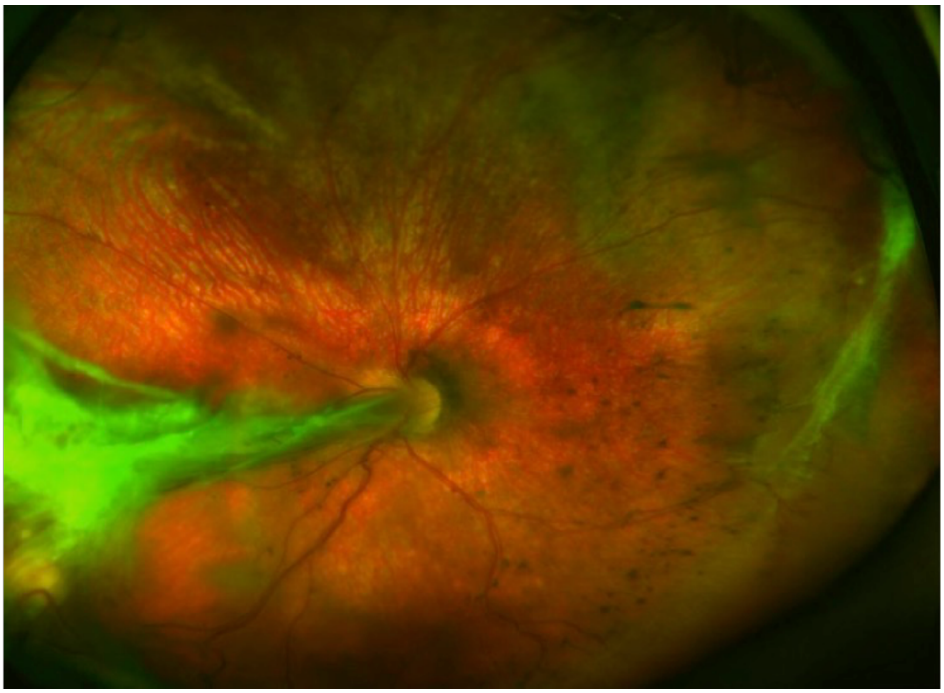

Figure 3 *A case of severe FEVR with retinal detachment and retinal folds*

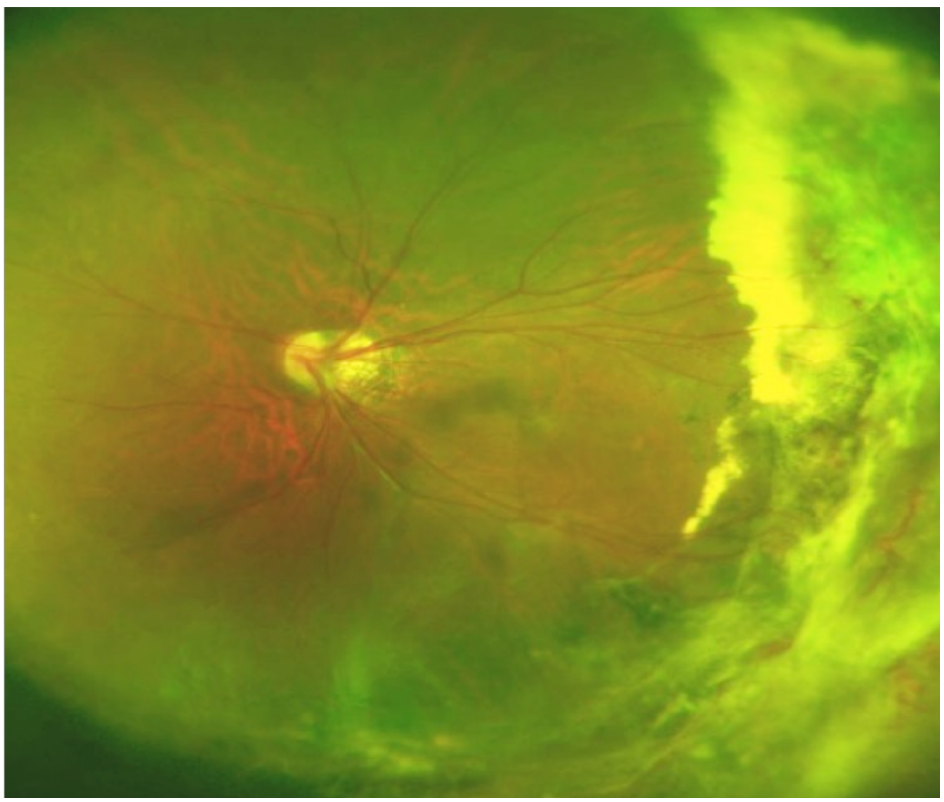

Figure 4 *Peripheral exudation and retinal detachment*

Table 1. Update clinical classification of familial exsudative vitreoretinopathy

Stage	Without exudation	With exudation	Clinical Features
1	A	B	Avascular retinal periphery
2	A	B	Extraretinal neovascularization
3	A	B	Retinal detachment not involving macula
4	A	B	Retinal detachment involving macula
5	A (open funnel)	B (closed funnel)	Total retinal detachment

Adapted from Kashani et al (2014)

6. Treatment

Due to the low prevalence of the disease, there is an absence of robust data to guide clinicians in managing FEVR patients. It is generally agreed that only patients that show signs of significant progression, or are at high risk of progression, should be treated. For Stage 1 disease, patients likely have a low likelihood of progression to advanced stages, so these patients may be observed at regular basis. However, treating the avascular zones with laser photocoagulation can be considered, especially if the other eye is at an advanced stage. For Stage 2 disease, the primary treatment of FEVR is laser photocoagulation. The peripheral avascular areas should be ablated with laser in case of neovascularization demonstrating leakage in FA, which can even be performed in fractionated sessions. In patients with RD, surgical intervention should be considered. Scleral buckling or pars plana vitrectomy can be considered depending on the clinical scenario with concurrent ablation of the avascular retina. Few studies have studied the use of anti-VEGF in the treatment of FEVR. Anti-VEGF therapy reduces retinal exudation and neovascularisation in FEVR patients but the rapid resolution of exudation can stimulate worsening vitreoretinal traction that often requires surgery. This treatment may have a role as an adjunctive therapy before surgery.

7. Prognosis

Children and adolescents diagnosed with the disease have a poorer visual prognosis when compared with adults and, generally, the earlier the disease presents, the more severe the manifestations. Nevertheless, most patients with FEVR retain good visual acuity with 64–74% of affected patients having vision of 6/12 or better. Macular ectopia, RDs and retinal folds are the main causes of reduced vision.

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STICKLER AND WAGNER SYNDROMES

Mafalda Mota, Susana Teixeira

1. Synonyms

Stickler Syndrome - Hereditary progressive arthroophthalmopathy

Wagner Syndrome - Wagner vitreoretinal degeneration, Hyaloideoretinal degeneration of Wagner

2. Epidemiology

Stickler syndrome refers to a group of rare collagenopathies, with a reported incidence of 1:7.500–9.000 births.[1,2] Early diagnosis in children is difficult because the phenotype develops over lifetime, especially in sporadic cases.[3] This syndrome is characterized by ophthalmic, skeletal, and orofacial abnormalities, but midfacial characteristics are more pronounced in children, and they become less distinctive in adult age.[1]

Wagner syndrome is a rare ocular-only syndrome, with an estimated prevalence of less than 1:1.000,000.[4,5,6] The syndrome starts frequently in childhood or during adolescence, but without the systemic manifestations of Stickler syndrome.[7,8]

3. Genetics

Stickler syndrome is subdivided based on the genetic collagen defect, with different phenotypes reflecting the mutations that affect the formation of collagen (Types II, IX, and XI).[2,9] Stickler syndrome type I (STL1, OMIM #108300) presents an autosomal dominant (AD) inheritance (chromosome 12q13.11; Gene/Locus *COL2A1*).[10] Another phenotype subtype: Stickler syndrome, type I, nonsyndromic ocular is known as OMIM #609508.[11] Stickler syndrome type II (STL2, OMIM #604841) also presents an AD inheritance (chromosome 1p21.1; Gene/Locus *COL11A1*).[12] The vitreous phenotype is a distinguishing feature between two types.[6] In the STL1, retrolental membranous vitreous is observed while SLT2 is described as having a fibrillar/beaded vitreous phenotype.[6] Ocular-

only variant shares its membranous vitreous phenotype.[6] There are still autosomal recessive forms of this disease, as Stickler syndrome type IV (OMIM #614134; gene *COL9A1*; chromosome 6q13) and Stickler syndrome type V (OMIM #614284; gene *COL9A2*; chromosome 1p34).[10] A disorder previously designated Stickler syndrome type III has been reclassified.[10]

Wagner vitreoretinopathy (OMIM #143200) is caused by mutation in the *VCAN* gene, on chromosome 5q14.2-q14.3, with AD inheritance with near complete penetrance.[4,6] *VCAN* encodes a chondroitin sulfate proteoglycan, where it represents 5–15% of the total protein content of the extracellular matrix of the vitreous gel.[5,13]

4. Signs and Symptoms

Stickler syndrome (Figures 1 and 2) is characterized by high myopia, severe vitreoretinal degeneration with vitreous liquefaction or syneresis (optically empty vitreous), circumferential membranes from the retina to the vitreous, reticular degeneration with retinal pigment epithelium hyperplasia and perivascular retinal degeneration (with very strong vitreous adhesions along the borders of these lesions), high incidence of retinal detachment, cataract and glaucoma due to congenital angle anomaly (dysgenesis) caused by prominent iris prolongations and iris root hypoplasia.[2,14,15] It is common for patients with Stickler syndrome to have a good corrected vision unless they have a retinal detachment, and high myopia is often the only sign of this disease in childhood.[15] In this early age, undiagnosed retinal detachments can lead to blindness.[15] The abnormal vitreoretinal interface predisposes patients to the development of giant retinal tears and associated rhegmatogenous retinal detachments early in life (childhood and first decades of life).[2] This syndrome is the most common inherited cause of retinal detachment.[2] The systemic manifestations of Stickler syndrome are sensorineural and/or conductive hearing loss, mild spondyloepiphyseal dysplasia, early-onset osteoarthritis, midfacial underdevelopment/hypoplasia, as micrognathia and cleft palate.[1,16,17]

Wagner syndrome is characterized by an optically empty vitreous, with avascular veils, strands and membranes.[4,5] Different chorioretinal abnormalities can be found, with the typical finding being chorioretinal atrophy with pigment migration into the retina.[13] These alterations cause abnormal equatorial vitreoretinal adhesions and may give rise to retinal detachment, which can be tractional or rhegmatogenous. Retinal detachment is caused by shrinkage of the preretinal membranes and the vitreous strands and veils.[4] Other common features of this disease are progressive night blindness, myopia, presenile cataract, ectopic fovea, inverted papilla (by tractional forces), uveitis and glaucoma.[4,5,6,7] Contrary to Stickler syndrome, Wagner's syndrome does not present systemic abnormalities.[4]

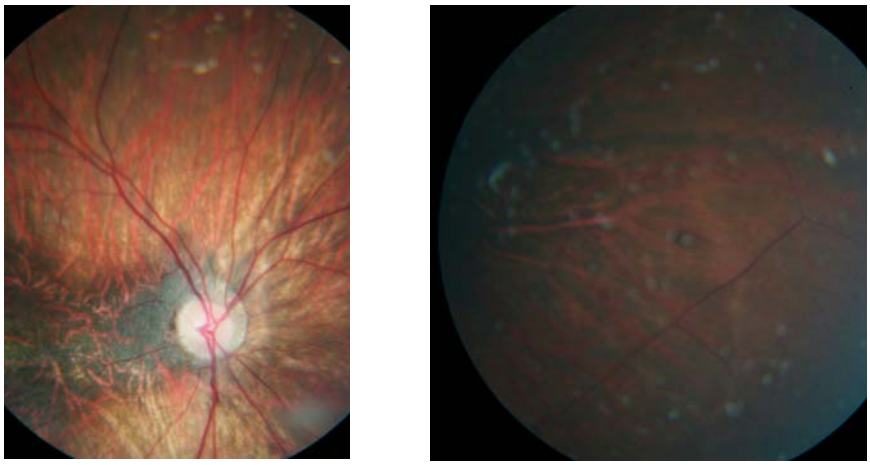

Figure 1 *Fundus photograph of significant chorioretinal atrophy (tessellated fundus) and severe vitreoretinal degeneration in a patient with Stickler syndrome. (Courtesy of João Pedro Marques, MD)*

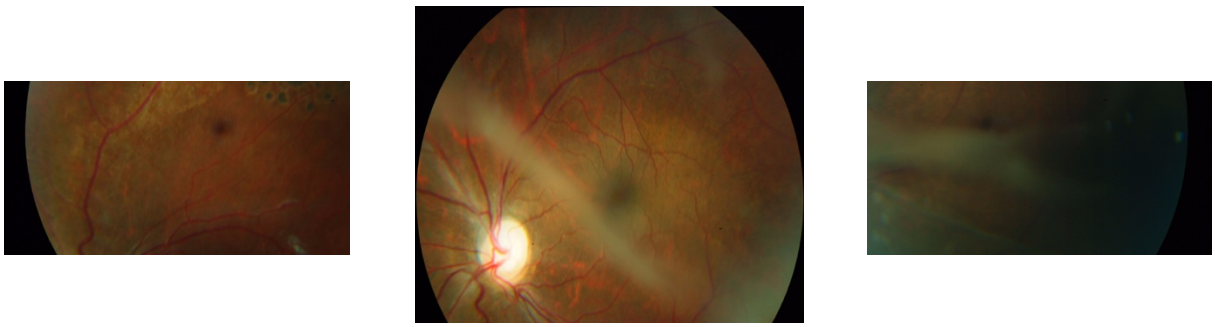

Figure 2 *Color fundus photographies of a patient with Stickler syndrome presenting with vitreous bands and retinal laser photocoagulation marks around an atrophic retinal hole in an area of posterior lattice degeneration.*

5. Diagnosis and Imaging

Diagnosis of Stickler syndrome is clinical, based on the ocular and systemic findings.[9] Typical ocular features can be observed with careful fundoscopy.[9] Differential diagnosis of the disease includes Wagner syndrome, with the same ocular phenotype but no systemic manifestations.[4, 19] Familial exudative vitreoretinopathy and Jansen Syndrome are other differential diagnoses.[4,6,19]

Genetic testing makes it possible to confirm the diagnosis in both Stickler and Wagner syndromes.[3]

Electroretinogram (ERG) may be important in the diagnosis of chorioretinal atrophy and evaluating its progression in Wagner syndrome.[4] Even though ERG may be normal in early disease stages, with disease progression the exam may show reduction in the scotopic b-wave or diffuse cone–rod loss. The responses may even become extinguished in later stages.[4] Several studies have shown that by age 45, 87% of the individuals with Wagner syndrome had electrophysiologic testing abnormalities.[6] The same is not true of Stickler syndrome, in which retinal function is

characteristically normal.[5,13] As the chorioretinal atrophy progresses, the visual field can suffer alterations, such as ring scotoma/constricted central visual fields.[4] In some cases, it is possible to observe outer retinal disruption on optical coherence tomography (OCT) and in patients with uveitis, OCT can reveal cystoid macular edema.[4] OCT can also reveal the ectopic fovea and inverted papilla in some patients with Wagner syndrome.[4] Fundus autofluorescence can show a perivascular pattern of chorioretinal atrophy.[4] However, some of these features are typical findings in other retinal dystrophies such as retinitis pigmentosa.

The clinical diagnosis of these two ocular diseases remains a challenge because clinical presentation, expressivity, and severity vary among patients and their families.[20]

6. Treatment

Stickler syndrome poses a significant risk for retinal detachment, so many studies propose treatment with prophylactic retinopexy (photocoagulation or cryotherapy) of suspected peripheral lesions.[3,14] These treatments significantly reduce the risk of retinal detachment and blindness from this syndrome.[3] Approximately 55–73% of patients with Stickler syndrome develop retinal detachment throughout your life.[3] The surgical treatment of these retinal detachments is very complex and difficult. Because these patients are younger, with high degree of vitreous liquefaction and degeneration, giant retinal tears are more frequent and the posterior vitreous membrane is firmly attached to the retina, surgical posterior vitreous detachment is difficult.[3,19] Results of the various surgical procedures are not consistent.[2] Reddy et al demonstrated that initial surgery with vitrectomy, scleral buckle or combining the two procedures has equal successful anatomical outcomes.[2] Abeysiri et al. showed superior anatomical outcomes with vitrectomy (84.2%), while other study suggested combined procedures with silicone oil tamponade to be the treatment of choice for retinal detachment in these patients.[2,19]

In patients with Wagner syndrome, retinal detachment can be a cause of blindness, and its prevalence varies from a few cases to 75% in some families.[4] Prophylactic treatment in these patients has not yet been well defined.[4] Contrary to Stickler syndrome, there are not many studies about the effectiveness of prophylactic interventions in Wagner syndrome.[4] In these two diseases there is no consensus: prophylactic cryopexy is performed in some series, while LASER retinopexy is favored by others authors.[4] When the loss of vision is due to progressive chorioretinal atrophy, there is still no treatment to offer.[4] However, adaptation to low vision devices and strategies for adaptation to low vision may improve the quality of life of patients.[4]

7. Prognosis

The early diagnosis of the Stickler or Wagner syndromes is essential, because prophylactic treatment of retinal lesions, seems to be the most effective way to improve the prognosis of these disease and decrease the risk of retinal detachment. [3,4,19] Retinal detachment can lead to a high incidence of blindness and decrease the quality of life.[3] After the correct diagnosis, adequate screening of family members should be performed.[4] This investigation is important both for genetic

counseling and to recognize the risk of RD, especially in children.[4] Careful ophthalmological follow-up of these patients is the key to achieving the best prognosis.[4]

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CHOROIDAL ATROPHY PHENOTYPES: CENTRAL AREOLAR CHOROIDAL DYSTROPHY, PERIPAPILLARY CHOROIDAL DYSTROPHY AND DIFFUSE CHOROIDAL DYSTROPHY

José Roque, Rita Flores

The term "choroidal dystrophy" is likely a misnomer as it implies a primary degenerative process involving the choroidal circulation. Current evidence focuses on the retinal pigment epithelium (RPE) as playing an important, if not pivotal, role in these disorders since genetic mutations that affect the RPE can lead to atrophic changes of both the RPE and choriocapillaris. The choroidal atrophy phenotypes can be subdivided into three clinical entities based on their geographical distribution. These include: central areolar choroidal dystrophy (CACD), peripapillary choroidal dystrophy and diffuse/generalized choroidal dystrophy. All can be inherited as either autosomal dominant (AD) or autosomal recessive (AR) traits. Since all of these phenotypes are rare, no prevalence data is available. Currently there is no defined treatment for hereditary choroidal dystrophies. Periodic ophthalmic examination to monitor progression of these diseases is warranted as affected individuals need counsel regarding their level of visual function loss and prognosis. Patients with severe visual impairment or blindness should be referred to a low-vision service.

