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September 2024

The Official Newsletter of the

VITREORETINAL SOCIETY-INDIA

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COVER PAGE IMAGE

Dr Tandava Krishnan
Vitreo-Retinal surgeon, Dr Agarwal's eye hospital,
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A 12 year old girl child presented to us with decreased vision. Her best corrected visual acuity was 6/9, N6 in both eyes (-2.00 D cylinder x 180 degrees in right eye, -2.50 D cylinder x 160 degrees in left eye)

She had depigmented skin and hair. Anterior segment evaluation was unremarkable, Fundus examination showed depigmented fundus with prominently visible choroidal vessels.

There was no history of consanguinity. A diagnosis of oculo-cutaneous albinism was made and the patient's parents were counselled about genetic evaluation.

GUIDELINES:
MANUSCRIPT SUBMISSION FOR VRSI NEWSLETTER

Original Articles :

These include randomized controlled trials, interventional studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 works (excluding Abstract, References and Tables) should be divided into sections with the headings: Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Case Reports / Challenging Case / Innovations / Instruments / Techniques:

New, interesting, challenging, rare cases, innovations, instruments and techniques can be reported. They should be unique and providing learning point for the readers. Manuscripts with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and References) and should have the following headings : Abstract (unstructured), Key-words, Introduction, Case, Discussion, Reference, Tables and Legends in that order. The manuscript could be supported with up to 10 references. Case Reports could be authored by up to four authors.

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INTRODUCTION TO THE ISSUE

Dr Deepika C Parameswarappa

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Dear Friends

It is my great pleasure to introduce this special edition of the VRSI newsletter, focusing on inherited retinal diseases/dystrophies (IRDs). I would like to sincerely thank Dr. P Mahesh Shanmugam and the entire VRSI scientific committee for bringing attention to this important topic. Special appreciation also goes to Dr. Pradeep Sagar for his efforts in coordinating contributions from various experts.

Although IRDs are considered rare, retinitis pigmentosa, a major phenotype of IRD, is quite prevalent in our country due to various cultural and ethnic practices. IRDs have a large social and economic impact. With advancements in treatments, many retinal diseases are now treatable. It is essential that we now prioritize the care of patients with IRD as well. IRD care begins with understanding the complexities of disease pathogenesis, providing precise phenotypic and genotypic diagnoses, and offering appropriate rehabilitation. Once deemed incurable, the success of gene therapy (Voretigene Neparvovec-rzyl; Luxturna™) for RPE65-related retinal dystrophy has sparked new hope for therapies to prevent blindness from IRDs. Research on treatments like cell therapy, optogenetics, and gene editing is rapidly advancing.

In this context, the current edition comprehensively covers various aspects of IRDs, including genetics, evaluation of nyctalopia, approach to macular dystrophy, management of associated macular complications, the vital role of electrophysiology, genetic counselling, genetic testing, and visual rehabilitation. Additionally, it addresses the myths and facts surrounding IRDs.

Readers will find it particularly exciting to explore the potential of gene therapy within the Indian context and to learn about real-world experiences with Luxturna™ in Canada. The newsletter also features spectacular images and case reports, showcasing the diversity of IRD cases and their associations.

I extend my sincere thanks to all the expert contributors for their invaluable role in advancing our understanding and care of IRD patients.

Thank you

Dr Deepika C Parameswarappa

GENES AND GENETICS OF INHERITED RETINAL DISEASES

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Genes are units of heredity transferred from parents to their offspring. They carry coded information required to produce proteins responsible for biological traits. The human genome contains approximately 20,000 genes coding for proteins, while some other portions of the genome are involved in regulating these genes.[1] Genes consist of specific nucleotide sequences, and variations in this genetic code can change the protein's structure and functional properties, leading to genetic disorders. Genetic variations/ mutations include insertions, deletions, and substitutions of the nucleotide sequence that can cause loss or toxic gain of protein function. This change in protein function may result in unfavourable phenotypes. Genetic variations can be inherited, or sometimes spontaneously occur in an individual (sporadic/ de novo mutations) and can manifest as disease.[2]

Inherited retinal disorders (IRDs) are a broad group of rare genetic disorders that result in photoreceptor degeneration. They can be stationary or progressive, causing visual impairment. Among the many genes identified in the retina, approximately 300 genes responsible for retinal cell development, function, maintenance, and survival are implicated in IRDs so far.[3] Figure 1 represents examples of different genes implicated in IRDs.[12]

IRDs follow autosomal dominant (AD), autosomal recessive (AR), X-linked dominant/ recessive (XL), or sometimes mitochondrial inheritance.[4,5] These inheritance types are documented in the family pedigrees in figure 2. IRDs are mostly monogenic i.e. they are caused by mutations in one gene, while sometimes digenic cases are also observed. For example, biallelic digenic retinitis pigmentosa (RP) is caused by the genes ROM1 and PRPH2[6] and triallelic digenic causation by BBS2 and BBS6 genes is observed in Bardet-Biedl syndrome (BBS) cases.[7] Some retina-specific genes are involved in non-syndromic

IRDs including retinitis pigmentosa, Leber congenital amaurosis (LCA) and Stargardt disease (STGD). Syndromic IRDs have extra-ocular presentation; an example is BBS, wherein obesity, polydactyly and developmental delay is seen in addition to progressive RP.[8,9]

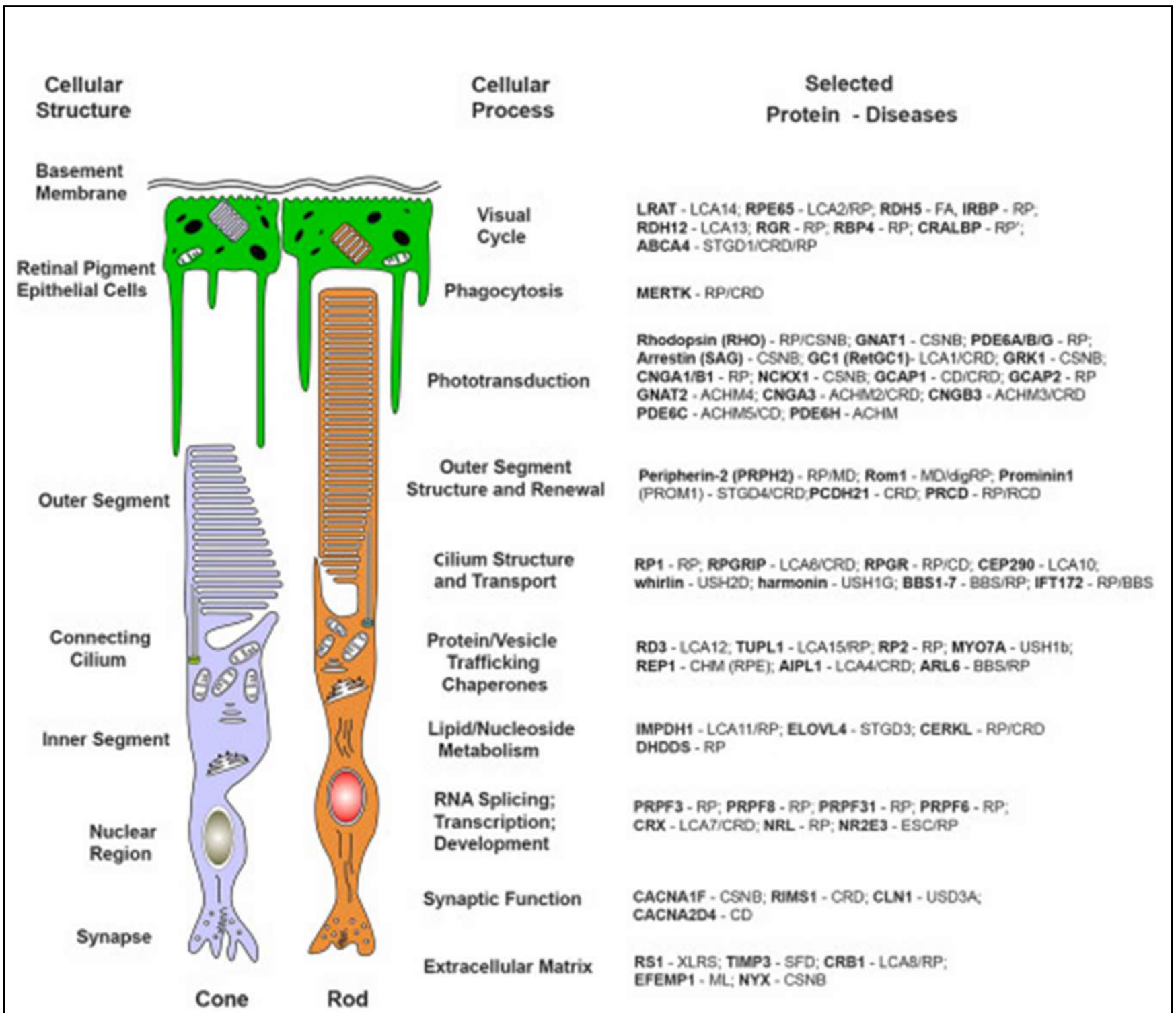

Figure 1: Genes implicated in IRDs, their cellular localization and function [12]

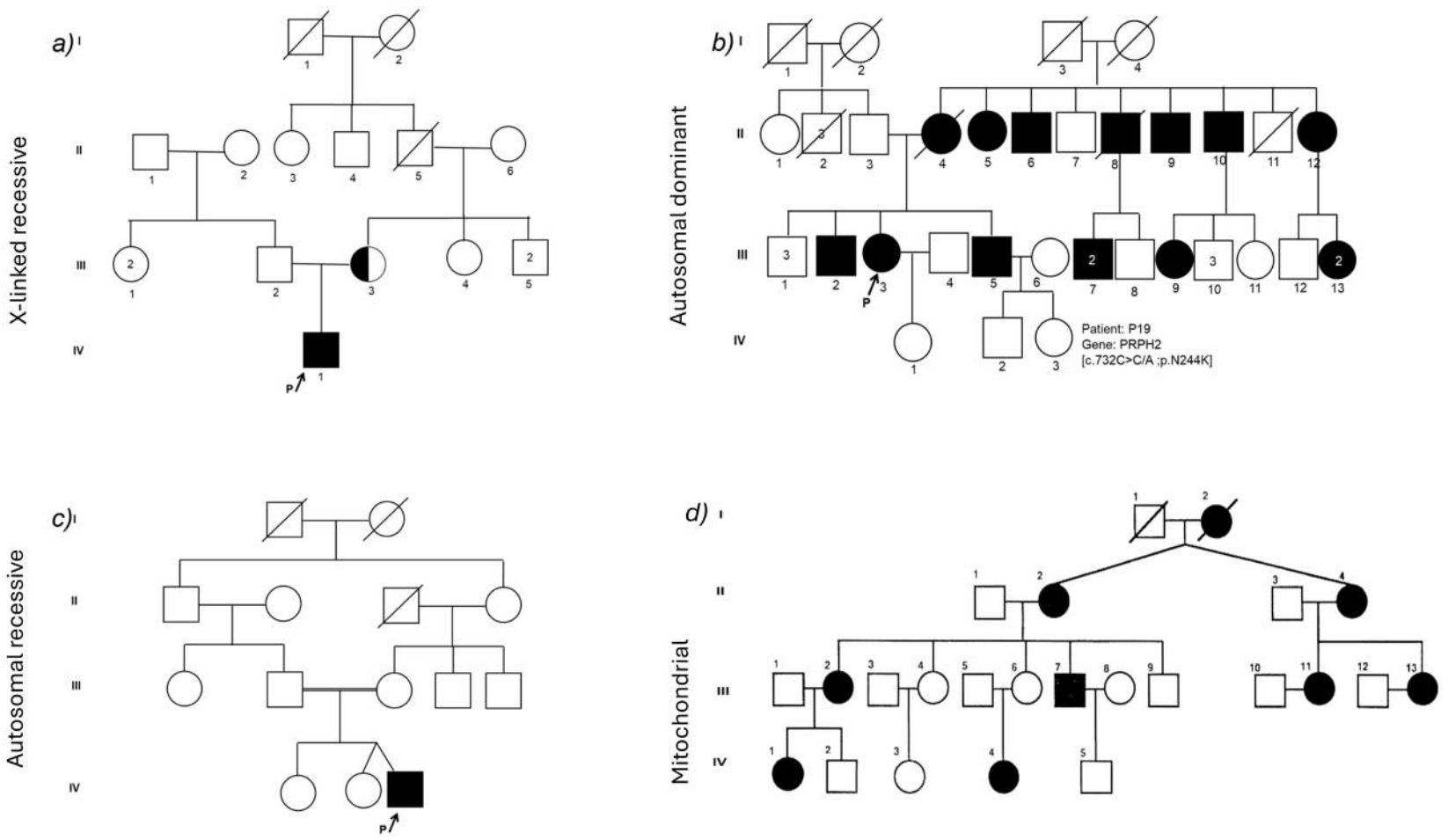

Figure 2: IRD patient pedigrees representing inheritance patterns [10,11]

IRDs are extensively reported to be clinically and genetically heterogeneous.[9] A mutation in one gene can cause different IRDs, while mutations in different genes can cause a specific type of IRD. For example, PROM1 gene mutations, can cause AD macular dystrophy-2 or STGD-4, while they can also cause an AR-RP.[13] Moreover, they can also cause AR/AD cone-rod dystrophy-12. Similarly, ABCA4, is involved in diverse phenotypes wherein, specific variants can directly be classified as mild, moderate, severe.[14] Other specific variants, like in the USH2A gene can be classified as syndromic vs non-syndromic [15]. Such “allelic hierarchy” is observed in genes with diverse phenotype associations.[16,17] An example of phenotype-genotype overlaps in an Indian cohort highlights such heterogeneity (figure 3).

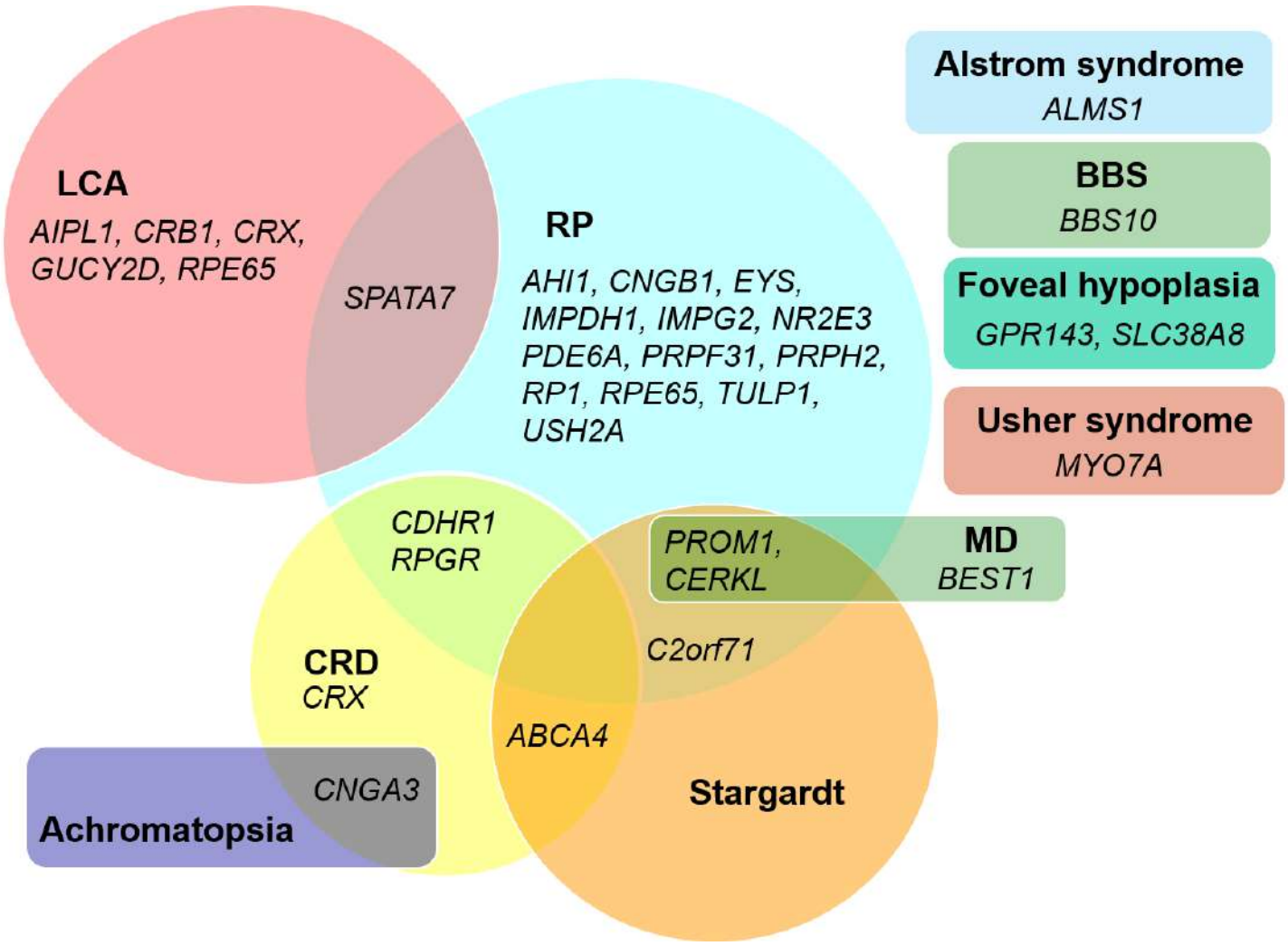

Figure 3: Genotype–phenotype overlaps from clinical and genetic findings of 117 IRD cases at Narayana Nethralaya, Bangalore (2014-2019). LCA, Leber congenital amaurosis; RP, retinitis pigmentosa; MD, macular degeneration; CRD, cone-rod dystrophy[10].

Genetic aspects of variable expressivity, haploinsufficiency, and incomplete penetrance of genetic mutations also govern the IRD phenotype and progression.[18] Many reports of familial exudative vitreoretinopathy patients identify 100% penetrance with highly variable clinical features, even within the same family.[19,20] An example of haploinsufficiency in IRDs is PRPF31-associated AD-RP exhibiting non-penetrance, wherein the disease skips generations despite being carriers (asymptomatic) of the mutation. The study also refers to epigenetic mechanisms as influencers of gene expression.[21] Further, variable phenotypic presentation of X-linked RP has been reported

in female carriers of the RPGR mutation.[22–24] Additionally, associated modifiers of the causative gene variant can also alter the penetrance or expressivity of the clinical phenotype.[25] Such intricacies can influence the onset, severity, order of involvement of rod vs cone photoreceptors, disease progression, and the mode of inheritance.[26–29]

Next-generation sequencing-based whole genome, whole exome, clinical exome, and targeted gene panels are used to identify disease-causing genes. These panels cover the genes studied to be responsible for IRDs and have genetically solved cases to a large extent. However, an Indian cohort shows that roughly 35% cases remain genetically unsolved, and approximately 50% genetic findings do not correlate with the clinical presentation.[10] Prescribed genetic test panels have their limitations, such as in cases caused by novel genetic variations, large deletions or insertions, deep intronic variations, promoter or regulatory elements sequence variations.[31] In such cases, alternate test methods like multiplex ligation-dependent probe amplification and chromosomal microarray may be useful. Accurate identification of the causative gene relies on available population databases, and in silico or functional evidence. Hence, genetic test screening panels need regular updates with evolving genetic information. Further, different ethnic and racial backgrounds, endogamous and consanguineous marriages make our population genetically diverse and distinct. While there is an increase in the number of IRD genetics reports/ publications, considering the heavy population of our country, the existing genetic landscape representation could be inadequate. Therefore, only Western population data may not always be applicable in the genetic diagnosis of IRDs in India. Also, when a genetic test report is available, it must be carefully dissected to understand the function of the causative gene, variant type, localization or proximity to important functional/regulatory domains. These can dictate the effect on the

molecular mechanism thereby affecting disease presentation. With the accumulation of segregation analysis from affected and unaffected family members and updated scientific evidence, genetically inconclusive reports have become conclusive over the years in many instances. Therefore, regular reanalysis and follow-ups of genetic reports are important.

While the availability and access to therapy for IRDs is presently faint, identifying the genetic cause underlying an IRD helps understand the likelihood of progression, risk of transmission to future generations, and stay informed in case of therapeutic developments. Gene and cell replacement, genome and RNA editing, mRNA targeting, and optogenetic strategies are being tested for IRD therapy.[33–35] Indian research organizations are working towards understanding phenotype-genotype correlations, deciphering molecular pathogenesis and designing therapeutic and management approaches for IRDs.[32,36] Even so, our country needs a detailed case-registry that can help reduce the genetic complexities involved in IRDs. In-depth genetic knowledge of IRDs is crucial to accelerate progress in holistic patient care.

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APPROACH TO NYCTALOPIA

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APPROACH TO NYCTALOPIA

Nyctalopia or night blindness, is the inability to see clearly in low-light conditions. Night vision relies on rod photoreceptors, which function through the rhodopsin pigment and vitamin A-dependent retinoid recycling pathway. The pupil's adaptation to reduced light also plays a role in enhancing night vision.[1,2] Night vision is achromatic (black and white). Impaired low-light vision can lead to various challenges in daily life, such as difficulty adjusting from bright to dim environments, blurry vision, halos, glare, bumping into things, frequent falls, and difficulty in driving.

Nyctalopia can be either congenital or acquired, and may present as stationary or progressive. The underlying causes are diverse, with the most common ones outlined in Table 1.[3-8] Broadly, nyctalopia occurs either due to dysfunction or degeneration of rod photoreceptors, defects in vitamin A recycling, or abnormalities in phototransduction signaling. A comprehensive discussion of the pathophysiology of each cause is beyond the scope of this short report.

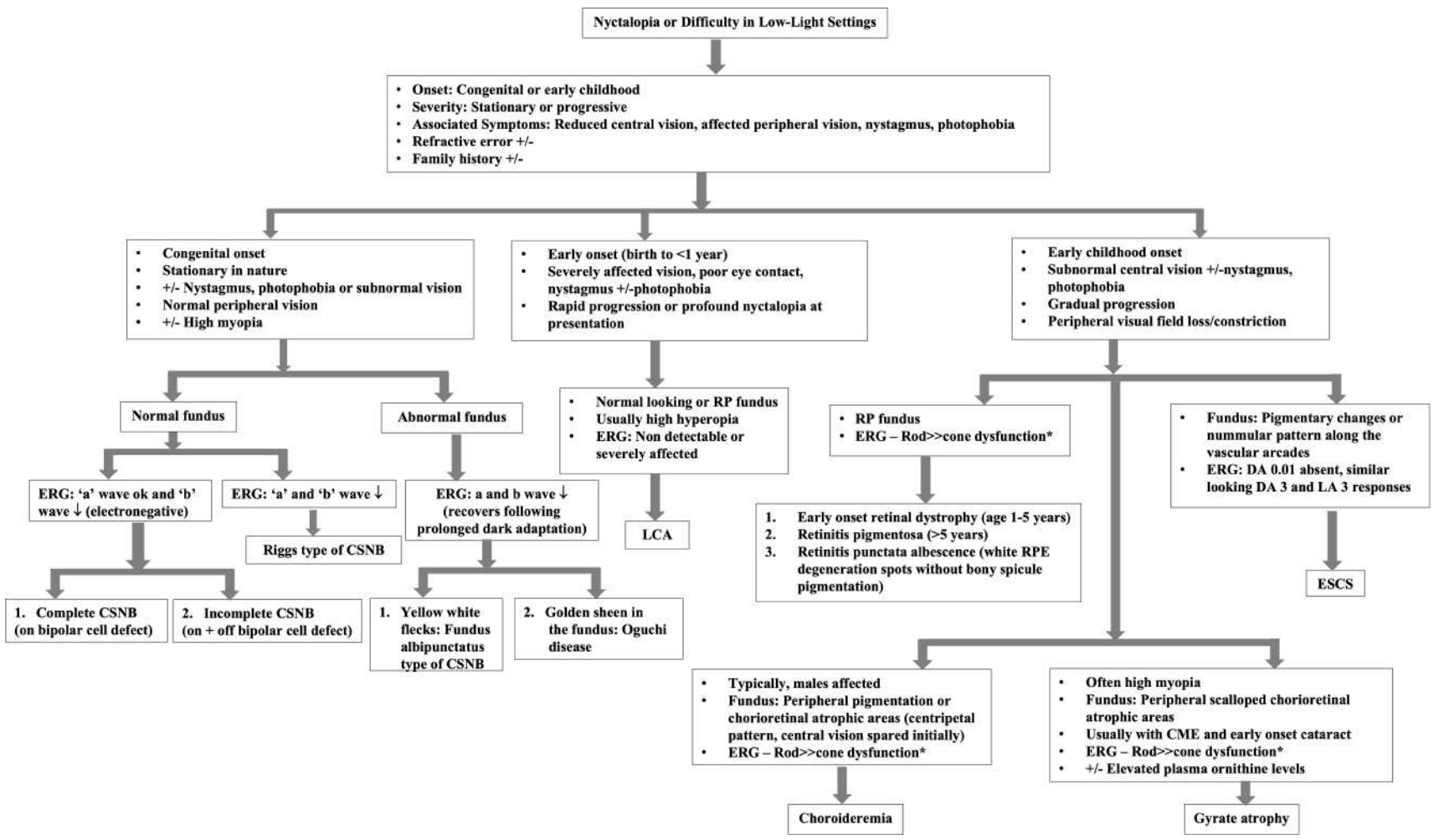
Patients presenting with nyctalopia should be assessed using a systematic approach that includes; thorough clinical and family history, as well as a detailed ocular and systemic examination. Complete refraction and slit-lamp examination are essential to identify cataracts and pupillary abnormalities. Structural and functional analysis of the retina is crucial for determining the underlying cause of nyctalopia. Retinal imaging techniques useful to asses structure include, fundus photography, fundus autofluorescence, and optical coherence tomography. Retinal function can be evaluated through electrophysiological tests and visual field analysis, with the flash electroretinogram (ERG) being the most critical investigation for all cases of nyctalopia.[4-6,8,9] Figures 1 and 2 illustrate the initial steps as flowchart for evaluation of common inherited and acquired causes of nyctalopia respectively. Both the figures show a simplified approach for the

purpose of this short report and do not replace a detailed evaluation for each cause of nyctalopia.

Congenital/Inherited		Acquired	
1	Congenital stationary night blindness	1	Nutritional (Vitamin A deficiency) · Malnutrition · Malabsorption syndromes (gastrointestinal or hepatic) · Post bariatric surgery
2	Progressive retinal dystrophies · Leber congenital amaurosis · Early onset retinal dystrophy · Retinitis pigmentosa · Retinitis punctata albescence · Enhanced S cone syndrome · Choroideremia · Gyrate atrophy	2	Malignancy (Paraneoplastic) · Melanoma (cutaneous, visceral, ocular) associated retinopathies · Cancer associated retinopathies (rarely)
		3	Traumatic · Ocular siderosis
		4	Iatrogenic · Lasered retinopathy of prematurity (aggressive peripheral laser) · Lasered (pan retinal photocoagulation) diabetic retinopathy
		5	Miscellaneous · Uncorrected refractive error/ High myopia · Cataract

Table 1: Various causes of nyctalopia.

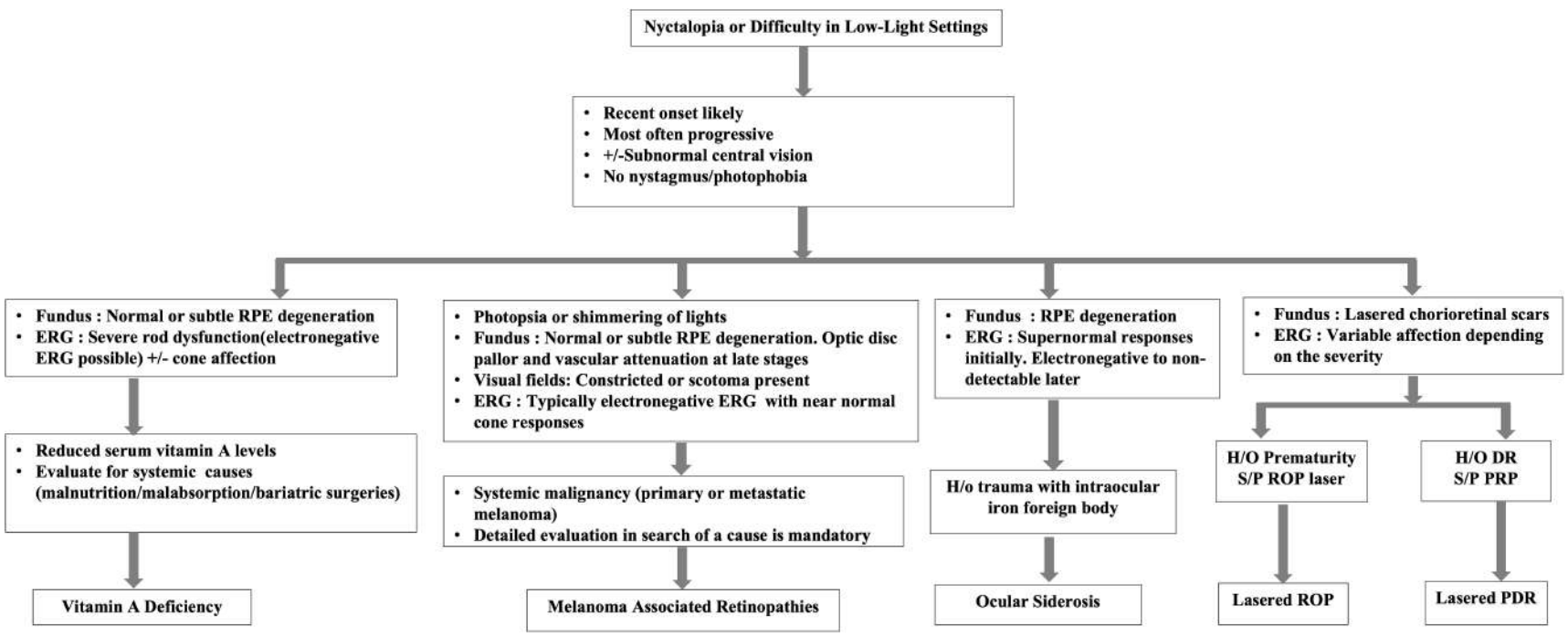
Figure 1: Flowchart for evaluation of congenital/inherited causes of nyctalopia



Footnotes figure 1: ERG; electroretinogram, CSNB; congenital stationary night blindness, RP; Retinitis pigmentosa, RP fundus; attenuated blood vessels with retinal pigment epithelial (RPE) degeneration/bony spicules and optic disc pallor, LCA; Leber congenital amaurosis, DA; dark adapted, LA; light adapted, ESCS; enhanced s cone syndrome, *Can be undetectable depending on age and severity.

For suspected congenital or inherited causes, genetic counselling and genetic testing should be initiated. Additional referral to paediatrician, endocrinologists or neurologists is recommended on identification of any syndromic inherited retinal diseases. Treatable acquired causes of nyctalopia require a multidisciplinary approach involving appropriate specialists. A repeat ERG may be beneficial if initial results are inconclusive or to monitor changes during follow-up in both inherited and acquired causes of nyctalopia.

Figure 2: Approach for acquired causes of nyctalopia



Footnotes figure 2: ERG; electroretinogram, RPE; retinal pigment epithelium, H/o; history of, ROP; retinopathy of prematurity, DR; diabetic retinopathy, PRP; pan retinal photocoagulation, PDR; proliferative diabetic retinopathy.

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PHOTO ESSAY:

PIGMENTED PARAVENOUS RETINOCHOROIDAL ATROPHY

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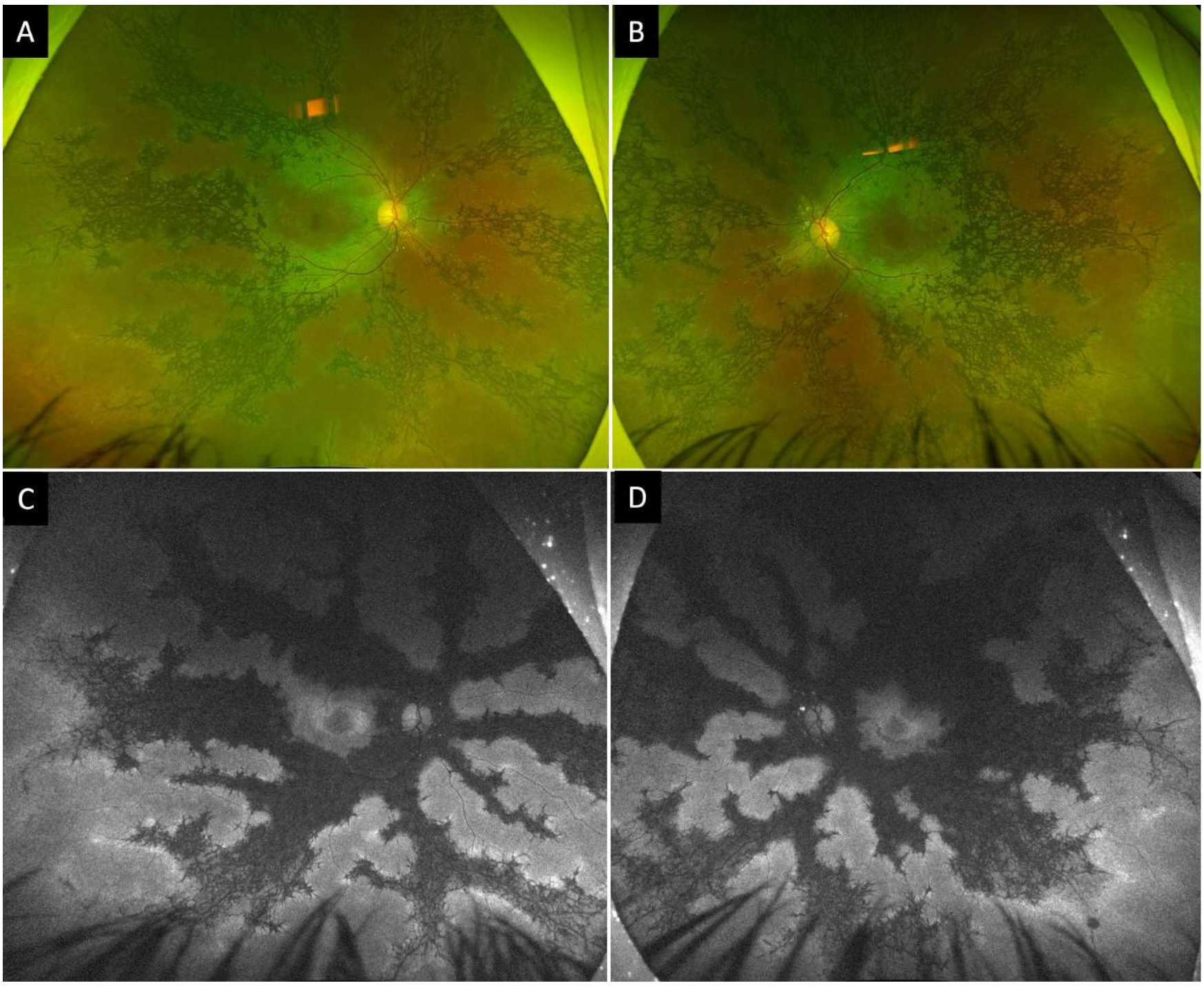

PIGMENTED PARAVENOUS RETINOCHOROIDAL ATROPHY

A 23-year-old male patient with night blindness and visual acuity of 6/6 in the right eye and 6/18 in the left eye was diagnosed with advanced pigmented paravenous retinochoroidal atrophy (PPRCA). The UWF fundus photographs (A, B) display paravenous pigment clumps associated with areas of retinal pigment epithelium (RPE) atrophy extending from the peripapillary area and distributed along the retinal veins in branching patterns, sparing the macula. The fundus autofluorescence images (C, D) show hypoautofluorescence corresponding to RPE atrophy and pigment clumping, surrounded by linear hyperautofluorescence extending to the periphery while sparing the macula. Spectral-domain optical coherence tomography (SD-OCT) revealed outer retinal thinning and loss of the ellipsoid zone sparing the fovea in both eyes, with intraretinal cystic spaces in the left eye. ERG showed grossly reduced and delayed scotopic and photopic responses in both eyes

APPROACH TO THE DIAGNOSIS OF MACULAR DYSTROPHY

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Introduction

Macular dystrophies (MDs) are inherited retinal disorders that cause progressive central vision loss predominantly due to macular atrophy. Although fundus findings are predominantly central, most MDs exhibit psychophysical, electrophysiological, or histopathological evidence of broader retinal involvement. Occasionally, the optic disc may show subtle pallor due to generalized retinal involvement, which can create a misleading impression of panretinal disease. Some conditions, such as cone dystrophy, rod monochromatism, and enhanced S cone syndrome, can initially mimic macular dystrophies. However, peripheral retinal abnormalities or additional diagnostic tests are needed to confirm the panretinal nature of these pathologies. Additionally, some diseases may appear advanced phenotypically but show minimal functional alterations, as seen in North Carolina macular dystrophy. While most macular dystrophies lack definitive treatments, some, like Stargardt's macular dystrophy, may benefit from dietary modifications. Advances in genetics have enhanced our understanding of these disorders, leading to potential treatments that could slow, halt, or restore vision. Many macular dystrophies are monogenic or linked to a few specific mutations, making them potential candidates for gene therapy. This underscores the importance of a systematic and targeted approach to diagnosing, classifying, and assessing macular dystrophies. Such an approach is essential to differentiate these conditions from mimickers, understand their extent, and prepare for potential gene therapy in the near future.