Molecular diagnosis (genetic testing) and genetic counseling can provide patients and their families with information on the genetic implications of these disorders which, in turn, can help them make informed personal decisions.

1. CENTRAL AREOLAR CHOROIDAL DYSTROPHY

1.1. Synonyms

Choroidal sclerosis; Central areolar pigment epithelial dystrophy: Choroidal angio-sclerosis

1.2. Genetics

Two similar subtypes have been described: CACD1 (OMIM #215500; chromosome 17p; *CACD1* gene; AR transmission) and CACD2 (OMIM #613105; chromosome 6p21.1; PRPH2 gene; AD transmission). Although genetically heterogeneous, most cases are caused by AD inheritance of PRPH2 gene mutations (CACD2). The mean age of onset varies with the underlying PRPH2 mutation. For instance, the age at onset is often in the third to fourth decades in the phenotype caused by the p.Arg172Trp mutation and the p.Arg195Leu mutation. On the other hand, the p.Arg142Trp mutation often leads to an onset of visual loss in the fifth to sixth decades.

1.3. Signs and Symptoms

The initial symptoms are diminished central vision that generally begins in the latter part of the second to the early part of the fourth decade. Characteristic bilateral macular lesions are solitary with well-defined margins and circular or ovoid in shape. They may increase in size and become irregular in shape, but they never involve the peripapillary region or extend beyond the vascular arcades (Figures 1 and 2).

Early fundus changes include a mottling of the retinal pigment epithelium (RPE) in the macula. The underlying choroid may appear ophthalmoscopically normal. With the progression of the disease and subsequent loss of RPE and choriocapillaris, the underlying choroidal vessels are more readily visualized. With continued loss of RPE and choriocapillaris, the larger choroidal vessels may be involved and undergo degeneration. As a consequence of choroidal atrophy, the sclera becomes visible in the late stages of the disease.

1.4. Diagnosis and Imaging

At the early stages, Fluorescein Angiography reveals hyperfluorescence due to increased transmission from the underlying normal choriocapillaris (window effect) along with no signs of involvement of the optic disc and retinal vessels. On full-field electroretinogram (ffERG), the amplitudes are normal. If reduced cone function is detected, the diagnosis of cone dystrophy should be considered. Differential diagnosis should include advanced stages of Stargardt disease, cone dystrophy, North Carolina macular dystrophy, pattern dystrophies and the geographic atrophy macular lesions of age-related macular degeneration. The absence of drusen and flecks may help in the differential diagnosis.

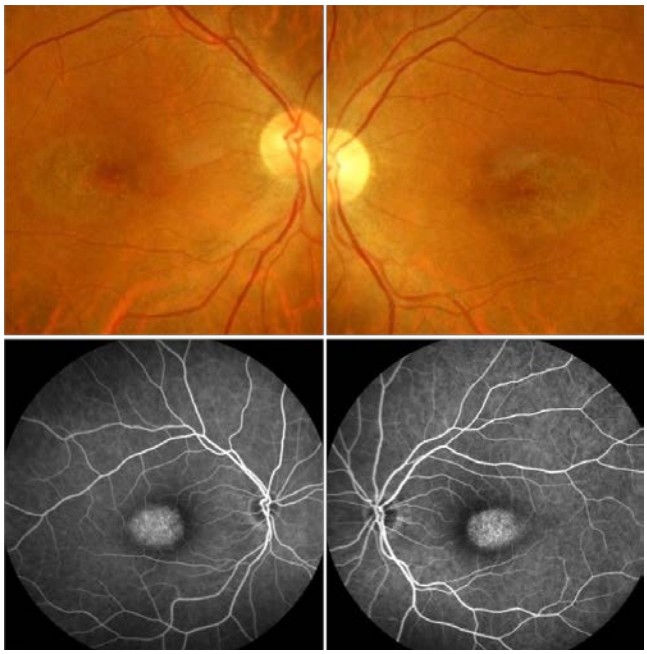

Figure 1 *Central Areolar Choroidal Dystrophy: color fundus photography (top) and fluorescein angiography (bottom), of the right and left eyes. Characteristic bilateral macular lesions are soli- tary with well-defined margins, and circular or ovoid in shape.*

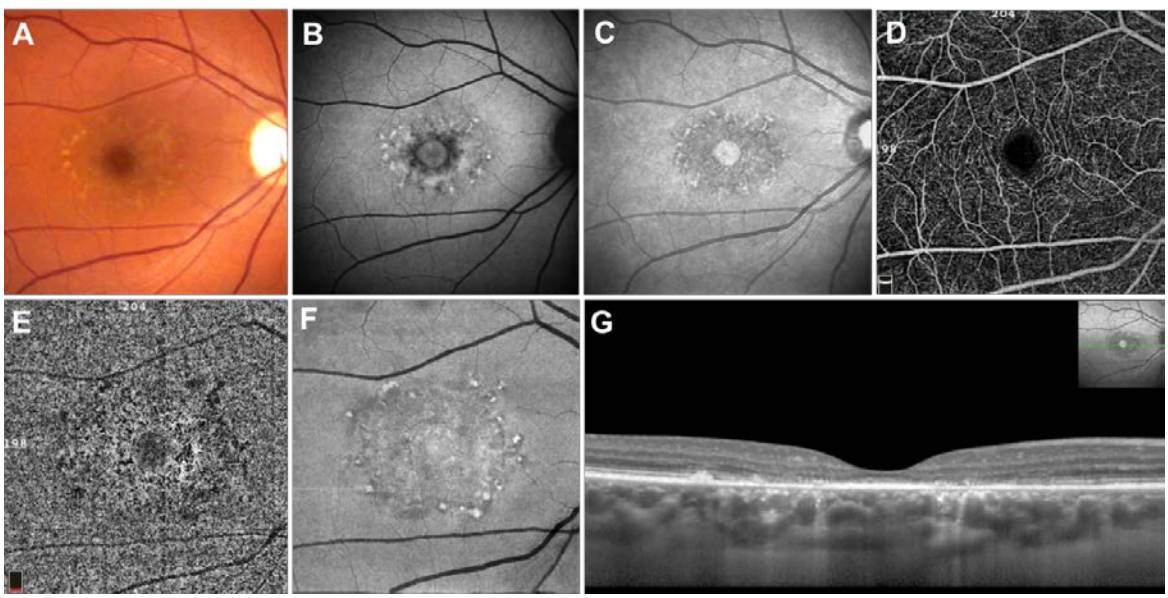

Figure 2 *Multimodal retinal imaging of another case of Central Areolar Choroidal Dystrophy.* **(A)** *Color fundus photography depicts the typical central mottling of the retinal pigment epithelium.* **(B)** *Fundus autofluorescence (FAF) and* **(C)** *near infrared (NIR) imaging highlight the central lesion.* **(D)** *Optical coherence tomography angiography (OCTA) of the superficial plexus shows no vascular changes in the inner retina but the choriopaillaris slab* **(E)** *evidences central choriocapillaris atrophy.* **(F)** *The enface OCT at the level of the outer retina is another imaging method that highlights the central changes observed in CACD.* **(G)** *Spectral domain optical coherence tomography (SD-OCT) shows paracentral atrophy of the outer retina and thinning of the RPE. (Courtesy of João Pedro Marques, MD)*

2. PERIPAPILLARY CHOROIDAL DYSTROPHY

2.1. Synonyms

Peripapillary chorioretinal degeneration; Sveinsson chorioretinal atrophy; Atrophia areata; helicoid peripapillary chorioretinal degeneration

2.2. Genetics

The peripapillary form of choroidal dystrophy (OMIM #108985) is caused by mutations in TEAD1 gene (chromosome 11p15.3). It can be inherited as an AD or AR trait.

2.3. Signs and Symptoms

The ophthalmoscopy in this form of choroidal dystrophy initially reveals changes in the RPE and later an apparent loss of RPE and choroidal tissue. The main difference between CACD and the peripapillary form is the location. The peripapillary form starts in the region surrounding the optic disc and slowly becomes larger, in finger-like projections, to the surrounding retina, eventually occupying the entire posterior pole. In some cases, the peripapillary form can progress to a clinical form similar to the diffuse form (Figure 3).

2.4. Diagnosis and Imaging

Peripheral to the fundoscopically involved area, retinal function is either normal or mildly impaired as demonstrated by visual field and dark-adapted final thresholds tests. The ffERG is either normal or only slightly reduced, according to the extent of the disease. In some cases, optical coherence tomography (OCT) may show foveal cysts.

Peripapillary pigment epithelial dystrophy in which there are well-defined areas of RPE loss, with direct visualization of the underlying choroidal vasculature is the main diagnostic challenge. In this case, fluorescein angiography shows intact choriocapillaris, thus differentiating it from those with choriocapillaris loss. Serpiginous choroiditis, which usually begins in the peripapillary region and then extends into the retina in pseudopod-like extensions sometimes involving the macula, is also a differential diagnosis.

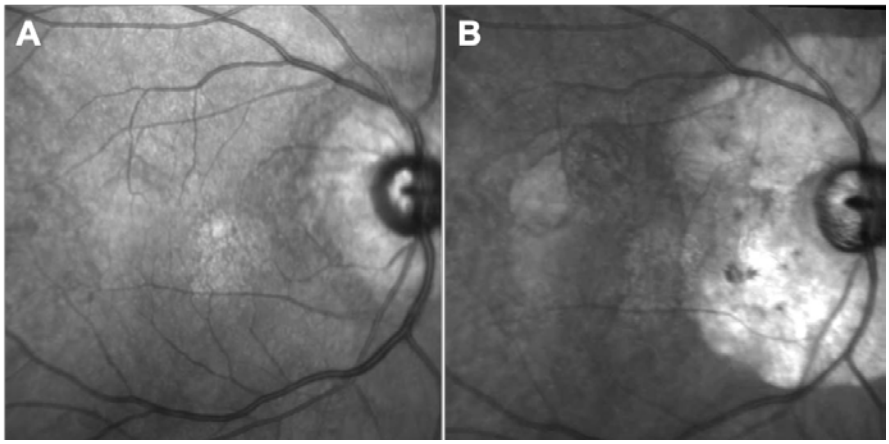

Figure 3 *Near infrared (NIR) imaging of a patient with peripapillary choroidal dystrophy depicting progression of the atrophy in a 6 year period.*

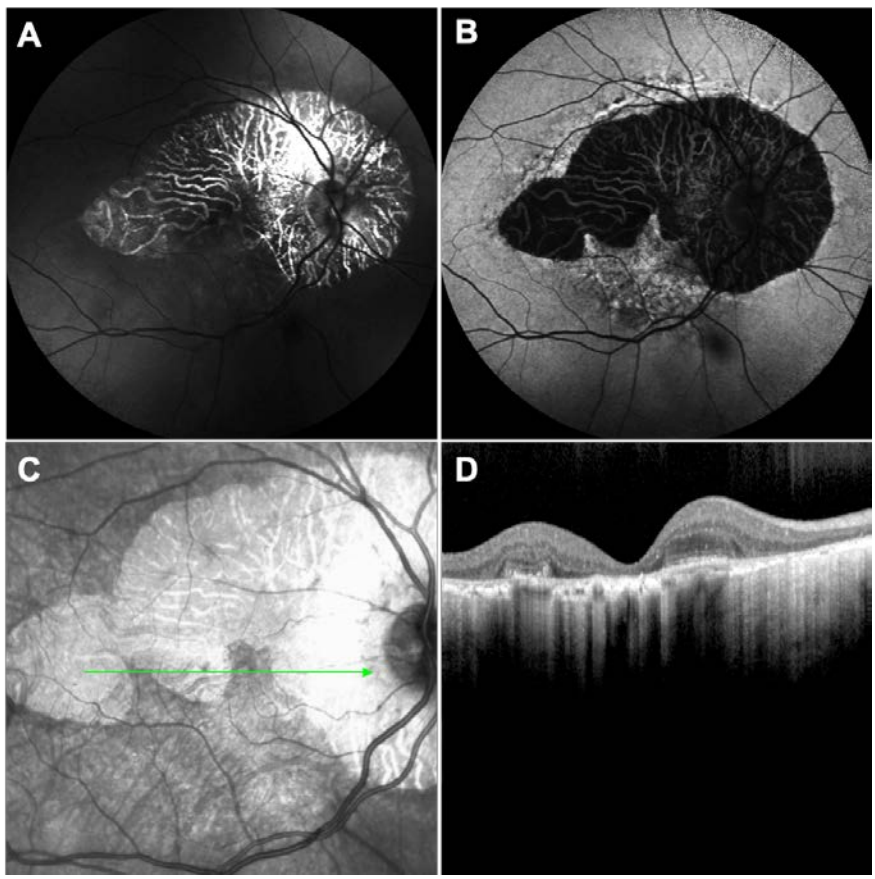

Figure 4 *Multimodal retinal imaging in a patient with peripapillary choroidal dystrophy.* **(A)** *Redfree imaging,* **(B)** *Fundus autofluorescence,* **(C)** *Near infrared imaging and* **(D)** *horizontal SD-OCT scan revealing extensive atrophy that involves the peripapillary area, the superior macula and the fovea. (Courtesy of João Pedro Marques, MD)*

3. DIFFUSE CHOROIDAL DYSTROPHY

This diffuse disorder of the RPE and choriocapillaris is more frequently inherited as an autosomal dominant trait but autosomal recessive transmission may occur. Clinical symptoms begin in the fourth or fifth decade and are usually manifested by poor central vision, impairment of night vision, or both.

Retinal pigment mottling and hypopigmentation are the early fundus findings. A predilection for the posterior pole is found initially before progression to the diffuse type. Late stages are characterized by diffuse atrophy of both the RPE and choriocapillaris with the larger choroidal vessels appearing sclerotic as yellowish-white bands in both the posterior pole and the periphery. The retinal vessels usually remain normal in all stages of the disease (Figure 4). In the end stages, diffuse choroidal dystrophy may be difficult to distinguish from other diffuse chorioretinal diseases such as thioridazine (Mellaril) retinal toxicity, advanced stages of both pattern dystrophy and Stargardt disease, as well to the advanced retinopathy seen in the Kearns–Sayre syndrome witch are the main differential diagnosis challenge.

The diffuse involvement is well demonstrated in the psychophysical and electrophysiological tests. Concentric peripheral constriction is found on the visual fields and ERG recordings are either subnormal or undetectable. Loss of the choriocapillaris and visualization of the larger choroidal vessels beneath atrophic-appearing pigment epithelium is found on fluorescein angiogram. Sometimes, a few scattered areas show a patchy choroidal flush pattern, indicative of some remnants of the choriocapillaris.

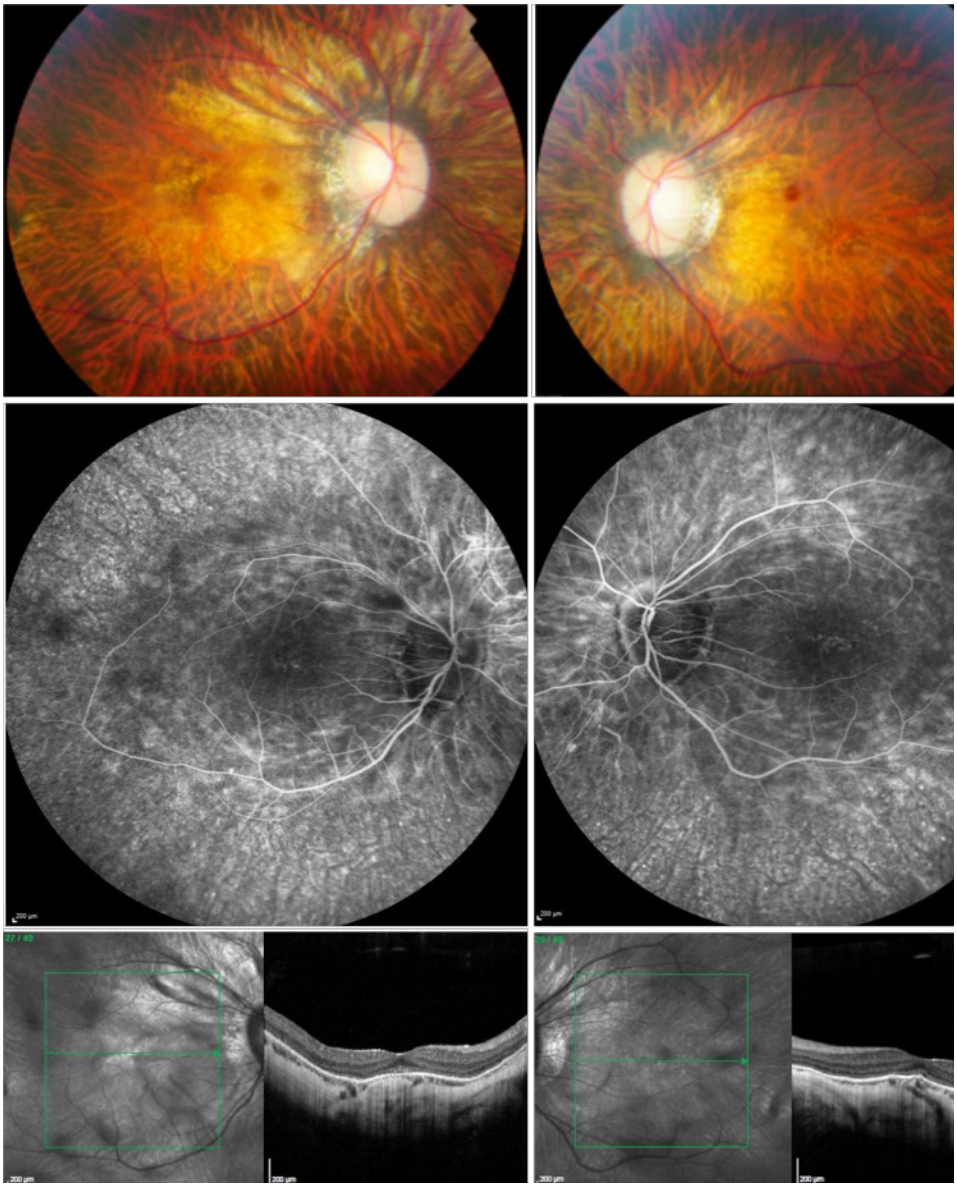

Figure 5 Diffuse choroidal dystrophy: color fundus photography (top), fluorescein angiography (middle) and spectral domain optical coherence tomography (bottom)

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GYRATE ATROPHY OF THE CHOROID AND RETINA

Pedro Reis

1. Synonyms

Gyrate atrophy; Hyperornithinemia with gyrate atrophy of choroid and retina; Ornithine aminotransferase deficiency; Ornithine keto acid aminotransferase deficiency; ornithine-delta-aminotransferase deficiency

2. Epidemiology

Gyrate Atrophy of the Choroid and Retina (GACR) is an inherited disease associated with hyperornithinemia, due to a deficiency of the enzyme ornithine aminotransferase (OAT). Jacobshon[1] first described the condition in 1888 as a variant of retinitis pigmentosa. Cutler[2] in 1895 and Fuchs[3] in 1896 characterized it as a separate entity. Since the initial description of this rare condition, only about 200 cases of clinically and biochemically confirmed cases have been reported[4]. A significantly high number of cases are from Finland, where prevalence of the disease is of about 1 in 50,000[5].