Approach to a Case of Macular Dystrophy- Flow chart approach

1. Detailed Ocular History: Gather comprehensive ocular history, including symptoms, onset, and progression.

2. Family History and Pedigree: Investigate family involvement and create a pedigree chart.
3. Illumination Preferences: Record preferences or aversions to different lighting conditions.
4. Initial Noninvasive Tests:
    a. Best corrected visual acuity
    b. Color vision
    c. Slit lamp image and Fundus photo documentation
    d. Pupillary reaction
    e. Autofluorescence
    f. Optical coherence tomography (OCT)
5. Dystrophy Workup:
    a. Full field ERG with Pattern ERG (refer table 1)
    b. Multifocal ERG
    c. Electrooculogram
    d. Visual field analysis (HVF)
    e. Additional tests based on initial findings (e.g. microperimetry)
6. Screening of Family Members: Examine the fundus of related family members.
7. Genetic Testing and Counselling: Provide genetic counselling (Pre and post test), and consider appropriate genetic tests (Refer Table2)
8. Low vision aids and visual rehabilitation
9. Periodic Review: Regularly review the case and explore new diagnostic avenues if needed.
10. Documentation and Reporting: Document and report any novel findings or entities not described in the literature.

Table 1: Electrophysiological Findings in Macular Dystrophies

Disease Type	Electrophysiological Findings
Stargardt Disease (STGD1)	ffERG: Normal to reduced cone responses, with progression to reduced cone and rod responses. PERG: Severely reduced. mfERG: Classification into Type 1-4 based on response distribution.
Stargardt Disease 3 (STGD3)	ffERG: Reduced cone and rod responses.
Stargardt Disease 4 (STGD4)	ffERG: Reduced cone and rod responses.
Early-onset STGD1	ffERG: Normal to reduced cone and rod responses. mfERG: Reduced central responses, preserved peripheral responses.
Late-onset STGD1	ffERG: Normal or reduced cone and rod responses. mfERG: Preserved central responses, reduced in peripheral areas.
Best Vitelliform Macular Dystrophy (BVMD)	ffERG: Typically normal. mfERG: Reduced amplitudes in areas with subretinal fluids. EOG: Absent light peak
Adult-onset Foveomacular Vitelliform Dystrophy (AOFMD)	ffERG: Reduced central and possibly peripheral responses. mfERG: Reduced central and peripheral responses. EOG: Typically normal.

Autosomal Dominant Vitreoretinochoroidopathy (ADVIRC)	ffERG: Normal to severely reduced photopic and scotopic amplitudes. EOG: Normal to borderline abnormal Arden ratio.
Autosomal Recessive Bestrophinopathy (ARB)	ffERG: Reduced cone and rod responses. mfERG: Reduced central amplitudes with preserved paracentral amplitudes. EOG: Severely reduced Arden ratio.
X-Linked Retinoschisis (XLRS)	ffERG: Electronegative response with reduced b-wave amplitudes; sometimes normal b-wave or reduced a-wave and b-wave. mfERG: Significant reduction in response densities in the retinal area of schisis.
Sorsby Fundus Dystrophy (SFD)	ffERG: Normal to reduced rod and cone responses. EOG: Normal or slightly reduced Arden ratio.
Doyne Honeycomb Retinal Dystrophy (DHRD)	ffERG: Normal or reduced b-wave amplitudes; reduced 30 Hz flicker response. PERG: Mild to moderate reduction in P50 and N95 components. mfERG: Reduced amplitudes near the macula. EOG: Normal to borderline reduced Arden ratio.
Occult Macular Dystrophy (OMD)	mfERG: Significant reduction in response densities in the central 7 degrees; slightly delayed implicit times. focal ERG: Reduced response with relatively smaller a-wave and larger b-wave amplitude. ffERG & EOG: Normal responses.

North Carolina Macular Dystrophy (NCMD)	ffERG: Typically normal. mfERG: Delayed implicit times in the central retina, reduced amplitudes in the lesion area. EOG: Reduced Arden ratio
Pattern Dystrophy (PD)	ffERG: Normal to reduced amplitudes depending on subtype. EOG: Varies by subtype. Specific Subtypes: - Butterfly-shaped Pigment Dystrophy (BPD): Normal ffERG and mfERG; EOG Arden ratio from 1.3 to 1.6. - Pseudo-Stargardt Pattern Dystrophy (PSPD): Normal to severely reduced ffERG amplitudes; EOG Arden ratio ranges from normal to severely reduced. - Sjogren's Reticular Pattern Dystrophy (RPD): Normal scotopic and photopic ffERG; EOG Arden ratio from 1.52 to 2.07.
Central Areolar Choroidal Dystrophy (CACD)	ffERG: Mostly normal scotopic and photopic responses; reduction in photopic amplitudes in advanced cases. mfERG: Reduced amplitudes and/or delayed implicit times, especially in advanced stages.

Abbreviations- ffERG: Full-field Electroretinography; mfERG: Multifocal Electroretinography; PERG: Pattern Electroretinography; EOG: Electrooculography; BPD: Butterfly-shaped Pigment Dystrophy; PSPD: Pseudo-Stargardt Pattern Dystrophy; RPD: Sjogren's Reticular Pattern Dystrophy; FP: Fundus Pulverulentus

Table 2: Genetics of Macular dystrophies

Disease	OMIM #	Gene	Inheritance Mode
Stargardt disease (STGD1)	248200	ABCA4	AR
Best disease	600110	BEST1	AD
X-linked Retinoschisis (XLRS)	312700	RS1	X-linked
Stargardt-like diseases			
- STGD3	600110	ELOVL4	AD
- STGD4	603786	PROM1	AD
Pattern dystrophy	169150	PRPH2	AD
Sorsby fundus dystrophy	188826	TIMP3	AD
Autosomal dominant drusen	601548	EFEMP1	AD
Central areolar choroidal dystrophy*	215500	PRPH2	AD
North Carolina macular dystrophy	136550	PRDM13	AD
Occult macular dystrophy*	613587	RP1L1	AD

* Only the commonest gene involved is mentioned here

The cases presented below serve an example of our approach to a case of macular dystrophy

a. Diseases where macular pathology is obvious phenotypically

Case 1: A 28-year-old male was referred with a suspected diagnosis of chronic central serous chorioretinopathy due to bilateral atrophic patches at the macula and a visual acuity of 20/25 in both eyes . Examination revealed bilaterally symmetrical, platyhelminth-shaped atrophic patches at the macula, bordered by brightly hyperautofluorescent deposits. Despite these findings, the visual acuity was disproportionately better than expected. Optical coherence tomography showed photoreceptor elongation and neurosensory separation. [Figure 1] Electroretinography results were normal, and electrooculography (EOG) showed no light rise, which confirmed the diagnosis of Best vitelliform macular dystrophy in its atrophic stage. The patient was counseled regarding the nature and progression of the disease. Recommendations included examining blood-related family members, even if they are asymptomatic, conducting genetic testing, and scheduling periodic follow-ups to monitor for choroidal neovascularization.

Remember:

- BVMD is the second most common macular dystrophy. Gass's staging system classifies the disease into five stages: Stage I (subclinical), Stage II (vitelliform), Stage III (pseudohypopyon), Stage IV (vitelliruptive), and Stage V (atrophic/fibrotic).
- Autosomal recessive bestrophinopathy present with extensive and variable autofluorescence patterns, including hyperautofluorescence in vitelliform deposition

areas and mottled hypoautofluorescence, which helps delineate it from Best vitelliform macular dystrophy. ERG is also subnormal.

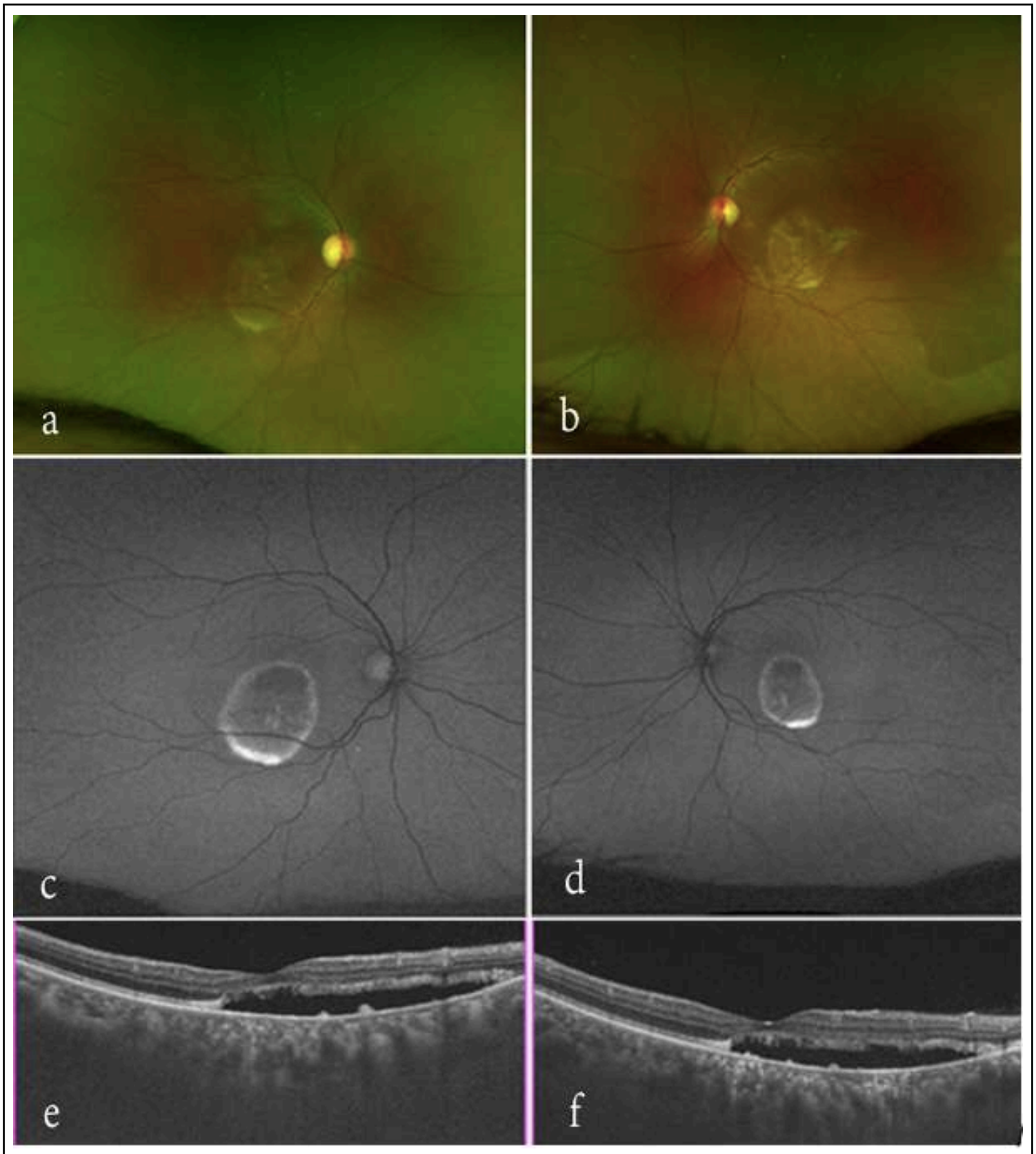


Figure 1

Case 2: A 40-year-old woman with worsening vision(BCVA 20/60) for 9 months was found to have yellowish macular lesions, neurosensory detachment, and hyperreflective

deposits at the retinal pigment epithelium on OCT. Autofluorescence showed mixed hypo- and hyperautofluorescence. Fluorescein angiography revealed a butterfly-shaped pattern of hypofluorescence, while the electrooculogram indicated a reduced Arden ratio. [Figure 2] Whole exome sequencing identified a missense variant, c.965C>T, in the CTNNA1 gene, confirming the diagnosis to be pattern dystrophy.

Remember:

- Pattern dystrophies, often caused by PRPH2 gene mutations, include adult-onset vitelliform macular dystrophy, multifocal pattern dystrophy, butterfly pigment dystrophy, reticular pattern dystrophy, and fundus pulverulentus. These typically exhibit a stable, benign course.
- Adult-onset vitelliform macular dystrophy is characterized by yellow-white subfoveal lesions with variable autofluorescence patterns, which represent different disease stages.

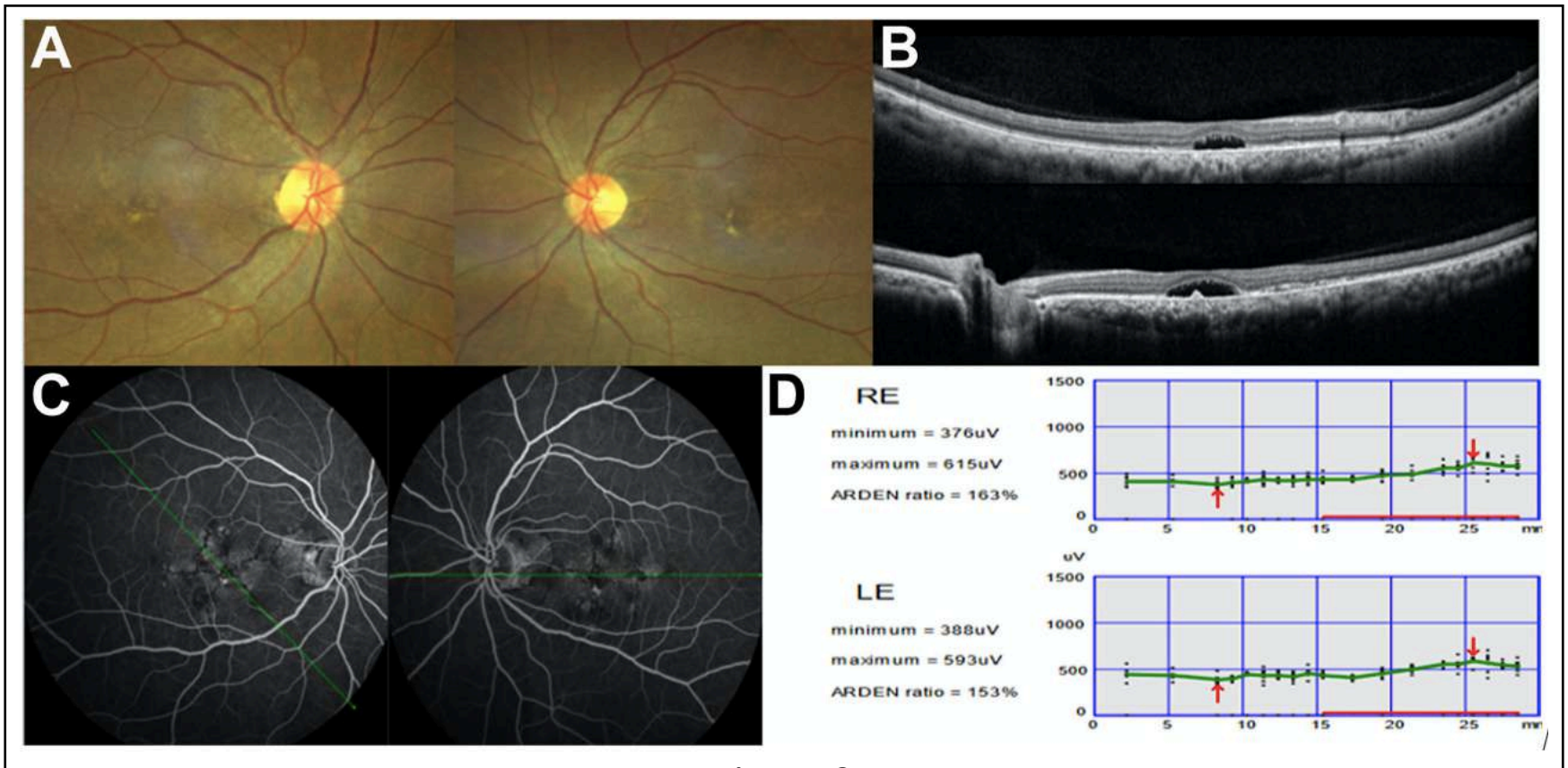


Figure 2

Case 3: A 24-year-old gentleman was found to have bilateral atrophic and slightly depressed lesions with multiple macular drusen during a routine fundus evaluation. Visual acuity was 20/20 in both eyes with N6 near vision and normal color vision. Optical coherence tomography showed loss of the photoreceptor layer, sparing the foveal center [Figure 3]. Multifocal ERG demonstrated a good foveal peak but stunted responses juxtafoveally, while full-field ERG showed normal scotopic and photopic responses in both eyes.

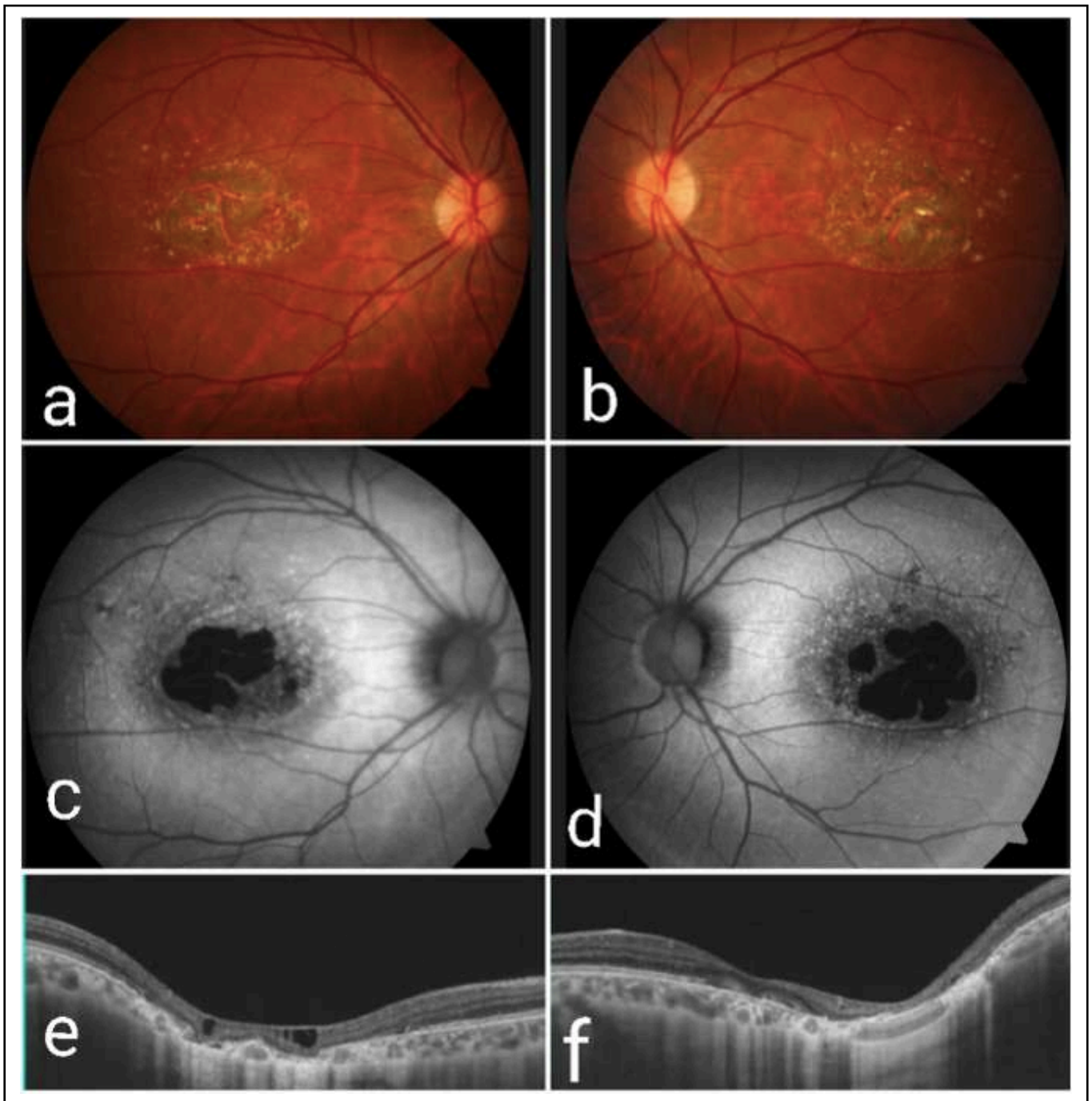


Figure 3

Fundus evaluation of the father revealed similar changes in both eyes. The patient was advised to undergo genetic testing to rule out North Carolina Macular Dystrophy (NCMD). The condition has remained stable over the past 10 years.

b. Phenotypically diseases restricted to macula but Pan retinal affection electrotypically

Case 4: A 42-year-old woman presented with bilateral central visual loss, photophobia, color vision abnormalities, central scotomas, and slow dark adaptation. Her best-corrected visual acuity was 20/200 in the right eye and 20/100 in the left eye. Fundus examination revealed pigment mottling, macular atrophy, a bull's eye maculopathy, sparing of the peripapillary retina, and fundus flecks. Autofluorescence imaging showed macular hypoautofluorescence with mixed hypo- and hyperautofluorescence flecks. [Figure 4] Full-field electroretinography (ERG) demonstrated notably abnormal scotopic and photopic responses. Clinical exome testing confirmed a mutation in the ABCA4 gene, diagnosing Stargardt disease. In addition to recommending low vision devices, the patient was advised to avoid excessive vitamin A and to use UV protective glasses outdoors. Given that both photopic and scotopic responses were affected in the full-field ERG, the patient was counseled about the potential for rapid vision deterioration and increasing scotoma size in the future.

Remember:

- Stargardt disease, commonest cause of macular dystrophy, is primarily caused by autosomal recessive mutations in the ABCA4 gene, located on chromosome 1p22.1.
- Clinical manifestations include variable macular degeneration with pigment mottling, bull's eye maculopathy, fundus flecks, and a characteristic sparing of the peripapillary retina. Early fundus examination may appear normal despite visual symptoms, leading to potential diagnostic delay. Fundus flecks, which are yellow-white lesions, represent lipofuscin accumulation in the retinal pigment epithelium and may also indicate

regional depigmentation and atrophy. Their distribution is variable and does not directly correlate with the degree of visual loss.

- Though the fundus suggests disease restriction to macula phenotypically, FAF and FF ERG may show extensive affection suggestive of pan retinal nature of the disease.

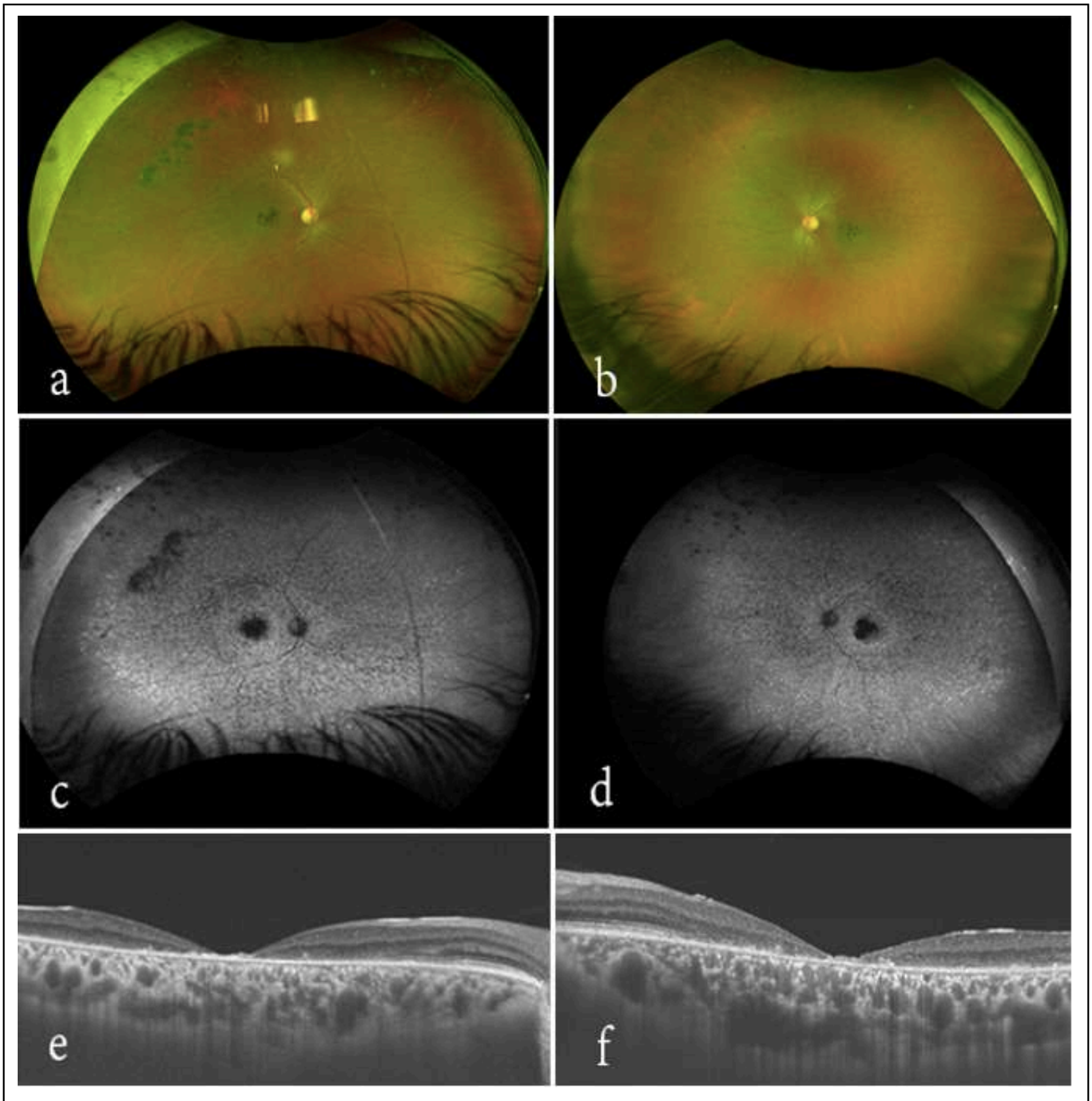


Figure 4

Case 5: A 20-year-old male presented with a best-corrected visual acuity of 20/80 in both eyes. There was no history of nyctalopia or familial history of similar conditions. Fundoscopic examination revealed a dull foveal reflex, a cartwheel macula, and a prominent tapetal reflex. Optical coherence tomography demonstrated multilayered schisis on either side of the outer plexiform layer. A full-field ERG revealed an electronegative b-wave response in scotopic 3.0 conditions [Figure 5]. Clinical exome sequencing identified a mutation in the RS1 gene, confirming a diagnosis of X-linked juvenile retinoschisis (XLRS). Topical carbonic anhydrase inhibitors were started for both eyes in addition to low vision devices.

Remember:

- X-Linked Juvenile Retinoschisis (XLRS) is the most common X-linked disorder affecting macular function in males, with a prevalence of 1 in 5,000 to 1 in 20,000. It often presents with bilateral reduced visual acuity, typically noticeable at school age but sometimes from infancy, and can be complicated by vitreous hemorrhage or retinal detachment. Diagnostically, fundoscopy reveals a distinctive spoke-wheel pattern of foveal schisis and may show peripheral retinoschisis, best visualized with red-free light.

- Optical Coherence Tomography (OCT) offers detailed cross-sectional imaging of the schisis within retinal layers. Full-Field Electroretinography (ERG) displays an electronegative response characterized by reduced b-wave amplitude relative to the a-wave, indicating abnormalities in ON and OFF bipolar cells.

- XLRS is linked to mutations in the RS1 gene, which encodes retinoschisin, crucial for retinal structural integrity.

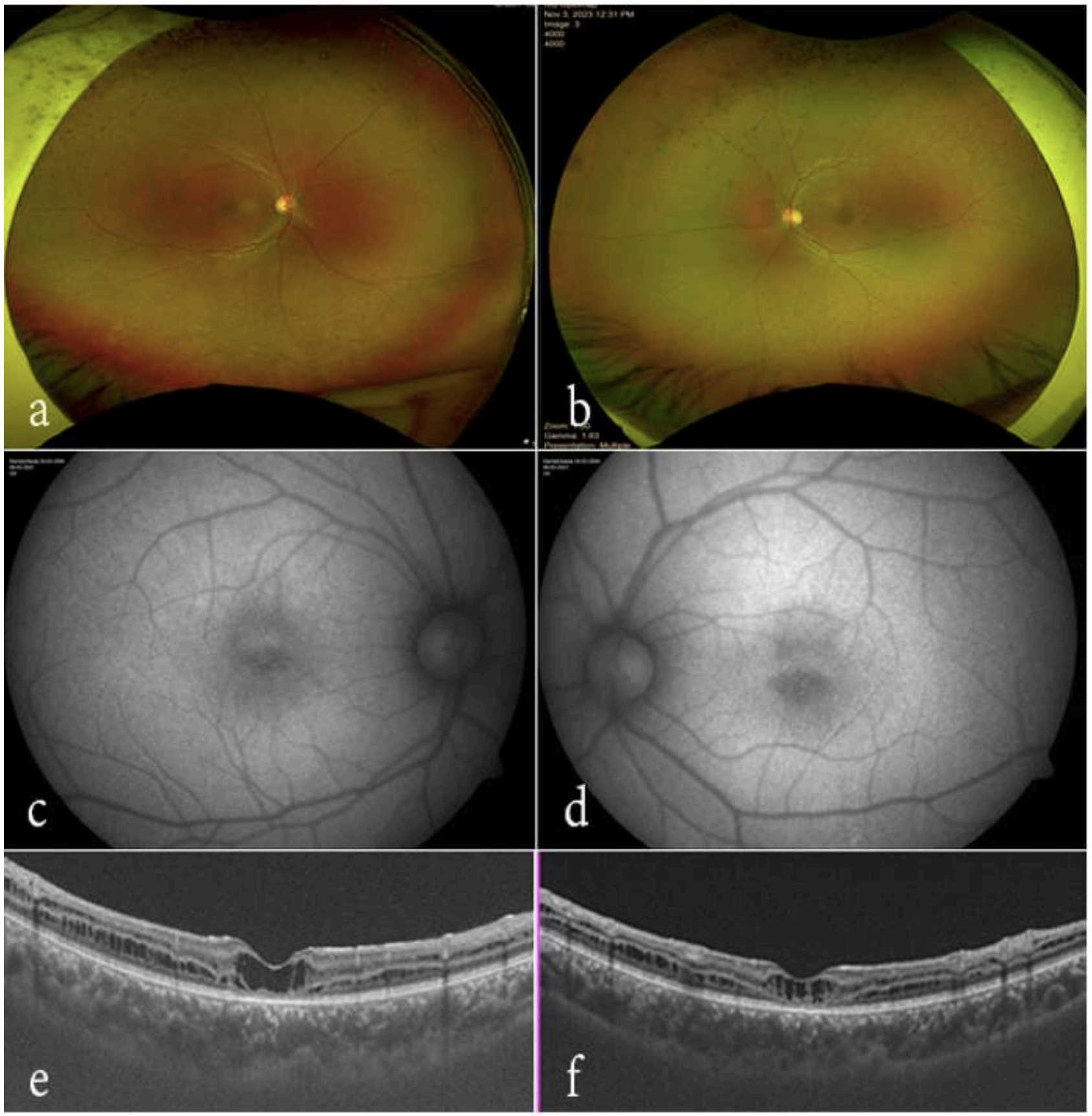


Figure 5

Case 6: A 41-year-old male with photophobia and minimal nyctalopia presented with coin-shaped macular atrophic lesions in both eyes. His family history included similar eye issues in his father and some eye problems in his son. Optical coherence tomography

revealed outer retinal loss confined to the macula, while autofluorescence showed central hypoautofluorescence surrounded by a ring of hyperautofluorescence. [Figure 6] Electroretinography indicated both scotopic and photopic dysfunction, with photopic responses more severely affected. Clinical exome testing identified a mutation in the GUCY2D gene, confirming cone-rod type retinal dystrophy.