In the review of 80 confirmed cases of GACR by Barrett et al. (1987), 55% were females and no significant quantitative difference in OAT deficiency in cultured cells was found between genders[6].

3. Genetics

GACR (OMIM #258870) is an inherited disease with autosomal recessive pattern of inheritance. The disorder is caused by a mutation in the *OAT* gene (OMIM #613349) mapped on chromosome 10 (10q26.13)[8]. Simell and Takki in 1973[13] first reported hyperornithinemia in patients with gyrate atrophy. Levels of plasma ornithine in these patients are up to 10 to 20 times higher than normal. Orinthine is an intermediate compound in the formation of urea (Kreb's Cycle). OAT is a pyridoxine (vitamin B6) dependant mitochondrial enzyme that catabolises ornithine forming pyrroline-5-carboxylate, ultimately converted into proline and glutamate.

4. Signs and Symptoms

Clinically, GACR is characterized by a slowly progressive chorioretinal atrophy starting in late childhood, associated with nyctalopia, myopia and early cataract formation. Progressive constriction of the visual fields and subsequent irreversible loss of central vision culminating in blindness are observed. Clinical manifestations usually begin with night blindness and constriction of the visual field by the first decade of life with progressive narrowing of peripheral vision until blindness is reached by the third to fifth decade[7]. GACR is a slowly progressive condition. The fundus exhibits patchy areas of atrophy of the RPE and choriocapillaris of round shape, well demarked borders and hyperpigmented margins. These atrophic areas of typical appearance (Figure 1A and 2A) are located in the midperipheral and peripheral retina and progress towards the far periphery and also centrally, becoming more confluent (usually during the second and third decades). Pigment clumping at the borders of the lesions is observed. Progression of the lesions further evolves to complete atrophy of the choroid and retina with exposition of the sclera. In the final stages, a ring of choroidal atrophy is observed as the lesions spread occupying all the fundus (including the peripapilary retina), even though relative spearing the macular area is observed.

Initially, retinal and optic disc vasculature may have normal appearance becoming attenuated in the advanced phases of the disease.

The condition is associated with other ocular manifestations like (generally high) myopia and early cataract formation (usually posterior subcapsular cataracts forming by the second decade of life)[9]. Zonular weakness[10] and retinal detachment[11] have been described in association with AGCR, as well as macular edema[12].

The majority of patients with GACR have only visual symptoms. Nonetheless, electromygraphic, electrocardiographic and electroencephalographic abnormalities have been reported[14]. Some patients with GACR may have complaints of mild muscular weakness. Muscle biopsy has shown abnormalities like atrophic type 2 muscle fibers and tubular aggregates[15].

5. Diagnosis and Imaging

Fluorescein Angiography shows large choroidal vessels in the areas corresponding to atrophy visible on fundoscopy. The clear demarcation between atrophic and non-atrophic areas of the retina and mild leakage at the margins of the areas of chorioretinal atrophy are typical. Macular leakage is observed when macular edema is present.

Spectral Domain Optical Coherence Tomography (SD-OCT) findings in GACR can include multiple bilateral macular cystic spaces and foveal thickening (macular edema) and hyperreflective deposits in the ganglion cell layer[16]. Outer retinal tubulations have also been described in association with the disease (round or ovoid hyporeflective spaces with hyperreflective borders in the outer nuclear layer that result from photoreceptor rearrangement after retinal injury) seen in the areas of transition between atrophic and non-atrophic retina. Areas of loss of the ellipsoid layer and thinning of the inner and outer retina are seen in structural OCT (Figure 2C). Loss of the focal hyperreflectivity of the inner choroid is also a described finding[17].

Fundus Autofluorescence imaging shows areas of well demarked hypoautofluorescence corresponding to the lesions of peripheral atrophy (Figures 2B and Figure 3). This is a noninvasive method of evaluating and monitoring the progression of RPE changes, making it an excellent tool for disease monitoring[18]. Full-field Electroretinogram (ffERG) testing of both scotopic and photopic responses may be only slightly altered in the early stages of GACR. Later in the course of the disease, ERG response deteriorates until showing eventually undetectable amplitudes. Static Perimetry shows bilateral progressive visual field constriction (Figure 2D). Blood tests confirm the increase in ornithine up to 20 times higher than normal.

The diagnosis can be confirmed by molecular genetic testing of the *OAT gene*.

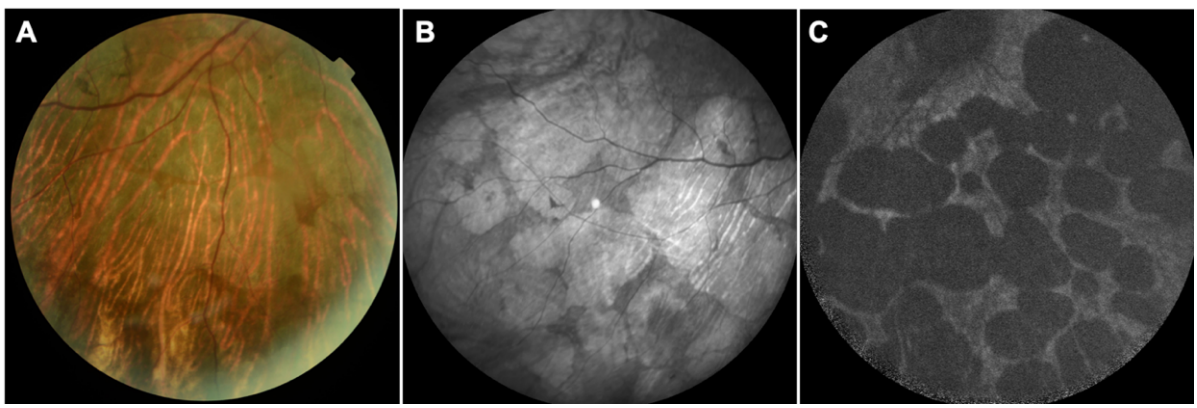

Figure 1 *Close-up view of the mid-periphery of a patient with GACR, emphasizing the patchy areas of atrophy on color fundus photography* ***(A)****, near infrared imaging* ***(B)*** *and fundus autofluorescence* ***(C)****. (Courtesy of João Pedro Marques, MD).*

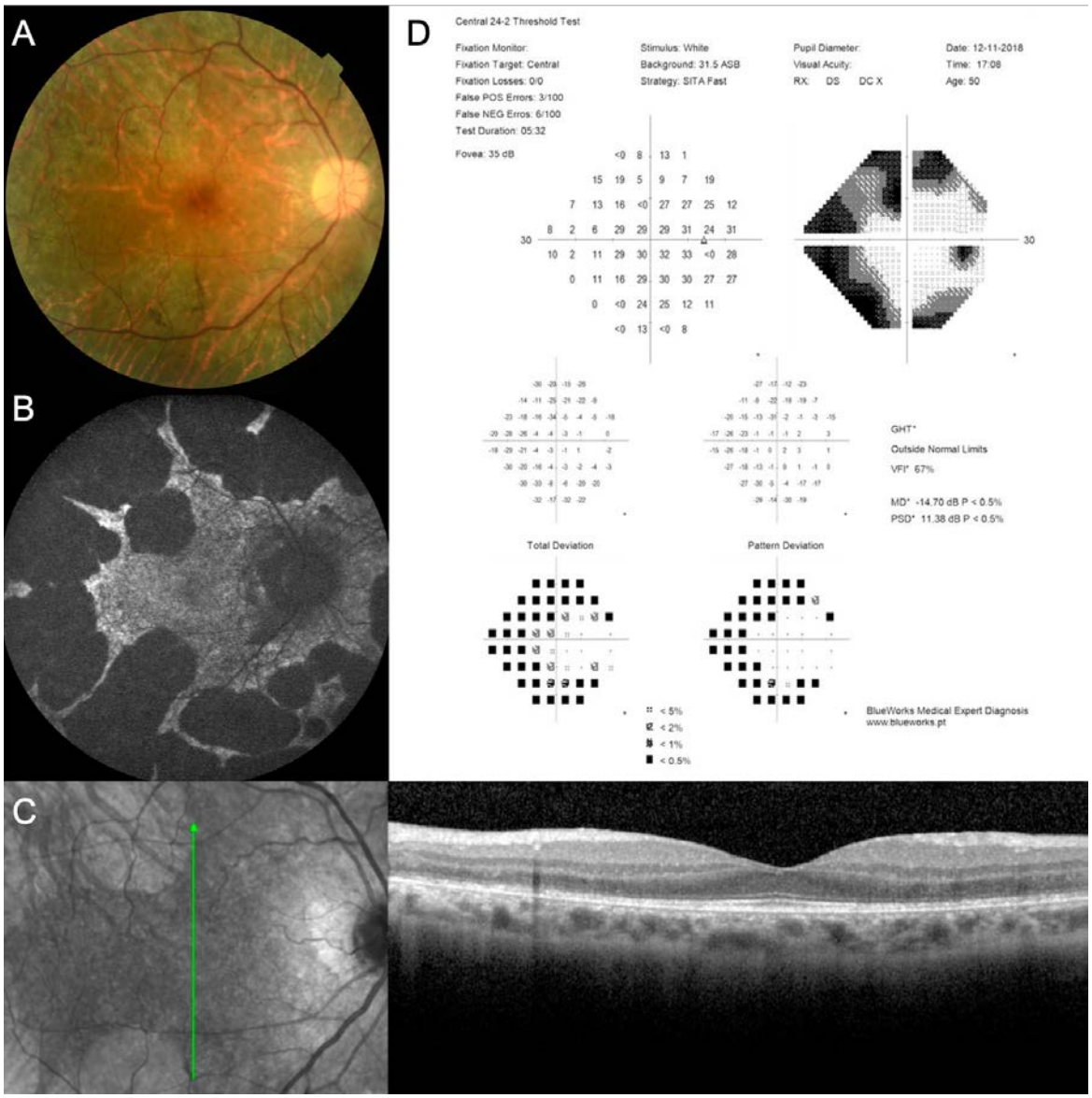

Figure 2 *Multimodal imaging of the same patient on Figure 1.* ***(A)*** *Color fundus photography (CFP) depicting patchy areas of atrophy of the RPE and choriocapillaris of round shape and well demarked borders that spare only the central macula. Pigment clumping is also seen.* ***(B)*** *Fundus autofluorescence (FAF) shows well demarked hypoautofluorescence areas corresponding to atrophic lesions seen of CFP.* ***(C)*** *Near infrared (NIR) imaging is another method of evaluating the patchy areas of atrophy. Structural OCT shows preservation of the central retina but areas of thinning of outer retina are seen inferiorly and supeiorly.* ***(D)*** *Humphrey visual field testing shows peripheral constriction. (Courtesy of João Pedro Marques, MD).*

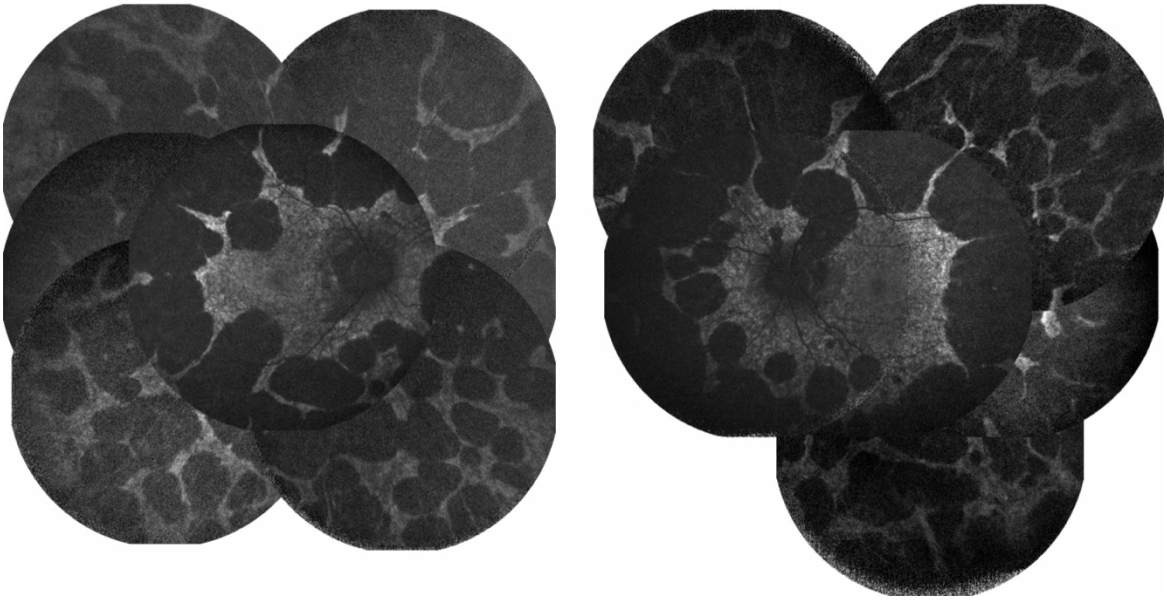

Figure 3 Composite fundus autofluorescence (FAF) images of the right and left eyes of a patient with GARC showing the typical pattern of atrophy (round shaped, well defined hypoautofluorescent areas) involving the equator and the periphery and beginning to involve the macular area. Foveal sparing is seen in both eyes. (Courtesy of João Pedro Marques, MD).

6. Treatment

OAT deficiency is the metabolic defect of AGCR, leading to excessive plasmatic levels of ornithine, which derives from dietary arginine. The reduction of ornithine blood levels by a strict and sustained arginine-restrited diet or a low-protein diet has been shown slow the progression of the retinal lesions of children with GACR[19, 20].

OAT requires vitamin B6 (pyridoxal phosphate) as a coenzyme. It has been found that some patients with AGCR associated with OAT deficiency respond to vitamin B6 dietary supplementation. Both a decrease to less than half of the serum ornithine levels, as in vivo and in vitro increase in OAT activity have been demonstrated. The difference of responsiveness to this therapy between patients is further evidence of the genetic heterogeneity of the groups of patients studied.[21, 22].

Gene therapy can, in the future, eventually become a valuable treatment option for these patients. One of the strategies investigated is the use of skin cells of AGCR patients modified in order to over express OAT [23, 24].

Cataract formation is a complication in eventually every GACR patient from the second decade of life[25]. The opacities are typically posterior subcapsuluar and their extraction may be necessary by the third or fourth decade. Zonular weakness is a per operative common finding[10]. Cystoid macular edema[12] and choroidal neovascularization[26] are also complications described in association with GACR. Macular edema treatment with intravitreal anti-VEFG has been proposed. In patients with advanced visual loss, low vision aids and training are useful.

7. Prognosis

Prognosis of GACR is poor. Extensive visual field constriction and central vision deterioration ultimately leads to blindness. Early diagnose and response to subsequent diet restriction or vitamin B6 supplementation may be considered prognostic factors.

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CHOROIDEREMIA

Rita Dinis da Gama

1. Synonyms

Choroideraemia

2. Epidemiology

Choroideremia is a progressive, bilateral condition that affects mainly males. The prevalence is estimated to be 1 in 50,000 to 100,000 people.[1] The symptoms usually start between 10-25 years of age and in some cases, even later.[2] There is a significant heterogeneity on the clinical features and the rate of progression, even within families.[3]

3. Genetics

Choroideremia (OMIM #303100), is an X-linked recessive disorder, transmitted on the long arm of the X-chromossome.[2] The choroideremia gene (*CHM*) is located at chromosome Xq21.2 and encodes the Rab escort protein 1 (REP1).[2] Rab proteins (REP1 and REP2) regulate the intracellular vesicular transport and all the genetic mutations identified so far origin stop codons that result in the absence of REP1.[4] *CHM* gene is ubiquitous, thus is found in all cell types however, the absence of REP1 on the choriocapillaris, the retinal pigment epithelium (RPE) and the photoreceptors is the only one that originates a progressive degeneration of the cells.[1,3]

On the carrier female the fundus signs are the result of random X-inactivation.[4]

4. Signs and Symptoms

There are 2 types of clinical features of choroideremia: the male hemizygotes and the female heterozygote.

The presenting sign on the affected male is poor night vision. Usually, best corrected visual acuity (BCVA) is preserved until late in the course of the disease. Typical fundoscopic signs are depicted in Figure 1.

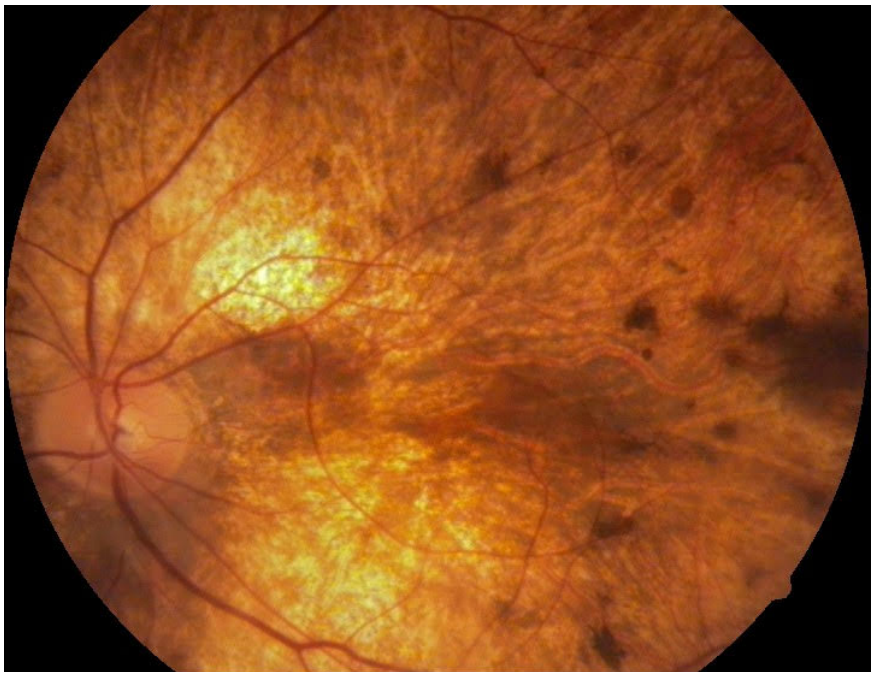

Figure 1 Fundus picture of a patient with choroideremia. Notice the pigment mottling at midperipheral retina, the scalloped atrophy of chorioretina, visualization of the choroidal large vessels and relative sparing of the central macular area. (Courtesy of João Pedro Marques, MD)

The initial changes affect the midperipheral retina in the form of patches of pigment mottling and hypopigmentation.[1,3] Later, yellow-white lesions with preservation of deep choroidal vessels, characteristic of the choriocapillaris atrophy, will extend to the extreme periphery.[1] These lesions will enlarge and areas of relatively well-preserved retina are found abruptly adjacent to areas of severe degeneration.[1,4] In the final stage, there are extensive degenerative changes of the RPE with only remnants of the choroidal vasculature apparent in the macula, far peripheral retina and near the optic disc.[5] Only in more advanced stages the arterioles became attenuated, but the optic disc does not become pale as in typical retinitis pigmentosa.[3]

The carrier female may complain of photophobia or difficulties in dark adaptation. The BCVA is not affected and the fundus has a reticular pigmentary mottling of the RPE mainly in the macular region, with additional RPE clumping and flecks of atrophy in the periphery.[3,6]

5. Diagnosis and imaging

AFFECTED MALES

The combination with nyctalopia, conserved BCVA, asymptomatic parents and a familiar history of "retinitis pigmentosa" in a young male patient should raise the suspicion of choroideremia [1]

The initial fundus changes begin at the midperiphery.[3] In the intermediate stages of the disease, the atrophy of RPE and choriocapillaris becomes more diffuse, sparing only the far retina periphery and the macula.[1-3]

Peripheral visual fields: Midperipheral ring scotoma that evolves concentrically to complete loss of peripheral field.[1-3]

Optical coherence tomography (OCT): On early stages the retina has either normal or increased thickness. Later on, photoreceptor degeneration and RPE depigmentation occur, but sparing the foveolar area (Figure 2). In late stages, the foveola is also affected and diffuse atrophy establishes.[1,2]

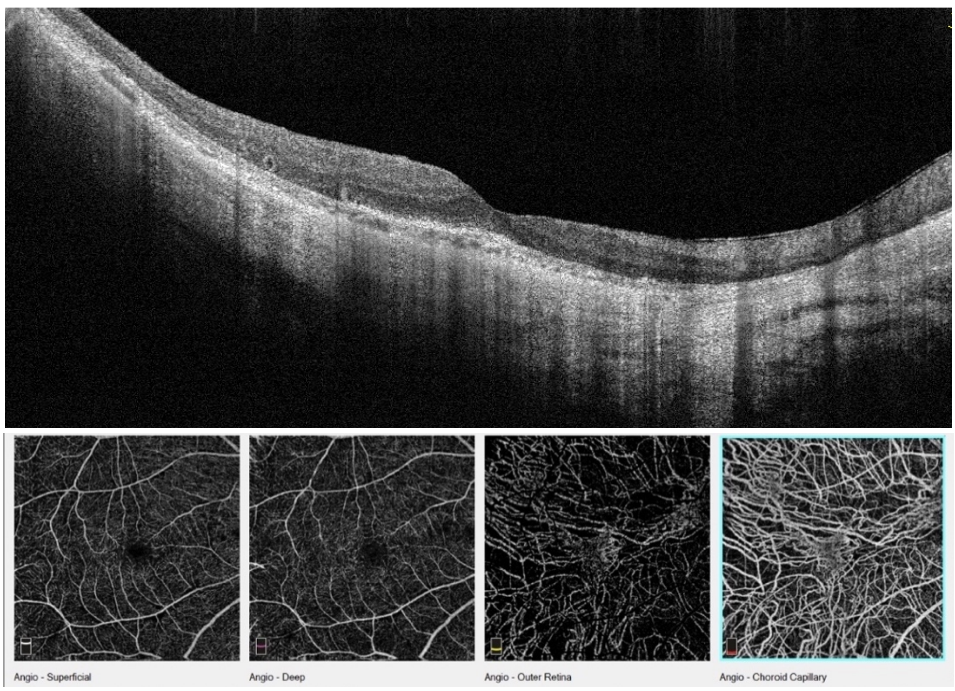

Figure 2 Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCT-A) of a patient with choroideremia. ***TOP:*** *B-Scan. Diffuse thinning of the choroidal layers and hypertransmission of the signal. Atrophy of the outer retina and outer retinal tubulations can be seen perifoveally, but the foveal architecture is relatively preserved.* ***BOTTOM:*** *OCT-A. The superficial and deep capillary plexus have normal vessel densities. However, due to outer retina and RPE atrophy, the choriocapillaris layer is almost absent and restricted to a small island at the foveal centre. The large choroidal vessels can be visualized due to absence of the choriocapillaries. (Courtesy of João Pedro Marques, MD)*

Autofluorescence: The atrophic lesions are hypo-autofluorescent round plaques surrounded with hyper-autofluorescent, scalloped borders. The macula is normo-autofluorescent and the typical perifoveal hyper-autofluorescent ring of retinitis pigmentosa is absent. [1,2]

Electrophysiology: Affected males have early reduced full-field electroretinogram of the rod-cone dystrophy type that ultimately evolves to complete extinction.[1-3]

Fluorescein angiography: Not useful for the diagnosis, it has been replaced by autofluorescence and OCT-A.

Molecular biology: The diagnosis is confirmed by an immunoblot analysis with anti-REP1 monoclonal antibody (2F1).[3,4]

CARRIER FEMALE

Optical coherence tomography: Usually normal

Autofluorescence: Irregular, small and hypo and hyper-autofluorescent speckles in the posterior pole that alternate with larger areas of atrophy in the periphery.[2]

Electrophysiology: Abnormal in 15% of the female carriers, with both rod or cone abnormalities.[2,6]

Molecular biology: Not useful for the diagnosis of a carrier.[3]

6. Treatment

A phase 1 gene therapy is currently ongoing. Preclinical data on the testing of the Adenovirus 2-REP1 gene therapy vector have been encouraging and the results of the human trial are awaited with great anticipation.[7,8]

7. Prognosis

BCVA declines very slowly and only 33% of the patients older 60 years has a central vision of 20/200 or worse.[1] The most severe visual acuity impairment (counting fingers or worse) does not occur until the seventh decade of life (after 60 years of age).[5]

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LEBER CONGENITAL AMAUROSIS

Amélia Martins, Dalila Coelho, Cláudia Farinha

1. Synonyms

Congenital retinal blindness (CRB); Congenital absence of rods and cones; Hereditary retinal aplasia.[1-3]

2. Epidemiology

Leber Congenital Amaurosis (LCA) was first described by Theodore Leber in 1869.[4] It is the earliest and most severe form of inherited retinal dystrophies. Its incidence is 2-3/100,000 births. Moreover, 5% of all retinal dystrophies and 20% of blindness in school age children, are related to LCA.[5-7]

3. Genetics

The genetic heterogeneity of LCA (MIM #204000) is extensive.[5] The majority of the mutations are in genes that affect development of the photoreceptors or the biochemical reactions of the visual cycle, including ciliary transport, phototransduction and retinoid cycling. Most often, LCA is inherited in an autosomal recessive pattern, and the most common mutations were detected in *GUCY2D* and *RPE65* genes, accounting for up to 21% and 16% of LCA cases, respectively.[8] Rarely, LCA can be autosomal dominant, and this can be caused by mutations in three genes: *CRX*, *IMPDH1* and *OTX2*.[7,9] Mutations in any one of at least 25 different genes are responsible for 70%-80% of all cases of LCA (**Table 1**).[5,6,10]

Table 1. Leber Congenital Amaurosis (LCA) pathogenic mutations, chromosome locus and its estimated prevalence.

Gene (Locus name, chromosome, gene MIM number*)	Inheritance	LCA attributed to this mutation (%)
GUCY2D (LCA1, 17p13.1, #600179)	AR	6 - 21
RPE65 (LCA2, 1p31.3, #180069)	AR	3 -16
SPATA7 (LCA3, 14q31.3, #609868)	Unknown	Unknown
AIPL1 (LCA4, 17p13.2, #604392)	AR	4 - 8
LCA5 (LCA5, 6q14.1, #611408)	Unknown	1 - 2
RPGRIP1 (LCA6, 14q11.2, #605446)	Unknown	5
CRX (LCA7, 19q13.33, #602225)	AD	3
CRB1 (LCA8, 1q31.3, #604210)	Unknown	Unknown
NMNAT1 (LCA9, 1p36.22, #608700)	AR	Unknown
CEP290 (LCA10, 12q21.32, #610142)	Unknown	15 - 20
IMPDH1 (LCA11, 7q32.1, #146690)	AD	Unknown
RD3 (LCA12, 1q32.3, #180040)	AR	Unknown
RDH12 (LCA13, 14q24.1, #608830)	AR, AD	4
LRAT (LCA14, 4q32.1, #604863)	AR	Unknown
TULP1 (LCA15, 6p21.31, #602280)	AR	Unknown
KCNJ13 (LCA16, 2q37.1, #603208)	AR	Unknown
GDF6 (LCA17, 8q22.1, #601147)	AR	Unknown
PRPH2 (LCA18, 6p21, #179605)	Unknown	3%
CABP4 (11q13.2)	AR	Unknown
IQCB1 (3q13.33)	AR	Unknown
OTX2 (14q22.3)	AD	Unknown
DTHD1 (4p14)	Unknown	Unknown
IFT140 (16p13.3)	AR	Unknown

AR, autosomal recessive; AD, autosomal dominant. *OMIM (www.omim.org) entries for Leber Congenital Amaurosis.

4. Signs and Symptoms

LCA is a severe dystrophy of the retina that generally becomes evident at birth or during the first year of life.[5,6] The clinical picture includes (1) severe visual impairment, usually stable or very slowly

progressive, rarely better than 20/400 and in 30% of patients no light perception; (2) Franceschetti's oculodigital sign, consisting of eye poking, pressing, and rubbing of the eyes; (3) pendular or roving nystagmus in all positions of gaze; (4) sluggish or near-absent pupillary responses; (5) photophobia; (6) normal fundoscopy (initially); and (7) high hyperopia, probably secondary to an impaired emmetropization.[5-7] Other ocular changes, likely associated to the oculodigital sign include keratoconus, cataract, keratoglobus and enophthalmos.[6,7] Although the retina may appear normal initially, the fundoscopic findings may evolve to different phenotypes: a pigmentary retinopathy similar to retinitis pigmentosa, subretinal flecks resembling retinitis punctata albescens, "marble fundus", pigmented nummular lesions at the level of the RPE, retinal vessel attenuation, widespread atrophy, macular atrophy, "macular coloboma", "Coats-like" reaction[6,7], and optic disc abnormalities (swelling, drusen and peripapillary neovascularization) (Figure 1).[6] The prevalence of some of these signs may vary according to the genetic mutation. Family history is typically congruent with autosomal recessive inheritance and occasionally there are non-ophthalmologic features associated: intellectual disability, neurodevelopmental delay, autism, oculomotor apraxia-type behavior, hearing loss and kidney dysfunction.[6]

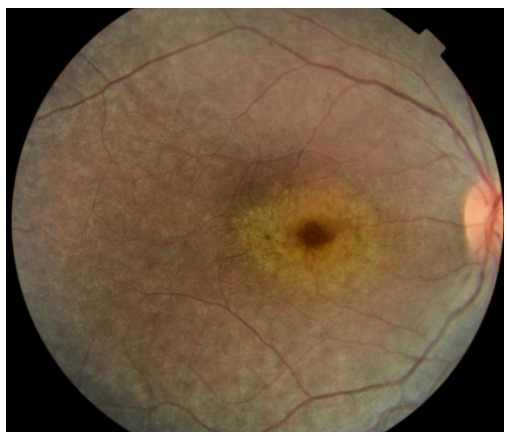

Figure 1. Color fundus photography of the right eye of an 8-year-old child with Leber Congenital Amaurosis. Subretinal flecks are visible in the posterior pole and in the periphery, as well as yellowish macular deposits and macular atrophy.

5. Diagnosis and Imaging

The diagnosis of LCA is established by clinical findings. Although there are no available diagnostic criteria for LCA, the signs and symptoms described above are highly suggestive of the disease. The scotopic and photopic electroretinogram (ERG) is characteristically non-recordable or severely subnormal (Figure 2).[5,6] Visual evoked responses can be altered or extinguished.[6,7]

To establish a genetic diagnosis, a multigene LCA panel should be performed. Similarly, the genetic test for relatives at-risk of autosomal recessive LCA carriers can be accomplished, as well as prenatal and preimplantation diagnosis, but they all require prior identification of the pathogenic variants in the family.[6]

Differential diagnosis of LCA includes: retinitis pigmentosa, achromatopsia, congenital stationary night blindness, Alstrom syndrome, Joubert syndrome, infantile neuronal ceroid lipofuscinosis, Zellweger syndrome, neonatal adrenoleukodystrophy, abetalipoproteinemia, hiperthreoninemia, severe early-childhood onset retinal dystrophy (SECORD).[10-12]

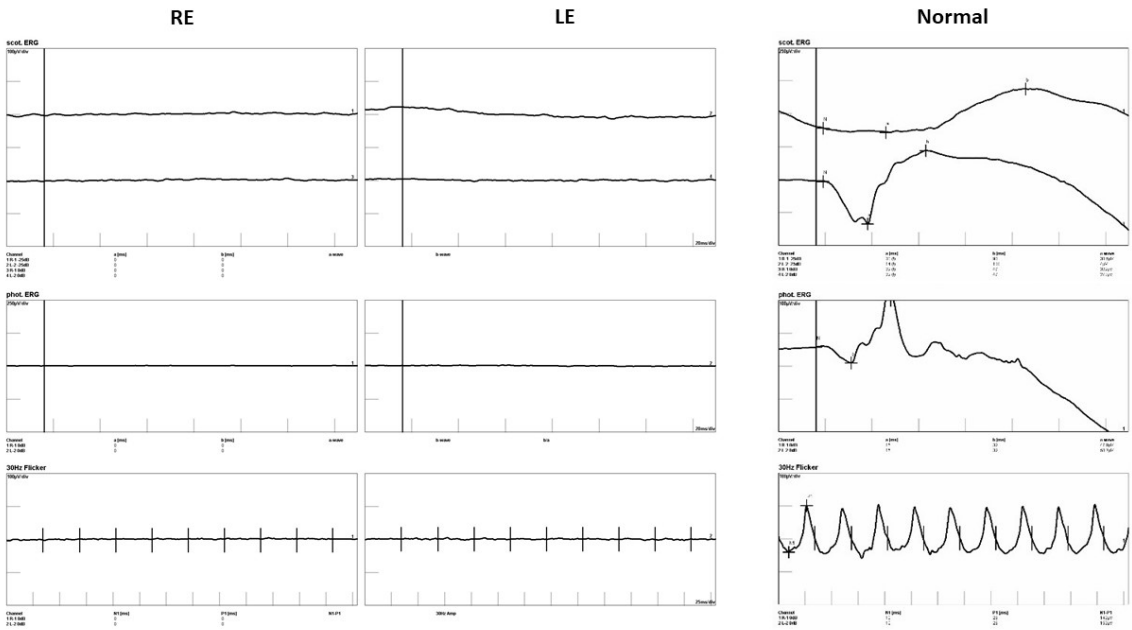

Figure 2. A non-recordable scotopic (rod response and maximal response) and photopic (single flash and 30 Hz flicker responses) electroretinogram (ERG) of the right (RE) and left eyes (LE) in a patient with Leber Congenital Amaurosis. Normal ERG is presented for comparison. (Courtesy of Miguel Raimundo, MD)

6. Treatment

Treatment has been mainly supportive. However, in december 2017, the US Food and Drug Administration (FDA) approved a cutting-edge gene therapy, called LUXTURNA™ (voretigene neparvovec-rzyl), an adeno-associated virus vector gene therapy, administered by subretinal injection, for patients with confirmed biallelic *RPE65* associated retinal dystrophy, with sufficient viable retinal cells.[3] The FDA approval was based on one open-label, dose-exploration Phase 1 safety study (n=12)[1,2,13-15]and one open-label, randomized, controlled Phase III efficacy and safety study (n=31) in pediatric and adult participants (range 4 to 44 years) with biallelic RPE65 mutation-associated retinal dystrophy.[3] This open-label phase 3 trial, included individuals over 3 years-old, with best corrected visual acuities of 20/60 or worse, and/or visual field less than 20 degrees in any meridian, sufficient viable retina, and ability to perform standardized multi-luminance mobility testing (MLMT). At 1 year, mean bilateral MLMT change score light levels were significantly higher in the intervention group versus in the control group. Thus, voretigene neparvovec gene replacement improved functional vision in *RPE65*-mediated inherited retinal dystrophy previously

medically untreatable.[3] The drug was granted approval in Europe in November 2018. Nevertheless, only the abovementioned restricted cases are targeted by this new treatment. Therefore, management in most cases is still based in periodic ophthalmic evaluation for correction of refractive errors and assessment of other ophthalmologic comorbidities (amblyopia, cataracts and glaucoma, among others). Discourage from repeatedly poking and pressing the eyes should be attempted. Low vision aids to maximize visual function can be very useful and children should be referred for a low vision clinic as early as possible.[6,7] Genetic testing and genetic counseling are recommended.

7. Prognosis

The visual acuity of patients with LCA is severely affected during the first year of life, with slow and gradual progression thereafter. The results reported in new gene therapies suggest that improvement of visual acuity may occur after treatment. However, its efficacy is reduced in cases of advanced stage of retinal disease at baseline, and for now only the *RPE65*-related LCA pathogenic variants are targeted by this new treatment.