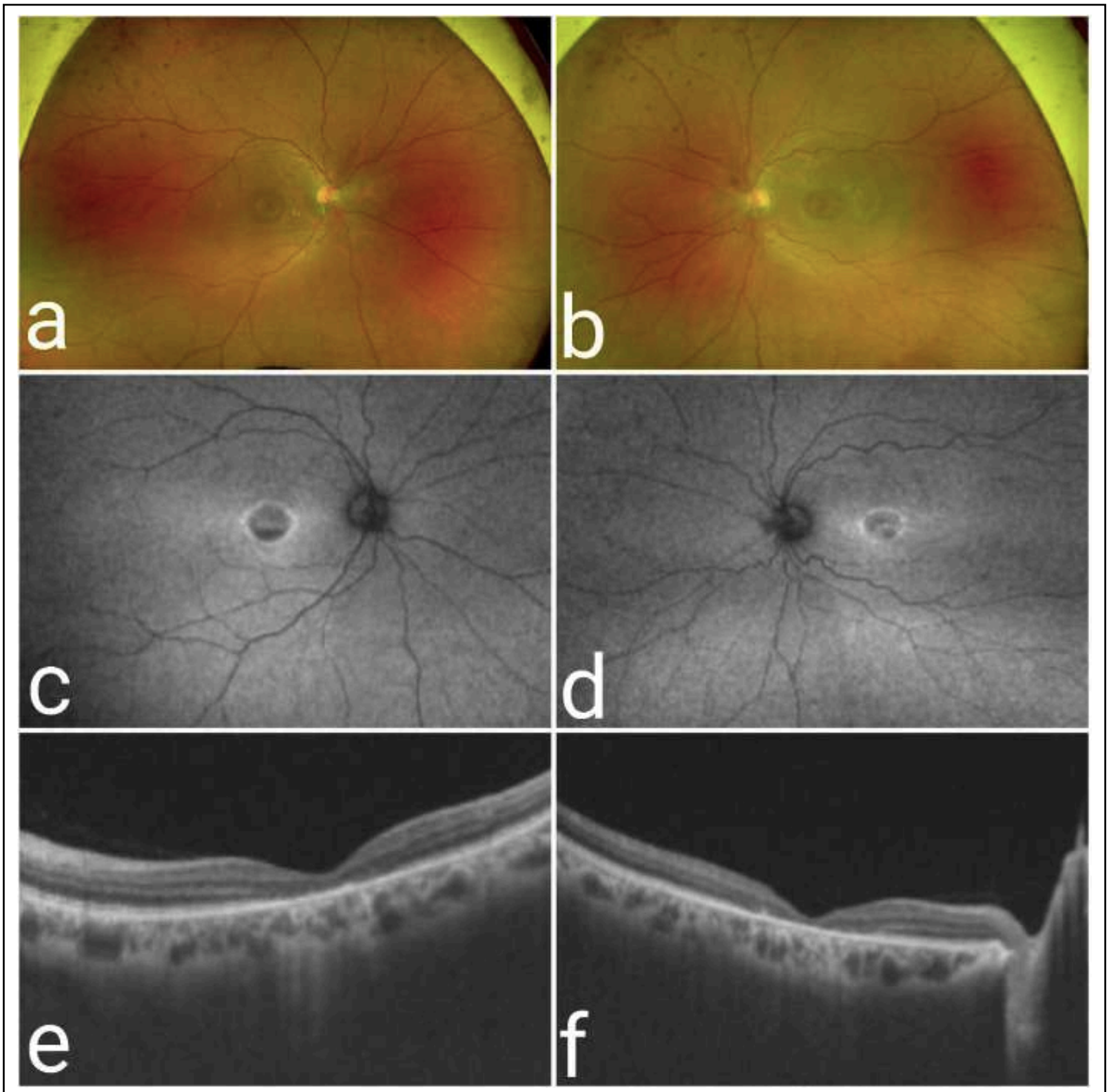


Figure 6

Remember:

- Cone-Rod Dystrophy (CRD) is characterized by early visual acuity decline, photophobia, and color vision defects, with night blindness appearing later. Fundoscopy may initially show normal or minimally affected macula, progressing to pigmentary deposits and optic disc pallor. Diagnostic tools such as OCT and ERG are critical for early detection, with ERG revealing reduced amplitudes of both a- and b-waves, particularly affecting photopic responses. Autofluorescence shows central hypoautofluorescence with peripheral hyperautofluorescence. Genetic testing, such as for GUCY2D mutations, helps confirm the diagnosis and differentiate CRD from other retinal dystrophies like Stargardt disease and cone dystrophies.
- Although Cone-Rod Dystrophy (CRD) clinically presents with macular lesions, indicating a localized appearance of the disease, full-field Electroretinography (ERG) reveals pan-retinal involvement.

c. Phenotypically and electrotypically difficult to diagnose macular dystrophies

Case 7: A 22-year-old female presented with blurred vision for 1.5 months. Best-corrected visual acuity was 20/50 in the right eye and 20/60 in the left eye. Autofluorescence was normal. Humphrey visual field showed a centrocaecal scotoma in both eyes. Optical coherence tomography revealed subfoveal disruption of the ellipsoid zone and an optically empty defect [Figure 7]. Multifocal ERG demonstrated overall reduced wave responses. Full-field ERG showed normal scotopic wave amplitudes with normal implicit times, while photopic phases exhibited minimally reduced wave amplitudes with normal implicit times. Genetic testing revealed a mutation in the RP1L1 gene, confirming occult macular dystrophy.

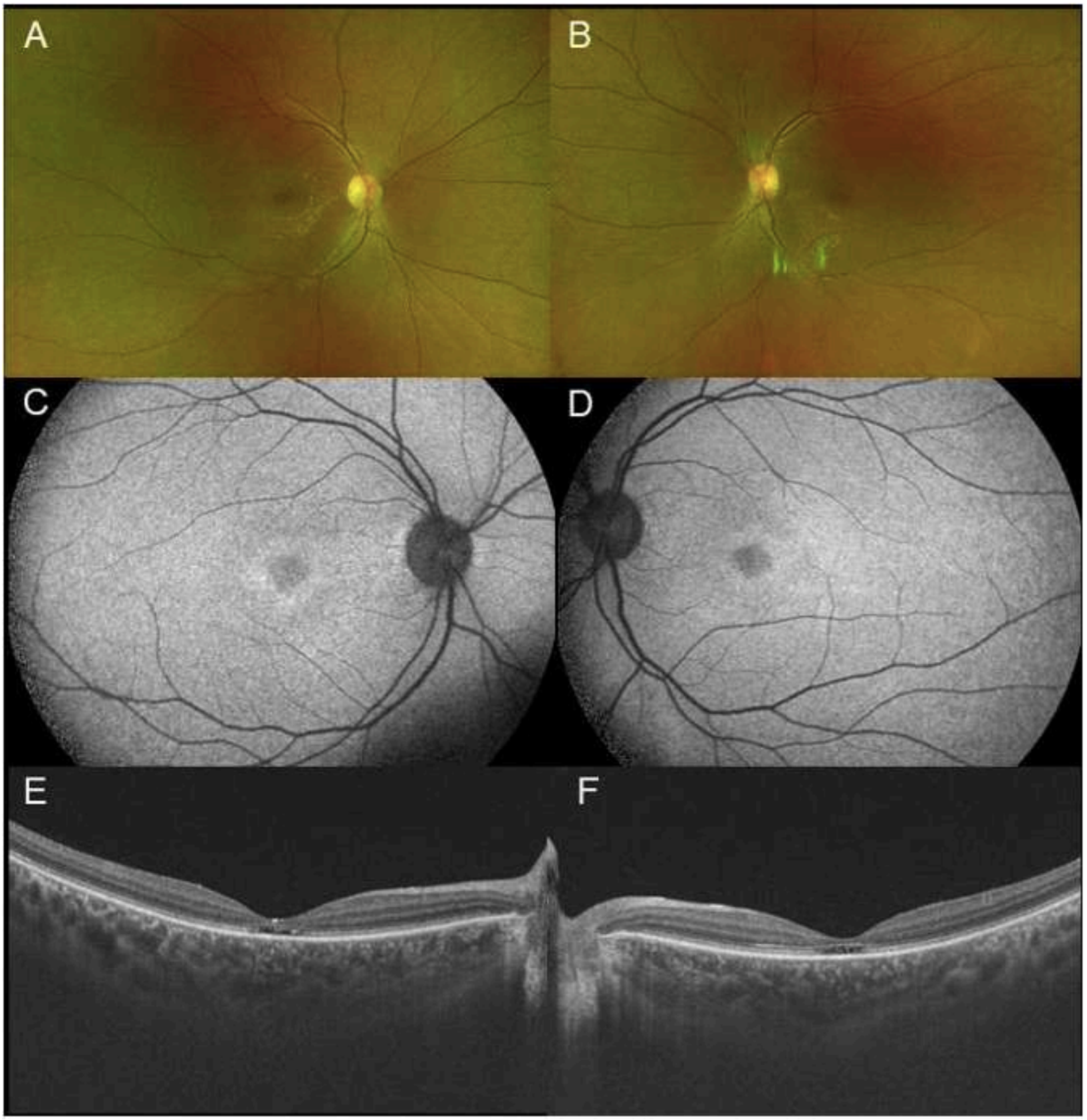


Figure 7

Conclusion

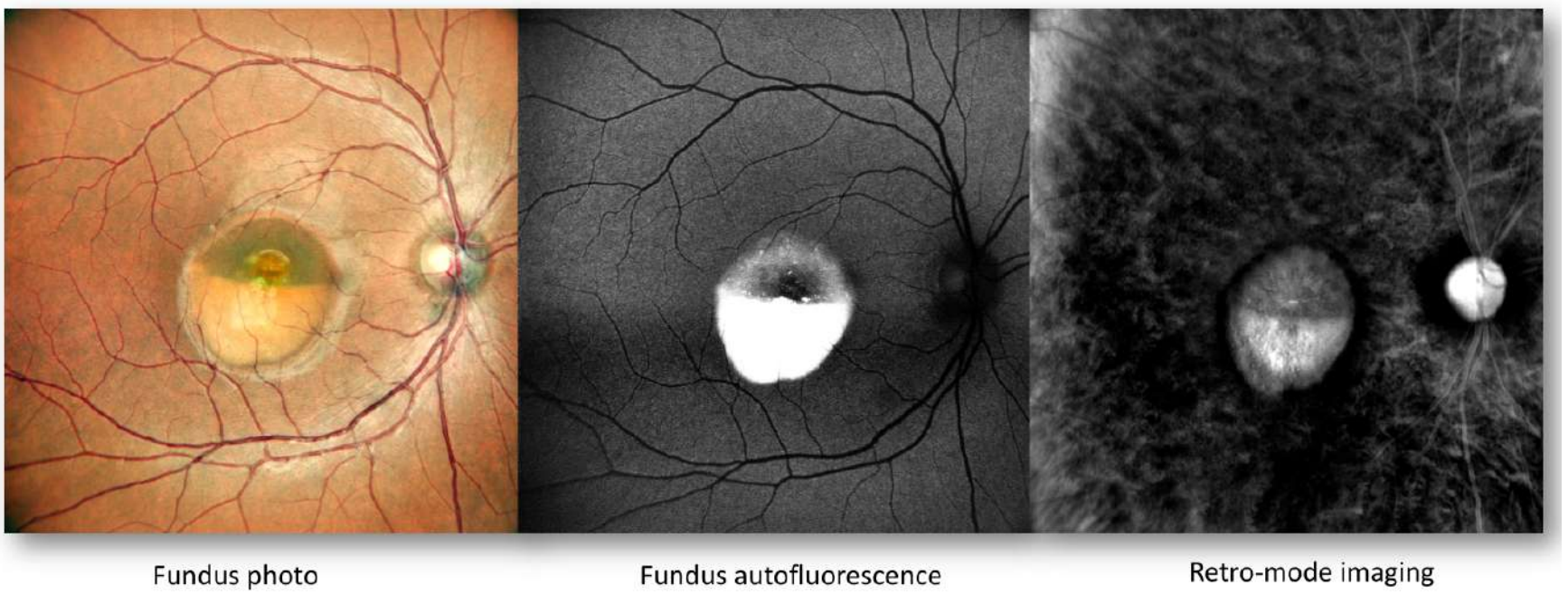
Approaching the diagnosis of macular dystrophy requires a comprehensive and systematic evaluation that integrates clinical examination, multimodal imaging, and

genetic testing. A thorough understanding of the patient's clinical history and detailed assessment through tools such as fundus photography, optical coherence tomography, fundus autofluorescence, and electroretinography can reveal characteristic features that guide the differential diagnosis. Genetic testing plays a pivotal role in confirming the diagnosis, identifying causative mutations, and enabling personalized management strategies. Collaboration with genetic counsellors is essential to provide patients with information on the inheritance patterns, prognosis, and potential therapeutic options.

INTERESTING IMAGE:

SUNNY SIDE DOWN

Dr Karishma Tendulkar, Dr. Anupama Kiran Kumar, Dr. Prathiba Hande
Narayana Nethralaya, Bengaluru

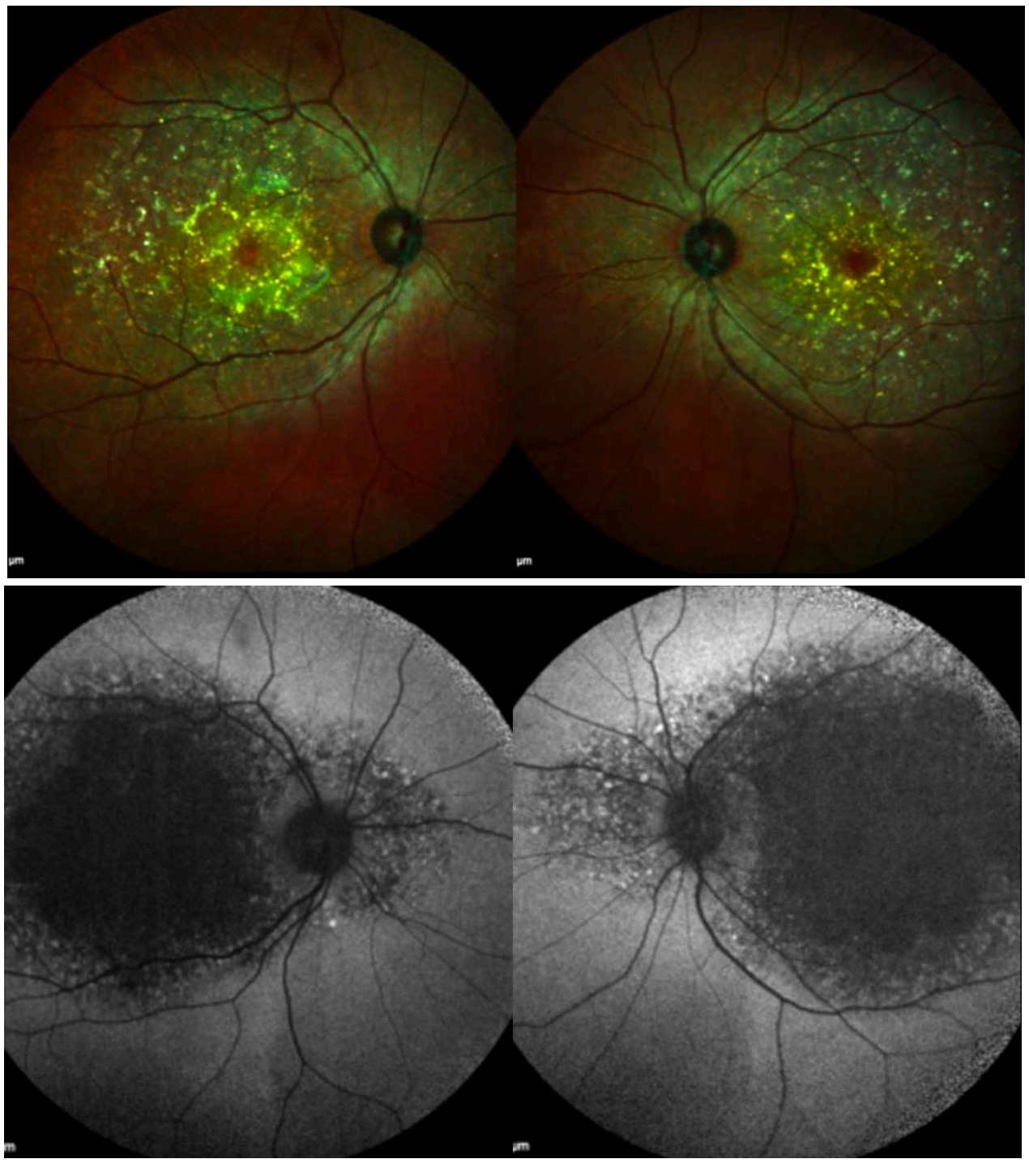


Imaging of a ‘pseudo-hypopyon’ vitelliform lesion in a young male with Best vitelliform macular dystrophy on Mirante, Nidek

INTERESTING IMAGE:

BEITTI'S CRYSTALLINE DYSTROPHY

Dr Lakshmi Prabha, Dr M Prabhu Shankar
Sankara eye hospital, Coimbatore



Multicolour and fundus autofluorescence images of a 28 yr old male diagnosed with Beitti's crystalline dystrophy

HOW ELECTROPHYSIOLOGICAL TESTS HELP IN MANAGEMENT OF IRD

Dr. Neha Goel

Assistant professor, Army college of Medical Sciences, New Delhi, Senior consultant vitreoretina and uvea, Synergy Eye Care, New Delhi

Introduction

Inherited retinal dystrophies (IRDs) are a diverse group of disorders with retinal degeneration, caused by pathogenic variation in proteins critical to retinal structure and function, resulting in vision impairment. They have been estimated to affect around 2 million individuals worldwide.[1] IRDs present diagnostic challenges to ophthalmologists and retina specialists due to their overlapping clinical presentations and variability in inheritance patterns. Sophisticated testing technologies for genetic disorders such as next-generation sequencing are allowing clinicians to better diagnose IRDs, however they are limited by their availability and cost.[2]

Advances in imaging modalities such as fundus autofluorescence (FAF) and OCT have allowed for accurate characterization of IRDs. However, electrophysiological testing remains a valuable tool as it identifies the site of damage, and the cell type involved in the visual degenerative process as well. Electroretinography (ERG) is the method of choice for objective evaluation of photoreceptors and bipolar cells in rod and cone pathways and enables the distinction between predominantly rod or cone system

dysfunction. While the full-field ERG (ffERG) represents a mass response, multifocal ERG (mfERG) can identify and monitor dysfunction in localized areas in the central retina. Pattern ERG (PERG) assesses the function of ganglion cells in the central retina. The international standards devised by the International Society for Clinical Electrophysiology of Vision (ISCEV) are of major importance for standardizing these electrophysiological examinations.[3]

IRDs have been classified into four categories, including rod-cone dystrophy, cone-rod dystrophy, inherited macular dystrophies and chorioretinal degenerations. [4] This article aims to provide a brief overview of the applications and limitations of electrophysiological tests in the diagnosis and management of these groups of disorders.

Rod-cone dystrophy

Retinitis pigmentosa (RP) is the commonest IRD characterized by initial symptoms of nyctalopia followed by progressive loss of visual field. ffERG can detect early characteristic photoreceptor degeneration, even before symptoms appear. This is also useful in cases where the typical fundus features may not be visible and in atypical variants like retinitis punctata albescens, where the fundus shows yellow-white deposits and peripheral areas of RPE atrophy. [4] ffERG shows decreased amplitudes and prolonged implicit times (IT) on all 5 dark adapted (DA) and light adapted (LA) protocols (Fig. 1), the LA 30 Hz correlates strongly with reduced visual acuity. [5] Extinguished ERG as seen in advanced RP can only be seen in a handful of conditions, such as Leber's congenital amaurosis, total retinal detachment, ophthalmic artery occlusion and retinal aplasia, most of which can be easily differentiated on clinical examination.

ffERG can identify up to 80% of examined carriers of X-linked RP, a condition with a lot of

phenotypic variability. Female carriers exhibit a delayed cone b-wave IT on 30 Hz flicker ERG. Identification of carriers in families with X-linked RP is important to be able to provide genetic counselling.[6]

mfERG and PERG allow objective evaluation of residual cone function, which correlates with visual acuity and shortening and thickening of the ellipsoid zone on OCT. This can guide prognosis and therapeutic monitoring.[7]

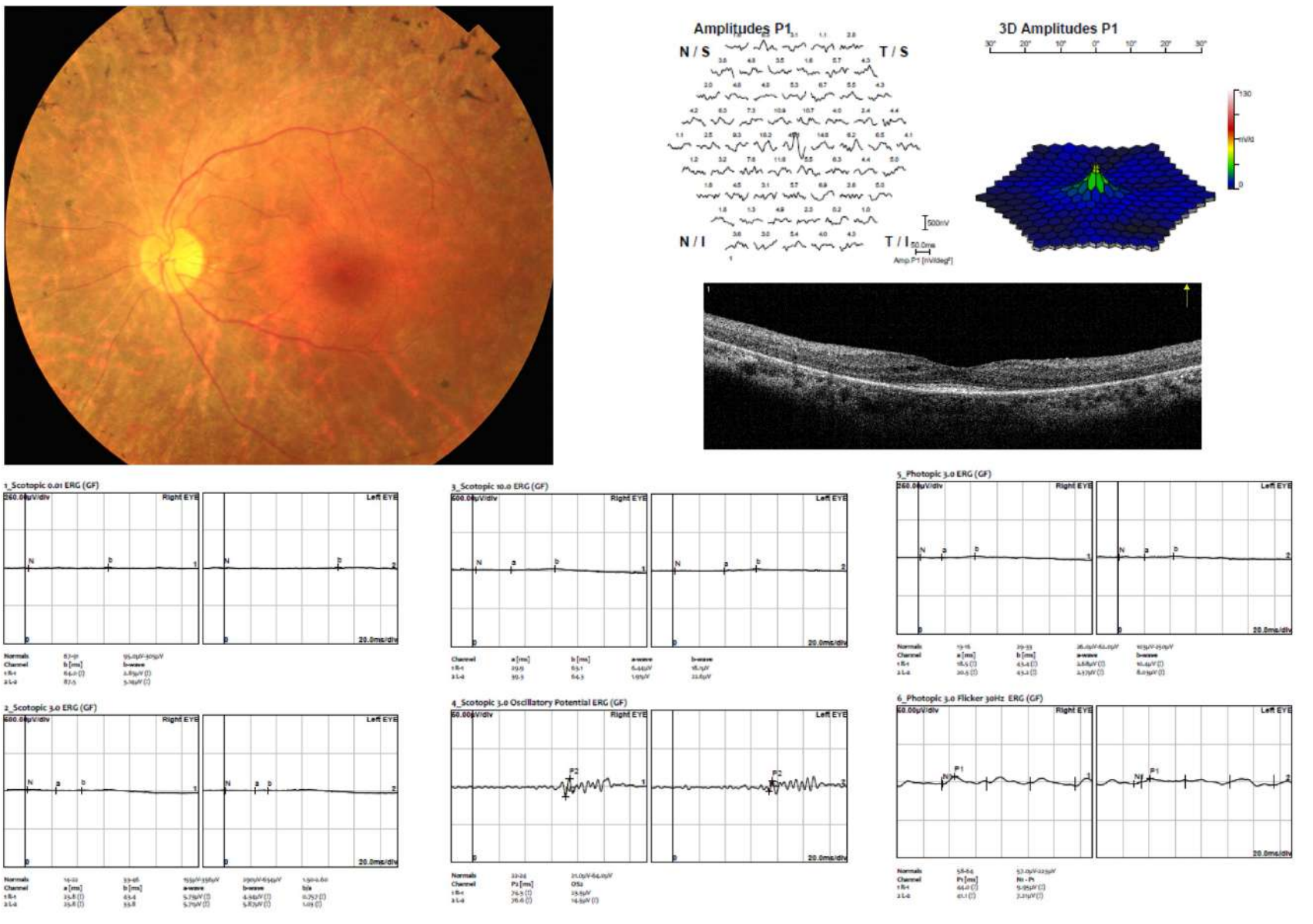


Fig. 1 – Color fundus photograph and OCT of a patient with retinitis pigmentosa. ffERG (bottom) shows extinguished scotopic and photopic responses. mfERG (top right) shows preserved foveal peak with decreased P1 amplitude in the outer 4 rings.

Progressive Cone / Cone-rod dystrophy

Inherited cone dystrophies are a heterogenous group of disorders characterized by decreased central visual acuity, color vision defects and varying degrees of nystagmus and photophobia. They may impair only cone function, or involve progressive rod photoreceptor loss as well, a distinction that can be made on ffERG. ffERG is particularly useful in early stages where fundus exam maybe normal. ERG findings of cone dystrophy include reduced amplitudes and IT delay in the photopic response and 30 Hz flicker ERG (Fig. 2). [8]

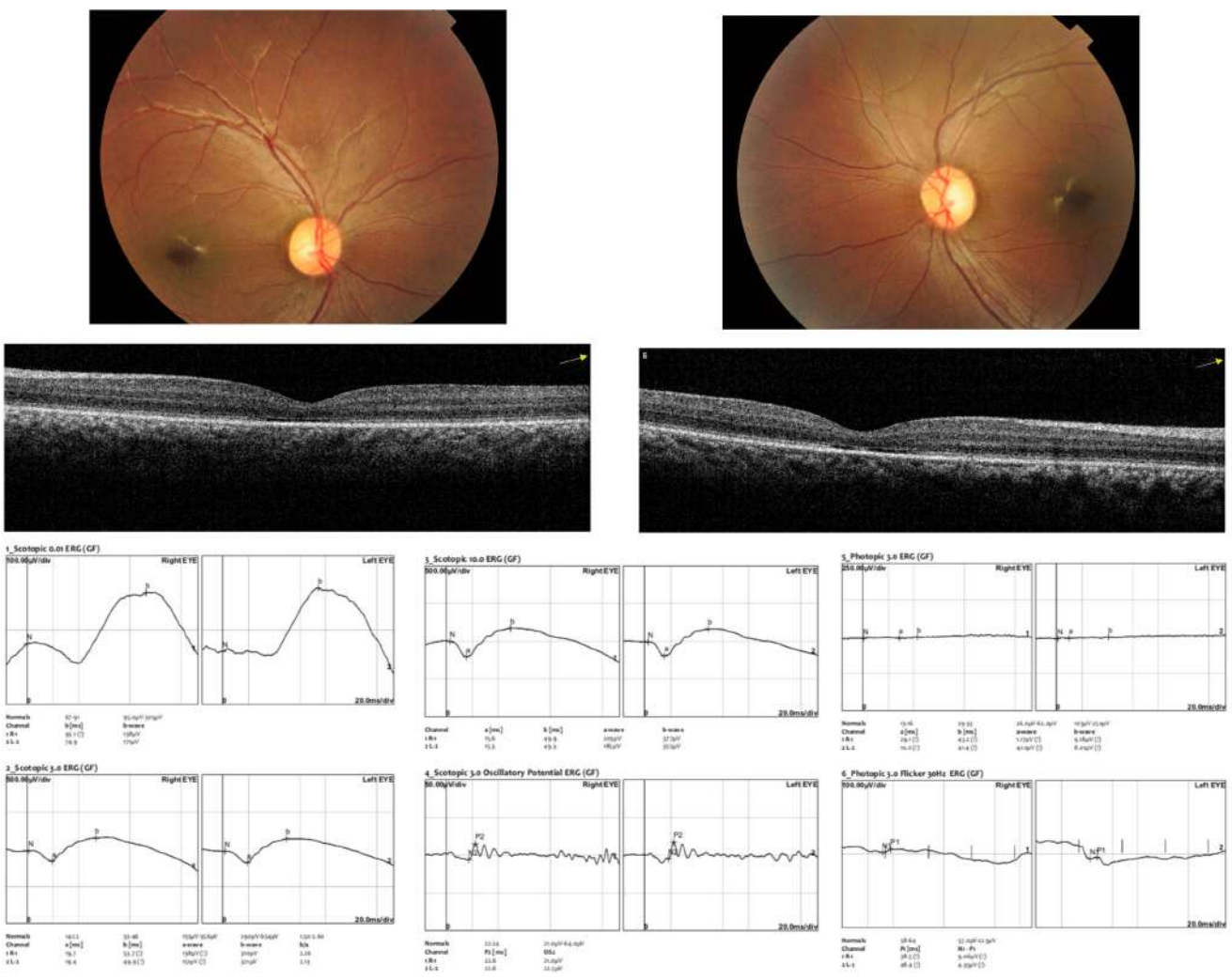


Fig. 2 – Color fundus photograph and OCT of a 13 year old male with decreased visual acuity (6/36 OU). ffERG (bottom) shows normal scotopic response and an extinguished photopic response suggestive of achromatopsia or rod monochromatism. Colour vision was found to be defective.

Cone dystrophy with supernormal rod response (CDSRR) is an autosomal recessive disease involving cone dysfunction with an abnormal rod ERG response, that is diagnostic and pathognomonic. The rod responses show insensitivity to dim light and increased responsiveness to suprathreshold light. CDSRR can be associated with cardiac abnormalities and genetic testing can confirm the mutations in either the KCNV2 or PDE6H genes. [9]

Enhanced S-cone syndrome (ESCS) is an autosomal recessive disorder due to mutations in NR2E3 that leads to excess S (blue) cones at the expense of other photoreceptor subtypes. The fundus shows characteristic nummular clumped pigmentary lesions around the vascular arcades with macular schisis. Electrophysiological testing is invaluable as the S-cone specific ON-/OFF ERGs show pathognomonic supernormal, higher amplitudes with simplified waveforms and delayed peak. Rod response maybe undetectable, combined rod-cone responses and 30 Hz flicker are delayed and reduced.[10]

Bradyopsia or “slow vision” is a rare disorder characterized by delayed dark to light adaptation due to defects in RGS9 or R9AP that play a critical role in the rate of recovery from phototransduction. In addition to the standard ISCEV protocols, a scotopic red flash ERG evokes normal DA rod and DA cone function but severely abnormal cone function under photopic conditions. [11]

Fundus albipunctatus is a type of congenital stationary night blindness, characterized by numerous dull white punctate lesions scattered throughout the fundus, without auto-fluorescence. Electrophysiological testing can differentiate it from retinitis punctata albescens and rule out associated cone dystrophy due to mutations in the RDH5 gene.

Scotopic dim flash ERGs are subnormal but can be normalized after prolonged dark adaptation, because of the slow rate of regeneration of photopigment (Fig. 3).[12] ffERG also aids in ruling out acquired and potentially reversible causes of nyctalopia, such as vitamin A deficiency, as it demonstrates a borderline reduction in cone function, in addition to a reduced rod response and a negative waveform on the combined rod-cone response.

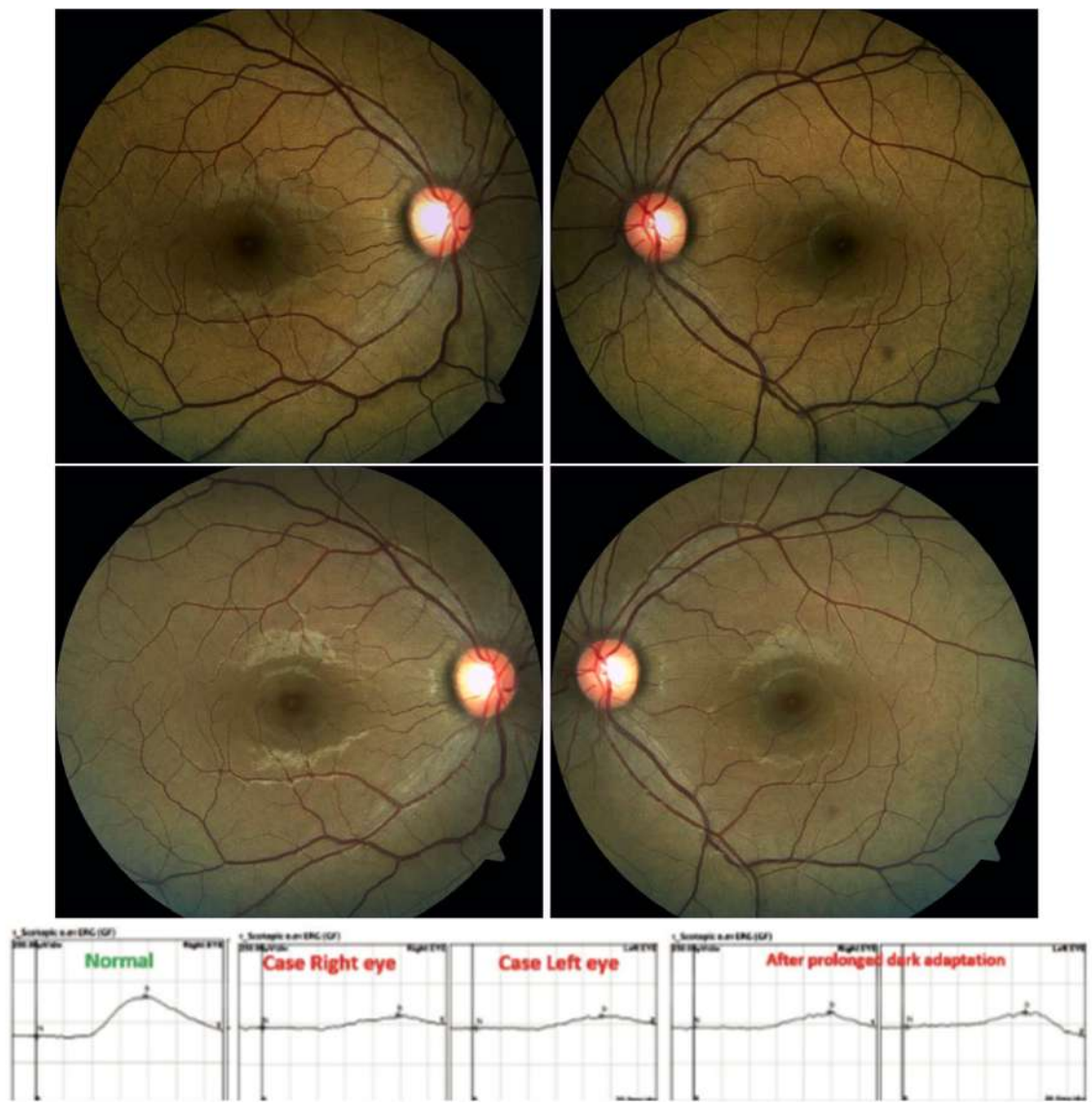


Fig. 3 – Color fundus photographs of a 25 year old male with congenital stationary night blindness showing the Mizuo Nakamura phenomenon (disappearance of golden metallic reflex after prolonged dark adaptation). ff ERG recordings of the case showing decreased rod response, and partial recovery in the scotopic responses following prolonged (two hours) dark adaptation.

Inherited macular dystrophies

Macular dystrophies (MDs) commonly present with bilateral central vision loss and electrophysiology remains the sole method to functionally differentiate them from generalized retinal dystrophies.

Stargardt disease is the commonest inherited juvenile macular dystrophy, associated with mutations in the ABCA4 gene. It can be classified into 3 groups based on electrophysiological features – in Group 1, the dysfunction is confined to the macula; in Group 2, there is macular and generalized cone dysfunction; in Group 3, there is generalized rod system dysfunction as well. Visual acuity worsens from Group 1 to 3. [13] This division of patients into subgroups allows to monitor for disease progression. mfERG provides another way to classify Stargardt disease according to the distribution of defective responses across the tested retina. However, electrophysiology cannot differentiate the autosomal recessive and dominant phenotypes.

Bestrophinopathies occur due to mutations in the BEST1 gene and are one of the commonest MDs in the world. Best vitelliform macular dystrophy (BVMD) or Best disease classically shows a normal ffERG and an abnormal EOG with a reduced light peak (LP) : dark trough (DT) ratio of 1.5 or lower, that signifies abnormal function of the RPE (Fig. 4). Patients with normal fundus in the early stages and carriers of the BEST1 mutation also show EOG abnormalities thus aiding in diagnosis. [14] Adult-onset foveomacular vitelliform dystrophy (AOFMD / AVMD) is clinically similar to BVMD, but can be differentiated on electrophysiology by a normal EOG. Autosomal recessive bestrophinopathy (ARB) on the other hand demonstrates reduction in both scotopic and photopic responses on ffERG and a severely reduced LP:DT ratio on EOG, reflecting

dysfunction not only in the RPE but also in the overlying retina. Thus, electrophysiological tests, especially EOG, provide an important tool to characterize the clinical presentation seen in different bestrophinopathies.