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ALBINISM

João Bernardes, Miguel Raimundo, João Pedro Marques

Albinism, from the Latin word, *albus*, meaning white, encompasses a group of genetically inherited diseases associated with a decreased or absent tissue melanin. Melanin, a polymeric pigment that colors skin, hair and eyes, is synthesized in melanocytes and retinal pigment epithelium (RPE) cells, in specialized intracellular melanin-producing organelles called melanosomes. The two major forms of melanin are eumelanin, responsible for brown or black tissue coloration and ultraviolet radiation B (UVB) skin protection, and pheomelanin, responsible for red or blond hair and light colored skin.

In albinism, biosynthesis or transport of melanin is impaired, but the number of melanocytes is preserved. Eyes and skin are the two main affected organs. Although initially different types of albinism were divided based on clinical and biochemical factors, with the advent of modern biomolecular techniques a more precise classification, based on the different genes affected, was adopted. Thus, this disorder may be classified as syndromic or non-syndromic, depending on whether or not, respectively, the mutated protein is implicated in extensive cell functions. The main syndromic types of albinism are the Hermansky-Pudlack syndrome (HPS) and the Chediak-Hihashi syndrome (CDH). Non-syndromic albinism can be further divided in oculocutaneous albinism (OCA) or ocular albinism (OA). The former, as the name implies, affects eyes and skin, with 7 different types (OCA1 to OCA7) having been described to date. In contrast, the latter has minimal skin involvement.

1. Epidemiology

The overall prevalence of OCA is estimated at 1/17,000 to 1/20,000, with 1 in 70 individuals carrying an OCA-mutated allele[1]. OCA1 has an estimated prevalence of 1/40,000. It is one of the most common forms found in China (70%) and the USA, although it is uncommon in African-Americans and in Africa[2-4]. OCA2 is the most common type worldwide, with an estimated prevalence of 1/39,000, mainly due to its high prevalence in sub-Saharan populations, where it reaches a prevalence of 1/3,900 (in selected Zimbabwean populations a prevalence as high as 1 in 1000 has been observed[3,5]). OCA3 has been reported to affect 1/8,500 people in southern Africa, but is extremely rare in Caucasian and Asian populations[3,4]. OCA4 is the third most common type of

OCA after OCA2 and OCA1, with an estimated prevalence of 1/100,000, being particularly common in Japan (24% of OCA)[6,7]. OCA 5, 6 and 7 are extremely rare, with scattered reports worldwide[8]. OA1 is the commonest form of ocular albinism with an estimated prevalence of 1/50,000 to 1/150,000. In contrast, OA2 is extremely rare. In fact, there is debate about whether or not OA2 and congenital stationary night blindness type 2A are the same entity[9-11]. Regarding syndromic albinism, Hermansky-Pudlack syndrome has an overall prevalence of 1/5,000,000, with increased prevalence observed among people of Swiss or Puerto Rican descent. Chediak-Higashi syndrome is extremely rare[8].

2. Genetics

2.1. Oculocutaneous albinism (OCA)

Inheritance: autosomal recessive pattern

OCA1

OMIM: OCA1A: 203100; OCA1B: 606952

Gene: *TYR* gene located at 11q14.3. Consists of a five-exon gene encoding a 529-amino acid protein called tyrosinase. Tyrosinase is a transmembrane domain protein involved in the first step of the melanin synthetic pathway by hydroxylating L-tyrosine to L-DOPA and then oxidating L-DOPA to DOPAquinone. OCA1A is caused by null variants in *TYR* associated with a total lack of tyrosinase enzyme function, thus no melanin is present in melanocytes; OCA1B is caused by mutations in *TYR* that produce a partially active enzyme[4,12].

OCA2

OMIM: 203200

Gene: *OCA2* gene (previously known as P gene) located at 15q12-q13. Consists of a twenty-four-exon gene encoding a 838-amino acid protein with twelve transmembrane domains called OCA2. Its precise function is unknown. It may be associated with tyrosinase maturation and activity regulation by interfering with melanosome pH [4,13,14].

OCA3

Synonym: Rufous OCA

OMIM: 203290

Gene: Tyrosinase-related protein 1 (*TYRP1*) gene located at 9p23. Consists of an eight-exon gene encoding a 547-amino acid protein. It may participate in the melanin synthetic pathway with enzymatic activity and contribute to melanosome integrity and tirosynase stability [4,15].

OCA4

OMIM: 606574

Gene: *SLC45A2* gene (also known as membrane-associated transporter protein – *MATP* – gene) located at 5p13.2. Consists of a seven-exon gene encoding a 530-amino acid protein. Its function is unknown, but it may act as a membrane transporter in melanosomes[8,13].

OCA5

OMIM: 615312

Gene: unknown. It has been linked to a locus on chromosome 4q24[16].

OCA6

OMIM: 113750

Gene: The *SLC24A5* gene located at 15q21.1 encodes a Na/K/Ca cation exchange protein whose function is thought to be similar to that of the gene responsible for OCA4[8].

OCA7

OMIM: 615170

Gene: *C10orf11* gene, also known as *LRMDA* (leucine-rich melanocyte differentiation associated protein) located at 10q22.2-q22.3. Encodes a 198 amino acid protein that may be involved in melanocyte differentiation[13,16].

2.2. Ocular albinism (OA)

Inheritance: x-linked recessive pattern

OA1

Synonym: Nettleship-Falls ocular albinism, Ocular Albinism X-linked, XLOA

OMIM: 300500

Gene: *GPR143* gene located at Xp22.2. Encodes an intracellular CPCR (G-protein coupled receptor) that may regulate melanosome biogenesis and transport. The pathogenic variant is associated with macromelanosomes observed in skin biopsy [17,18].

OA2

Synonym: Aland Island; Forsius-Eriksson type ocular albinism

OMIM: 300600

Gene: *CACNA1F* gene located at Xp11.23[19].

2.3. Syndromic Albinism

Hermansky-Pudlack syndrome

Inheritance: autosomal recessive pattern

OMIM: 203300, 608233, 614072, 614073, 614074, 614075, 614076, 614077, 614171

Gene: *PS1* gene (HPS1), *AP3B1* gene (HPS2), *HPS3* gene (HPS3), *HPS4* gene (HPS4), *HPS5* gene (HPS5), *HPS6* gene (HPS6), *DTNBP1* gene (HPS7), *BLOC1S3* gene (HPS8), *BLOC1S6* gene (PLDN), *AP3D1* gene (HPS10). *HPS* genes are associated with impaired intracellular vesicle biogenesis[8].

Chediak-Higashi Syndrome

Inheritance: autosomal recessive pattern

OMIM: 214500

Gene: *CHS1 /LYST* gene located at 1q42.3. Encodes a protein associated with trafficking material into lysosomes, leading to the formation of giant cytoplasmic granules[8,20].

3. Signs and Symptoms

Hypopigmentation of scalp hair, brows, lashes, skin and eye, particularly in comparison with relatives or individuals from the same ethnic background, is a common feature of OCA. However, the spectrum of pigmentation varies considerably depending on the gene involved. For example, due to the complete lack of tyrosinase activity, OCA1A patients manifest white hair and skin and pink eyes throughout their whole lives. OCA1B has residual tyrosinase function so the proband, although similar to OCA1A in the first years of life, will progressively accumulate melanin, which in this case is predominantly pheomelanin. This pigment is responsible for the characteristic yellow coloration of their skin. Among the other types of OCA, there are characteristic phenotypes such as the Brown OCA2 (BOCA) albinism, part of the clinical spectrum of OCA2 associated with light brown hair and skin, and the Rufous OCA3 (ROCA), associated with red-bronze skin color, ginger hair and blue to brown irises.

On the other hand, OA, as the name indicates, affects mainly the eye. However, a slightly pale skin is generally observed when compared to relatives.

Similar ophthalmologic findings are present in all albinism types and are the most debilitating features of the disease:

- Poor visual acuity: Near vision is usually better than distance vision, presumably as a consequence of reduced nystagmus when converging [1,18].
- Iris transillumination: Observed when a beam of light reflects back at the retina. Although characteristic, it is not specific, occurring in diseases like pseudoexfolation syndrome or pigment dispersion syndrome.
- Photophobia/Photodysphoria: Often the most debilitating symptom, associated with light scattering within the eye due to the lack of iris, retina and choroid pigment.
- Nystagmus: Predominantly horizontal, although vertical or torsional nystagmus have been observed. It may develop as early as 6 weeks of age. Characteristically with larger amplitude in the beginning, although later it acquires a uniform pendular form with smaller amplitudes. Nystagmus may have a null point leading to an anomalous head position. Usually convergence also damps nystagmus [12].

- Strabismus: Often associated with a positive angle kappa, so esotropia may appear diminished whereas exotropia may appear larger [21].
- Refractive errors: Including myopia, hyperopia and/or astigmatism.
- Foveal hypoplasia: The most important contributor to poor vision, presumably associated with the absence of melanin in the RPE. However, it is not specific as it may occur in other diseases like aniridia[12].
- Yellow or orange retina: Diminished melanin in RPE cells may allow the visualization of prominent choroidal vessels, particularly in the mid periphery, due to the presence of other non-melanin pigments like lutein in the macula (Figure 1A, 2A, 4A and 4B).
- Abnormal decussation of the visual pathways: In normal individuals, approximately 55% of the optic nerve fibers decussate to the contralateral side of the brain, but in patients with albinism, up to 90% of the optic nerve fibers crossover to the contralateral side, leading to an imbalance of the information between the visual fields of both eyes that arrives at the visual cortex. This abnormality results in the loss of stereopsis and probably contributes to the development of strabismus[12].

Hermanasky-Pudlak syndrome: Patients with HPS have OCA, bleeding diathesis due to a lack of dense granules in platelets, and in some severe forms pulmonary fibrosis and granulomatous colitis.

Chediak-Higashi Syndrome: CHS is characterized by OCA, an increased susceptibility to pyogenic infections, neutropenia, peripheral neuropathy and mild coagulopathy.

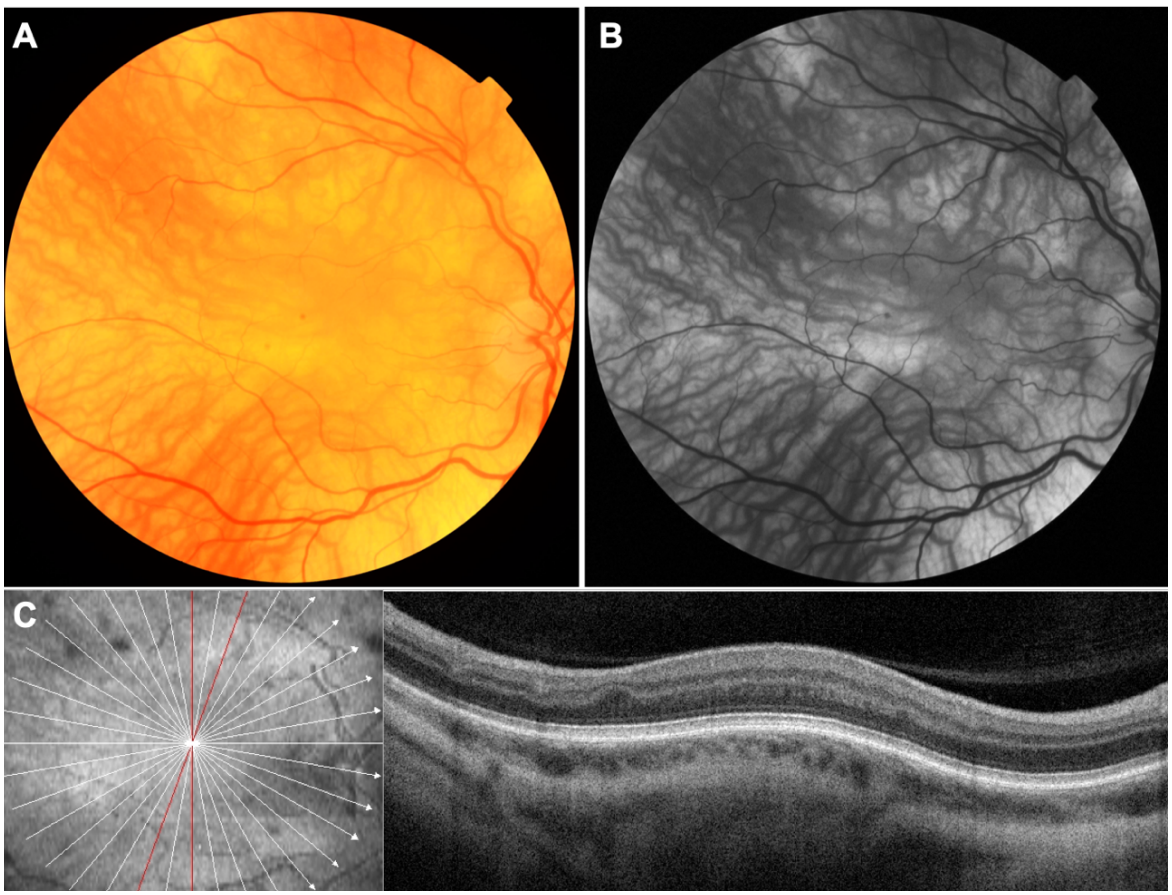

Figure 1 *Multimodal imaging of a male patient with ocular albinism.* ***(A)*** *Color Fundus Photography depicting the typical changes in the retina: diminished melanin in RPE cells allow visualization of prominent choroidal vessels. This is even better appreciated in the near infrared image* ***(B)****. Note the foveal hypoplasia in the SD-OCT scan (absence of the foveal pit)* ***(C)****.*

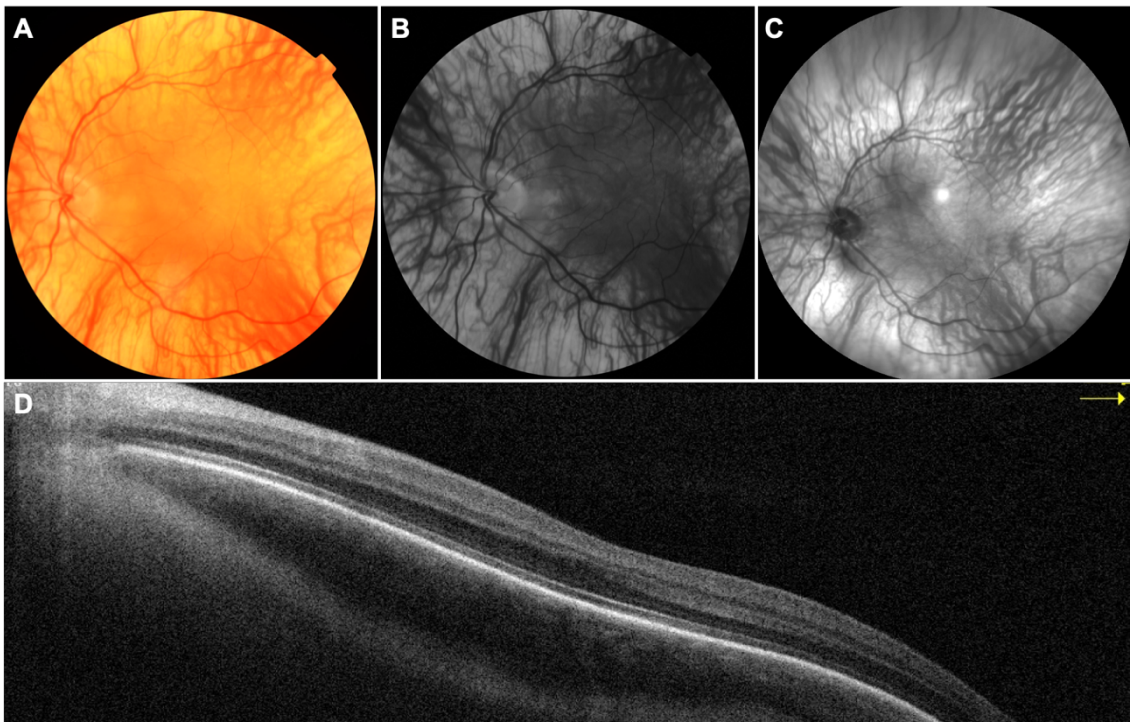

Figure 2 *Multimodal imaging of a female patient with oculocutaneous albinism.* ***(A), (B)*** *and* ***(C)*** *highlight the visualization of the choroidal vessels due to diminished melanin in the RPE cells in color fundus photography, near infrared and red free imaging, respectively.* ***(D)*** *SD-OCT scan showing the absence of the normal foveal anatomy*

4. Diagnosis and Imaging

Diagnosis of albinism is fundamentally clinical, based on dermatologic and ophthalmologic examination. When facing a presumed patient with OA, a posterior segment evaluation of the obligate female carrier reveals in 90% of cases a characteristic "mud-splatter" pattern in the mid-periphery, associated with hypopigmented patches of retina[18]. In Caucasian patients with OCA pigmented types, complementary exams as optical coherence tomography (OCT), visually evoked potentials (VEP) or magnetic resonance imaging (MRI) may help achieve the correct diagnosis.

Anterior segment OCT reveals a diminished thickness of the iris[22]. Posterior segment OCT is remarkable for the absence of both the foveal depression and the normal foveal thinning (Figure 1C and 2D).[23]

Full-field VEP, based on pattern or flash stimulation, is a useful exam that demonstrates the abnormal optic fiber decussation by comparing the interhemispheric asymmetry of the positive peak (P100) in terms of amplitude and latency (Figure 1). [24]

MRI reveals smaller optic nerves, optic chiasm and optic tracts[25]. Functional MRI based in asymmetrical indexes of cortical responses to monocular stimulation appears to deliver similar results to VEP[26].

Finally, molecular testing confirms the diagnosis. Multigene panel or comprehensive genomic testing are the preferred methods due to the overlapping phenotypes of OCA[7].

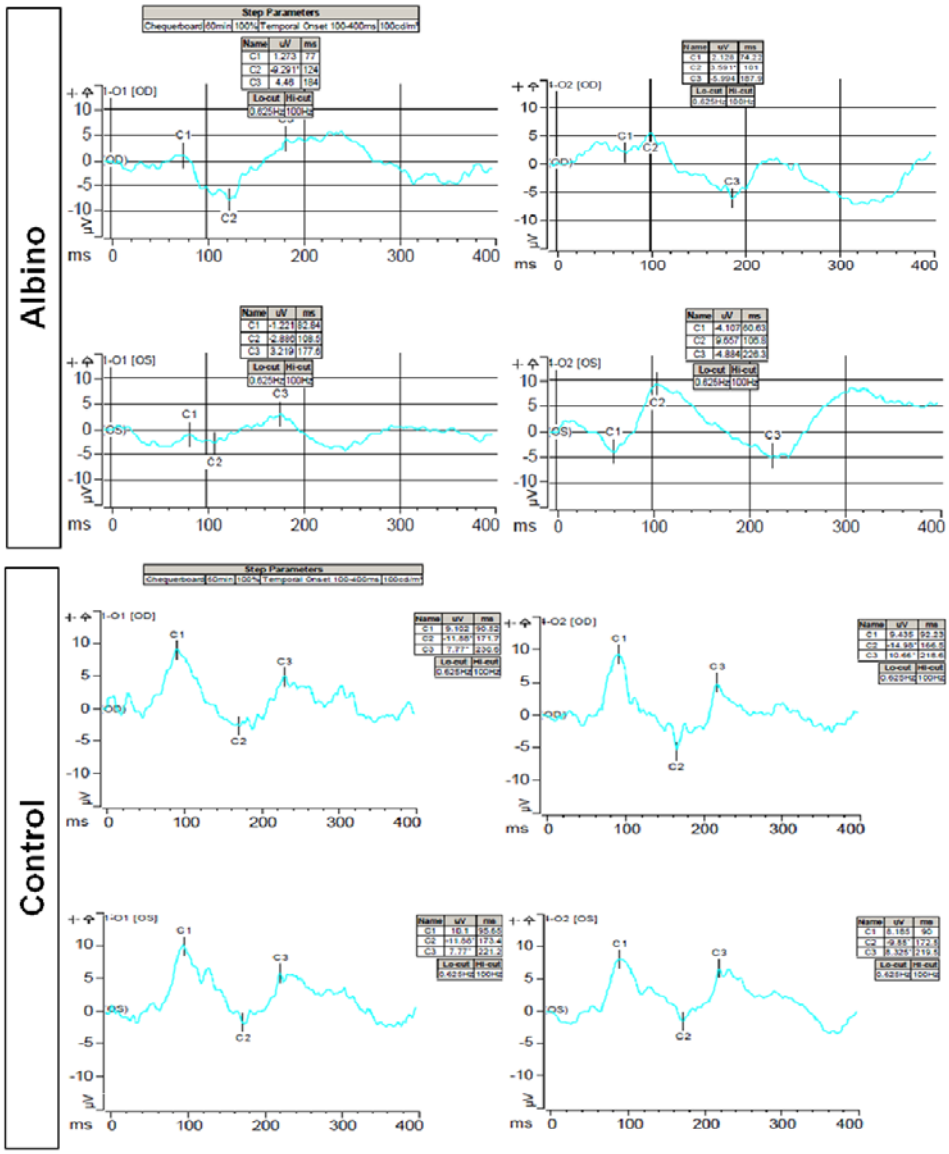

Figure 3 *Pattern-onset VEP in an albino subject and a control subject, using a monocular full-field checkerboard stimulus. The O1/O2 electrode refer to scalp electrodes 3 cm to the left and right of the midline, respectively. By visually inspecting the VEP responses, under monocular stimulation of the right eye (OD), a greater response is observed on the left electrode (O1). The inverse is seen for monocular stimulation of the left eye (OS), with a greater response in the right electrode (O2). These findings suggest increased projection to the contralateral hemisphere through chiasmal misrouting. Meanwhile, in a normal control subject, symmetrical activation under monocular stimulation can be appreciated.*

5. Treatment

To date, there is no definitive treatment for albinism. Therefore, treatment is aimed at controlling debilitating symptoms like photophobia, promote the adoption of sun protection measures (given the increased incidence of skin cancer) and maximizing the visual potential with regular refractive error correction and referral to a low vision clinic (Figure 4). Patients may benefit from small hand-held telescopes or other low-vision aids. Pre-school and school environments are particularly important for the normal development of the child with albinism. Therefore, teaching aids like high contrast material, large print texts and prompt usage of computers should be adopted.

Nitisinone, an inhibitor of tyrosine degradation used for hereditary tyrosinemia, was used in mouse models with improvement of their pigmentation. These results suggest that it may benefit OCA1A patients [27].

Future gene therapy may play an important role in albinism treatment.

Finally, patients with albinism and their families should be offered genetic counseling in order to explain the natural course of the disease, to access the family members' carrier status and to discuss prenatal testing and preimplantation genetic diagnosis.

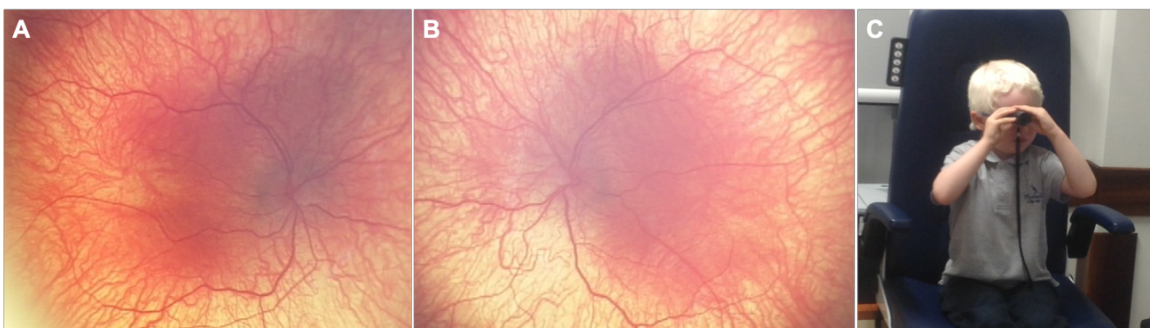

Figure 4 Color fundus photography of the right (A) and left (B) eyes of a 4-year old child with oculocutaneous albinism (images acquired with Retcam). (C) In the low vision clinic, the child receives training to use a hand-held telescope. (Courtesy of Catarina Paiva, MD)

6. Prognosis

Patients with non-syndromic albinism, if correctly monitored and carefully compliant of the skin-cancer prophylactic measures, appear to have a life expectancy comparable to the general population (4). Despite delayed visual maturation, normal intelligence and normal global development are the norm (28). Psychologically, patients with albinism may suffer from isolation and depression due to the stigma associated with this disease. Furthermore, an increased rate of hyperactivity disorder and attention deficit have been observed (8, 29).

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VISUAL REHABILITATION IN PATIENTS WITH INHERITED RETINAL DYSTROPHIES

Tiago M. Rodrigues, Catarina Paiva

The World Health Organization (WHO) defines low vision as "a visual acuity of less than 6/18 to light perception, or a visual field less than 10 degrees from the point of fixation [...] even after treatment and/or standard refractive correction". This definition explicitly includes only those cases that cannot be improved by surgical and/or medical therapies. Hence, it concerns many of the patients with retinal dystrophies, for whom there are still few to no therapies available.

Low vision reduces the ability to perform activities of daily living, reduces independence, decreases self-esteem and leads to social isolation and depressive states.[1] Visual Rehabilitation (VR) has the potential to maximize the visual performance of low vision patients, allowing them to perform their everyday tasks as independently as possible, not only at a defined point in time, but particularly as vision loss progresses.[2]

VR strategies are not specific to disease processes; rather, they are tailored to the needs and difficulties of each individual patient. [3] Even rehabilitation goals are not universal; instead, they are defined in terms of what matters most in a person's life. Therefore, not only is it necessary to perform a complete ophthalmological examination, but also to assess the functional visual performance (e.g., reading, writing, and mobility skills) within the context of specific lifestyles (e.g., professional and household activities). Additionally, knowledge of the natural history of the diseases allows us to already predict some of the difficulties patients will encounter.

For macular dystrophies, e.g. Stargardt Disease (STGD) and Progressive Cone Dystrophy, the central scotoma greatly hampers reading ability – particularly if located on the right side of the central visual field, as it leads to difficulty in tracking the text. Reading is an elementary skill needed for education, work and many daily activities. Specifically in STGD, reduced reading ability was shown to significantly worsen quality of life.[4] And even within the broader population of low vision patients, improving reading ability is the most common goal of VR;[5] to this end, several options can be explored.

First, spectacle refraction should not be overlooked. Even when distance visual acuity (VA) cannot be improved significantly, it is important to have the best possible correction for intermediate and near tasks. If needed, high addition spectacles can be prescribed; these are

aesthetically acceptable, allow both hands to remain free, but are only available in additions up to 12 D. Second, lighting conditions should be optimized; as luminance decreases exponentially with increasing distance from the light source, using an appropriate desk lamp correctly positioned above the text is more beneficial for reading than increasing the power of a ceiling light. The use of a reading stand (Figure 1A) should be encouraged to avoid harmful body postures (e.g., hunchback); patients with low vision already tend to get close to the text, and magnification devices often further decrease the working distance for reading. Additionally, large print books and audio books are readily available from public libraries. Contrast manipulation is also of benefit, even for household activities; for example, it is far easier to eat rice from a dark plate than against a white background.

Regardless, strategies to maximize reading speed often involve provision and training of low vision aids (LVAs).[2] LVAs include optical, nonoptical and electronic devices that maximize visual perception by increasing magnification and/or improving contrast. Particularly for STGD, several case series have demonstrated the usefulness of LVAs in improving visual performance.[6-10] These include (i) ruler- and dome-shaped bright field magnifiers (Figure 1A-B), which rest against the page but provide low magnification and require presbyopes to wear reading spectacles; (ii) hand-held and stand magnifiers (Figure 1C), which are held just above the object of interest, may incorporate a light source and are available in higher ampliations (generally, up to 39 D); and (iii) microscopes (Figure 1D), which are spectacle-mounted, have a wider field of view than magnifiers and allow both hands to remain free. However, as the magnification of these devices increases, the field of view gets smaller; thus, the lowest magnification consistent with best vision should be preferred.

Electronic magnifiers offer a high and variable amount of magnification over a relatively large field of view, and the contrast, color and brightness of the observed text can be manipulated to suit the observer. Conventional desktop closed circuit television systems (CCTV) (Figure 1E) consist of a camera mounted above a moveable table, whilst a screen displays an enlarged image of whatever is placed on the table. There are also hand-held CCTV systems (Figure 1F) which exploit new developments in screen and battery technology to provide portable magnification in systems aesthetically pleasing. However, these often work poorly on non-flat surfaces (e.g., a price tag on a supermarket shelf) and are usually expensive.

Be it an optical or an electronic device, there are several methods to calculate the magnification a patient requires, such as that validated by Lovie-Kitchin and Whittaker. [5] Briefly, this method considers the visual reserve and the execution goal (reading speed and print size). As a rule of thumb, the magnification required can be calculated by multiplying near VA (in Metric notation) by 4 D. Furthermore, required magnification and achievable reading rate for STGD patients can be informed from morpho-functional parameters from optical coherence tomography (OCT) and microperimetry testing. [11]

Patients with central scotoma often develop eccentric fixation. Eccentric viewing (EV) refers to the technique of extra-foveal fixation; due to the lower density of photoreceptor cells and higher photoreceptor:ganglion cell ratio than in the fovea, the spatial resolution is far less, but an obstructed view of the scene is possible. Reading ability with EV can be optimized by establishing a preferred retinal locus (PRL),[12] training eye movements (e.g., saccade and refixation),[13] and enhancing the 'perceptual span' within one fixation.[14] EV training was shown to double the reading

speed of low vision patients with central scotoma, despite no objective improvements in VA were observed.[15] A small randomized clinical trial (RCT) suggested that both rapid serial visual presentation (RSVP) and sensomotoric training (SM) are effective training methods in exploiting EV to improve the reading performance of patients with STGD.[16] However, EV should not be encouraged when some form of foveal function still exists.

Besides reducing reading speed, the central scotoma can interfere with many activities performed at intermediate-to-far viewing distances, such as watching television, going to a football match or recognizing faces or signs on the street. Besides some of the measures outlined above and other simple measures (e.g., changing the viewing distance to the television), telescopic magnifiers are available and may be helpful. Keplerian telescopes (KT) (Figure 1G) have a weak positive objective lens a strong positive eyepiece lens that are separated by the sum of their focal lengths, while Galilean telescopes (GT) (Figure 1H) have a weak positive objective lens and a strong negative eyepiece lens that are separated by the difference of their focal lengths.[17] These improve VA by increasing the angular magnification subtended by objects in the retina. KTs are lightweight devices usually worn around the neck and held in front of the preferred eye for spot-reading tasks (e.g., looking at airport departure boards), while GTs can be spectacle-mounted and used for prolonged tasks (e.g., watching television). Head-mounted electronic magnifiers have also been available for some years but remain unpopular due to their cost, weight and cosmetic appearance. However, telescopic devices cannot be used when walking due to their effect on the vestibulo-ocular reflex; small head or body movements are magnified such that they appear much larger, severely affecting balance.

On the other hand, the implications of peripheral dystrophies, such as Retinitis Pigmentosa (RP) and related syndromes (e.g., Usher syndrome), at least initially, can be markedly different from those discussed above. RP is among the most common causes of low vision in some series,[18] and these patients mainly complain of (i) peripheral visual field loss, leading to difficulty in spatial navigation and mobility, and (ii) debilitating glare and extreme photophobia. Thus, several aspects of the VR strategy will also differ.

First, VA must be tested at an appropriate distance not to overwhelm the field of view; RP patients have difficulty seeing a large object at near. Accordingly, only the minimal magnification required should be provided, because it will further constrict the field of view. The use of magnification devices should be delayed to later stages of the disease.

Figure 1 *Optical, nonoptical and electronic low vision aids (LVAs) available for visual rehabilitation of patients with retinal dystrophies. These include: use of reading stand and appropriate lighting (A); bright-field magnifiers (B); hand-held magnifiers with incorporated light sources (C); spectacle-mounted microscopes (D); desktop closed circuit television systems (CCTVs) (E); hand-held CCTVs (F); Keplerian telescopes (G); Galilean telescopes (H); and tinted lenses (I).*

For visual field expansion, the use of spectacle-mounted prisms, such as Peli's prism glasses, was more common in the past. The overall purpose of prism use is to pick up images which would fall within impaired regions of the retina and direct them into the still-functioning part of the visual field. Although, these were shown to effectively expand the functional visual field and to improve spatial orientation in patients with RP,[19] prisms are often very difficult for patients to adapt to and impracticable to wear.

Additionally, (i) also target image minification using reversed telescopes,[20] negative lenses,[21] and amorphic lenses[22] may be useful for visual field expansion; (ii) night vision devices [23] may improve nyctalopia; and (iii) orientation and mobility training (OMT) can improve functional spatial navigation. For glare control, tinted lenses that absorb wavelengths towards the blue end of the visual spectrum can be helpful; although these filters have been argued to protect against phototoxic damage to the retinal pigment epithelium and photoreceptors, this remains controversial.

In summary, there are ample resources available that can be adapted and customized to improve the visual performance of patients with retinal dystrophies. VR requires a multidisciplinary approach, which can include provision and training of LVAs, contrast enhancement techniques, lighting modifications, EV training, OMT, training for employment and assistance with activities of daily living. Furthermore, it is of utmost importance to be aware that, because of sight loss, these patients often fear ostracism, are susceptible to harassment and suicidal ideation; thus, psychological support and counselling may also be warranted.

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GENE THERAPY IN INHERITED RETINAL DYSTROPHIES

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Inherited retinal dystrophies (IRDs) comprise a clinically and genetically heterogeneous group of hereditary retinal degenerations, which affect around 1 in 3000 people worldwide and are caused by mutations in any one of more than 220 different genes. IRDs may occur both in syndromic and non-syndromic forms, and can be inherited in all the Mendelian inheritance patterns. Since they are monogenic conditions, gene replacement or silencing have gained more and more interest as potential therapies[1,2] and gene therapy research is currently being investigated in retinitis pigmentosa (RP), Stargardt disease, Leber congenital amaurosis (LCA), Usher syndrome, Best macular dystrophy, X-linked retinoschisis, achromatopsia and Choroideremia (see therapy in respective chapters).

But what exactly is gene therapy? How does it work and why use it in the eye? Gene therapy consists in introducing genetic material into cells to compensate for abnormal genes or to produce a helpful protein, by inactivating or replacing the mutated gene with a healthy copy. For a gene to be delivered to a cell, it has to be carried by a vector. As the vector releases the healthy human gene in the target cell, a functional protein is generated, restoring the target cell to a normal state. If the target cell is of germline (egg or sperm) kind, therapeutic effect is offered to all cells who inherit the target gene. This may give the opportunity of eradicating a disease from an entire family, which raises much controversy, and is currently prohibited in the European Union. If the target cell is of somatic kind, gene therapy affect only the targeted cells in that patient, and cannot be passed on to future generations. However, the effects of somatic cell therapy are usually transient (as cells die and are replaced by new ones), requiring repeated treatments to keep the therapeutic outcome over patient's life. The eye is a great organ for gene therapy as it is easily accessible, small and enclosed, which enables the need of only small amounts of vector to act, minimizing toxicity risks. Tight junctions between retinal pigment epithelial (RPE) cells and blood-retina barrier are responsible for its unique immunological properties, which limits adverse systemic effects of local treatments. Moreover, as these diseases are bilateral, it is possible to compare the effects of gene therapy in one eye to the normal disease progression in the other. There are many animal models available for retinal dystrophies, which make preclinical assessment of therapy efficacy easier to follow[1,2].

Gene therapy can be performed in two ways: *ex vivo*, where some cells are removed from the patient, genetically modified outside the body and then returned to the patient body; *in vivo*, where genes are genetically modified in cells still in the body[1,2].

Two kinds of vectors have been used: viral and non viral[1-9]. As viruses infect cells, viruses used in gene therapy are manipulated to be able to carry and deliver normal human genes to target human cells, like photoreceptor cells and RPE cells. Although viruses are modified to make them safer, gene therapy has still some risks. Viral vectors can be retroviruses, adenoviruses and, the most promising and frequently used, adeno-associated viruses. Retroviruses have two single-stranded RNAs. Among the retroviral family, lentivirus is the most commonly used as vector, as its intraocular administration does not generate an immune response and it has packaging capacity of 8 kilobases (kb), which enables it to carry multiple therapeutic proteins. Nevertheless, since it is not possible to predict the target cell genome location where retroviruses will insert its genetic material, it can lead to mutations in target cells and even to uncontrolled cell division (like cancer). There has been an effort to fight against this issue, by using zinc finger nucleases or by including specific sequences to try to direct the integration site to determined chromosomal locations. Adenoviruses have linear double-stranded DNA. Since their DNA is not integrated into the target cell's genome, they do not lead to mutations in target cells. They have packaging capacity of more than 8 kb. An adeno-associated virus consists of a parvovirus assisted by an adenovirus. It does not seem to have pathogenicity and does not generate an immune response, but its packaging capacity is only 4.7 kb. The only approved gene therapy in Ophthalmology – Voretigene neparvovec (Luxturna®) – uses an adeno-associated virus. Non-viral vectors (like liposomes and DNA nanoparticles) are safer and have more vector capacity than viral vectors (packing capacity of DNA nanoparticles is 20 kb). However, they have lower gene transfer efficiency for retinal cells, which may require repeated injections.