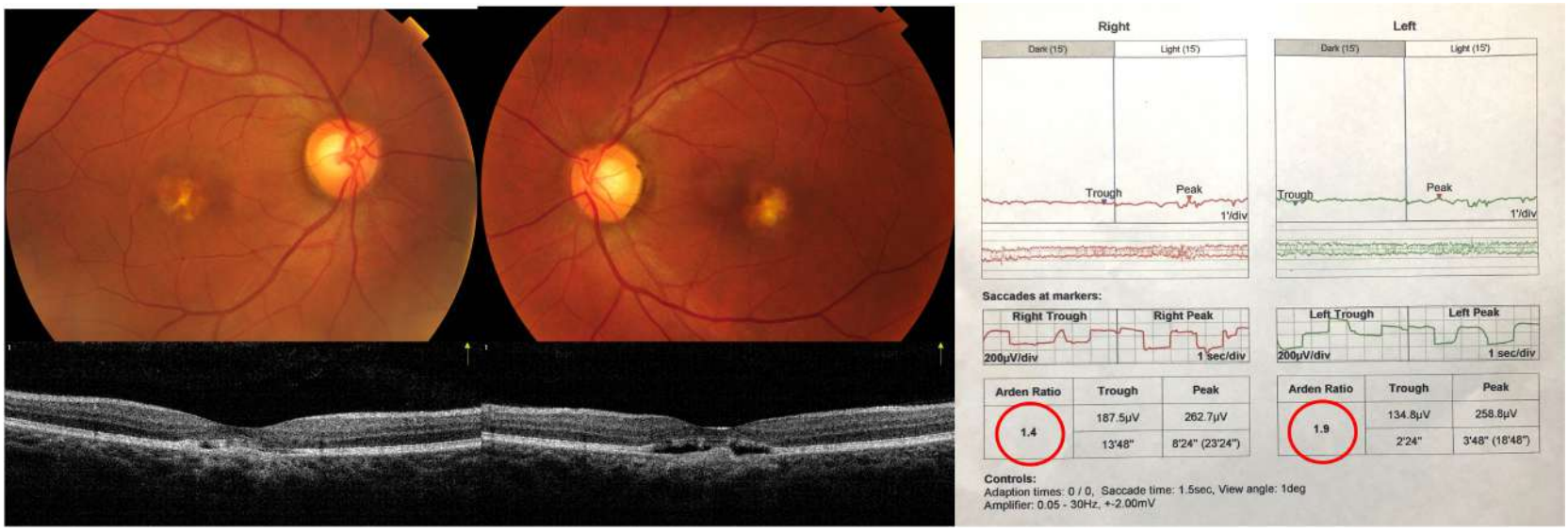


Fig. 4 – Color fundus photograph and OCT of a 32 year old male with BVMD (6/9 OU) showing vitelliform lesion. EOG showed a decreased light peak (LP) : dark trough (DT) ratio. ffERG was normal.

X-linked juvenile retinoschisis (XLRS) is the commonest IRD affecting the macula in males. OCT is currently the mainstay of diagnosis. On ffERG, XLRS patients have a classic electronegative response in a dark adapted retina (Fig. 5), but this feature can be associated with a host of other disorders like congenital stationary night blindness, retinal ischemia, paraneoplastic autoimmune retinopathy. mfERG shows reduced response densities in the schitic areas, and delayed IT in much larger areas. [15]

Occult macular dystrophy (OMD) is characterized by bilateral progressive vision loss along with a normal fundus appearance. OCT can pick up loss of the interdigitation zone in this condition, but mfERG better reflects the functional change across the OMD retina (Fig. 6). The response densities significantly decrease in the central 7 degrees and gradually approach normal values towards the peripheral retina. IT remain prolonged

over the entire tested retinal area.[16]

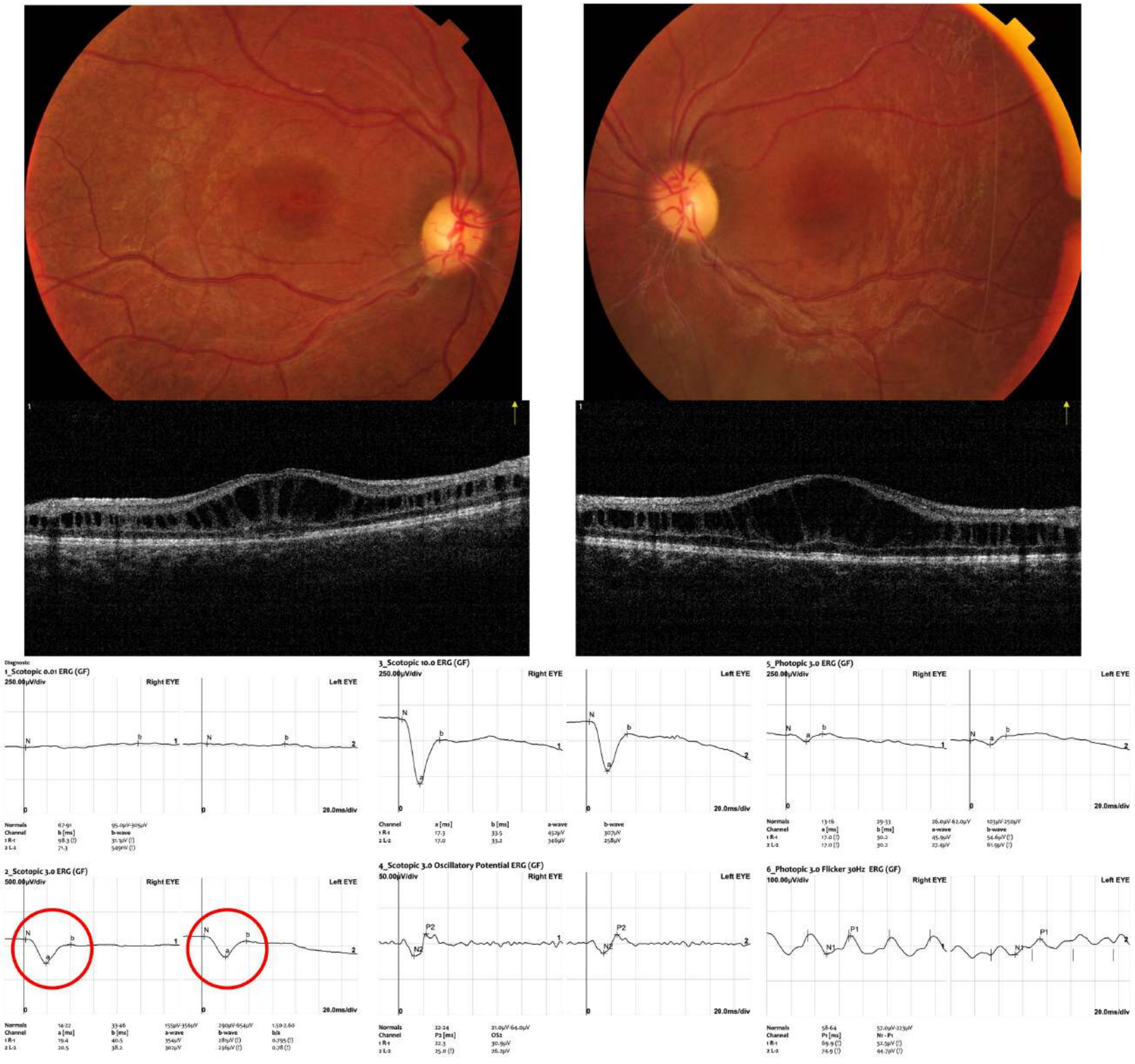


Fig. 5 – Color fundus photograph and OCT of a 12 year old male with decreased visual acuity (6/24 OU) showing foveoschisis. ffERG (bottom) shows “negative waveform” in the combined rod cone response.

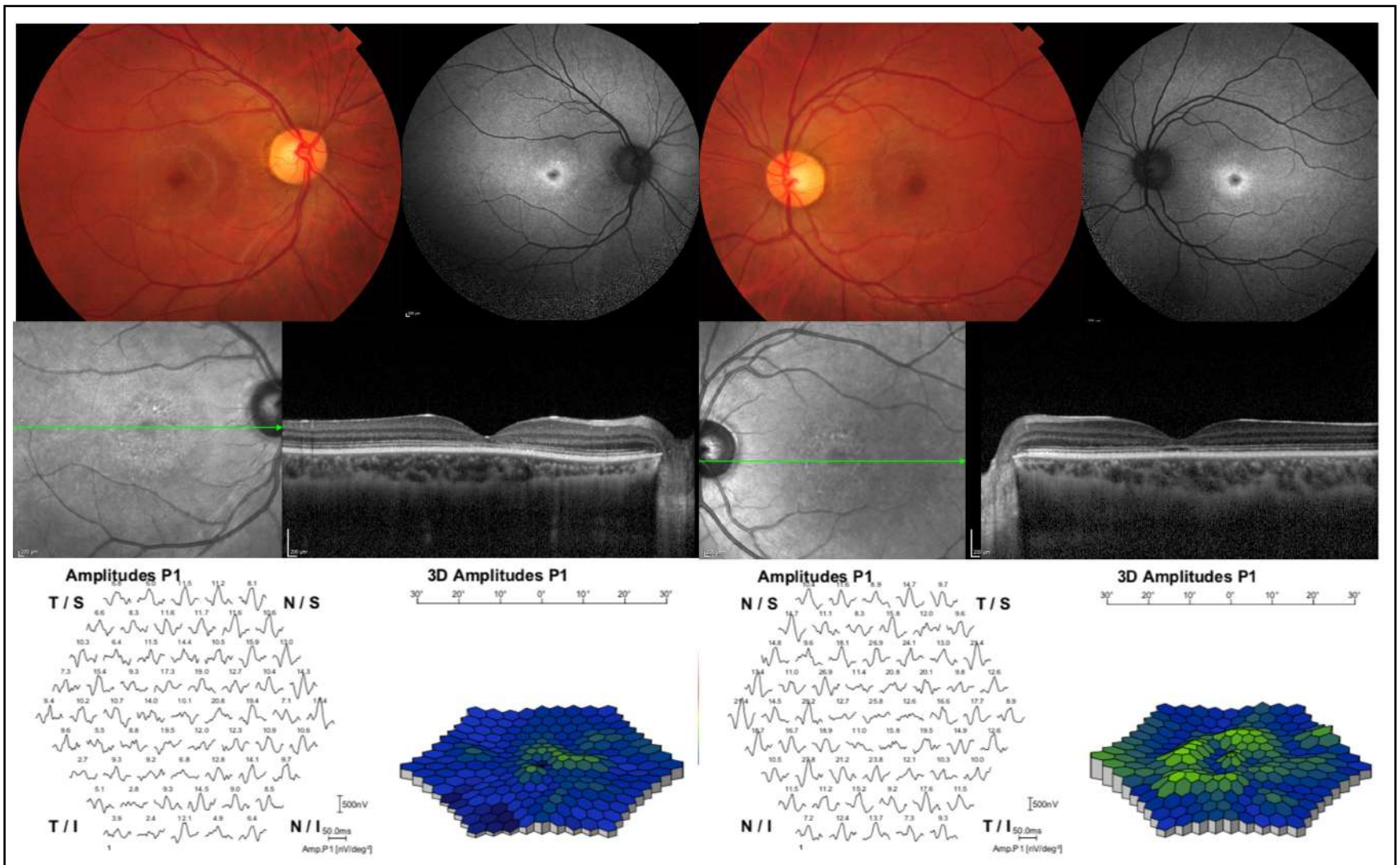


Fig. 6 – Color fundus photographs and fundus autofluorescence (top) of a 23 year old male, referred as “unexplained visual loss” (OD 6/24, OS 6/36). OCT (middle) shows abnormal ellipsoid zone (EZ). mfERG (bottom) shows depressed central responses (amplitude)

Conclusion

Electrophysiology testing allows for further understanding of IRDs and can be used for early detection, prognosis prediction, and therapeutic monitoring in this subset of patients. Some disorders such as CDSRR, enhanced S-cone syndrome and bradyopsia show pathognomonic findings in ffERG clinching the diagnosis. Combining electrophysiological testing with other imaging modalities provides additional information especially in pre-symptomatic patients or those with atypical features and

identifies patients for targeted specific molecular screening to confirm the diagnosis. Overall, electrophysiological features add to the clinical and genetic characterization of IRDs.

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INTERESTING IMAGE:

GIANT RPE RIP IN CASE OF BUTTERFLY-SHAPED PATTERN DYSTROPHY

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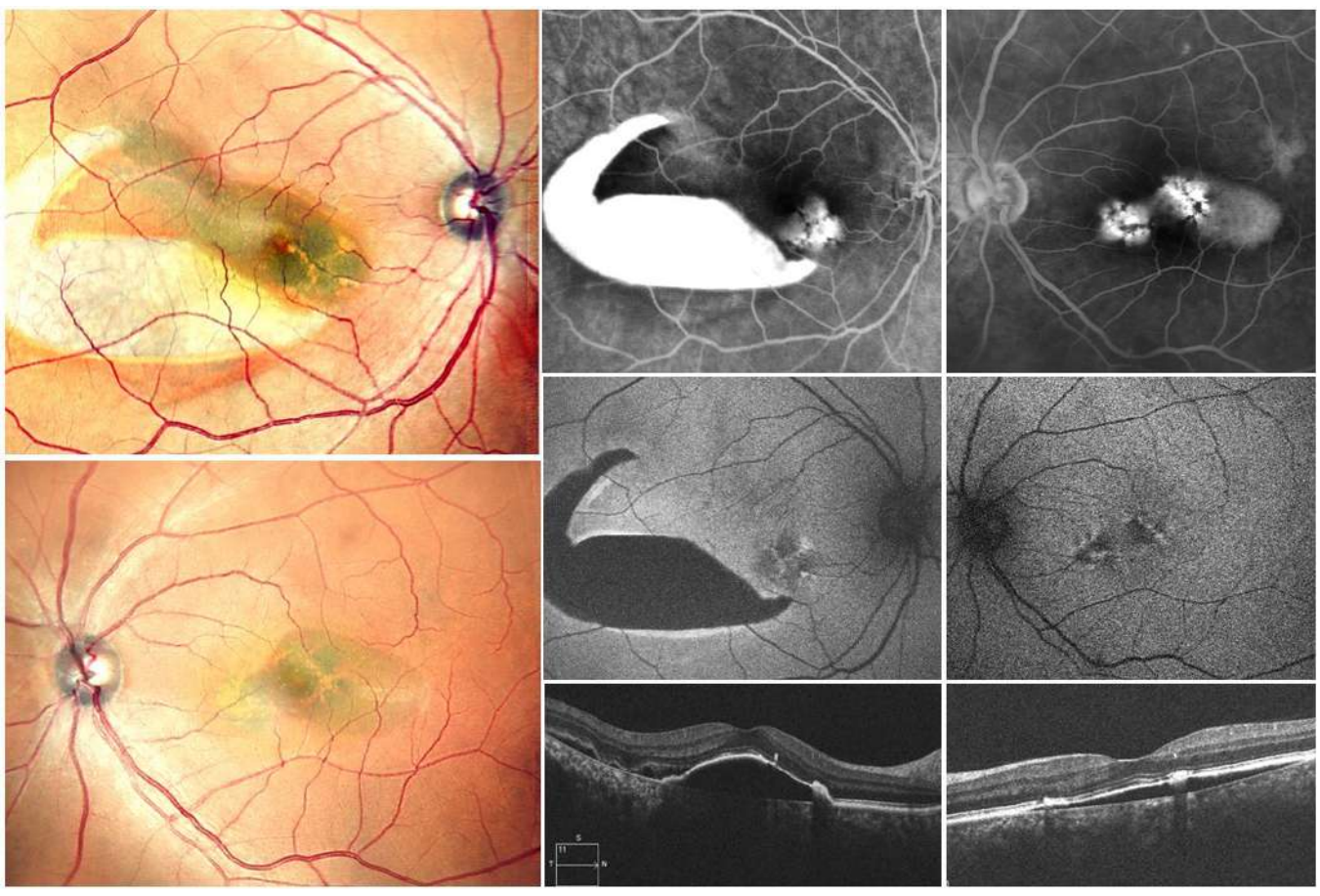

A 44-year-old male patient presented with a complaint of disturbance in vision in the right eye of 15 days duration. Best corrected visual acuity was 6/6, N6 in both eyes. Right eye fundus evaluation revealed large RPE rip and left eye showed idiopathic flat topped serous pigment epithelium detachment along with typical features of butterfly-shaped pattern dystrophy. Fundus autofluorescence and fundus fluorescein angiography imaging confirmed the diagnosis.

INCORPORATING GENETIC TESTING AND GENETIC COUNSELLING INTO CLINICAL PRACTICE

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With increase in awareness and better understanding of inherited retinal disorders (IRDs), there is now an urgency amongst the clinicians to incorporate care of these disorders also into their practice. Because of perceived financial and phycological barriers, so far these facilities have been limited to tertiary care centres. To allow better access to a large number of patients in need, it is imperative that these services become a part of primary care. The AAO's Task Force of Genetic Testing and the European Reference Network for Rare Eye Disease recommends that all patients with presumed or suspected IRDs undergo genetic testing.(1)

Incorporating genetic testing and genetic counselling into clinical practice involves a multi-faceted approach to ensure accurate diagnosis, personalized management and allow access to FDA approved future treatments and clinical trials, ultimately improving patient satisfaction.

The roadblocks in such an endeavour include:

1. Patient ignorance
2. Genetic testing and counselling has to be advised by ophthalmologists who are non-geneticists and are unfamiliar with these.
3. Ignorance about accredited labs that offer genetic testing in their region.
4. Perception that these genetic diseases are rare so investment in their care may not be cost effective. But it is important to remember that Inherited eye diseases are not so uncommon. Nearly 1 in 1000 people are affected with genetic eye disease worldwide.[2] Prevalence of IRDs have been reported to be 1 in 2000 to 1 in 3000 individuals.[3]
5. Lack of/limited access to trained personnel (clinical geneticist, ophthalmic geneticist, genetic counsellors) for pre-test genetic counselling to guide appropriate systemic work up and genetic testing[4]
6. General belief that “Nothing can be done” or “there is no treatment for IRD” and that genetic testing is very costly. With advancing technologies many new treatments are on the horizon. Also, with the advent of gene therapy for biallelic RPE65 variants implicated in Leber congenital amaurosis (LCA), accurate genetic diagnosis is becoming increasingly important to determine who will benefit from treatment. In paediatric population, wherein IRDs are major cause of visual impairment[5] and may be the presenting symptom of a syndromic condition, early genetic diagnosis may help prevent extraocular morbidity.

A complete genetic work up does not only involve genetic testing but also includes providing pre-test and post-test genetic counselling, genetic test interpretation, extended family testing and prenatal diagnosis where implied, gene based prognosis and providing patients with the information and follow up regarding ongoing clinical trials and newer treatments.

Various types of genetic tests may be used. These vary from targeted tests like Sanger sequencing and disease specific panels to pan genomic tests like the chromosomal microarray analysis (CMA) and Whole genome/ exome analysis using Next-generation sequencing (NGS) to look for single-nucleotide variants(SNVs) and/or small insertions and deletions.(6)

Choosing the correct test is of utmost significance. The choice of appropriate genetic testing is determined by underlying genetic etiology and knowledge of molecular genetics. Pre-test genetic counselling/ discussion with a clinical or molecular geneticist can aid in genotype-phenotype correlation, determining syndromic or isolated genetic disorder and choosing the most appropriate genetic test.

Most tests in IRD will be NGS based which screens multiple genes and is especially useful in diseases like RP that can be caused by more than 100 genes. NGS can be:

a. Single gene testing-like RPE65 for LCA or RB1 for retinoblastoma.

b. Gene panel Sequencing. Panel based targeted sequencing is the most commonly used approach. This tests specific exons and flanking intronic gene regions that have been implicated in IRDs. List of genes covered in the specific panel is provided by the lab doing the test.

c. Whole Exome Sequencing (WES) captures all the coding exons in the genome

d. Whole Genome Sequencing (WGS) tests entire genome including exons, introns,

regulatory and promoter DNA and large structural variations.

Panel-based NGS testing has a detection rate of approximately 60-70%.[7] The test as well as the solve rate of genetic testing increases with the use of exome and genome sequencing but so does the added cost of the procedure, with WGS being almost 5 times the cost of gene panel based tests. Also, false discovery rates may be higher which may make test interpretation more difficult. [8]

Here's a comprehensive structured strategy for integrating these services:

1. Understand Inherited Retinal Disorders:

   A basic knowledge of types of IRDs including conditions like retinitis pigmentosa, Leber congenital amaurosis, and Stargardt disease, which have different genetic causes and inheritance patterns is important. Some IRDs are caused by mutations in specific genes, and phenotypic recognition of these can guide appropriate genetic testing.

2. Clinical Assessment :

   The process of good genetic diagnosis begins with careful clinical examination.

   a. Good ocular history taking to record symptoms as well as onset and pace of progression of symptoms.
   b. Relevant medical history and systemic examination to look for obesity, hearing loss, polydactyly, dental abnormalities, etc.
   c. Drug history and history of trauma to rule out any masquerades like drug toxicity with drugs like hydroxychloroquine or solar retinopathy where in genetic testing will be totally confusing.
   d. Assess visual impairment in terms of best corrected visual acuity, color vision and field examination.

e. History of night blindness or difficulty in dark adaptation

3. Good Phenotyping of disease:

a. Precise ocular examination along with appropriate diagnostic testing, such as wide field fundus photography, electroretinogram, optical coherence tomography (OCT) , fundus autofluorescence (FAF), and visual fields.

b. Establish the topography of disease. This is best seen on FAF by looking at the distribution of the RPE granularity or pigment dispersal.

c. Quantify macular involvement with OCT and correlate it with best corrected visual acuity.

4. Genetic Testing:

Highest yield with NGS based genetic testing is obtained when following complete work up, a list of differential diagnosis and complete summary is submitted to genetic lab. Collection of Samples for genetic analysis involves extraction of DNA obtained from blood or saliva from patients after obtaining informed consent. These samples are then sent to accredited labs for DNA testing and analysis.

Genetic testing includes:

A. Pretest Counselling

B. Interpretation of Results

C. Post test Counselling

A. Pretest counselling includes: Pre-test genetic counselling should be done by trained ophthalmologist, ophthalmic geneticist, clinical geneticist or a genetic counsellor. It includes

a. Discussion on hereditary nature of disease and its possible effect on the

next generation.

b. Determine family history and construction of at least a three generation pedigree.

c. To summarize disease features and provide a list of differentials to the lab to attain maximum yield from genetic testing.

d. Discuss the potential benefits and implications of genetic testing with patients and their families.

e. Discuss with the patient the limitation of genetic testing and that the final report may in some cases be non-diagnostic (no variants identified or variants of uncertain significance-VUS) in case the selected test panel did not include the causative gene or the variant has not yet been classified as disease-causing.

f. In case of non-conclusive test result, repeat testing or testing of the family or periodic re-analysis of genetic report may be required.

g. Informed Consent: Ensure patients understand what genetic testing involves and the possible outcomes.

B. <u>Interpretation of Results:</u>

The genetic labs in accordance to American college of medical genetics and genomics (ACMG) guidelines reports a variant as pathogenic/likely pathogenic, or variants of uncertain significance(VUS). [9]

This process is dynamic, as variant interpretation may also change over time based on new reports and findings published by the scientific community. Ideally,

disclosure of results and genetic counselling should only ensue after validation of functional consequences of "VUS". Repeat genetic testing after 3-5 years may increase the diagnostic yield. (10)

C. Post-test genetic counselling:

This is best provided by trained ophthalmologist/ ophthalmic geneticist/clinical geneticist/genetic counsellor who provided pre-test genetic counselling. He/She should explain the report to the patient in simple words and also discuss the report with the referring clinician. Counselling must include:

a. Discussion of the implications of the diagnosis with the patient.
b. Explanation of the gene variant based precise prognosis and natural disease history.
c. Identification of at-risk family members.
d. Genetic counselling can also discuss options of gene therapy or other newer treatment options where available .
e. Explanation on how the genetic results may affect their family planning options.

All this should be done while ensuring confidentiality and ethical handling of sensitive genetic information.

5. Collaborate with Clinical Geneticists/Molecular Geneticists/Genetic Counsellors:

Collaboration with Genetic Counsellors (GC) is required for not only pre-test and post -test genetic counselling but also to provide multidisciplinary care and family

support, to identify new genes and genetic diseases and provide prenatal diagnosis where necessary. In places where access to GC on site facilities is limited, tele-consultation can be an alternative.

6. Incorporate Results into Management Plans

a. To fully utilise the results of the genetic tests, clinicians need to keep abreast of advancements in treatment of IRDs and facilitate eligible patients to participate in ongoing clinical trials.

b. Provide accessible resources about IRDs

c. Provide connect with support groups if available.

d. Train healthcare providers like optometrists on the basics of genetic testing. Some knowledge and education about IRDs can allow them to give better care especially when providing low vision care.

e. Patients with multisystem involvement need to be guided to be under the care of internists.

f. Regularly assess the effectiveness of genetic testing and counselling services and seek feedback from patients and providers.

Last but not the least, these tests are not covered under insurance in India, so a connection with research organisations and NGOs can help support the cause of genetic testing for patients with IRD.

Genetic testing comes with a responsibility. Our patients deserve accurate clinical diagnoses and genotype confirmation to allow a better understanding of their disease and hopefully, someday, treatment for their condition.

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INTERESTING IMAGE:

THE ECLIPSE WITHIN: STARGARDT SILENT SHADOW

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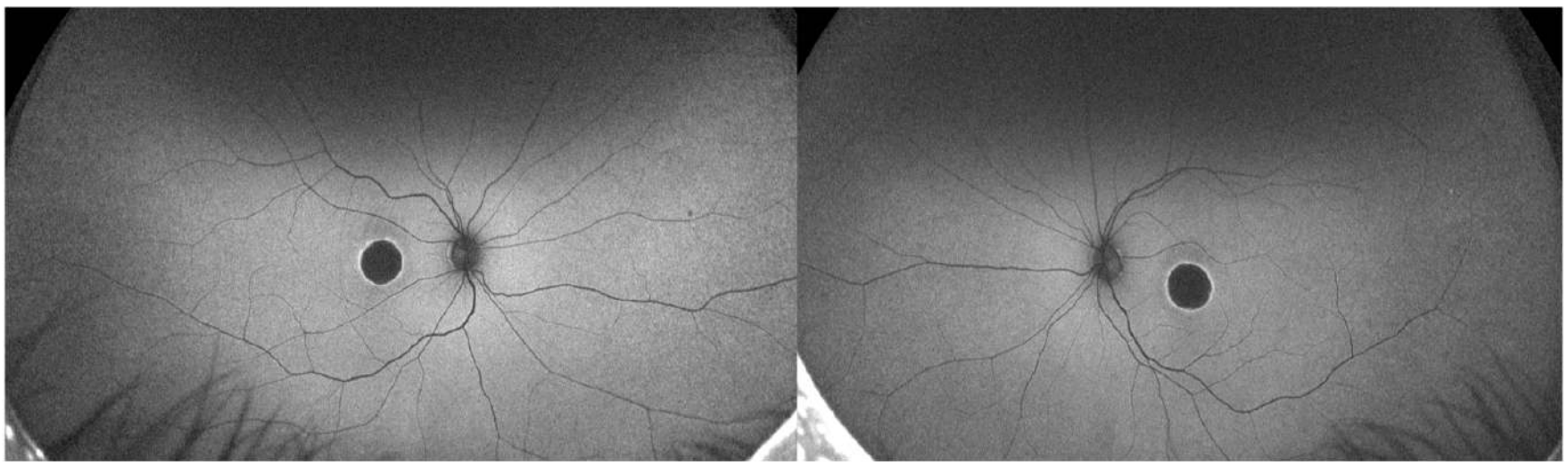

Fundus autofluorescence image of a patient with Stargardt disease

TREATMENT OPTIONS, MYTHS AND FACTS IN RETINAL DYSTROPHIES

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Introduction

Retinal dystrophies are a group of degenerative disorders of retina which show genetic and phenotypic heterogeneity [1] even within the same family, characterized by progressive degeneration of the outer retinal layers- photoreceptors and/or RPE leading to significant disability in the patients. This article will concise our current understanding of retinal dystrophies and briefly discuss the treatment options.

Physiology of vision

Perception begins with phototransduction, i.e. conversion of light to electrical energy. This occurs via a chain of reactions within the outer segment discs of photoreceptors containing 11-cis-retinal which gets converted to all trans retinal, the byproduct opsin converts into metarhodopsin 2 causing hyperpolarization of disc plasma membrane which depolarises the bipolar cells and creates an action potential[2] These metabolically active discs of outer segments undergo shedding and phagocytosis by Retinal Pigment Epithelial (RPE) cells, which can then be used up for photoreceptor regeneration. Thus, RPE and photoreceptors function as a single unit to ensure good vision. Defect in anyone leads to defect in the other. (Figure 1)

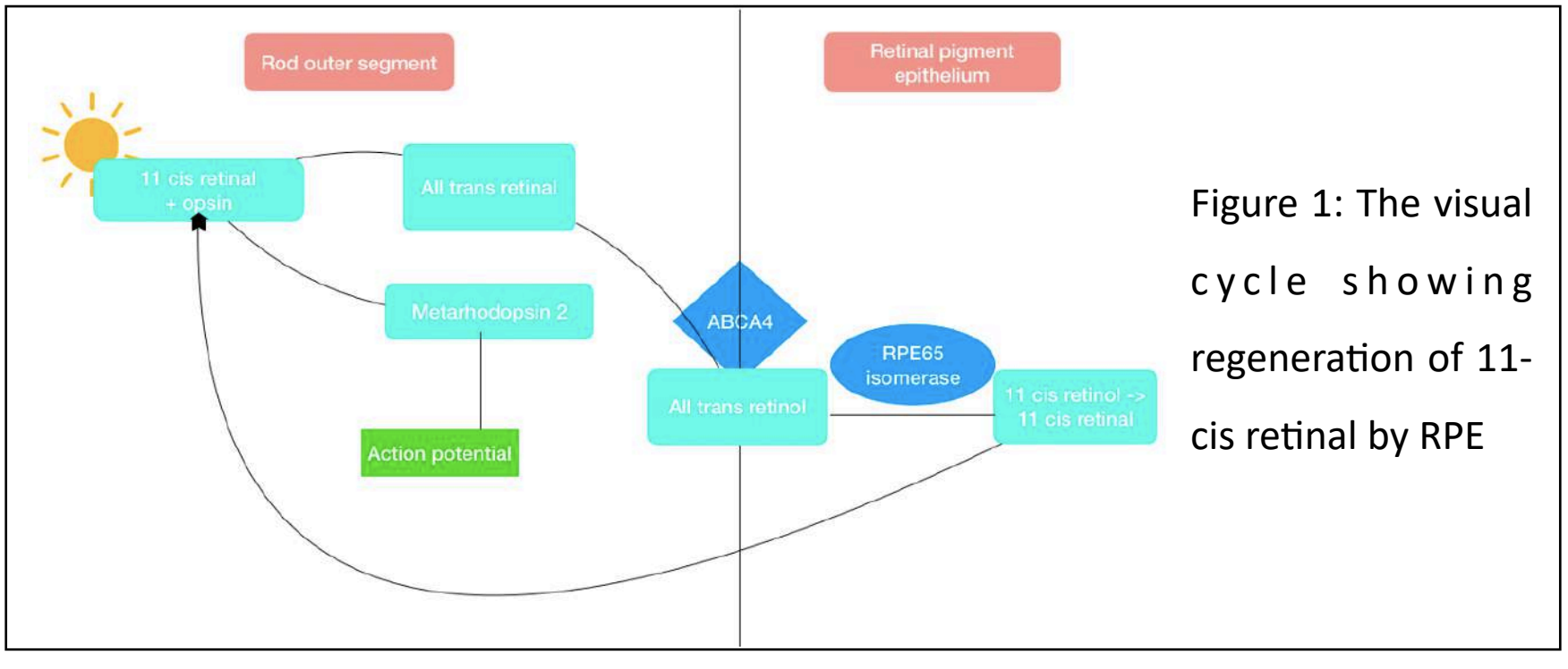

Figure 1: The visual cycle showing regeneration of 11-cis retinal by RPE

Retinal dystrophies can be broadly classified into 3 types based on which cell type is involved-

1. Rod cone dystrophy, i.e. rod predominant

2. Cone rod dystrophy, i.e. cone predominant

3. Macular dystrophy, which involves both rods and cones in the macula

Presentation

Based on the pattern of inheritance, the onset and extent of visual impairment can vary even within a family owing to incomplete penetrance and variable gene expressibility. Dominantly inherited mutated genes will present late and have slightly better prognosis than the recessive one where both the genes are non functional. In X linked inheritance, the females will be spared and are mostly carriers. Males will be more severely affected in that case.

Typical rod cone dystrophy or Retinitis pigmentosa presents with early onset night blindness followed by contraction of peripheral visual fields, which are often ignored initially as the visual acuity is normal. Once the disease progresses and significant loss of photoreceptors has occurred, they start noticing the symptoms which makes it difficult to drive at night, frequently bumping into objects as the peripheral field starts to constrict.[3] Visual acuity can be reduced due to macular edema or posterior subcapsular cataract. [4,5] Fundus findings include a triad of arteriolar attenuation, bony spicules, and a waxy pale optic disc which is seen in very late stages. ERG is diagnostic as dark adapted response is affected much more than the light adapted one.

Cone dystrophies present with early onset vision complaints such as central scotoma

with symptoms getting worse during daytime, photophobia which is perceived by some as pain on opening eyes in normal lightning and color vision abnormalities which may later extend to involve the peripheral fields as in cone-rod dystrophies.[6] Fundus can be normal in early stages, later on pigmentary and atrophic changes in the macula and a pattern mimicking RP can be seen. ERG shows selective lowering of cone response much more than rod response.

Macular dystrophies affect both rods and cones in the macula thus causing low vision in both day and night, color vision difficulties and characteristic fundus findings- pisciform flecks which appear hyperautofluorescent on FAF with peripapillary sparing, beaten bronze appearance at macula as in Stargardt's disease[7] or yellowish, vitelliform lesion in the macula as in Best's macular dystrophy.

Treatment options

Given the progressive and irreversible nature of retinal dystrophies, it becomes even more important to diagnose and salvage the remaining functioning cells, to slow down / arrest the speed of photoreceptor degeneration. With ongoing research, multiple treatment options are available, and many new advances are upcoming for the treatment of inherited dystrophies.