Intraocular vector administration can usually be done by intravitreal or subretinal injections[1,2,6-10]. In an intravitreal administration, the vector is released in the vitreous and it has to diffuse through the internal retina to get to photoreceptor cells and RPE cells. Due to the different barriers it has to cross, the amount of vector delivered to outer retina is limited. This kind of administration seems to be adequate in inner retina dystrophies (as X-linked Retinoschisis) and in ganglion cell diseases (as Leber hereditary optic neuropathy). In subretinal administration, a vitrectomy is performed and the vector is injected with a subretinal cannula in a "bleb", which is a small pocket of retinal detachment (between the RPE and the neuroretina). As the vector is released closer to photoreceptor cells and to RPE cells in the outer retina (the target cells for the treatment of most retinal dystrophies), this kind of administration seems to be more efficient for outer retinal, RPE and choroid diseases.

After the landmark publication in the Lancet of the 3-year results of efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy[11], the Food and Drug Administration (FDA) approved voretigene neparvovec (Luxturna®, Spark Therapeutics Inc.) for the treatment of LCA/ar-RP patients with confirmed biallelic *RPE65* mutations and sufficient viable retinal cells in December 2017. Novartis has the license to commercialise Luxturna® outside the USA and in November 2018, the product has been granted drug marketing authorisation approval from the European Medicines Agency (EMA). This represents

a first-of-its-kind breakthrough that will hopefully lay the groundwork for the development of gene therapies for other genes and other conditions that are not adequately addressed today. A large number of genes and loci have been identified and can be accessed at RetNet[15], predicting future opportunities for treatment.

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GENE/GENOME EDITING TECHNIQUES: INTRODUCING CRISPR

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1. Introduction

For many years retinal degenerative diseases, whether inherited or acquired have been one of the major causes of vision loss. From retinitis pigmentosa to acquired macular degeneration several treatments, including different drugs, macular transposition surgery and gene therapy have been investigated.

In recent years, the development of genome editing tools experienced an explosive growth with the discovery of a group of different techniques used to modify the genome of a cell or organism. It involves the introduction of an engineered nuclease leading to the generation of a double strand break (DSB) at a desired location on the genome. This process is followed by an endogenous DNA repair through non-homologous end joining (NHEJ) or homologous recombination (HR). During NHEJ, insertion or deletion of random nucleotides can be introduced into the DSB site, which usually causes a reading frame-shift if the DSB is located in a coding sequence. Therefore, NHEJ although efficient for DNA repair in quiescent cells, is error-prone and often utilized to conduct gene disruption (or gene knock-out). In contrast, the repair of DSBs by HR involves the copying of DNA from a homologous template, is error-free, but far less efficient and only occurs in late S phase or G2 phase of the cell cycle. Precise genome modification can be achieved by the HR pathway if a DNA template with homology arms is introduced to the cell together with the engineered nuclease, a process called homology directed repair (HDR). Thus far, four types of engineered nucleases have been developed, namely meganucleases, zinc-finger nucleases (ZFNs), transcription activator like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas nucleases. Unlike the others, the newly discovered CRISPR-Cas9 endonuclease is guided by an RNA of 20 nucleotides that recognizes the target DNA via Watson-Crick base paring. Because of the simplicity of its design, CRISPR/Cas9 has become the most popular genome editing tool and has been applied for a variety of research purposes including disease modeling, genetic screening, epigenome editing, cell labeling, and gene therapy.[1] CRISPR/Cas systems are categorized into three major types (I, II and III), but the type II is the most widely used. The Cas9 endonuclease

gene, either alone, or together with the small guide RNA (sgRNA) expression cassette, is small enough to be packed into one or two adeno-associated viral (AAV) vectors that are capable of transducing retinal cells efficiently. In this regard, *in vivo* application of CRISPR/Cas9 genome editing in the retina, though only at its infant stage, represents a significant step forward in developing new treatments for retinal diseases.

2. Delivery of CRISPR components and present challenges

As the CRISPR components originate from prokaryotic cells, their expression may cause cytotoxicity and trigger immune responses in mammalians with tissue or organ damage. However, CRISPR applications in the retina might be able to avoid the pre-existing immune responses if subretinal vector administration is used, as the subretinal space is segregated from the blood circulation[1].

Another confounding issue is the possibility for cleavage at other sites that may share similar sequence to the targeted locus. These off-target sites pose serious consequences since they may introduce mutations in unintended locations of the genome such as inactivating a tumor suppressor gene[2].

Both viral and non-viral methods have been used for the delivery of CRISPR components to the retina. Adeno-associated viral (AAV) vectors have been the most efficient for *in vivo* gene delivery to the retina. The most commonly used Cas9 nuclease is *Streptococcus pyogenes* Cas 9 (SpCas9), and its coding sequence approaches the packaging limit of an AAV vector, therefore a dual vector system is usually employed, one for the SpCas9 and another for the single-guide RNA (sgRNA). Subretinal injection has been the most successful approach since the AAV vector is delivered closer to retinal cells, especially the photoreceptors. However several studies have presented promising results using intravitreal injections, even though the vector system needs to go through a series of membranes and spaces throughout the posterior hyaloid and whole retina.

Genome editing can be attempted in photoreceptors, bipolar cells, Müller cells and amacrine cells. However, in animal studies efficiency can only be achieved when electroporation is performed on newborn specimens in which retinal cells are in mitotic phase. This creates a problem in human studies as most retinal diseases are usually diagnosed when retinal cells are in the post-mitotic stage.

Finally it is desirable that CRISPR components are no longer effective once they have fulfilled their task of generating a DSB[3].

In this way several problems arise from the recent gene editing techniques discovered including cytotoxicity, off-target responses, the accessibility of cells to the viral vectors, the fact that most cells in the human body are not in mitotic phase, and the immune response that our organism can mount against these treatments. Presently, these are the major concerns for the *in vivo* application of CRISPR technology.

Scientists have tried to minimize off-target effects engineering nucleases that are more target specific; encountering ways of disrupting and repairing DNA that are effective even in somatic cells

that are not in mitotic phase; delivering the vectors as close as possible to the cell and in tissues with immune privilege.

3. Therapeutic Applications and Future Perspectives

The unique anatomy of the eye and its physiological and anatomical barriers make it an immune privileged site in the human body providing a quite favorable environment in which to apply gene therapy. Inherited ocular diseases affect millions of people worldwide and have an enormous socio-economic impact. Unfortunately, the majority of these conditions are as yet currently untreatable. In this way, the eye is an ideal target for early clinical trials using CRISPR technology. Inherited retinal disorders are mostly caused by a mutation in one or more genes. Several techniques of gene disruption have been attempted for dominant diseases and gene augmentation for recessive diseases with some success, but precise gene repair by genome editing would definitely be more successful and long-lasting and therefore more attractive. Gene intervention could also modulate the disease pathways of multifactorial retinal diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and glaucoma.

Retinitis Pigmentosa

Bakondi et al used CRISPR to knock out mutant rhodopsin gene in rodent models. Disruption of the murine allele prevented retinal degeneration and improved visual function[4]. Latella et al significantly reduced the amount of mutant RHO protein with CRISPR delivery by electroporation, however the sgRNAs were not mutant-specific[5]. Giannelli et al after extensive testing of different Cas 9 variants, and using an improved version of SpCas9, managed to efficiently knock-out only the mutant allele thanks to a single mismatch to the wild-type allele in the sgRNA[6].

Leber Congenital Amaurosis

Ruan et al showed that a pair of sgRNAs coupled with SpCas9 were highly efficient at removing the mutation and restoring the expression of wild-type CEP290[7].

AMD, Diabetic Retinopathy and Glaucoma

To obviate the problem of repetitive frequent anti-VEGF administration to control neovascularization in AMD and DR, two studies reported the disruption of the mouse VEGFA in RPE cells using either AAV9 or RNP–mediated delivery of Cas9. Both systems induce indels at 20-30% of RPE cells resulting in reduced area of coroidal neovascularization[8,9]. In other studies CRISPR-mediated depletion of VEGF receptor 2 in vascular endothelial cells by intravitreal delivery of AAV vectors abrogated angiogenesis[10]. Jain et al used CRISPR to knock down Myocilin in primary open-angle glaucoma cases with a gain of function mutation, and in a transgenic mouse model the expression of the mutant protein in the trabecular meshwork was reduced, resulting in alleviated stress, partial correction of the intraocular pressure phenotype and improved ganglion cell function[11].

4. Conclusions

Given that the eye is an ideal target for early clinical trials using CRISPR/Cas, it is imperative that the ophthalmic community has a firm appreciation of these issues. Retinal diseases are likely to be one of the earliest targets of CRISPR/Cas9 therapy. *In vivo* studies show promising results but there is still a long way to go. Moral and ethical considerations will be particularly pertinent during translation into human trials.

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RETINAL IMPLANT TECHNOLOGY

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1. Introduction

Outer retinal degenerations caused by primary and secondary loss of photoreceptor cells are accountable for most causes of untreatable blindness in developed countries. Amongst these are age-related macular degeneration (AMD) and retinitis pigmentosa (RP). Indeed, RP has become the most common cause of untreatable blindness in people at working age in the United Kingdom[1]. This has led to increasing interest in finding therapeutic approaches for these disorders, including gene therapy, electronic retinal implants, and stem cell therapy.

In RP, there is loss of photoreceptor cells and collapse of the outer nuclear layer, and eventually retinal ganglion cell (RGC) loss [2]. However, in end-stage RP there is partial preservation of RGCs, bipolar cells, and other inner retinal cells, which has led to the suggestion that at least some visual signal might be transmitted by the RGCs should there be some sort of photoreceptor replacement or "photoreceptor cell bypassing" [3,4]. This was the rationale for the development of electronic retinal implants (RI), implantable devices designed to supplant phototransduction by bypassing the defective photoreceptor cells.

Neurobionics is the direct interfacing of electronic devices with the nervous system, and has played an increasingly greater role in the treatment of several diseases, including epilepsy, chronic pain, psychiatric disorders, movement disorders, and neural deafness [5]. Specifically in Ophthalmology, neurobionics has been an area of intense research in order to restore vision.

Retinal implants are classified on the basis of two criteria [6]:

1. Position relative to the retina: two types of RI gave been proposed: sub-retinal (SRI) and epi-retinal implants (ERI). SRI are positioned behind the retina, whereas ERI are directly in contact with the ganglion cell layer. More recently, a suprachoroidal device has been developed and has been implanted in human subjects [5];
2. Functional principle: based on this criterion, RI have been classified as micro-photodiode arrays (MPDA) or micro-electrode arrays (MEA); MEAs have met greater clinical and research interest. MEA-based devices consist of an implanted electrode array chip connected to a multichannel stimulator. Images are collected by a digital camera and

processed by an image-processing unit, which will generate a stimulation pattern that is wirelessly transmitted to the chip.

Currently there are three devices which have received the EU CE mark: the Argus II Retinal Prosthesis System, the IRIS 2 and the Alpha-AMS.

2. Argus II Retinal Prosthesis System

The Argus II Retinal Prosthesis System (Second Sight Medical Product, Inc., Sylmar, CA, USA) is a surgically implantable device designed to provide visual perception in patients with outer retinal degenerations such as RP[7,8]. The Argus-II is the most widely used RI, having received the EU CE mark in 2011 and US FDA approval in 2013 for the visual improvement of patients with severe to profound RP. Over 300 Argus-II devices have been implanted worldwide, mostly in patients with RP and to a lesser extent in patients with choroideremia and geographic atrophy from AMD [9,10]. It is a ERI, MEA-based device consisting of an implantable 60- platinum electrode array with a 575 μm spacing (center-to-center) embedded in a thin film of polyimide, and a receiver coil using an external video-processing unit that converts optical data captured from an eye-glass mounted video camera into electrical signals [7].

Ideal candidates for treatment are those with outer retinal degenerative diseases with at least partially preserved inner retinal layers (bipolar cells, RGCs, horizontal cells, and amacrine cells). Patients should be older than 25 years old and have bilateral, profound vision impairment (bare light or no light perception, NLP).

Potential candidates for the Argus-II implant must undergo comprehensive clinical ophthalmic examination, including assessment of visual function, anterior segment examination, and posterior segment examination. Adjunctive testing is recommended, including wide-field fundus photography, optical coherence tomography (OCT), ocular ultrasonography (A- and B- scan), ocular biometry for determination of axial globe length. If the patient has NLP, ocular electrophysiology tests are indicated to assess optic nerve and inner retina functions. If dark-adapted flash test and visual evoked potentials (VEP) are negative, the patient should not be considered for surgery[7, 9-11]. Finally, potential candidates for surgery must undergo systemic evaluation for general anesthaesia, as well as psychological counseling. [9]

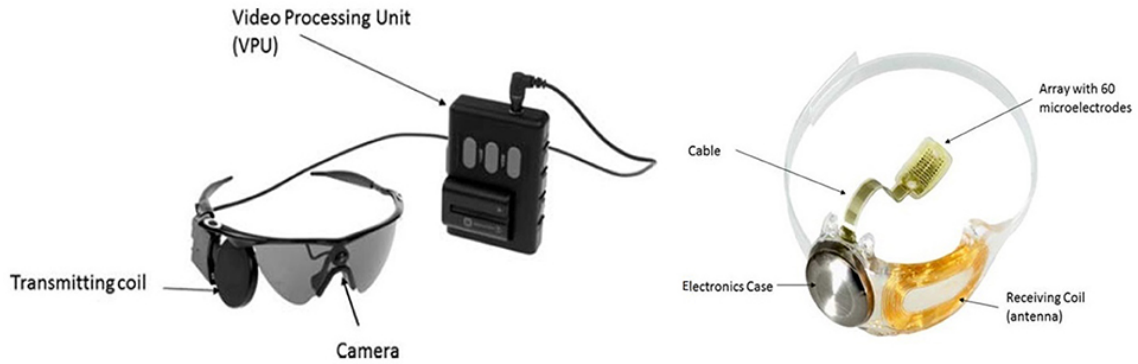

Figure 1 *Argus II retinal implant. It includes a receiver, electronics, and an electrode array that are surgically implanted in and around the eye. The array has 60 electrodes arranged in a rectangular grid, of which 55 are enabled. It is attached to the retina over the macula with a retinal tack. The external equipment includes glasses, a video processing unit (VPU) and a cable.*

Surgical technique

The Argus-II is implanted in the worst-seeing eye of the patient, under general anesthaesia. If the patient is phakic, lens surgery (cataract extraction or lensectomy) is performed first. Next, an inferonasal relaxing incision and a 360º conjunctival peritomy is performed, and the four recti muscles are isolated with silk sutures. The encircling band is threaded under the recti muscles and held with a Watzke's sleeve, much like a scleral buckling procedure. The electronic case is then positioned in the superotemporal quadrants, its location based on axial length measurements. Next, a standard pars plana vitrectomy is performed, with particular attention to shaving of the superotemporal vitreous base where the cable will pass. The array is then inserted through a 5.2-mm superotemporal sclerotomy, positioned and secured in the center of the macula (retina-choroid-sclera) using a retinal tack. The sclerotomies are finally sealed. [7,10] Patients are given steroid and antibiotic eye drops and are kept under close, regular postoperative clinical follow-up schedules[7.]

Outcomes of the Argus-II implant

The Argus-II has shown to increase patient's ability to recognize characters or short words, to perform activities of daily living, and to succeed in orientation and mobility tasks. The largest clinical trial conducted to date sought to assess the safety and efficacy profile of the Argus II implant (n=30). The long term studies at 3- and 5-year assessments found that implanted patients performed tasks requiring vision significantly better when the system was "on" than when it was "off" [12-13].

Surgery-related adverse events include conjunctival erosion, hypotony, endophthalmitis, and retinal detachments [11]. A multicenter, prospective clinical trial was conducted (n=30) and found that at 3 years post-implantation, 29/30 patients remained implanted, and that 11/30 experienced a total of 23 serious surgery or device-related adverse events [12]. The 5-year extension study found that 24/30

patients remained implanted with only one additional complication [13]. These findings support the long term safety profile of the procedure/implant.

Patient motivation and adherence to visual rehabilitation play a major role in the success of this implant. Potential candidates must be highly motivated and comply with visual rehabilitation programmes that seek to optimize the visual benefits [14].

The Argus-II implant was shown to be a cost-effective device to treat RP patients comparing to the usual care in RP, even accounting for the high initial cost of this treatment [15]. It fell below the societal willingness to pay in most EU countries, and with significant health gain in terms of QALYs at an affordable cost in the Eurozone [15].

3. Alpha-IMS Retinal Implant

The Alpha-IMS (Retina Implant AGy, GmbH, Germany) is a SRI developed by Zrenner *et al.* in Germany. This RI consists of a light-capturing part composed of a complementary metal-oxide semiconductor camera-like chip with 1500 pixels, embedded in a polyimide band; a photodiode which acts like the outer segment of photoreceptor cells; and an electrode which stimulates the overlying retina, acting like the photoreceptor synapse with the inner retina. The major difference between Alpha-IMS and the Argus-II implant is that whilst the latter uses a camera with an image processor to convert the image into electrical stimuli, the former directly senses intraocular light and then converts it to electrical energy to control the intensity of the stimulation [8].

Surgical technique

Implantation of the Alpha-IMS involves an extraocular and an intraocular component [8,16]. The procedure is performed under general anesthaesia. The extraocular component comprises the creation of a subperiosteal tunnel from the infraorbital region extending to the retroauricular area, through which a cable is directed from the SRI to a coil positioned externally behind the ear. A tunnel is then prepared from the conjunctival space in the upper temporal quadrant to the skin incision at the orbital rim; the SRI is then pulled through this tunnel. The intraocular procedure involves the creation of a superior temporal quadrant scleral flap, vitrectomy, elevation of the retina, and then insertion of the implant through the choroid into de sub-retinal, subfoveal space; the globe is then closed, and silicone oil tamponade is performed.