Pharmacological treatment

Carbonic anhydrase inhibitors given by topical or oral route help to reduce macular edema by acidifying the sub retinal space, thereby increasing the adhesiveness. A clinical starting dose of 500 mg/d oral acetazolamide for at least a month is required to see an effect.[8]

Emixustat is a visual cycle modulator, targeting the enzyme- RPE65 which is involved in the production of 11 cis retinal from all trans retinal in RPE. By depleting 11-cis retinal, it indirectly suppresses the production of all trans retinal as well which reduces the production of its toxic by product- bis retinoids (A2E) and prevents RPE degeneration, and could potentially slow down macular atrophy in Stargardt's disease [9]

Gene therapy

Using a specific viral or non viral vector, the gene of interest is introduced into the target cell which then starts to express the desired protein. Thus an adequate vector is the principal requirement for any successful gene transfer. Most commonly used viral vector, adeno associated viral vector 2 (AAV2) is non immunogenic and doesn't integrate into the host cell, but when a large gene needs to be inserted such as ABCA4, then a vector with larger cargo capacity is needed such as lentivirus. However, the production of these viral vectors is costly and some of these can trigger an immune response. These problems are less with non-viral vectors, nanoparticles coated with plasmid DNA, metal bound DNA or direct injection of naked plasmid DNA into the target cells.[10] These vectors can be introduced into the retina through subretinal or intravitreal injection. Subretinal technique, the most common one, is more invasive but also more accurate in reaching the RPE. Intravitreal approach targets a larger area of inner retinal layers.[11]

The required gene can be simply inserted in the DNA of the host cell to take over the function of the defective gene by a process called gene augmentation. Voretigene Neparvovec (Luxturna) has received FDA approval for treatment of LCA with biallelic RPE65 mutation. It utilizes recombinant adenovirus vector to introduce a functioning copy of the gene into the host cells administered via subretinal injection.[12] In early

stage of X linked recessive RP, subretinal injection of AAV2 vector containing a functioning copy of the RPGR gene has shown to prevent photoreceptor degeneration. [13]

However, in diseases with dominant inheritance, the defective gene needs to be silenced to allow the functional gene to express which can be achieved via CRISPR Cas9 technology. Here Cas9 binds to the target DNA sequence with the help of a guide RNA. Then dsDNA cuts are made by CRISPR Cas9 endonuclease, followed by repair via non homologous end joining. This technique has shown to prevent photoreceptor degeneration in autosomal dominant RP. [14]

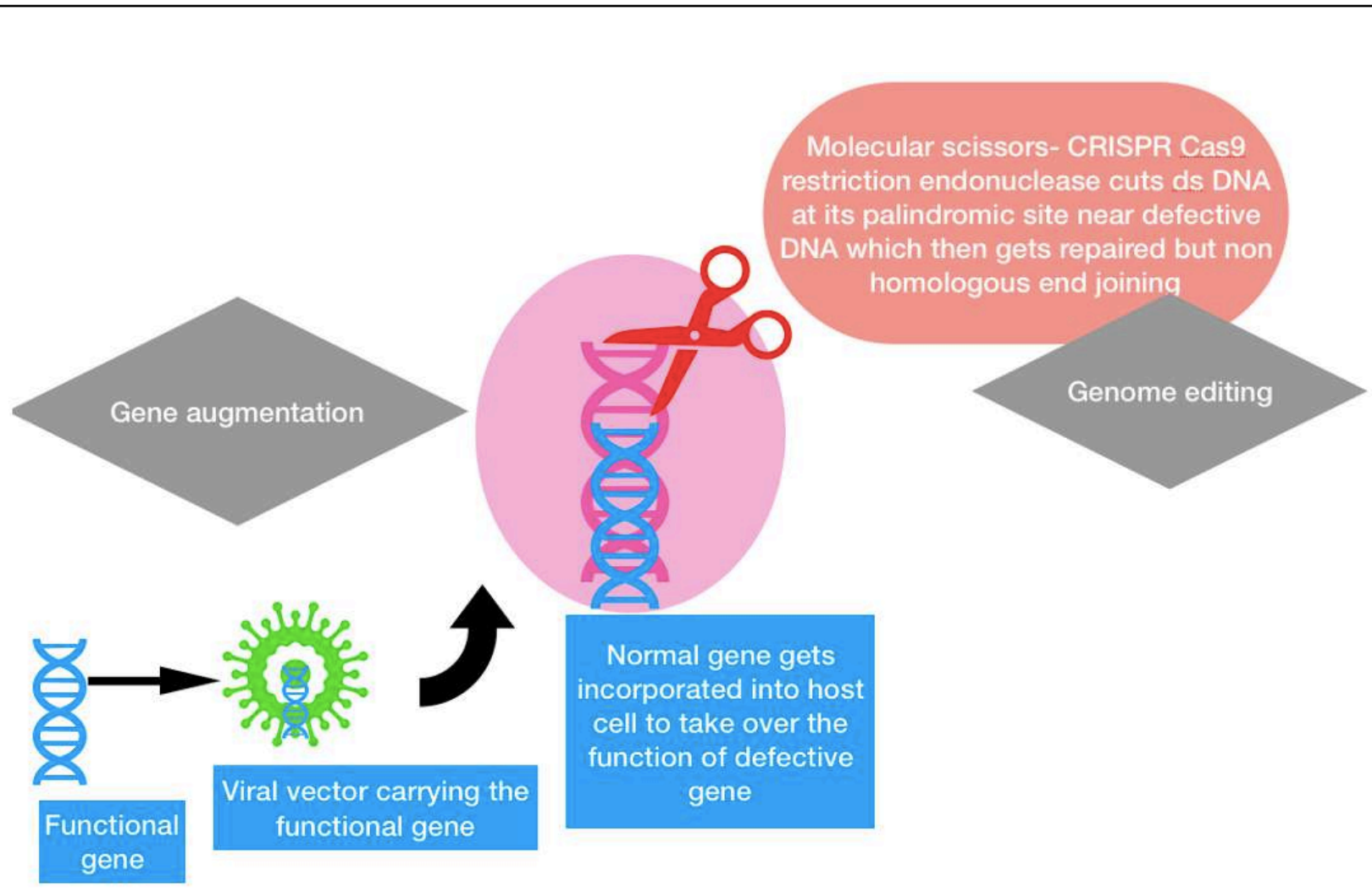

Figure 2: Different types of gene therapy

Optogenetics

Most patients present late to the clinic. By the time, most photoreceptors have already degenerated, however the second and third-order neurons are spared in these diseases. Using an adenovirus vector, channel rhodopsin can be expressed in the third-order neurons, i.e. retinal ganglion cells which then start phototransduction taking over the function of photoreceptors (Figure 3).[15]

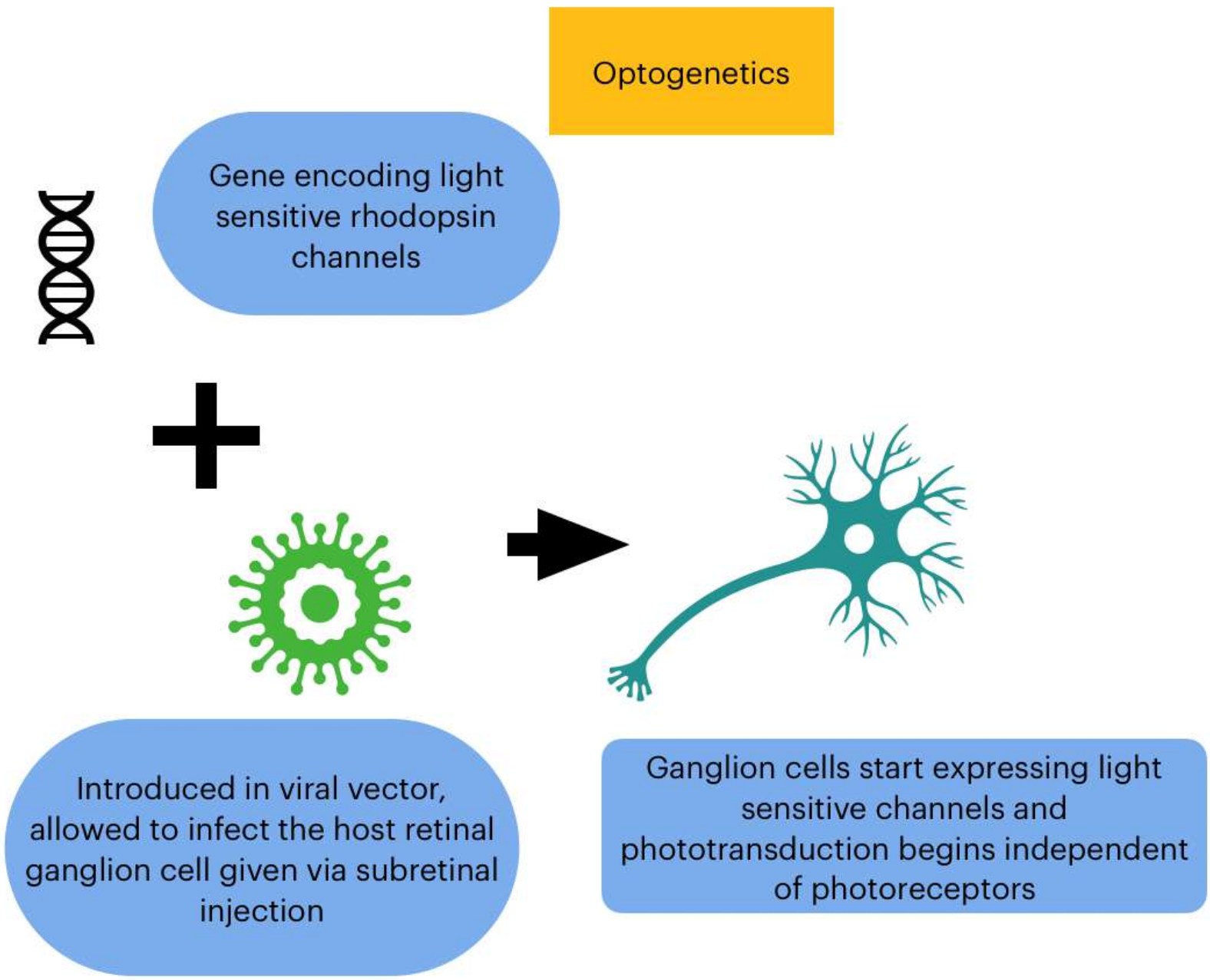

Figure 3: Principle of optogenetics

Mesenchymal Stem cell therapy

Stem cells can be used to directly replace the damaged RPE cells or take over their function and produce essential growth factors and trophic factors. This is achieved using human embryonic stem cell derived RPE cells to take over the function of damaged cells. Phase I/II trials have shown encouraging results in Retinitis Pigmentosa (RP), Stargardt disease and even AMD [16]

Immunotherapy

Microglia are the major immune cells in the retina which undergo sustained activation leading to progressive recruitment of immune cells leading to destruction of retinal layers. Immune based therapies which target microglia such as TSPO ligands and INF-B can help to reduce the inflammatory process.[17]

Autologous platelet rich plasma (PRP) injected in suprachoroidal or subtenon space, especially in cases where functional vision is preserved, helps to slow down the disease process. Negligible treatment costs and affordability will give power to economically disadvantaged patients.[18]

Treatment of complications and Low vision aids

In order to limit the disability in these patients, regular follow ups should be done to correct underlying refractive error, surgery for cataract especially in RP, and low vision aids such as magnifiers, telescopes and reading frames.

Myths and facts related to retinal dystrophies

MYTH	FACT
Retinal dystrophies are always passed onto the next generation	The type of inheritance decides whether the offsprings will receive the mutated allele, clinical presentation may still be variable due to variable expressibility and incomplete penetrance
All retinal dystrophies lead to total blindness	While retinal dystrophies can cause significant vision loss, the severity and progression of vision loss can vary depending upon the type of dystrophy and individual factors, and the type of inheritance: dominantly inherited usually present late and show slower progression than recessive counterparts. Complete progression to blindness is rare, especially in RP
All retinal dystrophies are progressive	While majority of the retinal dystrophies are slowly progressive, a significant number of cases including congenital stationary night blindness and achromatopsia are non-progressive and remain stable for a long time. Detailed phenotyping and genotyping is required for all IRD patients to identify and prognosticate such cases.
High dose vitamin A supplementation is protective in retinal dystrophies	The by-products of retinol metabolism can cause worsening in patients of Stargardt disease where the retinol transporter ABCA4 is already defective. Risks of vit. A toxicity must be considered as well which include raised intracranial pressure, liver toxicity and teratogenicity.
Only retina is affected in these dystrophies	Besides retina, systemic involvement can be seen based on the gene involved and needs adequate workup and treatment

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GENE THERAPY FOR IRD: PROSPECTS AND CHALLENGES IN THE INDIAN CONTEXT

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Introduction:

Inherited retinal disorders are group of disorder that leads to visual impairment in the early stage of life and most common childhood blindness in high- and middle-income countries. The worldwide prevalence rate of IRDs is 1 in 2000.[1] IRDs comprise a spectrum of clinical phenotype and inheritance pattern followed by autosomal recessive, dominant, x-linked and mitochondrial mode. Currently, neuroprotection, pharmacology, and optogenetics offer avenues for maintaining vision from further deterioration.[2] But globally, AAV-based gene therapy has shown promising results, leading to the approval of several gene therapy products for inherited disorders[2]. However, in the Indian context, the development and application of gene therapy, particularly for retinal dystrophies, face unique challenges. These include limited industrial and scientific infrastructure, a lack of organized patient databases, and financial constraints that hinder large-scale clinical trials and therapy development.[3] Despite these challenges, recent years have seen growing awareness and efforts within Indian research and clinical communities to advance gene therapy for retinal dystrophies. Indian organizations are increasingly engaging in gene therapy research, aiming to bridge the gap between global advancements and local applications. This progress is crucial for addressing the unmet needs of patients with genetic disorders in India, particularly those with inherited retinal dystrophies, which are a significant cause of visual impairment in the country. As India continues to build its capacity in gene therapy, rAAVs remain a leading platform for delivering wild-type gene copies. However, the path forward requires addressing critical questions related to the pathophysiology of retinal diseases, optimizing delivery methods, and ensuring the affordability and accessibility of these therapies for the Indian population.

Table 1: List of clinical trials for retinal disorders

Target disease	Target	Vector	Delivery	Phase	Sponsor	NTN No.
Achromatopsia	CNGA3	AAV2/8	Subretinal	I/II	MeiraGTx	03758404
	CNGA3	rAAV	Subretinal	I/II, active	STZ eyetrial	02610582
	CNGA3	rAAV2fYF	Subretinal	I/II	AGTC	02935571
	CNGB3	AAV2/8	Subretinal	I/II	MeiraGTx EMAS	03001310
				I/II (5 year f/u)		03278873
	CNGB3	rAAV2fYF	Subretinal	I/II	AGTC, NEI	02599922
Choroideremia	REP1	AAV2 (Gemini)	Subretinal	II	Nightstar	03507686
				III		03496012
	REP1	AAV2	Subretinal	II	Oxford, UCL	02407678
	REP1	AAV2-Hchm	Subretinal	I/II, active	Spark	02341807
	REP1	rAAV2	Subretinal	II, active	STZ eyetrial	02671539
	REP1	rAAV2	Subretinal	I/II, active	Alberta, Ian MacDonald	02077361
	REP1	AAV2	Subretinal	II, completed	BPEI, B. Lam	02553135
	REP1	rAAV2	Subretinal	I/II, completed	Oxford	01461213
LCA	RPE165	AAV5	Subretinal	I/II	MeiraGTx	02781480
				I/II (5 year f/u)		02946879
	RPE165	AAV2 (Luxturna)	Subretinal	I/II, active (follow-up)	Spark	01208389
	RPE165	AAV2 (Luxturna)	Subretinal	III, FDA approved	Spark, CHOP, Ulowa	00999609
	RPE165	AAV2 (Luxturna)	Subretinal	I/II, active (LTFU)	Spark	00516477
	RPE165	rAAV2	Subretinal	I, active	Upenn, NEI	00481546
	RPE165	rAAV2/4	Subretinal	I/II, completed	Nantes	01496040
	RPE165	rAAV2	Subretinal	I, completed	Hadassah	00821340
	RPE165	rAAV2	Subretinal	I/II, completed	AGTA	00749957
	RPE165	rAAV2	Subretinal	I/II, completed	UCL	00643747
LHON	ND4	rAAV2 (Reverse)	Intravitreal	III, completed	Gensight	02652780
				III (5 year f/u)		03406104
	ND4	rAAV2 (Rescue)	Intravitreal	III, active	Gensight	02652767
				III (5 year f/u)		03406104
	ND4	rAAV2 (Reflect)	Intravitreal	III	Gensight	03293524
	ND4	rAAV2	Intravitreal	I/II, active	Gensight	02064569
	ND4	rAAV2	Intravitreal	II/III, active	Huazhong, Shiyan	03153293
	ND4	rAAV2	Intravitreal	I/II, completed	Huazhong	01267422
	ND4	AAV2	Intravitreal	I	BPEI, NEI	02161380
Retinitis Pigmentosa	RLBP1	rAAV8 [CPK850]	Subretinal	I/II	Novartis	03374657
	PDE68	AAV2/5	Subretinal	I/II	Horama S.A.	03328130
Advanced RP[a]	ChR2	AAV2 [RST-001]	Intravitreal	I/II	Allergan	02556736
Autosomal dominant RP[b]	RHO	QR-1123 [Aurora]	Intravitreal	I/II	ProQR Therapeutics	04122626
Mertk-associated RP	MERTK	rAAV2	Subretinal	I	King Khaled, Fowzan	01482195
Non-syndromic RP	ChrR-dt	rAAV2.7m8	Intravitreal	I/II	Gensight	03326336
Stargardt disease	ABCA4	Lentivirus [SAR422459]	Subretinal	I/II	Sanofi	01367444
				I/II (15 year f/u)		01736529
Usher type-1B	MYO7A	Lentivirus [UshStat]	Subretinal	I/II	Sanofi	01505062
				I/II (15 year f/u)		02065011
Usher type-2A[b]	USH2A	QR-421a [Stellar]	Intravitreal	I/II	ProQR Therapeutics	03780257
XLRP	RPGR	AAV2/5	Subretinal	I/II	MeiraGTx	03252847
	RPGR	rAAV2fYF	Subretinal	I/II	AGTC	03316560
	RPGR	AAV8	Subretinal	I/II/III	Nightstar	03116113
XLRS	RS1	rAAV2fYF	Intravitreal	I/II, active	AGTC	02416622
	RS1	AAV8	Intravitreal	I/II	NEI	02317887

AGTC, Applied Genetic Technologies Corp; BPEI, Bascom Palmer Eye Institute; CHOP, Children's Hospital of Philadelphia; FDA, U.S. Food and Drug Administration; Hadassah, Hadassah Medical Organization; Huazhong, Huazhong University of Science and Technology; King Khaled, King Khaled Eye Specialist Hospital; LCA, Leber congenital amaurosis; LHON, Leber hereditary optic neuropathy; LTFU, long-term follow-up; LUXTURNA, voretigene neparvovec-rzyl; Nantes, Nantes University Hospital; NEI, National Eye Institute; Oxford, University of Oxford; RP, Retinitis pigmentosa; Shiyan, Shiyan Taihe Hospital; UCL, University College, London; Ulowa, University of Iowa; UPenn, University of Pennsylvania; XLRP, X-linked retinitis pigmentosa; XLRS, X-linked retinoschisis.
[a]Indicates optogenetics-based gene therapy.
[b]Indicates use of antisense oligonucleotides (AONs) as gene therapy modality.

Retina as an ideal candidate for gene therapy

Retina is a circular disc around 30 to 40 mm diameter in size and 0.5 mm thick and lines the back of the eye.[4] Due to the established surgical procedures and clinical practices, retina is considered an excellent target for gene therapy. Easy real-time ocular monitoring by optical coherence tomography and fundus imaging allows monitoring the drug effects in both animal models and clinical trial participants. Further, the lesser volume of vector used and immune privilege reduces the risk of immune rejection, allowing gene and cell therapies to have a better chance of survival and effectiveness within the eye.[2]

Vector selection in gene therapy:

The success of gene therapy largely depends on selecting the most suitable vector. Adenovirus, lentivirus, and adeno-associated virus (AAV) are three commonly employed recombinant viral vectors used to deliver therapeutic genes into target cells. The ideal vector should possess several key attributes, including prolonged transgene expression, low immunogenicity, non-integration into the host genome, and high cellular specificity to ensure precise and effective transduction in the targeted tissues, cells, or organs (Fig 1a).[5]

Adenovirus in gene therapy:

Adenoviruses are widely used as vectors in gene therapy for delivering therapeutic genes into target cells. Their ability to transduce a broad range of cell types, including both dividing and non-dividing cells, makes them versatile for various applications. A key advantage is their capacity to deliver large amounts of genetic material, leading to high

levels of gene expression, which is crucial for achieving therapeutic effects. Unlike some other viral vectors, adenoviruses do not integrate into the host genome, reducing the risk of insertional mutagenesis, which can potentially lead to cancer. Instead, they exist as episomes within the cell nucleus, allowing for transient gene expression. This is beneficial in scenarios where temporary gene activity is desired. However, their strong immunogenicity can limit the duration of gene expression, as the immune system may clear the vector. Despite this challenge, adenoviruses are also used in cancer therapies to stimulate an immune response against tumors. Ongoing research aims to improve adenovirus vectors by reducing immunogenicity, enhancing tissue-specific targeting, and extending the duration of gene expression, broadening their potential in gene therapy.[6]

Adeno associated virus:

Adeno-associated virus (AAVs) was discovered from contaminant of adenovirus preparations in human tissues by Atchison. It is a member of Parvoviridae family; belongs to genus of dependovirus. It is replication defective and depends on the presence of a helper virus, such as adenovirus or herpes viruses, for effective and productive replication in mammalian cells. Preliminary investigation shown, AAV life cycle does not cause any disease in mammals. AAV has a single-stranded DNA genome, which is small compared to other viruses, allowing it to carry only limited genetic material (about 4.7 to 5.0 kb).[7,8]

Lentivirus (LVs)

Lentiviruses play a crucial role in gene therapy, particularly due to their ability to deliver therapeutic genes into both dividing and non-dividing cells with high efficiency. Unlike

other viral vectors, lentiviruses can integrate their genetic material into the host cell genome, which allows for stable, long-term expression of the therapeutic gene. This feature is particularly advantageous in treatments where sustained gene expression is essential, such as in chronic diseases or genetic disorders. Lentiviral vectors have a large cargo capacity, enabling them to carry relatively large therapeutic genes. They also exhibit a relatively low immunogenicity, which means they are less likely to trigger a strong immune response, making them suitable for repeated administration in some cases. Additionally, because lentiviruses can be engineered to target specific cell types, they offer precision in gene delivery, minimizing off-target effects. Lentiviral vectors have been widely used in clinical trials for treating various genetic disorders, cancers, and blood-related diseases, and are considered promising tools for advancing gene therapy due to their safety profile and ability to provide durable therapeutic outcomes.[9,10]

Route of delivery:

The success of gene therapy depends not only on the choice of vector but also on the selection of the appropriate gene delivery route. Early gene therapy attempts employed viral vectors for systemic delivery, which often led to severe immunologic reactions and multi-organ failure. Consequently, the focus has shifted to targeted gene delivery, aiming to administer genes specifically to relevant cells. In the realm of ocular diseases, gene therapy commonly utilizes intravitreal, subretinal, and suprachoroidal injections. The choice of delivery route is crucial and depends on the target cell type (Fig 1 b), (Table 2).

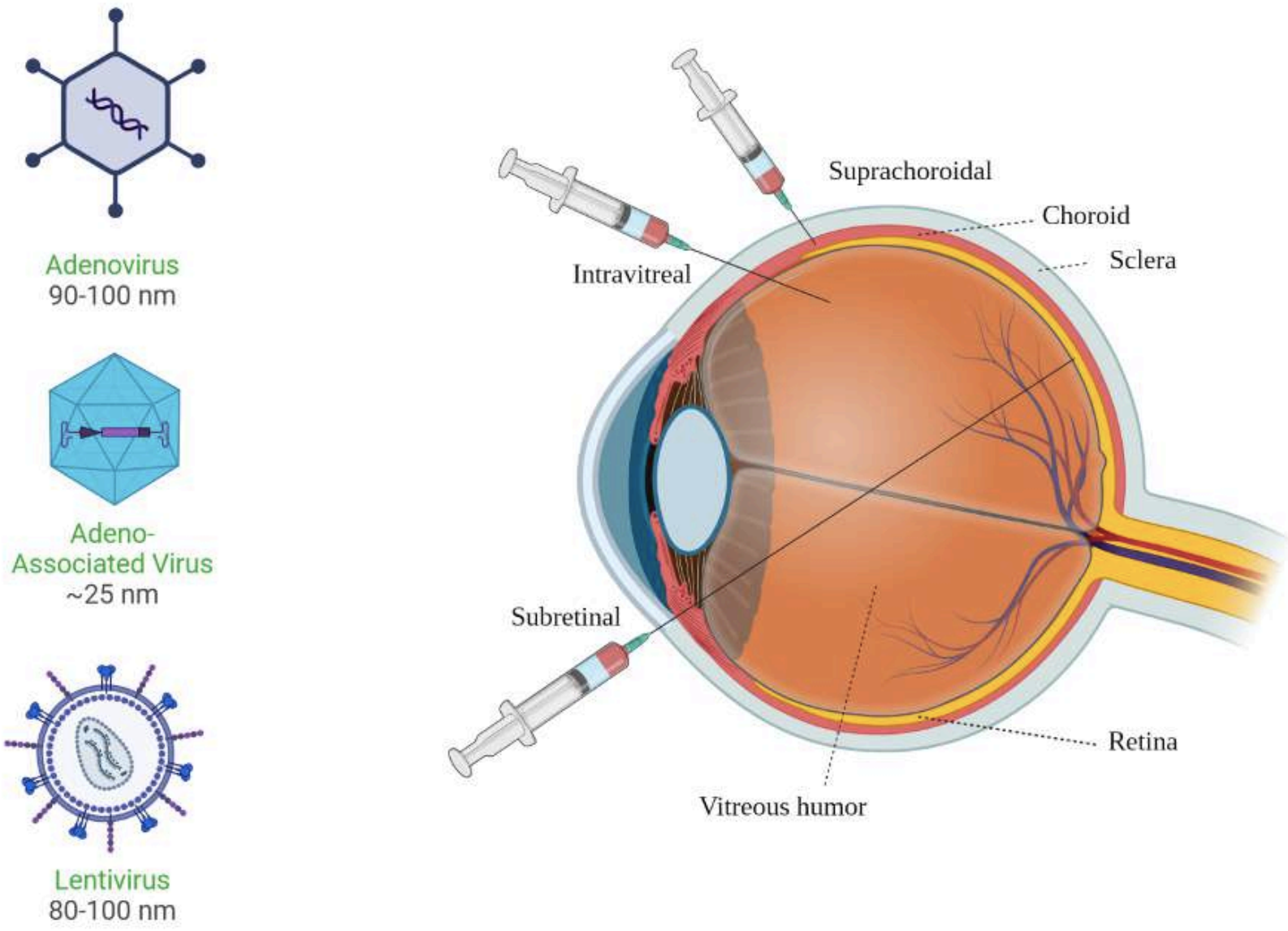

Figure 1: Three common viral vectors and route of delivery used in ocular gene therapy: a) Adenovirus (90–100 nm), Adeno-Associated Virus (AAV, ~25 nm), and Lentivirus (80–100 nm), each varying in size and application. b) Three different routes of delivery in ocular system: intravitreal, subretinal, and suprachoroidal injections, each targeting different retinal layers for gene therapy.

Table 2: Overview of gene therapy injection techniques

Injection Method	Description	Target	Advantages	Limitations
Intravitreal Injection [11]	A minimally invasive procedure where the gene therapy product is injected directly into the vitreous humor.	Primarily targets the inner retinal layer, including retinal ganglion cells.	Relatively simple and low-risk; widely used in clinical settings.	Limited ability to reach the outer retina (photoreceptors and RPE cells); potential for inflammation.
Subretinal Injection [12]	The gene therapy product is delivered into the subretinal space, between the retina and the RPE.	Directly targets photoreceptors and RPE cells.	Provides precise delivery to outer retinal layers; highly effective for targeting photoreceptors.	Requires more complex surgical procedures; potential for retinal detachment and other surgical risks.
Supra choroidal Injection[13]	The gene therapy product is injected into the suprachoroidal space, between the sclera and the choroid.	Targets the choroid, retina, and RPE.	Minimally invasive with fewer risks compared to subretinal injection; can reach broader areas of the retina.	Limited by the diffusion of the therapeutic agent; currently under investigation in clinical trials.

Current gene therapy approaches and their applications in retinal diseases

Current gene therapy approaches for retinal diseases include gene replacement, gene editing, and optogenetics, each targeting specific genetic mutations and disease stages. These innovative methods aim to restore vision by addressing underlying genetic defects or enhancing remaining retinal cell functions.

Gene augmentation: Gene replacement therapy, also known as gene addition or augmentation, is a widely used technique for treating genetic diseases. This method involves delivering a normal gene copy into target cells to replace defective DNA, making it particularly effective for biallelic loss-of-function recessive diseases (Figure 2). Gene replacement is currently used for treating various inherited retinal diseases (IRDs), such as RPE-mediated LCA2, choroideremia, and MERTK-associated retinitis pigmentosa with AAV vectors, as well as Stargardt disease and Usher syndrome using EIAV-based lentiviral vectors.[14] However, this approach is most beneficial for early-stage diseases, as it requires that some functional cells remain; it is less suitable for advanced retinal degeneration.[15]

RNAi therapeutics: For diseases caused by gain-of-function mutations, like rhodopsin-linked autosomal dominant retinitis pigmentosa (RHO-adRP), a combined strategy of gene suppression and replacement is often necessary. This approach typically involves using an AAV vector to deliver RNA interference (RNAi)-based suppressor to down-regulate the target gene, followed by a separate AAV vector to introduce a functional, codon-modified replacement gene (Figure 3).[16]

CRISPR approach: Gene editing has emerged as a promising alternative, particularly for diseases with dominant mutations or large genes. CRISPR technology allows precise modification of the genome by cutting out defective genes and inserting functional ones,

offering a cost-effective and efficient solution.[17] This method is being explored in clinical trials for conditions like CEP290-associated LCA (LCA10), RHO-adRP, and wet age-related macular degeneration.

Optogenetics: It presents a novel approach by introducing light-sensitive proteins into retinal cells to convert them into artificial photoreceptors. This method is particularly useful for diseases with significant photoreceptor loss, such as advanced retinitis pigmentosa. Unlike other gene therapies, optogenetics does not rely on specific genetic mutations, making it versatile for treating a broad range of retinal diseases.[18]

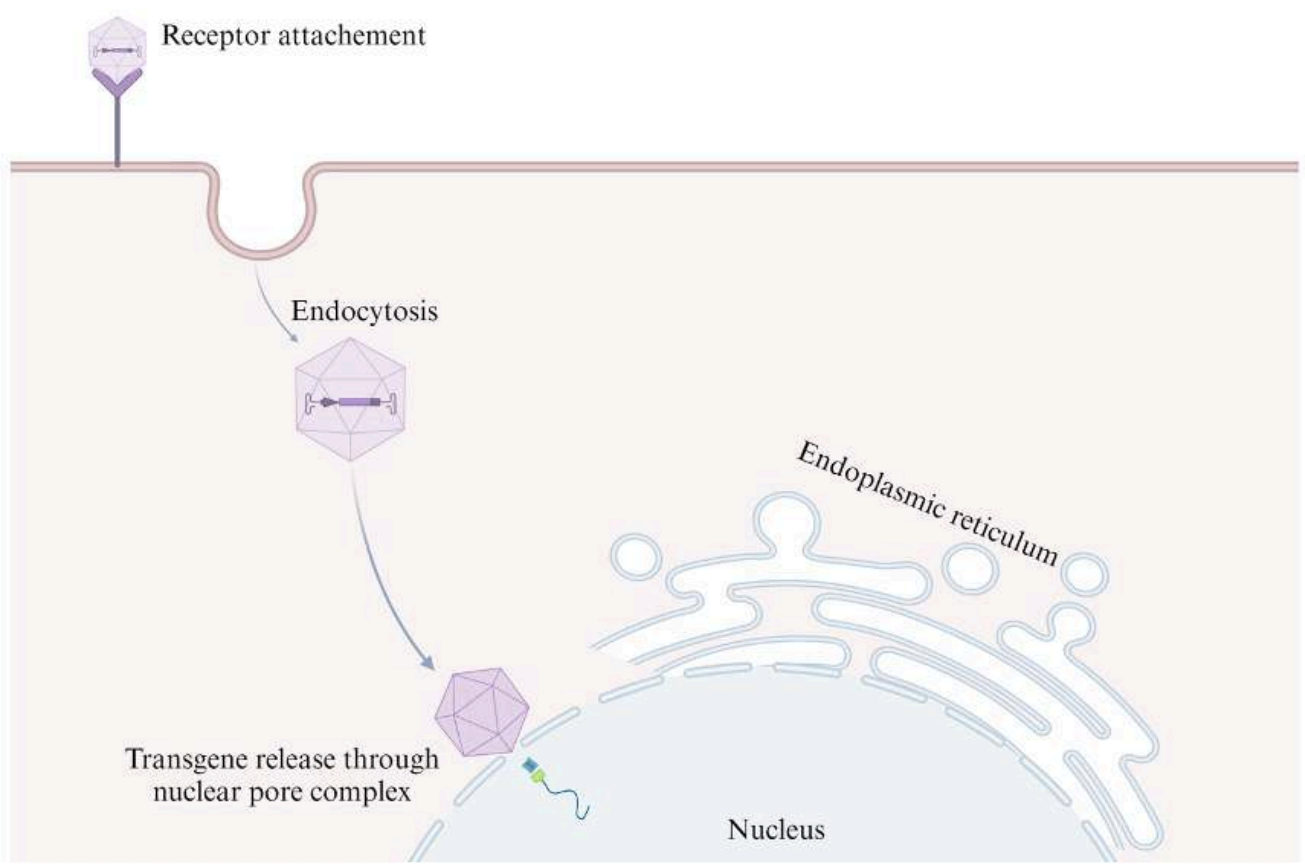

Figure 2: Gene replacement: Gene replacement involves introducing a functional copy of a defective gene into the patient's cells. The vector used for gene delivery contains the normal gene sequence, which can be a cDNA or a modified version of the gene. Once inside the target cells, the therapeutic gene unwinds from capsid and remains episomal, leading to the expression of the functional protein, thereby correcting the genetic defect.

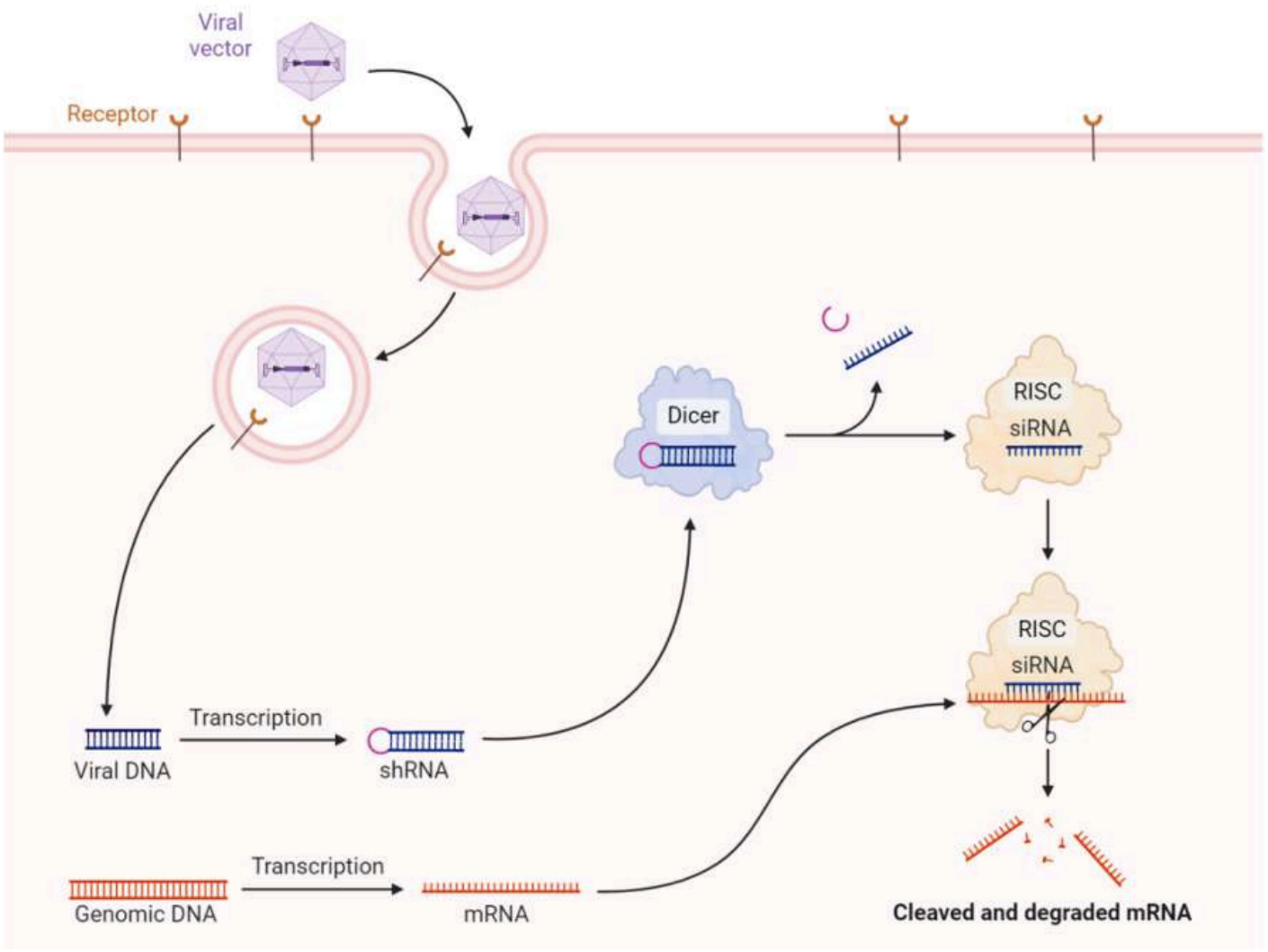

Figure 3: Gene silencing by RNA Interference: Gene silencing through RNA interference is a mechanism used in gene therapy to interrupt the expression of a specific mutation. The process begins with the introduction of RNA interference via lenti viral vector. Once inside the cell, a ribonuclease called DICER cleaves the viral RNA strands, resulting in the production of the antisense strand. Within the cell nucleus, the nuclear DNA is undergoing transcription and may encounter errors. Subsequently, the nuclear DNA can take two different paths. In the first scenario, it is complemented by the antisense strand of RNA interference, effectively silencing the expression of the targeted gene and enabling the production of corrected functional products. In the second scenario, the sequence continues to produce a nonfunctional product within the cell. Gene silencing through RNA interference offers a promising approach in gene therapy for selectively modulating gene expression and correcting mutations. RISC- RNA induced silencing complex, shRNA- Short hairpin RNA, siRNA- small interfering RNA

Challenges in Gene Therapy for Inherited Retinal Diseases (IRDs) in India

Gene therapy has emerged as a promising treatment for inherited retinal diseases (IRDs) due to significant scientific advancements and successful trials. However, several challenges must be addressed before this technology can become a practical option in India. IRDs encompass a range of rare, blinding conditions caused by over 270 different genes.[19] Effective genetic testing is crucial to identify potential candidates for gene therapy. Unfortunately, only a limited number of these genes are currently targeted by available therapies, leaving many patients without viable options. Additionally, most gene therapies, including Luxturna, are effective only for patients with viable retinal cells, underscoring the importance of early genetic testing for potential treatment eligibility. Several other issues complicate the implementation of gene therapy. Safety risks are a primary concern, as once delivered, the effects of gene therapy are challenging to reverse. Moreover, gene therapy requires viable cells, making it less effective in advanced stages of IRDs where photoreceptor degeneration is severe. While cell therapy might be a better option for later stages, it is uncertain whether it can halt disease progression. Gene therapy is gene-specific, necessitating extensive development, including animal studies, clinical trials, and regulatory approvals for each target gene. The capacity of viral vectors to deliver genes is limited, and the presence of anti-AAV antibodies in the eye may reduce treatment efficacy. For autosomal dominant conditions like those caused by rhodopsin mutations, disrupting the mutated allele while introducing a functional copy is complex.[20] Cell therapy also demands prolonged systemic immunosuppression, which carries its own risks and side effects. Although short-term results are promising, long-term safety data is still lacking. Additionally, gene therapy often requires surgical procedures, such as pars plana vitrectomy, which come

with risks of complications like macular holes, retinal tears, cataracts, and in rare cases, permanent vision loss.[21] This necessitates specialized surgical skills and training, limiting the number of providers capable of administering these treatments. Cost is another significant barrier. Gene therapies are expensive, with Luxturna costing approximately $450,000 per eye.[22] This high price, coupled with the limited long-term safety and efficacy data, poses a substantial financial challenge for patients and the healthcare system. While emerging technologies like CRISPR and optogenetics show promise for more affordable treatments, gene therapy remains a costly and evolving field.

Table 4: FDA-approved gene therapy

Product (Company)	Technology	Target Disease	Price
Zolgensma (Novartis)	AAV vector	Spinal muscular atrophy	$2000000
Luxturna (Spark Therapeutics)	AAV vector	RPE 65-mediated retinal dystrophy	$850000
Kymriah (Novartis)	CAR T-cell therapy	Acute lymphoblastic leukemia	$475000
Yescarta (Gilead)	CAR T-cell therapy	Nonhodgkin Lymphoma	$373000

*Price not confirmed, based on analytic predictions. AAV, adeno-associated virus; CAR, chimeric antigen receptor.

Future prospects:

India has a large population with a diverse genetic pool, including a substantial number of individuals affected by inherited retinal diseases. There is a need to improve various aspects of gene and cell therapy in India.

Expanding genetic screening:

Expanding genetic screening in India is vital for advancing gene therapy by identifying patients with specific genetic mutations, enabling early and personalized treatment, reducing the burden of genetic disorders, and supporting research and development. This expansion will also aid in identifying suitable candidates for clinical trials.

Patient Awareness and Advocacy:

Conducting workshops and webinars, will provide clear information about the condition

and treatment options. Online communities can offer emotional support and facilitate knowledge sharing among patients and families. Collaboration with healthcare providers is important for delivering comprehensive education and up-to-date information during consultations.

Regulatory and Ethical Framework:

Developing comprehensive regulations specific to gene therapy and cell therapy is crucial, including guidelines such as informed consent, patient autonomy, privacy, reinforcing the role of ethics review boards to oversee research that will be helpful for conducting clinical trials, product approval, and post-market surveillance. Safety and long term follow-up studies will help manage risks and monitor the ongoing effects of gene therapies. Additionally, training for regulators, researchers, and healthcare professionals is essential to keep pace with advancements in gene therapy, and investing in research capacity will support high-quality development. These measures will help create a robust regulatory and ethical environment that ensures gene therapy innovations are safe, effective, and ethically sound.

Conclusion:

In summary, the future of gene and cell therapy for retinal dystrophies in India is bright, with the country poised to play a significant role in both the development and delivery of these cutting-edge treatments. With the right investments in research, infrastructure, and regulatory frameworks, along with a focus on affordability and accessibility, India has the potential to offer life-changing therapies to millions of patients.

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EXPERIENCE WITH VORETIGENE NEPARVOVEC-RZYL (LUXTURNA™) GENE REPLACEMENT THERAPY

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EXPERIENCE WITH VORETIGENE NEPARVOVEC-RZYL (LUXTURNA™) GENE REPLACEMENT THERAPY

Inherited retinal diseases (IRDs) are clinically and genetically heterogenous disorders due to pathogenic variants in >300 genes (https://retnet.org).[1,2] Biallelic pathogenic variants in RPE65 account for 3-10% of IRDs.[3,4] RPE65, expressed in retinal pigment epithelium (RPE) encodes 65kD retinoid isomerase which converts all-trans retinyl ester to 11-cis retinol in the visual cycle, responsible for phototransduction.[5] Defective RPE65 gene and enzyme lead to profound nyctalopia, low vision, nystagmus and severe functional deficits (undetectable or barely detectable electroretinogram). Severe forms of RPE65 IRDs include Leber congenital amaurosis (LCA; age of onset < 1 year) and early onset severe retinal degeneration (EOSRD; age of onset 1-5 years).[3,6]

Voretigene neparvovec gene replacement therapy, marketed as Luxturna™, was approved by US Food and Drug Administration in 2017 for treating IRDs due to biallelic pathogenic variants in RPE65.[7] Luxturna™ is a recombinant adeno associated viral (AAV2) vector with millions of copies ($1.5X10^{11}$vg) of normal human RPE65 cDNA. Delivered subretinally, Luxturna™ transduces RPE to regain function of the retinoid cycle pathway.[7] Following treatment, most patients show improved retinal sensitivity and navigation ability.[7] Luxturna ™ was approved by European Medicines Agency in 2018 and Health Canada in 2020. Since then, various real-world studies have reported its safety and efficacy.[8-12] Here, we briefly describe the experience using Luxturna™ at The Hospital for Sick Children and Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

From March 2022 to July 2024, 23 patients were treated with subretinal injections of Luxturna™. The inclusion criteria for Luxturna ™ treatment were; i) age >4 years with a diagnosis of LCA or EOSRD, ii) presence of biallelic (autosomal recessive) disease causing

variants in RPE65, and iii) presence of viable photoreceptor cells in spectral domain optical coherence tomography (SD-OCT;>100um of retinal thickness in the posterior pole).[7]

Three days before the first eye surgery, all patients received 40mg oral prednisone which was continued the day of surgery and post op according to a strict protocol.[7] Pre and postoperative evaluations included visual acuity, refractive error, fundus photography, SD-OCT, full-field stimulus test (FST), and Goldmann visual field (GVF) when possible. Standard FST (using Diagnosys espion™) was recorded for blue, red and white stimuli. GVF was analysed for I4e, III4e and/or V4e stimuli.

The procedure consisted of a standard 23 gauge three-port pars plana vitrectomy. Sites of injection were determined pre-op based on viable ellipzoid zone/outer nuclear layer in OCT macula and areas of residual visual fields in GVF. A total volume of 0.3ml ($1.5X10^{11}$vg) Luxturna drug was delivered subretinally with the creation of a bleb aiming the central macula via a 38-gauge cannula.[7] Fluid air exchange followed, with closure of the ports. Patients maintained a strict supine position for six hours post-surgery.

A standard postoperative regimen included rest, oral steroids as per protocol, topical corticosteroid, antibiotic, and cycloplegic drops.[7] Oral and topical corticosteroids were tapered weekly according to the inflammation. Raised intraocular pressure was managed medically. The second eye surgery was performed within 1-3 weeks of the first eye surgery.

The average age of patients at treatment was 19 years (range 9-44 yrs.). All were treated bilaterally except for one, who had one eye treated in an earlier phase 2 trial. BCVA pre-op varied from ≤20/60 to hand motion appreciation.

Functional assessment: Central vision remained stable postoperatively. Patients <40 years showed significant improvement in rod mediated FST (≥ 5db or ≥ 0.5log units) as early as one-month post-surgery (7). The average pre and postoperative white FST was -10.40dB and -32.03db respectively. While a non-significant (considering 20-30% inter-test variability[13, 14]) decrease in visual fields was observed postoperatively in few cases, patients did not observe decline in visual fields.

Structural assessment: Nummular and touchdown chorioretinal atrophies were noted in a few cases with no functional implications. From patients with over 6 months follow up, central subfield thickness showed a decreasing trend in the analysed cases so far (n=15 eyes of 9 patients, range -2 to -59 µm). Detailed OCT parameters analysis was challenging in many patients due to difficulty in scan acquisition, inappreciable retinal layers, nystagmus and poor fixation.

Subjective assessment: All the patients with significant FST improvement were very satisfied with improved vision in the dark and better navigation postoperatively. Both children and parents described the procedure as life-changing. The children became more confident, less reliant on their parents at dusk and were able to go out with friends on their own.

Two older adults in their fifth decade (≥40years) had low FST response preoperatively and did not show significant improvement in retinal sensitivity postoperatively. These two older patients reported non-refractive reduced reading vision, affecting their quality of life. Localized retinal detachment was noted intraoperatively in two eyes which was

treated with laser barrage and fluid gas exchange. Subretinal hemorrhage was noted in three eyes while creation of blebs. Despite eventful surgery in these eyes, the vision remained stable and retinal sensitivity improved.

In summary, Luxturna™ gene replacement therapy is safe, significantly improves retinal sensitivity, and is life-changing when performed at early stages of retinal degeneration. This marks a new era in medicine, and patients' expectations vs outcomes of a therapy must be clearly communicated preoperatively. Steroids should be tapered carefully, especially for overweight patients. Older patients with severe retinal degeneration should be counseled about the potential non-improvement in retinal sensitivity or even vision loss.

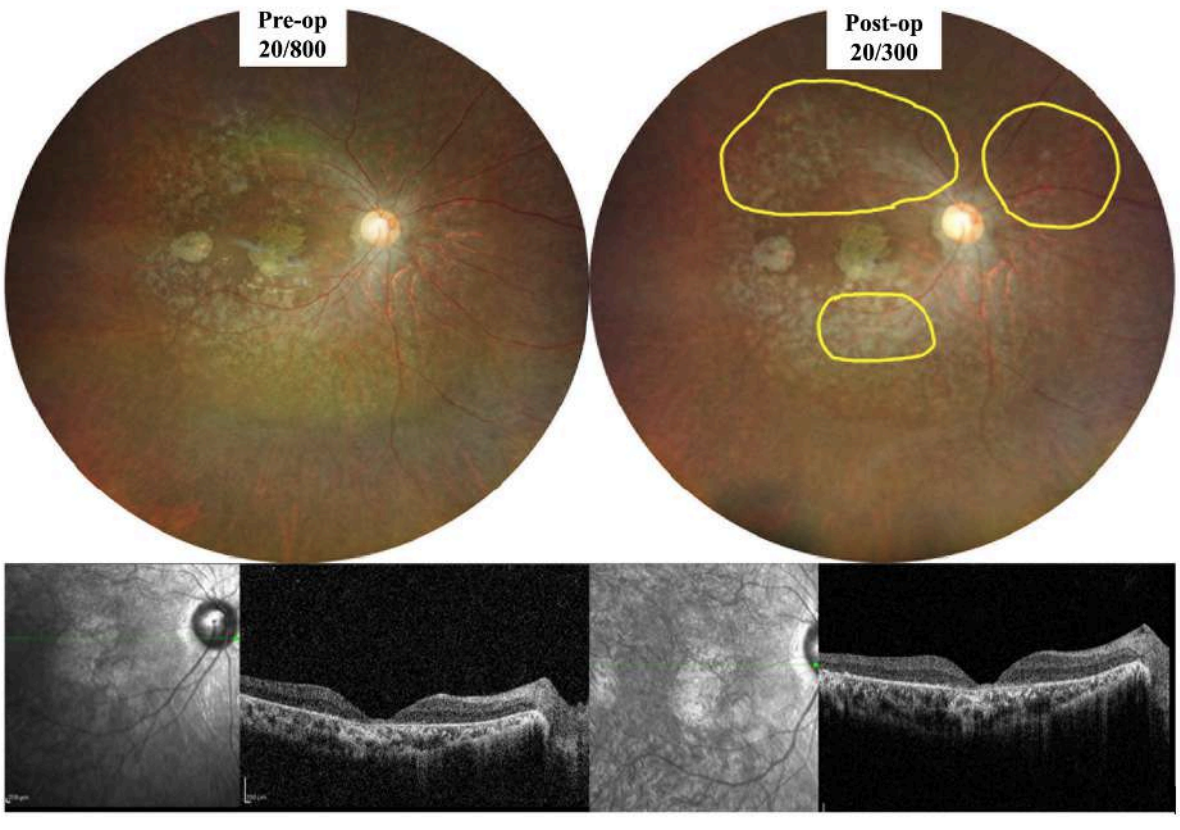

Figure 1: 18-year-old-female with RPE65 early onset retinal dystrophy, treated with Luxturna™. Fundus and optical coherence tomography images of right eye at pre- and post-operative one month. Yellow marked areas in the post-op fundus images represent the location of intraoperative subretinal blebs. Pre-surgery full-field stimulus test value for white light was -4.00dB which improved to -42.10dB at one-month post-surgery.

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MANAGEMENT OF MACULAR COMPLICATIONS IN RETINAL DYSTROPHIES

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Inherited retinal dystrophies (IRD) can have a myriad of macular complications such as cystoid lesions, macular holes (MH), macular neovascularization (MNV), and epiretinal membranes (ERM). Clinical detection is often challenging in the background of pre-existing retinal pathology, but, multimodal imaging has increased detection of these lesions in recent years.

Cystoid changes in the macula

Cystoid changes of the macula in IRDs can be either cystoid macular edema (CME) or non-leaking macular cystoid spaces (MCS). CME is caused by fluid accumulation due to retinal pigment epithelium (RPE) pump failure or a non-immune response to toxic by-products of a degenerating retina[1] (Figure 1). In contrast, MCS are fluid-filled spaces created due to structural changes in retinal architecture (Figure 2). Unlike CME, MCS do not leak on fluorescein angiography.[1] CME occurs in 25%-38% of retinitis pigmentosa (RP) cases while MCS has been associated with Usher syndrome, juvenile X-linked retinoschisis (XLRS), NR2E3 retinopathies (enhanced S-cone syndrome [ESCS], Goldmann-Favre syndrome, clumped pigmentary retinal dystrophy) and CRB1 retinopathy.[2,3] Carbonic anhydrase inhibitors (CAI), both oral (acetazolamide, 7-15mg/kg/day up to a maximum of 500mg in a single daily dose) and topical (2% dorzolamide, twice daily), have proven effective in treating these cystoid changes.[1,2] However, due to underlying degenerative changes, a decrease in central foveal thickness (CFT) does not always translate to visual improvement. Moreover, cessation of CAIs can often cause rebound fluid accumulation, necessitating reinstitution of drugs. Spontaneous improvement without any treatment has been noted infrequently, but usually, vision does not improve in these cases, possibly due to photoreceptor damage. Therefore early treatment, prolonged therapy, and slow weaning of CAI are recommended.[1,2] A few authors have indicated that oral acetazolamide may be more effective than topical dorzolamide.[2] Less commonly, local steroids (intravitreal dexamethasone, intravitreal triamcinolone, sub-tenon triamcinolone, topical betamethasone) have been used to treat CME. Some authors have reported more improvement in CFT with intravitreal dexamethasone (Ozurdex, 0.7mg) than with CAI.[4]

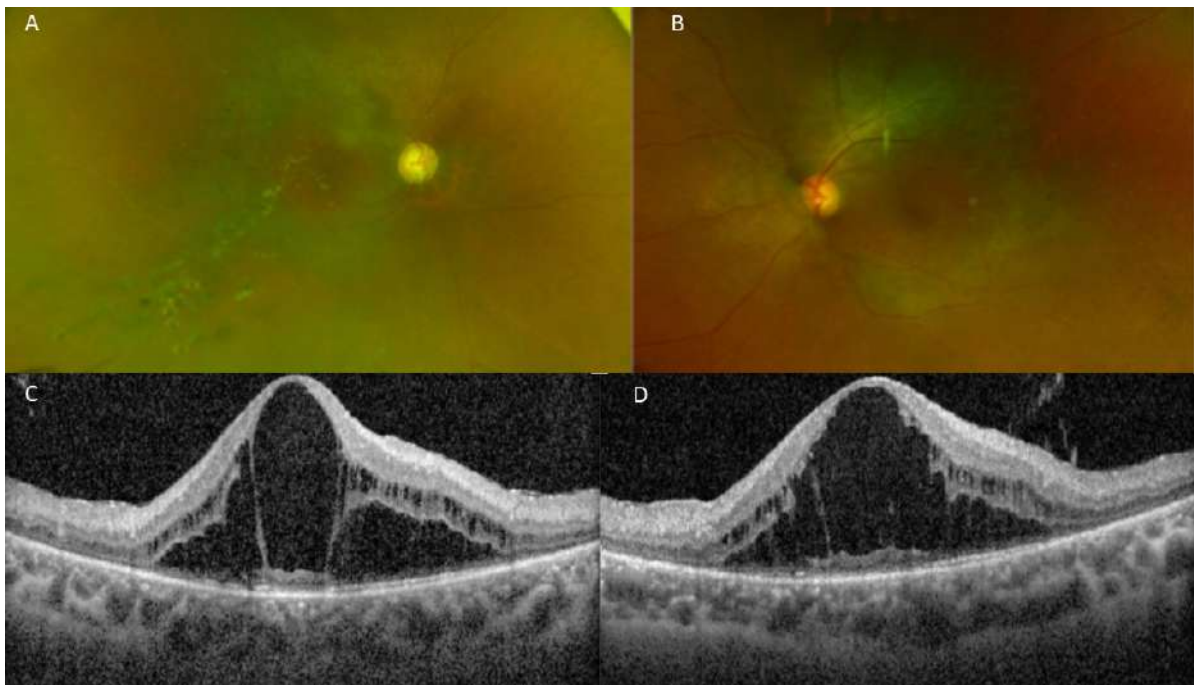

Figure 1: Panels A & B are widefield pseudocolor (Optos) photos showing features of retinitis pigmentosa with pale discs, attenuated arterioles, outer retinal atrophy in midperiphery, and a few bony spicule pigments. Panels C & D are OCT scans of the same patient depicting long-standing cystoid macular edema. Schisis and atrophy are seen in the outer retinal layers. Visual acuity was less than 20/200 and it was nonresponsive to treatment.

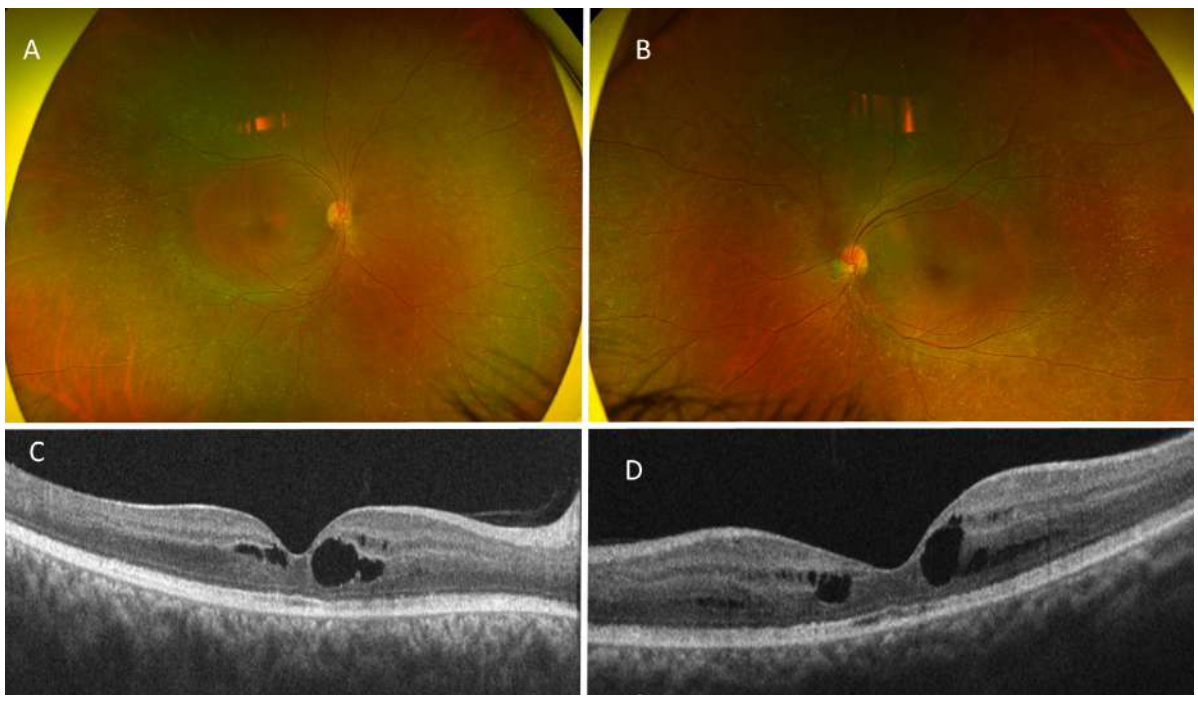

Figure 2: Panels A & B depict Optos images of a patient with a confirmed diagnosis of enhanced S cone syndrome. The discs and vessels are normal. Nummular yellow deposits are seen along arcades. The night blindness was stationary and ERG was diagnostic. Panels C & D show the macular cystoid spaces on OCT which remained stable over a 5-year follow-up period.

Macular holes

MHs can occur secondary to IRDs like RP, Usher syndrome, Best Vitelliform Macular Dystrophy (BVMD) and XLRS, and less commonly, in Bietti corneoretinal dystrophy (BCRD), pericentral pigmentary retinopathy and Stargardt dystrophy.[3] The development of a MH is especially threatening in IRDs with constricted peripheral visual fields, like RP, as it endangers the preserved island of central vision (Figure 3). Unlike typical idiopathic MHs caused by vitreomacular traction, holes in IRDs occur due to outer retinal degeneration. MHs have been reported in 0.5-10.5% of RP patients, caused by degeneration of large coalesced cysts in eyes with pre-existing CME. In BVMD or autosomal recessive (AR) bestrophinopathy, we see large MHs as a result of rupture of cysts in the vitelliform stage or atrophy in the vitelliruptive stage (Figure 4). In both these IRDs, MHs are associated with intraretinal cysts and subretinal fluid (SRF); additionally, retinal detachment (RD) occurs in more than 50% of cases of BVMD with MH.[3] Standard treatment for MHs in IRDs involves pars plana vitrectomy (PPV) with brilliant blue-green dye-assisted internal limiting membrane (ILM) peeling and gas tamponade (C3F8 or SF6). Surgical outcomes are not available for all the IRD-associated MHs. Anatomical closure post-ILM peeling ranges from 70-100% within the reported pool of cases, which include: RP (7/10 eyes), BVMD (3/3 cases) and BCRD (1/1 eye).[3,5–11] However, visual improvement is often limited due to pre-existing retinal dysfunction. In RP, only 50% of the reported cases (5/10 eyes) achieved a final best corrected visual acuity better than or equal to 20/80.[3,5–8] In BVMD, large MHs with associated RD make surgery more challenging. Poor prognosis has been reported with vitrectomy alone; it is advisable to laser the edges of the MH to prevent redetachment.[3] The inverted ILM flap technique may prove effective in these cases as a primary treatment.[9] One author reported

success with RD surgery and silicone oil (SO) tamponade followed by ILM peeling at the time of SO removal.[12] Recently, retinal autograft has been attempted successfully to close the large MHs in retinal dystrophies.

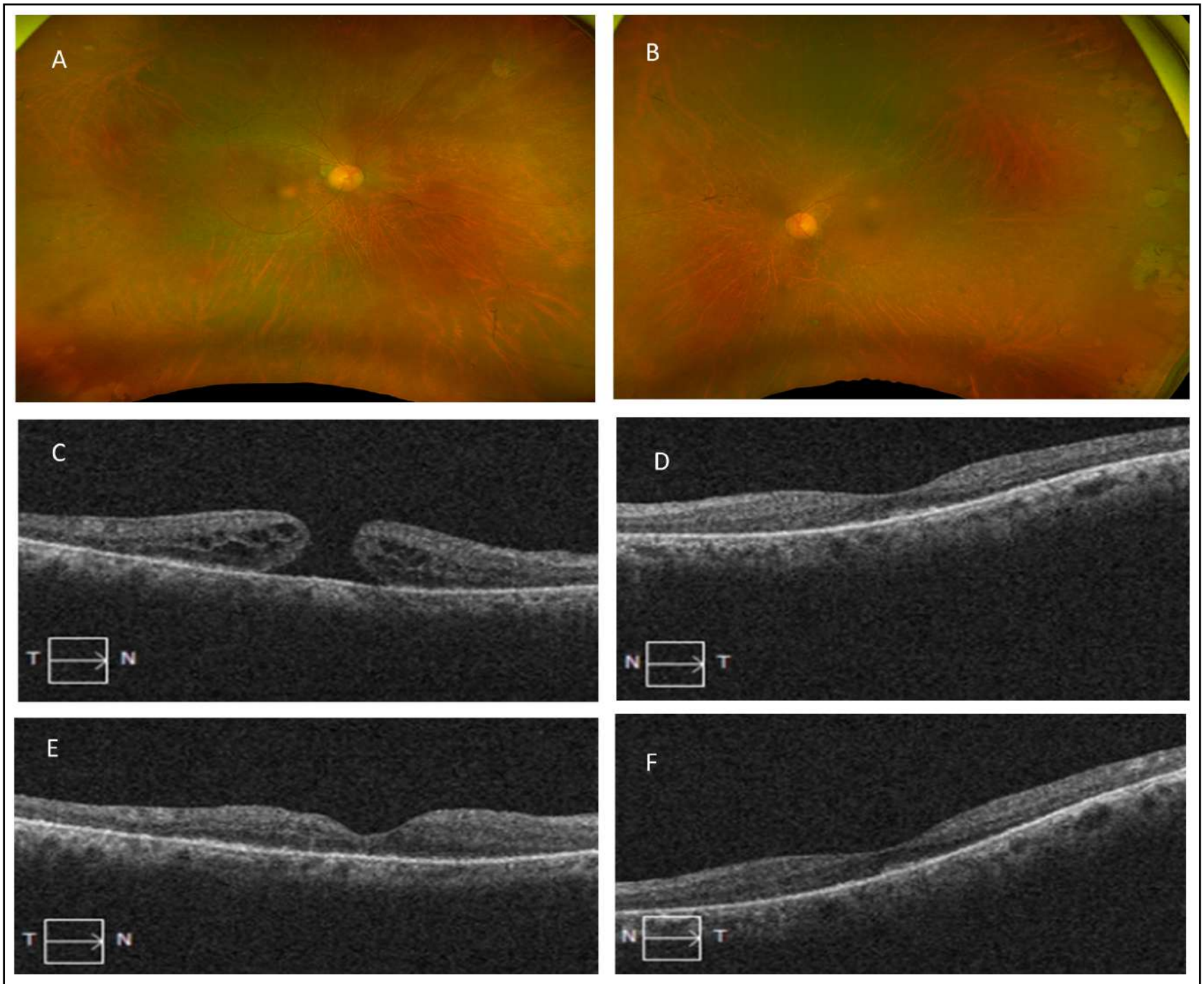

Figure 3: Panels A & B are Optos photos showing features of retinitis pigmentosa. Panels C & E are OCT scans demonstrating a full-thickness macular hole in the right eye before surgery and its successful closure after vitrectomy, ILM peeling and gas tamponade. The vision improved from 20/200 to 20/60. Panels D & F show OCT scans of the left eye with thinning of the fovea and outer retinal atrophy beyond the perifoveal area.

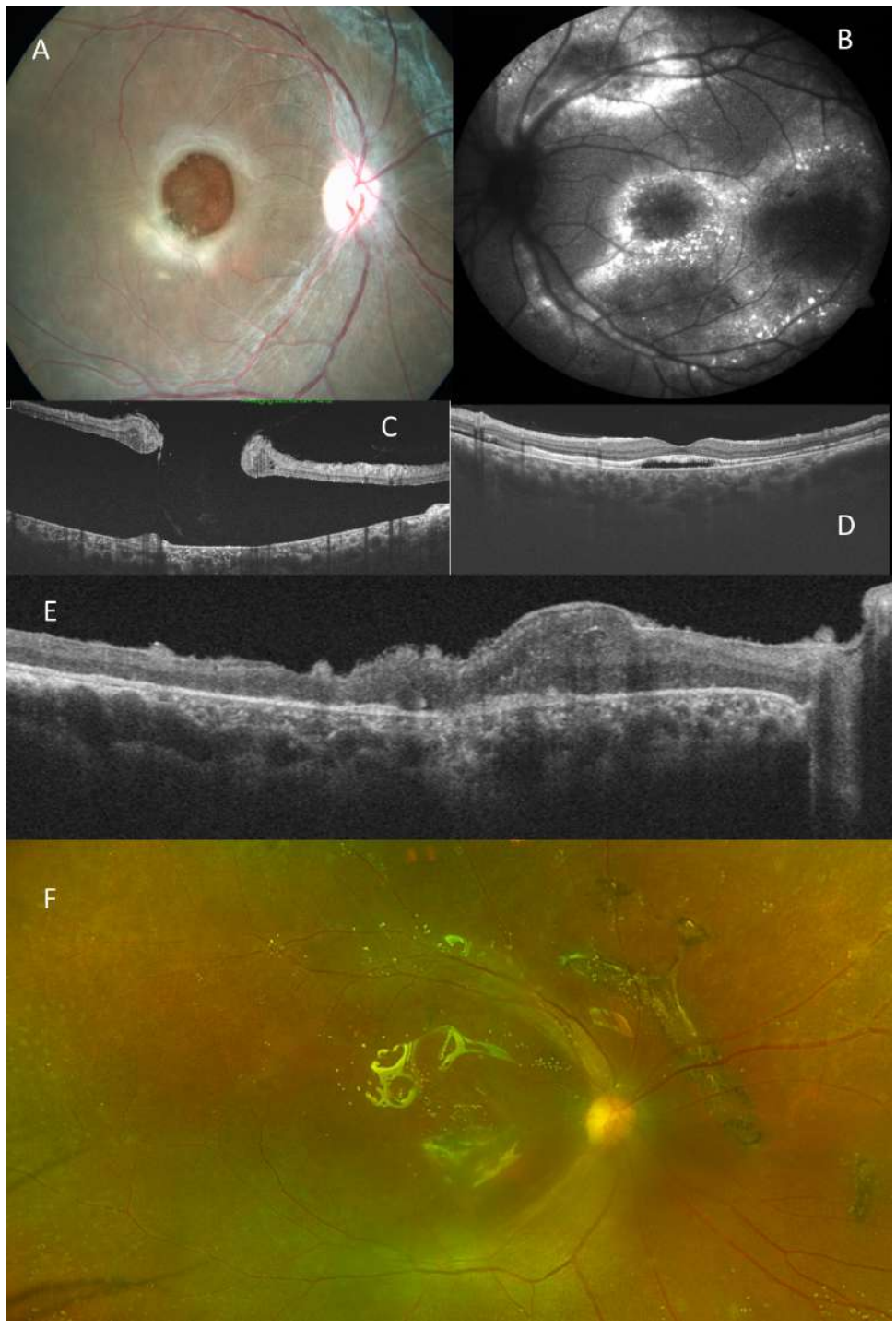

Figure 4: Panel A depicts the right eye of a patient with autosomal recessive bestrophinopathy with a large full-thickness macular hole measuring 1800 microns. Panel B depicts the left eye with typical hyperautofluorescent material deposition throughout the retina. Panel C shows a large macular hole with retinal detachment on OCT. Panel D shows vitelliform deposit under the fovea in the left eye OCT scan. E & F panels show OCT and fundus photo after successful surgery with vitrectomy, closure of macular hole with a retinal autograft and silicone oil tamponade.