Outcomes of the Alpha-IMS /AMS retinal implants

A multicenter trial was conducted to assess the efficacy and safety profile of the Alpha-IMS implant (n=29) in patients with RP and patients with cone-rod dystrophy [17]. 72% of patients reached the primary endpoint of a significant improvement in activities of daily living; 86% of patients had some sort of improvement in visual acuity; although the theoretical potential to reach 6/75 visual acuity, the maximum visual acuity achieved was 6/160 [17].

The major limitation of Alpha-IMS was its short-life. Most implants began to fail at 12-month follow-up [8]; Although theoretical visual resolution with the Alpha-IMS has been said to be superior to the Argus-II implant, real-world differences have been found to be marginal [8].

4. IRIS®II

The Intelligent Retinal Implants System (IRIS®II, Pixium Vision SA, Paris) is an ERI currently CE-approved for the treatment of retinal dystrophies (Figure 2). It is a bionic vision system composed of three components: an epiretinal implant attached to a built-in wireless receiver; a camera and transmitter unit built into a pair of glasses; and a pocket computer for optimization of visual signals [18]. There is an ongoing clinical trial which will evaluate the 36-month safety and effectiveness of the IRIS II implant in patients with RP, cone-rod dystrophy, and choroideremia [19]. The 6-month interim results have found that light perception was confirmed in all patients, improvement in visually-related tasks, and a good safety profile (0.4 adverse events per patient) [20].

5. Future Perspectives

The Argus-II is the RI which has gathered most clinical experience and best clinical results to date. However, there are an increasing number of RIs currently under intense research, including the EPIRET3 System (EPI-RET Project Group, Germany), the Boston Retinal Implant, and the Bionic Vision Australia Suprachoroidal Retinal prosthesis [5,8].

The previously mentioned RIs require coils to deliver energy and signals via intraocular cables to the implantable electrode array (photoelectric). This limits the number of electrodes that can be addressed and requires complex surgical techniques. To overcome these limitations, newer technologies have emerged. The PRIMA implant (Pixium Vision SA, Paris) is a wireless SRI (Figure 3). Is it composed of a 2x2 mm wide, 30 microns thick photovoltaic chip containing 378 electrodes which is powered by pulsed near-infrared light projected from augmented reality glasses, along with a mini-camera [21].

The PRIMA Feasibility study is a clinical trial is currently being conducted in the US and in Europe to assess the safety and outcomes of the PRIMA implant in patients with atrophic dry AMD [21].

Figure 2 *The IRIS®II retinal implant is an epi-retinal implant (attached on the surface of the retina) with 150 electrodes. It has a bioinspired camera sensor and was designed for explantability.*

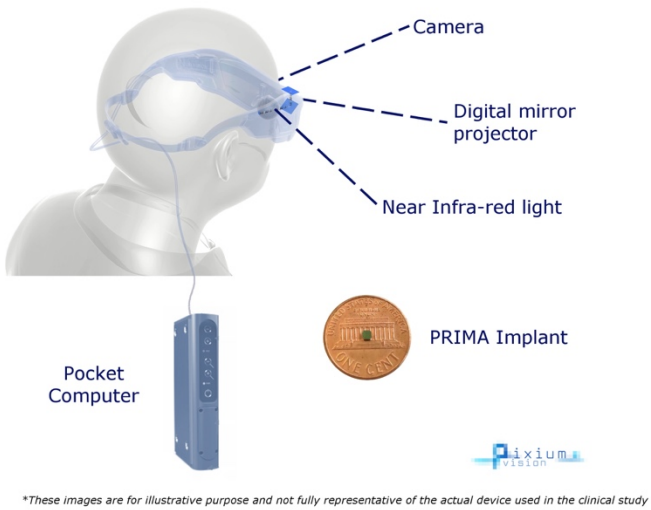

Figure 3 *The PRIMA retinal implant is a tiny wireless photovoltaic implant of 2x2 mm and 30µ thick, comprising 378 electrodes, each with its own local return circuit potentially enabling higher resolution. Physiological signal processing from sub-retinal space, directly replaces the degenerated photoreceptors. It is shorter, thus less invasive than the epi-retinal IRIS®*

6. Conclusion

RIs have shown favorable results with a good safety profile in patients with outer retinal degenerative diseases, rendering them a promising approach to visual restoration in these patients, particularly in patients with RP given their long life expectancy. Important limitations that must be overcome include longer lifetime of the RIs, wider retinal area coverage of the implant, and cost. Interestingly however, a currently available RI has already shown to be cost-effective compared to usual care in patients with RP despite its cost. These findings highlight the clinical and socio-economic importance of clinical research in the area of retinal prostheses.

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STEM CELL THERAPY IN RETINAL DYSTROPHIES

Maria Picoto, Ana Almeida, João Nascimento

1. Introduction

Stem cell transplant studies aiming to restore visual function and improve the natural history of several retinal degenerative diseases have gained momentum, representing a novel class of potential therapies. [1,2] While some early-phase trials of cell therapies suggest acceptable safety profiles, others have been linked to severe blinding complications. As of now, there is no Food and Drug Administration (FDA) approved stem cell therapies for retinal disease.[1]

Stem cells are precursor, undifferentiated, immature cells that are able to self-renew and differentiate into more mature and specialized cell types, such as retinal cells.[1, 2] They have also the potential to repair tissue and restore function after injury.[2]

The 3 main types of stem cells used in retina studies are: human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), and adult stem cells.[1, 2] Stem cells can also be categorized in: pluripotent (PSCs), fetal and postnatal (adult) stem cells.[1] PSCs have the capacity to self renew indefinitely and to differentiate into any cell type belonging to the three germ layers and include hESCs and hiPSCs.[1] Both can be converted to neural retinal or EPR cells.

hESCs are pluripotent cells cultivated from the inner cell mass of early embryo at the late blastocyst stage (Figure 1). In 2009, the FDA approved the first hESC clinical trial for spinal cord injury. In 2010, a phase I/II clinical trial to treat Stargardt disease was approved followed by a phase I/II clinical trial to treat advanced dry age-related macular degeneration in 2011.[3]

hiPSCs are also pluripotent stem cells, similar to hESCs in appearance and behavior, but are generated from differentiated reprogrammed adult somatic tissues. The creation of hiPSCs may enable the production of grafts that are autologous or donor-matched (HLA-typed). The major benefit of this strategy is that autologous iPSC-derived RPE theoretically induce smaller immunogenic response than allogeneic PSC-derived RPE, with less risk of rejection or need for imunosupression. [1,2] However, due to their abnormal genetic composition, some iPSCs may trigger the T cell-mediated immune response and both iPSCs and ESCs can give rise to an increased risk of tumor formation, by stimulation of X-linked oncogenes, suppression of tumor suppressor genes, and due to the high in vitro growth rate.[2]

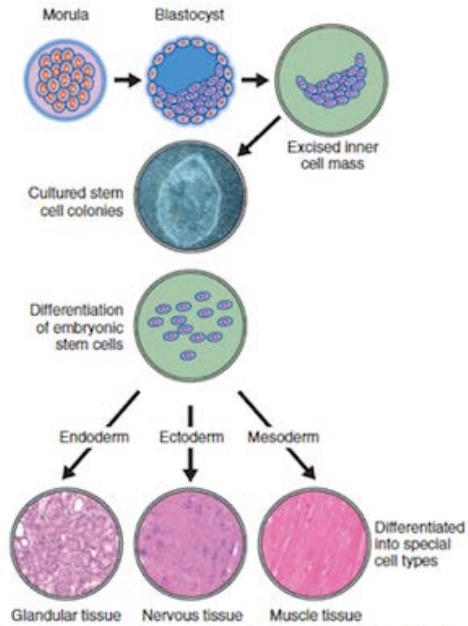

Figure 1 *Culture of human embryonic stem cells and their differentiation*[3]

Adult stem cells are non-pluripotent post-natal cells that can generate the cell types comprising the organs from witch they originate.[2] These cells presumably represent a pool of progenitor, quiescent and undifferentiated cells, that under appropriate stimuli will divide and differentiate into the cell type of the tissue in which they reside, repairing them following injury and if appropriately stimulated, differentiating into other cell types.

There are four basic populations of retina cells that may contain dormant progenitor cells and have therapeutic application: (1) Retinal stem cells that can give rise to photoreceptors and other retinal neurons; (2) Müller glial stem cells that can differentiate into retinal neurons; (3) RPE stem cells that can replace diseased RPE and perhaps be stimulated to differentiate into photoreceptors; and (4) endothelial progenitor cells (EPC) that can contribute to the retinal vasculature and exert a neurotrophic effect. Müller glial cells, RPE stem cells and adult bone marrow-derived hematopoietic stem cells containing EPCs have great therapeutic potential.

Stem cells can be delivered to the retina trough intravitreous injection (IVT), vitrectomy with subretinal transplantation and "external" subretinal delivery across the sclera and choroid (Figure 2). [2]

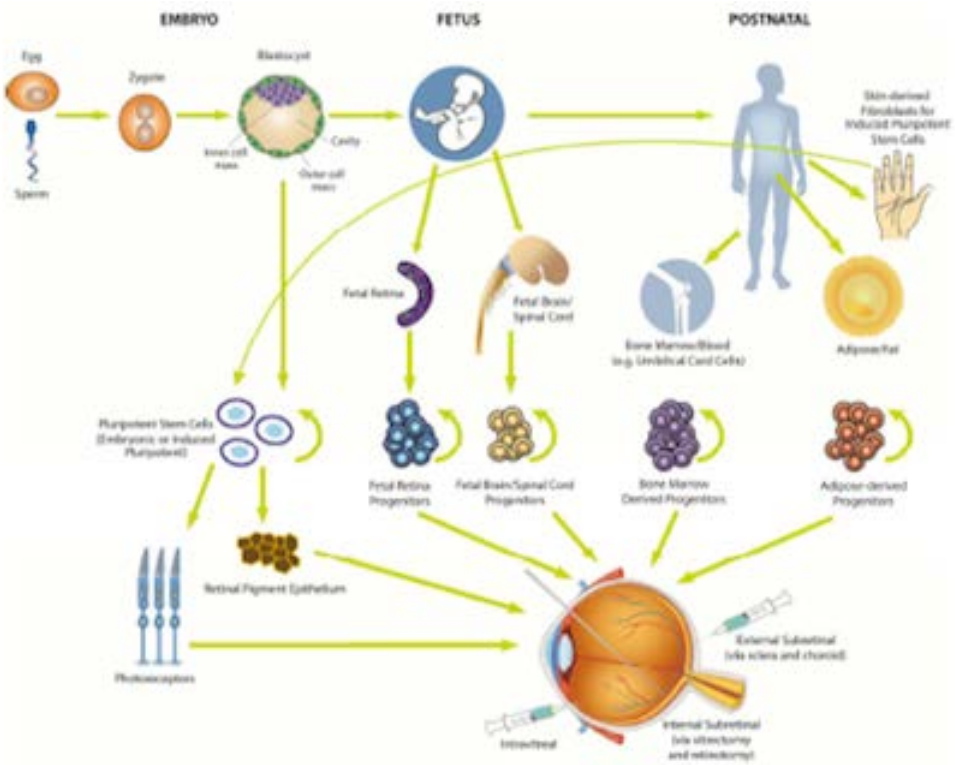

Figure 2 *Sources of stem/progenitor cells and their delivery to the retina*[1]

2. Research Findings and Trends

The eye is an ideal target choice for initial stem cell therapy due to easy accessibility, immune privilege and the ability to use noninvasive methods for structural engraftment and monitor functional outcome.

Most stem cell-based interventions for the retina do not seek to replace dying cells, but rather to indirectly promote survival of the host's retinal cells through "trophic" effects. To date, only stem cell trials involving the use of PSCs differentiated to RPE transplanted subretinally are being tested with the aim of replacing dying cells in eyes with AMD, Stargardt disease or myopic degeneration.[1]

2.1. Studies on the use of Embrionic Stem Cells

The first study to report the safety of stem cell application (hESC-RPE) in degenerative retinal diseases was a phase I/II clinical trial that enrolled 9 AMD and 9 Stargardt macular dystrophy patients. None of the patients had an adverse intraocular or systemic event. The anatomical and functional results were encouraging, with more than half of treated patients experiencing sustained improvements in visual acuity and demonstrating evidence of possible cellular engraftment. However, some patients had adverse events related to the surgery or the immunosuppressive regimen. The lack of a masked control group, advanced disease at baseline, small cohort, difficult

to correlate functional improvements without clear anatomic changes and use of solid organ transplant-dose immunosuppressive regimens hindered conclusions. Future studies must include microperimetry, OCT and autofluorescence enabling more rigorous structure-function correlations and attempt to minimize/abolish immunosuppression. [4, 5]

Another report [6] supported the safety of ESC-derived RPE cells applied to the subretinal space in 2 cases of dry AMD and 2 cases of Stargardt macular dystrophy. At 1-year follow-up, no adverse side effects were observed. Visual acuity improved in 3 patients and remained stable in the other.

Mehat *et al*, [7] submitted 12 patients with advanced Stargardt disease to subretinal transplantation of hESC-derived RPE cells. No evidence of uncontrolled proliferation or inflammatory responses was found. Borderline improvements in VA in 4 participants either were unsustained or matched by a similar improvement in the untreated contralateral eye. Microperimetry demonstrated no evidence of benefit at 12 months. Participants reported no significant change in quality of life. Focal areas of subretinal hyperpigmentation developed in all participants in the recipient retina and persisted after withdrawal of immunosuppression, consistent with the survival of viable transplanted hESC-derived RPE cells, but may also reflect released pigment in their absence.

2.2. Studies on the use of Induced Pluripotent Stem Cells

In 2014 a study investigated autologous use of iPSCs in a woman with exudative AMD. Epithelial cells collected from the patient were transformed into RPE cells in vitro and transplanted subretinally. The study was discontinued in 2015 because the iPSCs did not pass a genomic validation step in the second patient. The trial resumed in 2016, although the iPSCs were not autologous but banked from allogeneic cell lines. In 2017, the researchers reported that the transplanted sheet remained intact in the first patient 1 year after surgery and VA had not declined.[8]

These trials have raised important caveats about the autologous iPSC strategy, as the immense costs in ensuring mutation-free reprogramming to iPSCs will preclude this approach from being scaled up to large trials. [9]Also, using iPSCs developed from a donor do not offer an exact genetic match, raising the prospect of immune rejection.

2.3. Studies on the Use of Adult Stem Cells

Huang et al. reported that Mesenchymal Stem Cells (MSCs) differentiated into RPE-like cells with similar morphological features and that they could replace damaged cells when applied to damaged retinas.[10] Castanheira et al., injected MSCs into the vitreous chamber in a model of laser-induced retinal damage. After 8 weeks, most of the MSCs had migrated to the ganglion cell layer and inner and outer nuclear layers, and expressed photoreceptor, bipolar cell, amacrine cell, and Müller glial cell markers.[11]

Recent preclinical and clinical trials suggest bone marrow-derived cells for the treatment of retinal degenerative diseases, through regenerative and trophic mechanisms.[12] In a prospective phase I study conducted by Siqueira et al, a single dose of IVT autologous bone marrow-derived

MSCs was applied to 3 patients with RP and 2 with cone-rod dystrophy. They reported no significant structural or functional impairment in 10 months of follow-up. Four of the patients had an increase of 1 row in BCVA at 1 week after injection and this increase was preserved in follow-up.[13] In the phase II trial, they demonstrated that MSCs had a positive effect on cystoid macular edema associated with RP.[14] In a continuation study, MSCs were applied IVT to 20 patients followed for 1 year. There was a statistically significant improvement in the patients' vision-related quality of life scores at 3 months, however this improvement disappeared over time.[15] Park et al. injected bone marrow-derived MSCs IVT into 6 eyes with irreversible vision loss. The treatment was well tolerated, with no intraocular inflammation or proliferation, and no decline in ERG and BCVA results after 6 months of follow-up. [16] In a recent study, evaluating the safety of a single IVT injection of autologous bone MSCs in patients with advanced RP, no adverse events were observed in eyes of 2 out of 3 patients. The patients reported improvements in light perception after 2 weeks, which lasted for 3 months. However, severe fibrous tissue proliferation was observed in the vitreous cavity and retrolental space of the third patient's eye, leading to tractional retinal detachment, iris neovascularization and development of a mature cataract. Injection of this patient's MSCs into the vitreous cavity of mice also resulted in fibrosis. Hence, a thorough evaluation of MSCs must be done in other to continue.[12]

Öner A., MD, presented at Euretina 2018, the 1-year results of a prospective case series of 14 patients with advanced stage RP who received subretinal adipose tissue derived MSC implantation. No systemic events were observed, and 8 patients had no ocular complications. One patient developed a choroidal neovascular membrane, which was treated with a single dose of anti-VEGF and 6 patients developed epiretinal membrane with localized peripheral tractional retinal detachment at the periphery. After 6 months, 1 of these patients developed mild band keratopathy and retrolental fibrous tissue was found at 12 months in another. To date, 4 patients have experienced visual acuity improvement. These findings offer some indication of mid-term safety of subretinal implantation of adipose tissue derived MSC but also highlight the potential ocular complications. [17] In fact, as MSC applications increase in number, so do reports of ocular complications related to this treatment. Kuriyan et al. described 3 patients in whom severe bilateral visual loss developed after IVT injections of autologous adipose tissue-derived "stem cells".[18] In another case report, autologous bone marrow-derived MSCs led to improved visual acuity in 2 of 3 patients with advanced RP; however, the other patient developed a total tractional retinal detachment and subsequently lost their vision within 3 months. [19]

The suprachoroidal application of adipose-derived MSCs described by Limoli et al. may prevent the vitreoretinal complications reported with IVT and subretinal applications. No complications were observed and visual function improved in 36 eyes of 25 patients with dry AMD at 6 months. [20] A fourth important research avenue involves tissue derived from the retina, spinal cord, and brain of the fetus but these have yet to show any results.

3. Concluding remarks

The potential use of stem cells in the treatment of a variety of retinal diseases remains tremendously exciting, with multiple potential approaches and many ongoing studies. The results

for phase I/II trials of stem cell applications are quite encouraging. No systemic or ocular side effects were observed.

However, it should not be forgotten that sight-threatening vitreoretinal complications could develop after IVT and subretinal applications. Also, significant problems that arise from poorly designed clinical trials and questionable practices could substantially hinder research.

Larger studies founded on solid preclinical research with a strong level of scientific design and longer follow-up periods are needed to determine the place that this treatment will hold in the future.

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