Macular neovascularization

MNV is being detected more frequently in IRDs with the advent of OCTA. MNV can be the first sign in late-onset fovea-sparing Stargardt disease, mimicking neovascular AMD due to the resemblance between flecks and drusen.[13] AntiVEGFs like Ranibizumab are effective in reducing exudation, leading to visual improvement, but need to be used judiciously as they can cause enlargement of the atrophic areas.[13,14] Outcomes with PDT are variable.[13] In bestrophinopathies, the incidence of MNV is 36%-63%.[13] In early

disease stages (2-3) of BVMD, active sub-RPE MNV (type 1) can be seen with stable vision, whereas in late stages (4-5), type 2 MNV develops with RPE breach and collapse of the vitelliform lesion, resulting in visual decline. Type 3 MNV has been reported in AR bestrophinopathy.[13] MNV in bestrophinopathies is often simply monitored, due to a high rate of spontaneous regression, but, significantly better visual outcomes can be achieved by treating with antiVEGF injections.[13,15,16] Other IRDs where MNV has been reported include RP, Sorsby fundus dystrophy, adult-onset foveomacular dystrophy and North Carolina Macular dystrophy.[13] In ESCS, almost 50% of patients can have type 3 MNV which regress into fibrotic submacular nodules.[17] Although laser photocoagulation and PDT have been used successfully in selected cases, anti-VEGFs are now the treatment of choice. It is important to note that MNV in IRD usually has a better prognosis and requires fewer injections than in AMD.[13]

Epiretinal membranes

ERMs are common in RP with an incidence of 1.4%-23%[18,19] (Figure 5). PPV with ERM removal was anatomically successful in 82% of cases but visual improvement was variable and limited.[19] Intact pre-operative ellipsoid zone on OCT has been proposed as an indicator of better visual prognosis post-PPV.[19] ERM is infrequently seen in Stargardt disease. (Figure 6) While one can opt to monitor these cases until spontaneous separation occurs, surgical removal has also achieved structural and functional success. [20]

The various macular manifestations in IRDs have different pathogenesis and natural history as compared to their primary counterparts. Realizing these differences can help in understanding the nuances in their management and predicting treatment outcomes.

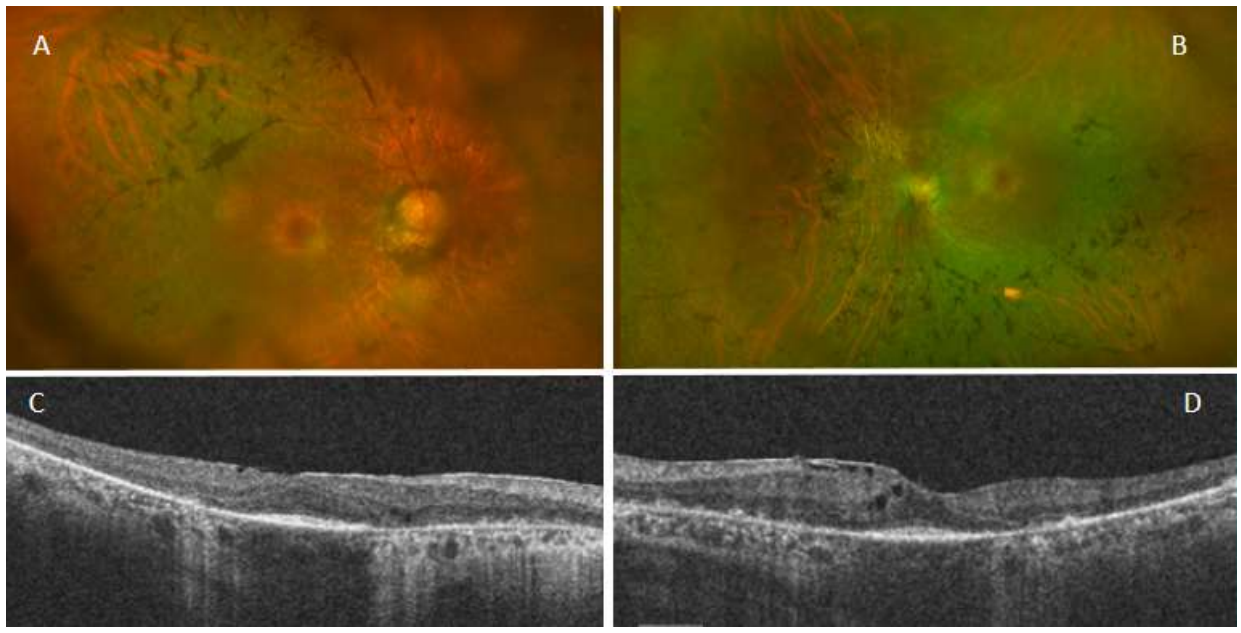

Figure 5: Panels A & B are fundus photos depicting typical retinitis pigmentosa. Panels C & D show OCT scans with gross outer retinal atrophy and hypertransmission defects. Photoreceptors are present only at the fovea. A thin ERM is seen in both eyes.

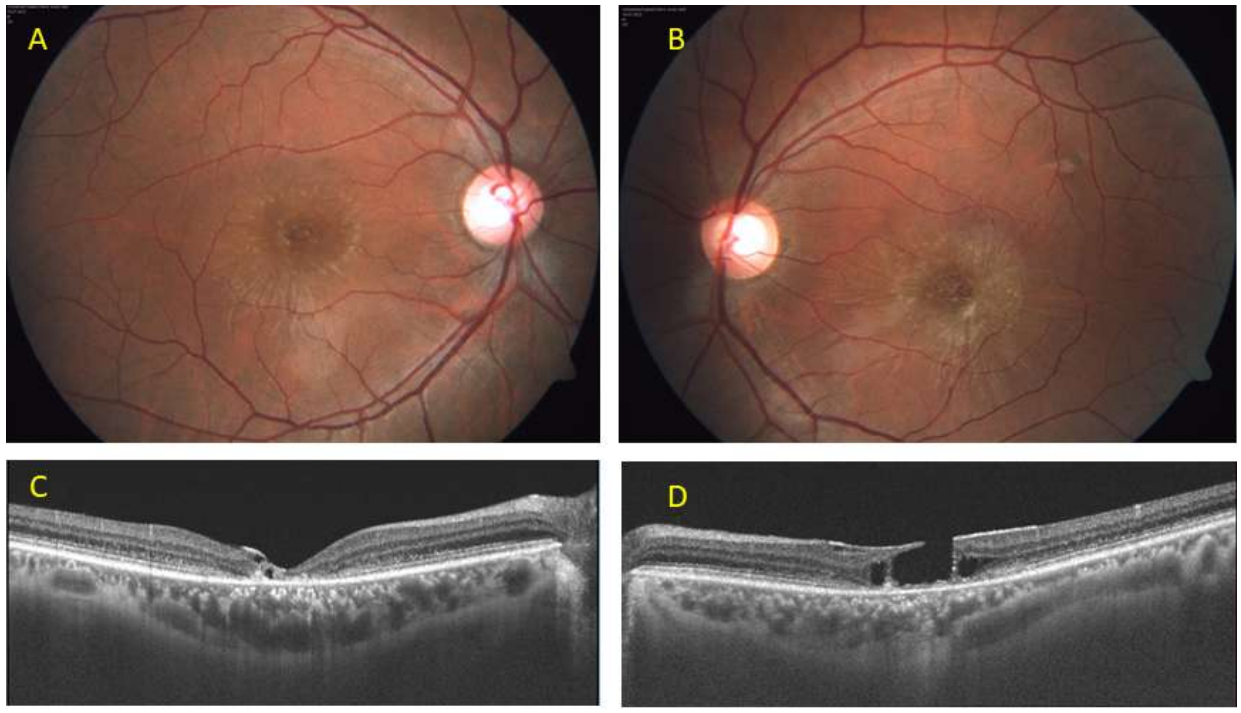

Figure 6: Panels A & B are fundus photos showing Stargardt disease with macular atrophy surrounded by flecks. Panels C & D are OCT scans showing macular thinning with photoreceptor loss in the right eye and a lamellar macular hole with thin ERM in the left eye.

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LOW VISION REHABILITATION IN A CASE OF RETINAL DYSTROPHY

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Introduction

Retinal dystrophies are degenerative disorders of the retina with clinical and genetic heterogeneity. The common presentations include night blindness, peripheral visual abnormalities, colour blindness and complete blindness. It is caused by abnormalities in the photoreceptors as well as defects in phototransduction. Depending on the photoreceptors affected it is of 3 types - rod dominated, cone dominated and generalised form.[1]

Low vision rehabilitation provides techniques to improve residual vision and enhance the quality of life for those affected by these conditions. This review gives a general overview of low vision rehabilitation concepts and procedures with a particular emphasis on retinal dystrophy.

Low vision Rehabilitation

The low vision rehabilitation of retinal dystrophies varies depending on the severity of the condition. As per the current ICD classification[2] we can classify them according to the severity of the visual impairment. Based on the category, the management is planned which includes the low vision devices (LVD), rehabilitation and counselling. Low vision rehabilitation is not done to restore the lost sight, but helps the patient to maintain an independent lifestyle with his/her remaining vision.[3] So to plan the management, a detailed low vision evaluation needs to be performed.

Low vision evaluation

The low vision evaluation starts with a detailed history which includes the patient's chief complaints, financial status, qualification, family support, associated disabilities and previous history of LVD usage. The low vision history is followed by task analysis where

the patient is asked about the difficulties they face due to low vision including difficulties in reading, daily living skills, ambulation, photosensitivity, glare and patient's lighting preferences, their priority for distance task, near task and intermediate task. The Low vision assessment includes visual acuity assessment using LogMAR chart for distance and Mn read chart for near. Functional vision assessment is most important to decide management. It includes visual field test, contrast sensitivity and colour vision assessment.

Based on the evaluation, the management plan will be decided. If the patient falls under mild to moderate visual impairment, the management includes low vision device trial for distance & near, field expanders, glare control, rehabilitation.

Distance devices (Figure 1)

- Telescopes: Telescopic systems magnify the apparent size of distant objects; they work on the principle of angular magnification. They can be prescribed for near, intermediate and distant tasks. Field of view decreases with magnification and it also varies with the design of the telescope. Effective use of telescopes need good coordination and training. Telescopes can be hand-held, clip-on or spectacle-mounted, and can be prescribed monocularly or binocularly. Telescopes can be fixed focus, focusable telescope, or autofocus.
- SEETV: The "SEETV" glasses will focus objects at an intermediate distance which can vary between 1m to 3m with a clear view of the enlarged image. The "SEETV" glasses are specially designed for watching TV.
- Bioptic telescope: In a bioptic telescope system, a telescope is typically mounted in the superior aspect of the spectacle lens.[4] These are specially designed for driving

where the patients view through the carrier lenses of the system for near and view through the telescope system for viewing street signs, traffic lights, and other distant obstacles. These designs could be helpful for people with defective distance vision for better mobility and in the classroom. Bioptic telescopes are not approved for driving in India.

Telescope (Monocular)

Telescope (Spectacle mounted)

SEETV

Bioptic telescope

Figure 1: Low vision devices for distance

Near devices (Figure 2)

- Spectacle magnifiers: These are binocular high-powered convex lenses mounted on a spectacle which could be useful for reading. Prisms will be incorporated into these

magnifiers to avoid fatigue due to excessive convergence. These are recommended for continuous reading and writing. The closer working distance restricts the illumination and writing through the magnifier.[5]

- Stand magnifiers: These are convex lenses with fixed focus stands. It is helpful for elderly people with tremors.[5]
- Handheld magnifiers: These are cheap and readily available, portable and foldable. The disadvantages are a reduced field of view, the need to be held with the hands and lesser acceptability than glasses.[5]
- Dome magnifiers: Dome-shaped convex lenses made up of glass or plastic.
- Video magnifiers: It provides a magnified image and also allows contrast enhancements. A wide range of magnification is possible with a video magnifier. It also provides a better field of view.

SEE TV is the most prescribed device in cases of retinal dystrophy for distance and dome magnifier for near.[6]

The acceptability of telescope or magnifiers depends on the visual field. Constricted visual poses mobility issues like bumping on objects and fall. A trial for expansion of field (field expanders) should be planned as per the visual field evaluation. It include

- Inverse telescope
- Prisms
- Fresnel prism (Eli Peli system)

The rehabilitation services are not limited to dispensing low-vision aids. It encompasses a wide range of efforts, including counselling on adjustment to disability, career guidance, employment skill training, rehabilitation therapies, or medical interventions to

lessen the effects of disability. People with vision impairment may benefit from learning and developing adapted skills that are an alternative technique for performing tasks and activities.[7] These include

- Independent living skills or daily living skill training which includes home and personal management. Home management tasks include housekeeping, planning and preparing meals, shopping, managing money and performing light home-maintenance chores. Personal management includes grooming and hygiene activities.
- Orientation and mobility training: Mobility devices and techniques are taught to increase an individual's safety while walking or travelling. Use of non-optical assistive devices and cane training are mostly practised.
- Glare and lighting: Glare and photophobia are one of the major issues associated with visual impairment which can restrict the visually challenged from achieving a normal life. So, these areas also need special consideration. Use of coning photochromic filters and polaroids can minimise the discomfort. Patients have to be trained for lighting adjustments according to personal preferences.

Though there is variability in the preference of filters, few studies suggest that grey filters were preferred by the patients with retinal dystrophy.[6]

Assistive Technologies

Advancements in technology have led to the development of various assistive devices for individuals with low vision:

- Electronic Magnification Systems: Devices such as closed-circuit televisions (CCTVs) and handheld electronic magnifiers provide adjustable magnification and contrast, aiding in reading and detailed work.

- Text-to-Speech Devices: Screen readers and text-to-speech software can convert written text into spoken words, assisting with reading and access to information.

- Smartphone Applications: Apps designed for low-vision users offer features like voice commands, magnification, and GPS navigation to support independent living.

- Smart Glasses: Spectacle or head-mounted wearable devices combining advanced technologies such as computer vision, sensors, and audio feedback to enhance the daily lives of the blind. By capturing and processing real-time visual information from the surroundings, smart glasses offer navigation support, object recognition, and obstacle detection.

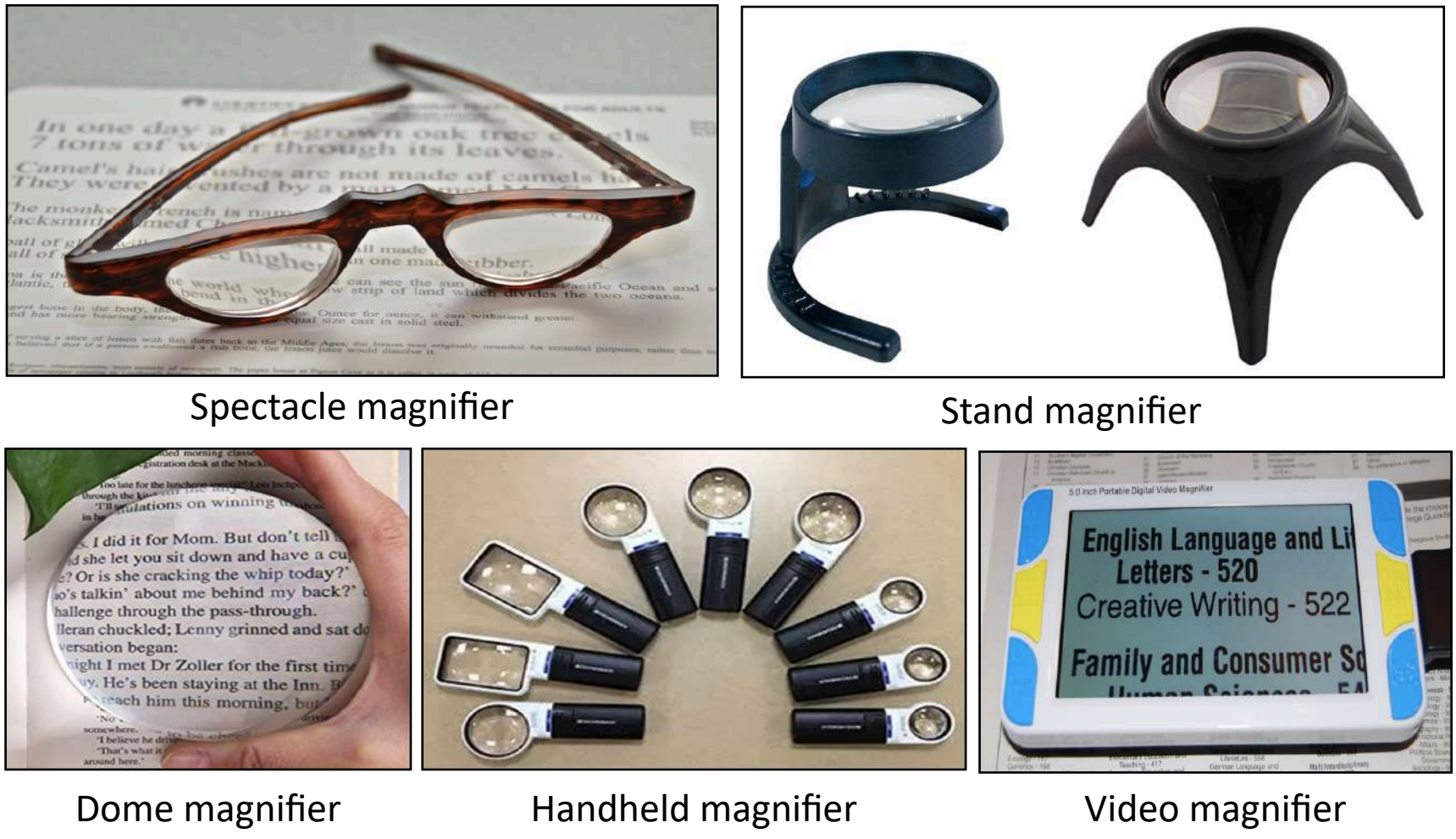

Figure 2: Low vision devices for near

Studies have shown that there is a significant improvement in the quality of life of the visually impaired who utilize the low vision services.[8]

Achieving the best possible outcomes for the patient requires a collaborative, multidisciplinary approach and dedicated effort to leverage new scientific advancements. Collaborative models are suggested for the best outcome, including co-management with other healthcare services like occupational therapy and speech therapy. The teachers and parents of visually impaired children should be actively involved in the training for the success of therapy.

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CASE REPORT

UNILATERAL PIGMENTARY RETINOPATHY: A RARE CASE REPORT AND DIAGNOSTIC CONSIDERATIONS

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Introduction:

Unilateral Pigmentary Retinopathy (UPR), also known as unilateral retinitis pigmentosa, is a rare, sporadic condition characterized by the degeneration and atrophy of the retina in one eye, particularly affecting the photoreceptors.[1] Although it resembles Retinitis Pigmentosa (RP) in appearance, UPR is distinct in that it usually affects only one eye, with the other eye remaining normal, whereas RP generally affects both eyes. Its prevalence is noted to be approximately 1 in 4000 and fewer than 100 cases are reported in the literature so far.[2] Careful consideration is needed before diagnosing UPR. We report a rare case of a 36-year-old apparently healthy female with UPR.

Case Report:

A 36-year-old lady presented with gradual progressive diminution of vision in her left eye for 6 months. She was apparently healthy with no systemic disorders. Best corrected vision in right eye (RE) was 6/6 (+0.50DS, -0.50DC) and left eye (LE) was 6/6 (-1.00DC). The fundus of LE had a pale waxy disc, arteriolar attenuation and a few mid-peripheral bony spicule pigmentary changes typically seen in retinitis pigmentosa. Fundus autofluorescence (FAF) revealed corresponding speckled hypoautofluorescence. (figure 1) Visual field examination of the same eye by a Humphrey perimeter (HVF)

demonstrated a generalized sensitivity reduction and severely restricted visual field (figure 2a and b) and electroretinogram (ERG) also revealed grossly reduced scotopic responses and photopic responses (figure 3). LE optical coherence tomography (OCT) showed atrophy of the outer retinal layers in the peripheral macula. (figure 2c and d) RE fundus, HVF, OCT and ERG were within normal limits.

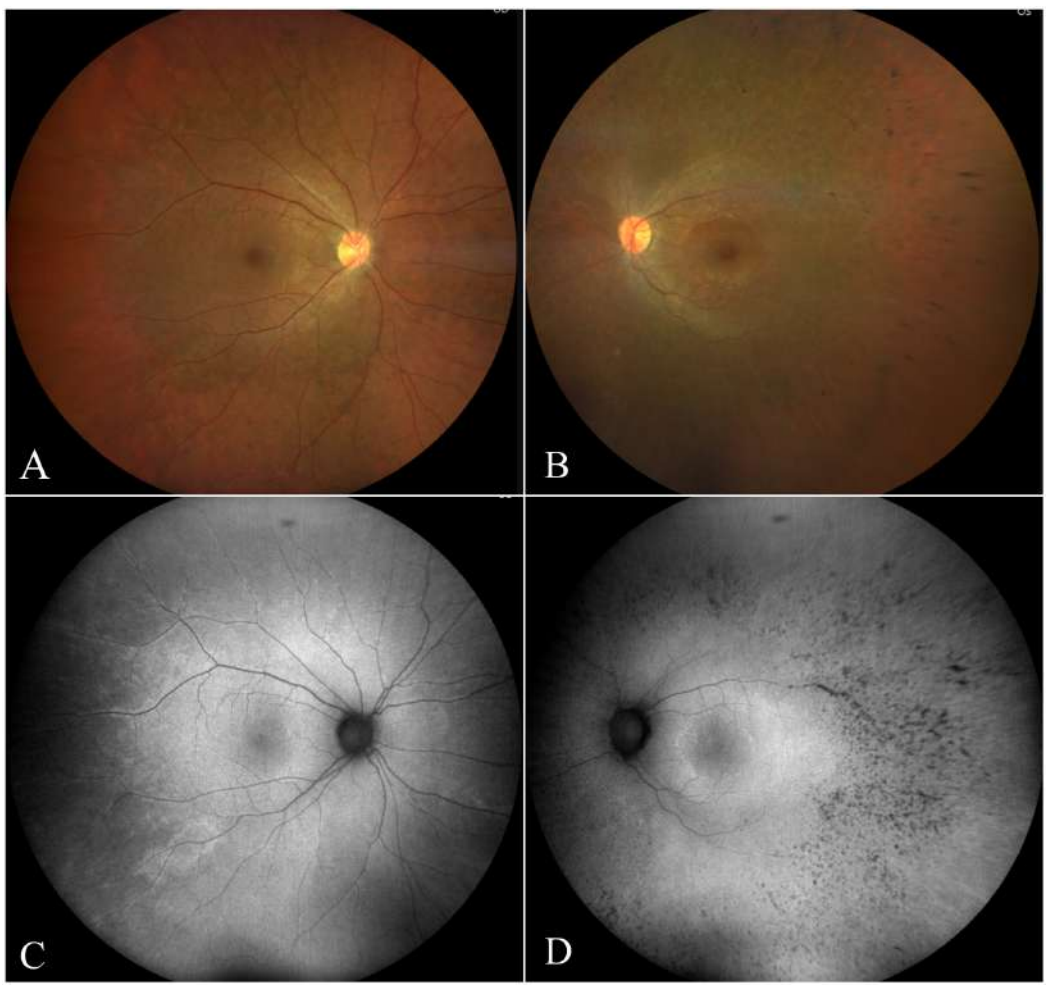

Figure 1: Panels A & C show normal features in the colour fundus photo and autofluorescence in the right eye while panels B & D show typical features of disc pallor, attenuated vessels, RPE atrophic spots and bony spicule pigments suggestive of unilateral retinitis pigmentosa in the left eye with corresponding changes in the autofluorescence

Detailed history and investigations were performed to rule out secondary causes of unilateral PR. The patient's history showed no previous episodes of ocular infections or inflammations, systemic drug intake, trauma, or retinal detachment. Serological tests for syphilis and toxoplasmosis were negative. Additionally, the patient's mother had no history of infection during pregnancy, and there was no family history of a similar condition. The patient did not undergo genetic testing because of financial constraints.

UNILATERAL PIGMENTARY RETINOPATHY: A RARE CASE REPORT AND DIAGNOSTIC CONSIDERATIONS

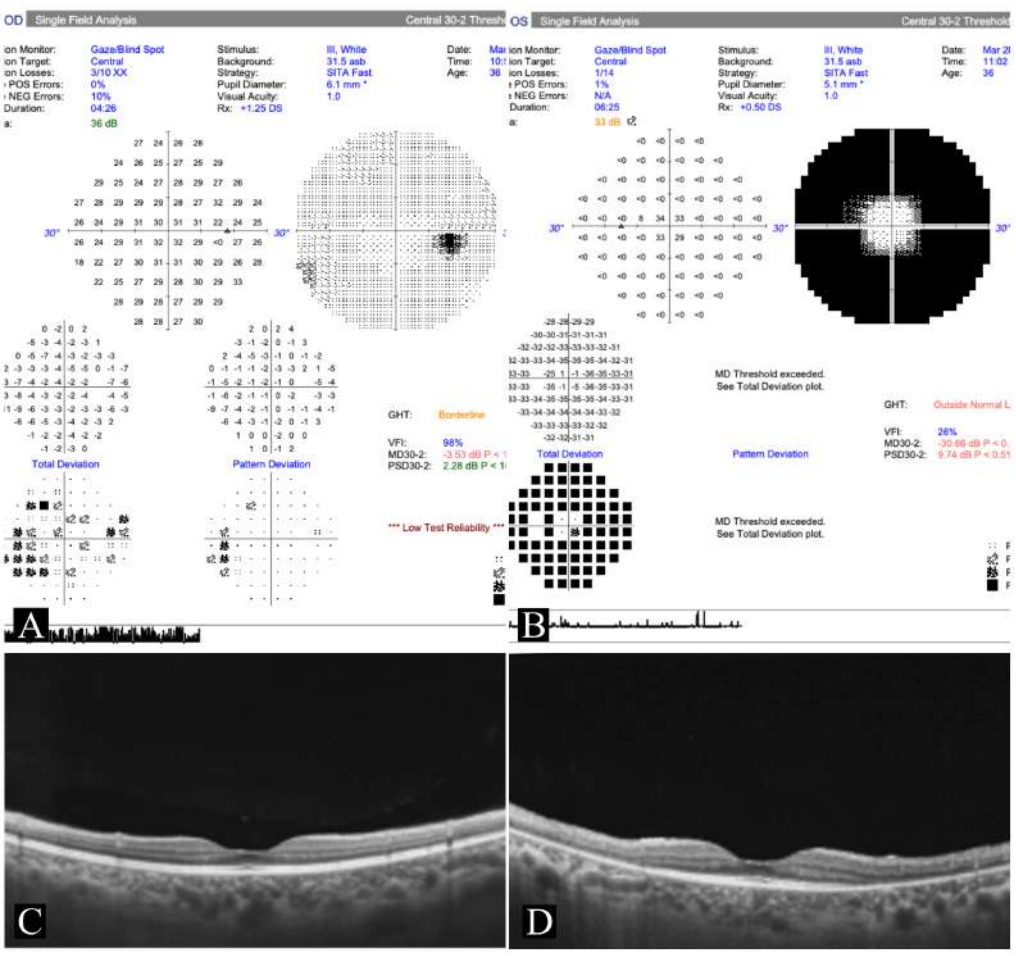

Figure 2 (A and B): Automated Humphrey perimetry demonstrated a normal visual field in the RE, with generalized sensitivity reduction and a severely restricted visual field in the LE. (C & D) show normal OCT in the right eye and the LE shows intact photoreceptors only at the macula, with para-macular and peripheral photo-receptor loss and outer retinal degeneration.

Based on the patient's history, distinct clinical findings, and functional examinations, a diagnosis of unilateral pigmentary retinopathy was made. However, to be certain, she was advised a regular and long follow-up to look for a delayed onset of an asymmetrical form of bilateral pigmentary retinopathy. No specific treatment was advised.

Discussion:

Unilateral Pigmentary Retinopathy (UPR) is one of several variants of classical pigmentary retinopathy, alongside sector, sine pigmento, and punctata albescens PR, each of which differs in morphology and electrophysiology.[1] The early symptoms of the disease include nyctalopia (night blindness), constriction of the peripheral visual field, and sometimes loss of central visual acuity or visual field. In patients with UPR, the fundus of one eye typically shows mottling of the retinal pigment epithelium (RPE),

followed by clumping of the disrupted RPE into bone-spicule formations, along with attenuated retinal vessels and waxy pallor of the optic disc while other eye remains within normal limits. Although case reports of RP in one eye and pigmented paravenous retinochoroidal atrophy (PPRCA) in the other eye have also been noted in the past, those were solitary cases.[3] The exact cause of UPR is unknown. It is believed that a somatic mutation during embryogenesis affects the cells forming the retina and retinal pigment epithelium (RPE). Since this mutation occurs early in embryogenesis, it has the potential to affect germ cell lines as well, posing a risk of passing the mutation to offspring.[4] According to Sharma et al., different etiological conditions with fundus appearances like RP are referred to as pseudoretinitis pigmentosa. Non-hereditary phenodeviants and other inherited disorders that closely resemble known RP mutant phenotypes are termed phenocopies. These often arise in response to triggers such as trauma or inflammation and vary depending on factors such as genetic predisposition, duration of exposure to the trigger, and the developmental stage at the time of exposure. To ensure an accurate diagnosis, it is important to consider differential diagnoses of uniocular pigmentary retinopathy and other RP phenocopies.[5]

Marsiglia et al have proposed 2 genetic mechanisms that could explain the unusual unilateral presentation of RP: mosaicism and somatic mutations.[4] Both mechanisms may cause asymmetric and partial involvement of a genetic disease throughout the body.[6] Cases have been documented with the p.R677X germline mutation in the RP1 gene, the USH2A W4149R mutation, and the PDE6B mutation.[6]

The nature of the pigmentary changes may not reliably predict the diagnosis or functional phenotype. Intraretinal pigmentary deposition, RPE depigmentation, disc

pallor, and vessel attenuation can occur in UPR depending on the stage of the disease but are not pathognomonic. The formation of bone spicules occurs due to apoptosis-induced photoreceptor cell death. This eventually leads to the degeneration of the outer retina, causing direct contact with the inner retinal vessels and migration of the RPE cells. Mislocalized RPE cells partially seal the contacting vessels, leading to extracellular matrix deposits.[6]

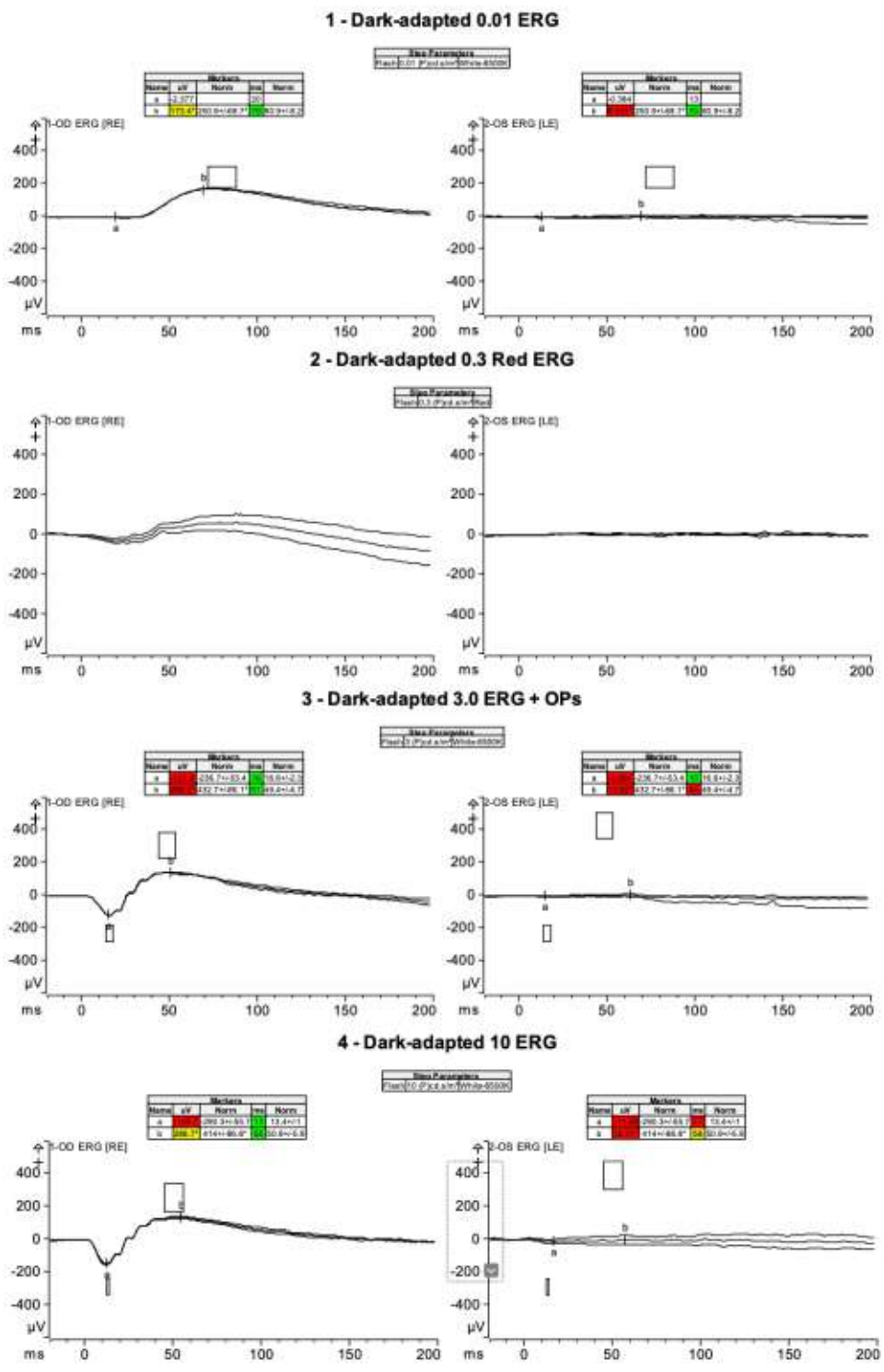

Figure 3: The left side panels show normal scotopic response in full-field electroretinogram (ERG) in the RE while the right side panels show grossly reduced scotopic responses in the LE.

To diagnose unilateral PR, the patient should be monitored over time using clinical, perimetric, and electroretinographic methods to ensure that retinal function in the unaffected eye remains stable. This approach helps to identify cases of bilateral but asymmetric PR.[7] Francois and Verriest's criteria for an authentic case of unilateral pigmentary retinopathy (idiopathic form) are as follows:

- Functional changes and fundoscopic appearance typical of primary pigmentary degeneration must be present in the affected eye.

- Symptoms of retinal degeneration must be absent in the unaffected eye, with a normal ERG.

- Inflammatory, infectious, and vascular causes in the affected eye must be excluded.

- The observation period must be long enough (over 5 years) to rule out the possibility of asymmetric inherited PR.

The case presented here met three out of the four criteria, with the only unmet criterion being the follow-up duration.

Many conditions can cause degenerative retinopathy that resembles UPR, making accurate differentiation crucial, as these conditions, unlike UPR, are typically treatable. Table 1 summarizes these differential diagnoses. High clinical suspicion is particularly important when dealing with a unilateral form of PR. In this case report, there were no previous episodes of ocular infections or inflammations, systemic drug intake, trauma, or retinal detachment. Additionally, serological tests for syphilis, toxoplasmosis, and Lyme disease were negative. UPR can be inherited through autosomal dominant, autosomal recessive, or X-linked recessive patterns.[6]

Table 1 : Differential diagnosis of UPR with distinguishing features

Conditions resembling UPR		Distinguishing features
Drug toxicity	Chloroquine Hydroxychloroquine Phenothiazine Thioridazine	- History of long-term medication use - Presence of Bull's eye maculopathy - Renal or liver disease - No family history of night blindness or retinal degeneration
Trauma	Foreign body (ie, siderosis) Blunt trauma (ie, commotio retinae, retinal detachment)	Traumatic retinopathies can be ruled out through a thorough medical history. Additionally, traumatic retinopathies typically do not progress in the same manner as RP.[8]
Post infectious state	Secondary to syphilis, toxoplasmosis, cytomegalovirus, Lyme disease, rubella, measles, tuberculosis	In RP, both the b-wave latency and amplitudes are abnormal, whereas in syphilitic retinopathy, only the amplitudes are reduced while the latencies remain normal.

Post inflammatory state	Secondary to retinal vasculitis, old posterior uveitis, diffuse unilateral subacute neuroretinitis, acute zonal occult outer retinopathy (AZOOR)	Young females with a history of autoimmune disease and characteristic retinal findings. Can be relapsing and remitting or progressive. Systemic workup may elucidate underlying rheumatologic conditions.
Autoimmune	Autoimmune Retinopathy	Autoantibodies circulate in the bloodstream, hence, both eyes are usually affected. ERG amplitudes are reduced, but the reduction is less severe than in UPR. Unlike UPR, where scotopic amplitudes are affected earlier than photopic amplitudes, in autoimmune retinopathy and CAR, both scotopic and photopic ERG results are equally reduced.[9]
Malignancy	Carcinoma related retinopathy (CAR)	

There is no definitive treatment for UPR, with supportive care being the primary approach; while treatments like antioxidants and vitamins have shown limited benefit, associated conditions like cystoid macular edema require appropriate medical therapies, and regular follow-up is necessary to monitor disease progression and the health of the unaffected eye.[7]

Conclusion:

In this case, characteristic features of pigmentary retinopathy were observed in only one eye, while the fellow eye remained unaffected. Diagnosing the condition requires a long follow-up period, along with visual field and electrophysiological testing, to rule out the possibility of a delayed onset of bilateral pigmentary retinopathy. Despite advancements in imaging and testing, UPR remains a diagnostic challenge due to its significant heterogeneity.

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CASE REPORT

EXTREME ENDS OF THE PHENOTYPIC SPECTRUM OF APPARENT PRPH2-RELATED RETINAL DYSTROPHY IN A MOTHER-DAUGHTER DYAD

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Introduction

Mutations in the Peripherin-2 (PRPH2) gene are among the most common inherited retinal diseases (IRD), with a larger percentage occurring in diseases primarily affecting the central retina with a large phenotypic variety.

Case report

A 74-year-old female presented with a history of progressive deterioration of vision in both eyes (OU) over the past 2 decades. Past history was significant for uncontrolled glaucoma in the right eye (OD) and two intravitreal injections in the left eye with no appreciable improvement. She denied light perception in OD while the best corrected visual acuity (BCVA) in OS was 6/36, N36. Both eyes were pseudophakic while OD showed a flat filtering bleb at 12 o clock position. The intra-ocular pressure in OD was 33 mmHg, and OS was 10 mmHg. Fundus view in OD was limited by posterior capsule opacification but showed a pale optic disc , severely attenuated retinal vessels and widespread areas of well-defined chorioretinal atrophy and pigment clumps (Fig 1a). OS

showed a normal appearing disc and mildly attenuated retinal vessels. The background retina had multiple circular well defined areas of chorioretinal atrophy with pigment clumping, also involving the peripapillary area and macula (Fig 1 B). Ultra-wide field autofluorescence (UWF-AF) (Fig 1C&D) showed numerous areas of loss of autofluorescence (AF) with a zone of sparing temporal to the arcades in OS. Spectral domain optical coherence tomography (SD-OCT) showed extensive outer retinal layer loss (Fig 2). The possibility of a retinal dystrophy was considered.

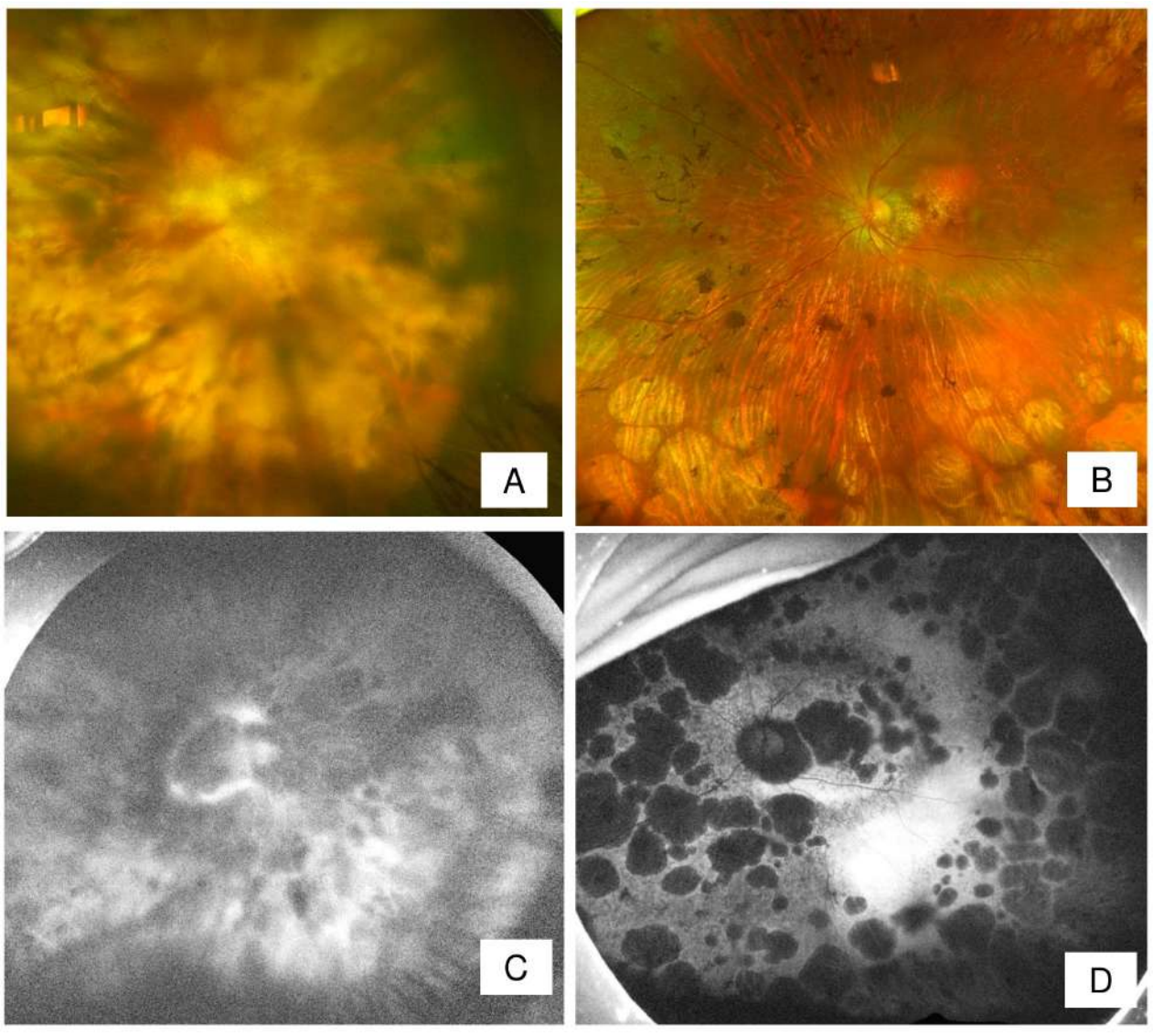

Figure 1: Figure 1.A and 1.B represents an ultra-wide field pseudo color Optos® California ((Optos, Marlborough, MA, USA) images with autofluorescence (1.C and 1.D) showing multiple discrete areas of extensive chorioretinal atrophy involving the entire fundus including the fovea with a crescentic pattern of hyperautofluorescence temporal to macula better visualized in the OS. OD details were hazy due to posterior capsule opacification.

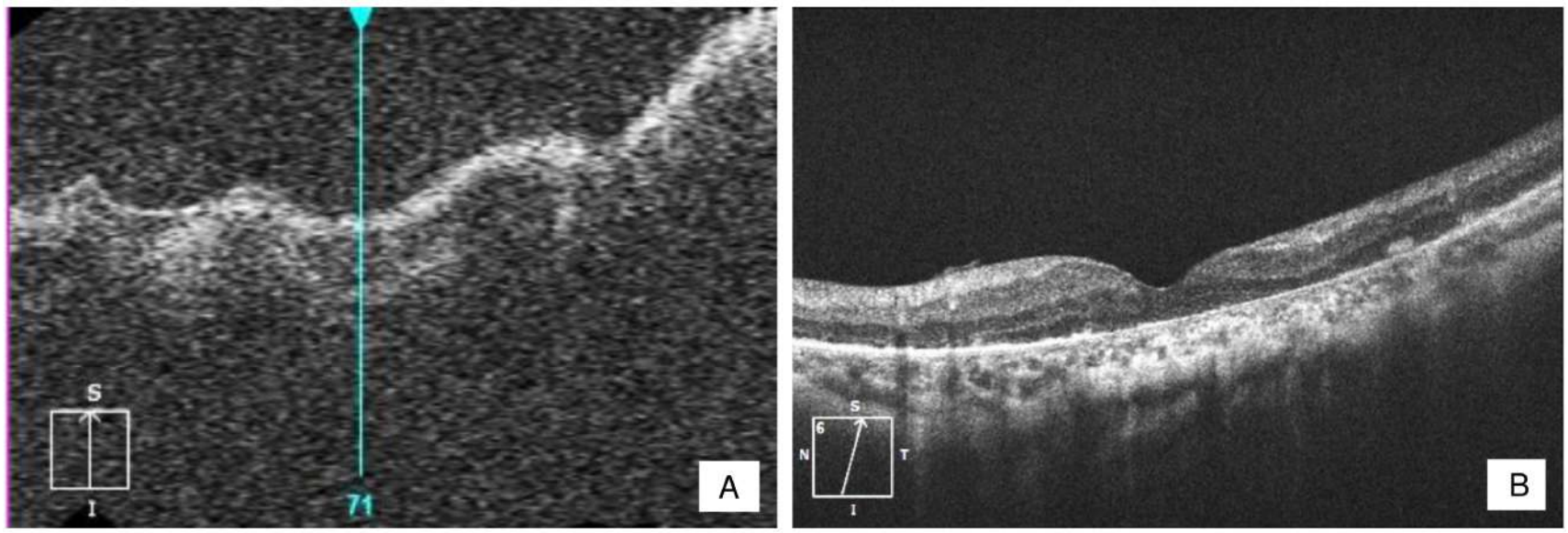

Figure 2: Figure 2.B SD OCT CIRRUS™ 6000 (ZEISS, Dublin, CA) of OS indicating a maintained foveal contour, retinal pigment epithelial atrophy, loss of ellipsoid zone and distortion of outer retinal architecture. Figure 2.A is a similar scan of the OD but the scan quality is poor due to media haze

Her accompanying 39-year-old daughter was evaluated for complaints of blurred vision and metamorphopsia in OU for the past 3-4 years. She had been advised in vitro fertilisation and wanted to know if her eye problem could be affected by the treatment. BCVA was 6/6, N6 OU with unremarkable anterior segment and IOP. Fundus OU revealed normal optic discs and retinal vessels with a butterfly pattern of yellowish vitelliform deposits subfoveally and fine drusenoid deposits in the periphery. AF images showed a localised mixed pattern of hyper and hypo AF at the macula (figure 3). Outer layer irregularity and elevated subretinal dome-shaped hyperreflective deposits were seen on SD OCT (figure 4). OU full-field electroretinogram showed reduced scotopic responses. A subnormal EOG with a reduced light peak-to-dark trough ratio (Arden's ratio- OD 1.24, OS -1.14) was noted (figure 5). The clinical picture and imaging findings were suggestive of butterfly pattern dystrophy of the retinal pigment epithelium.

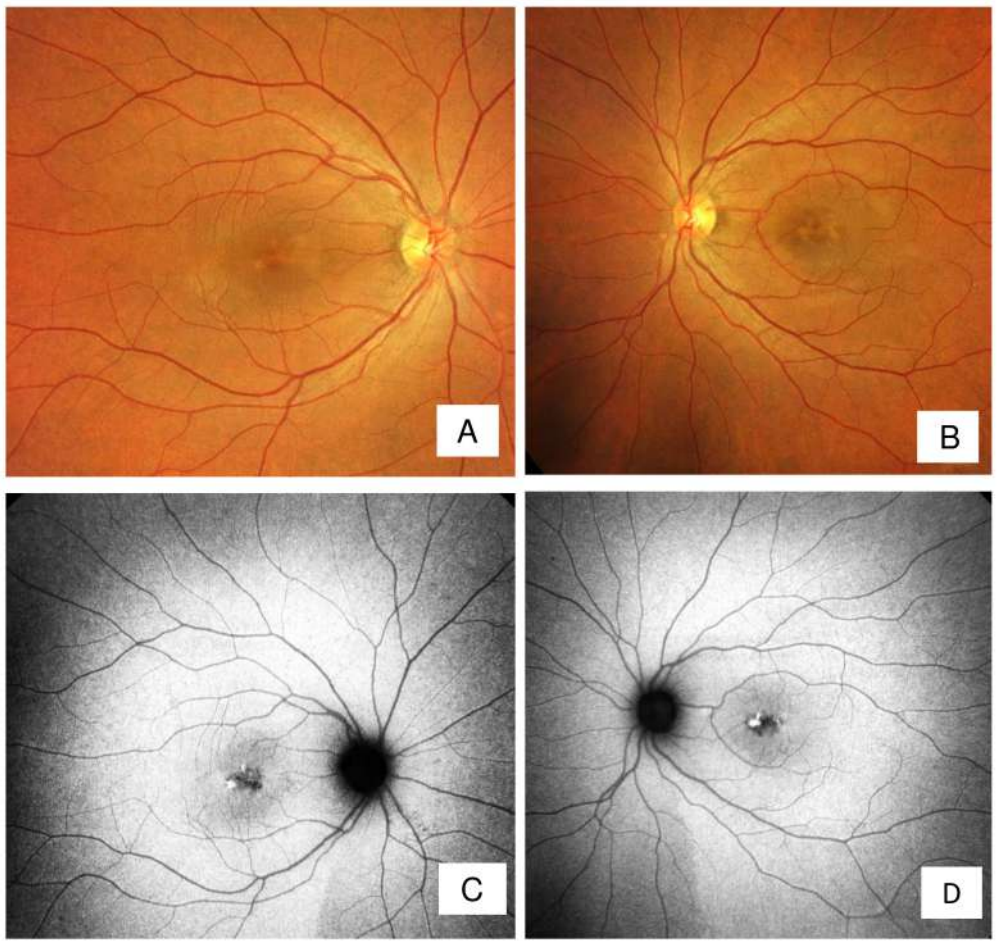

Figure 3: Figure 3.A and 3.B are color fundus photos of the patient's daughter which show normal optic discs and vasculature with yellowish vitelliform deposits subfoveally in a butterfly pattern in both the eyes. The fundus autofluorescence images (Figure 3.C and 3.D) show a bilateral symmetric mixed pattern of hyper and hypoautofluorescence at the macula. Focal hyperautofluorescent areas correspond to the areas of yellow vitelliform deposits seen on the fundus

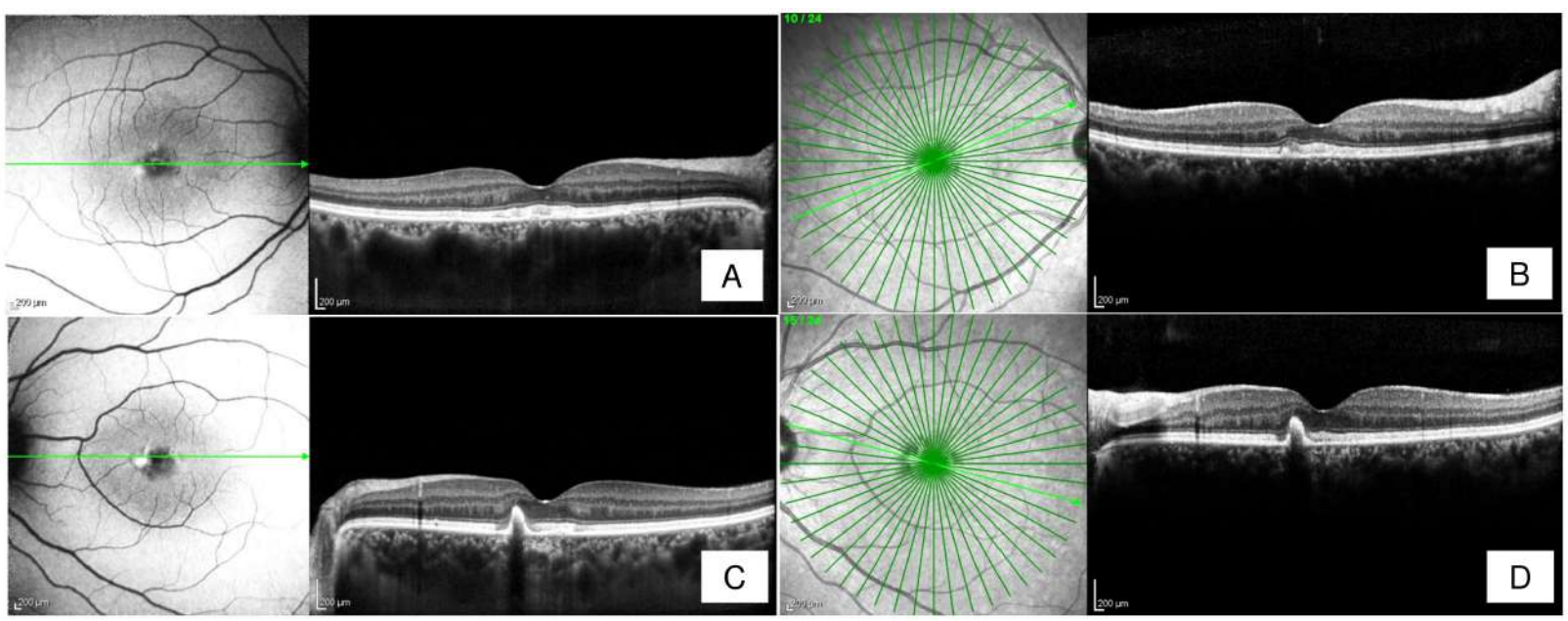

Figure 4: Figure 4.A and 4.B SD OCT OD of the patient's daughter showing outer layer irregularity and elevated subretinal dome-shaped hyperreflective deposits. These deposits had led to the disruption of the ellipsoid zone more evidently seen in OS. (Figure 4.C and 4.D).

EXTREME ENDS OF THE PHENOTYPIC SPECTRUM OF APPARENT PRPH2-RELATED RETINAL DYSTROPHY IN A MOTHER-DAUGHTER DYAD

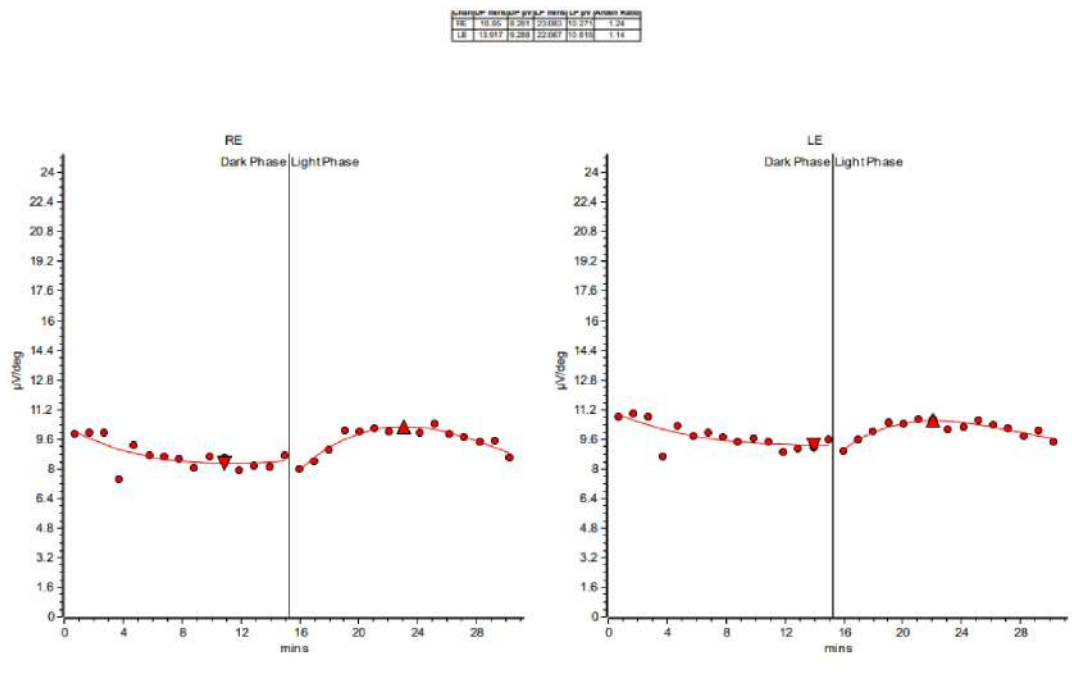

Figure 5: A subnormal EOG with a reduced light peak-to-dark trough ratio (Arden's ratio- OD 1.24, OS -1.14) was seen in OU.

As both mother and daughter had features suggestive of a dystrophy , the possibility of different phenotypes of PRPH2 mutation was considered.

Discussion

Mutations in the Peripherin-2 (PRPH2) gene (OMIM: 179605) are among the most common inherited retinal diseases (IRD),[1] with a larger percentage occurring in diseases primarily affecting the central retina with a large phenotypic variety.[2]

The 74-year-old female patient had gradually deteriorating vision, extensive retinal degeneration, and macular atrophy in her left eye. Her 39-year-old daughter had milder symptoms such as bilateral impaired vision and metamorphopsia. Both patients had clinical features suggestive of PRPH2 mutations but at two ends of the described spectrum.

The guarded prognosis was explained to the mother and option of low vision aids was given. The daughter being of child bearing age and considering assisted reproduction was explained about the possible inheritance pattern and given the option for genetic testing to confirm the diagnosis.

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CASE REPORT

MULTIMODAL IMAGING OF A CASE OF BUTTERFLY PATTERN DYSTROPHY

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Introduction

Butterfly shaped pattern dystrophy is a rare autosomal dominant pattern dystrophy of the retina first described by Deutman,[1] characterized by abnormal accumulation of lipofuscin at the level of the retinal pigment epithelium(RPE) due to RDS/Peripherin gene mutation affecting the photoreceptor outer segments. In early stages it can be picked up by multimodal imaging which highlights the butterfly pattern of lipofuscin accumulation like – yellowish pigmentary change on colour photo with corresponding hyperautofluorescence on Fundus Auto Fluorescence (FAF) and shadowing artefact on Optical coherence tomography angiography (OCTA), while in late stages it may be confused with Age related macular degeneration. Though asymptomatic in early age group most patients become symptomatic in late twenties or thirties [2] due to extension of the atrophy to the peripapillary area or development of CNVM. [3,4] Here we present a case of butterfly pattern dystrophy presenting in seventh decade without any visual symptoms.

Case report

A 70 year old hypertensive male patient presented to our centre for routine eye

examination. At presentation his best corrected visual acuity was 20/20 in both eyes and had immature cataract. Fundus examination showed normal disc with abnormal yellow pigmentary change at macula with 4-5 arms resembling the shape of a butterfly [figure 1a] which was well demarcated on red free [figure 1b] and FAF images [Figure 1c]. FAF imaging showed hyperautofluorescent central lesion with radiating hyperautofluorescent arms.

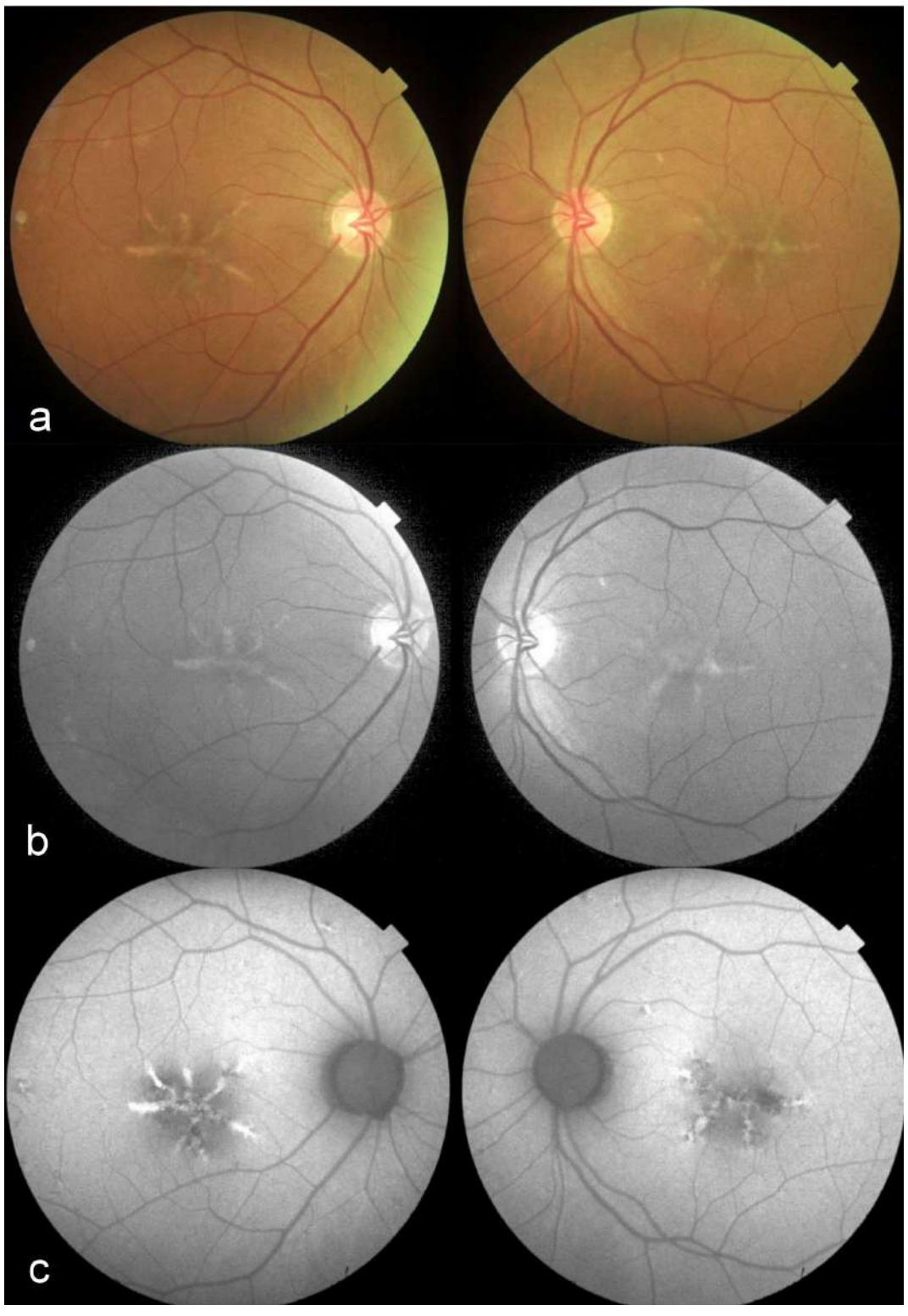

Figure 1: a. Fundus colour photo showing yellowish lesion at the posterior pole with radiating arms with adjacent hyperpigmented borders. b. Red free image showing better delineation of the butterfly pattern of retinal dystrophy as bright signal when compared to background retina. c. Fundus autofluorescence imaging showing central hyperautofluorescent lesion with hyperautofluorescent radiating arms corresponding to areas of lipofuscin accumulation and yellow lesion in colour photo

Swept source OCT showed areas of ellipsoid layer discontinuity and abnormal accumulation of debris as evident by hyperreflective material accumulation at the level of photoreceptors and RPE [Figure 2]. Perifoveal capillary network was normal in both superficial and deep capillary plexus. However, choriocapillaris slab showed shadowing artefact in the form of a butterfly due to lipofuscin accumulation in RPE [Figure 3]. As Patient was asymptomatic he was advised to be on periodic follow up.

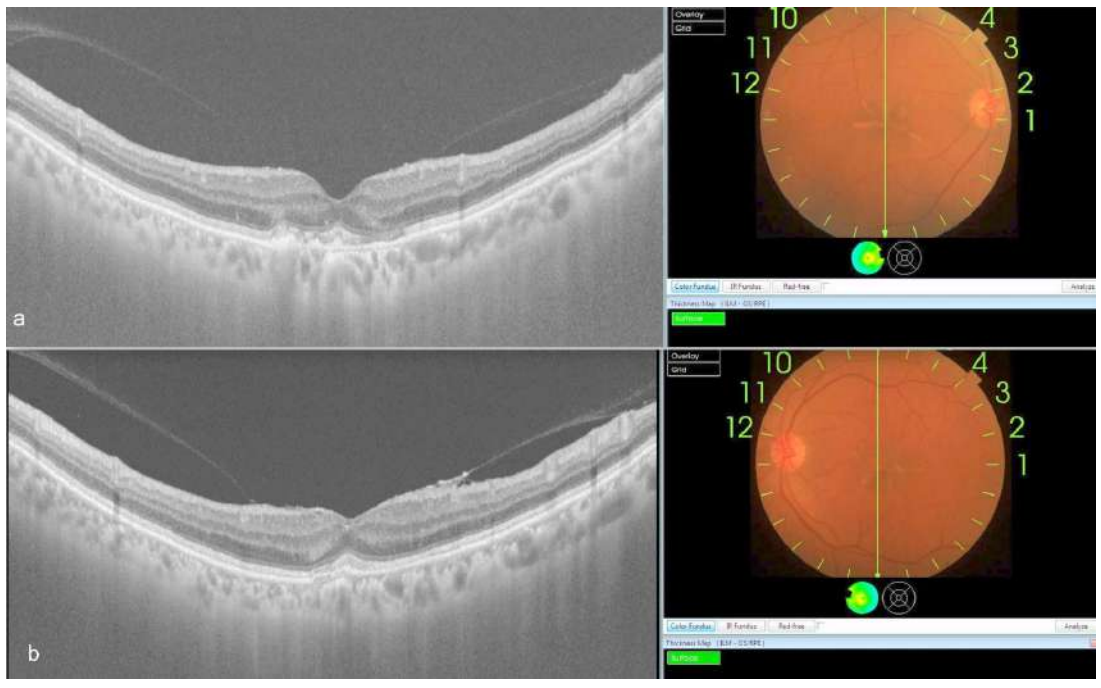

Figure 2: Swept source OCT showing a) OD: ellipsoid layer discontinuity and hyperreflective material between RPE and ellipsoid zone b) OS: areas of ellipsoid layer discontinuity and RPE irregularity

Discussion

Butterfly pattern dystrophy is characterized by lipofuscin accumulation in RPE in a characteristic pattern of central lesion with radiating arms in early stages with progressive atrophy. The lesion appears yellowish with pigmented borders on colour images and appears hyperautofluorescent on FAF with hypoautofluorescent margins of atrophy. OCTA shows shadowing in choriocapillaris slab. The main purpose of OCTA is to monitor the development of choroidal neovascular membrane. In our case, the lesion was not complicated by CNV or atrophy which explains good visual symptoms.

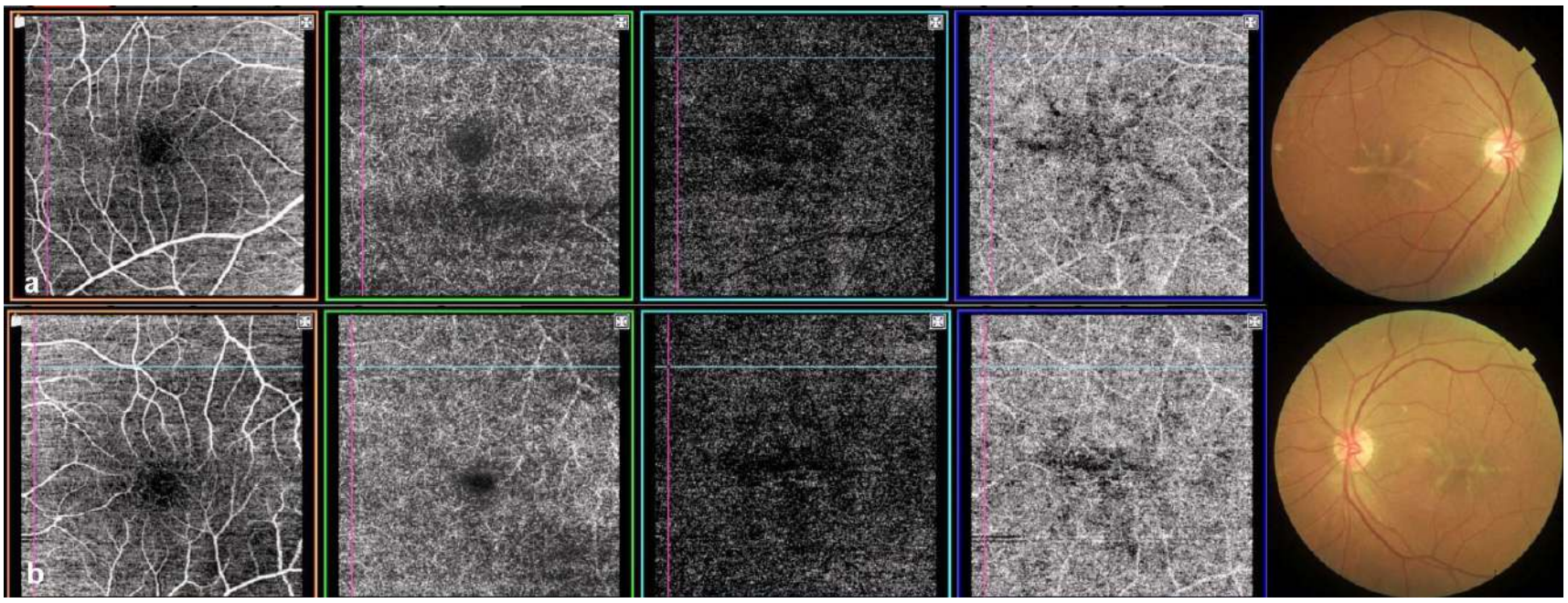

Figure 3: OCT angiography of right (a) and left eye (b) demonstrating superficial slab (Orange Square), deep slab (Green Square), outer retina (light blue), choriocapillaris slab (dark blue). Both eyes demonstrate well maintained perifoveal capillary plexus in superficial and deep slab, choriocapillaris slab demonstrates shadowing effect due to lipofuscin accumulation in overlying RPE layer.

Conclusion

This case report describes a case of butterfly pattern dystrophy using multimodal imaging.

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