Approach to inherited retinal diseases

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Inherited retinal diseases (IRDs) are a group of phenotypically diverse disorders with varied genetic mutations, which result in retinal degeneration leading to visual impairment. When a patient presents to a clinician who is not an IRD expert, establishing a correct diagnosis can be challenging. The patient and the family members are often anxious about further vision loss. They are eager to know the prognosis and chance of further worsening of the vision. It is important for every eye specialist to educate himself/ herself about the basics of IRD. It would help to familiarize oneself about how to approach a patient with an IRD. An early and accurate diagnosis can help predict the vision loss and also help the patient plan his/ her education and choose appropriate career choices. An updated knowledge about the genetic mutations, mode of inheritance, and possible therapies would empower the eye specialist to help his/her patients. This article gives a broad plan of how to approach a patient with IRD with regards to characterization and diagnosis of the disorder, visual rehabilitation, and possible therapy.

Key words: Inherited retinal diseases, rare eye diseases, retinitis pigmentosa, retinal dystrophies, electroretinography

Inherited retinal diseases (IRDs) are a group of disorders affecting the retinal cells, which lead to severe vision loss and sometimes blindness. Various mutations of genes involved in the function or structure of the outer retinal elements have been identified as the causative factors for these IRDs. The vast heterogeneity in the genotype as well as the phenotypic features of these diseases makes it difficult to characterize them. The patients and their families are often bewildered by the vision loss and are worried about the disease progression to blindness. They are anxious to know about the therapeutic options and inheritability of the disease. An early accurate diagnosis is desirable as it can help the patients and their families to plan the education and choose appropriate professional courses for the affected persons. It can also help predict the rate of vision loss and the inheritance pattern. The process of obtaining a correct diagnosis can be challenging even to a clinician who is well versed in IRDs. It includes detailed ocular history, medical and family history, multimodal imaging, and molecular testing. A multidisciplinary approach might be needed involving the internist, pediatrician, geneticist, and genetic counselor. This review helps in detailing the systematic way to approach a patient suspected to have an IRD, so that the most likely diagnosis can be arrived at easily.

Overview and Epidemiology

Most of the IRDs belong to the rare eye disease category, wherein the disease is seen to affect less than 200,000 people. Despite being rare, they are the most common cause of visual impairment in childhood and in young adults. About 20%–25% of blindness in the working age population is due to IRDs.[1] The disease burden is higher in India than in the Western population. Various studies have reported the prevalence of retinitis pigmentosa (RP) to be around 1 in 750 in urban population.[2] The prevalence was reported to be higher in rural population and tribals (20%).[3] This might be due to the high rate of consanguinity in these populations. In one study, the consanguinity rate was 24.7% in the rural subjects.[4] Among the consanguineous families, the prevalence of RP could be as high as 64%.[5]

Clinical Characterization: Medical History

It is important to suspect or identify an IRD at an early stage, so that proper assessment with specialized investigations can help characterize the disease accurately. A detailed medical history forms the cornerstone of assessment and can often point the diagnosis, which can then be confirmed by appropriate investigations. It should include the age of onset, the symptoms at the onset, and whether the symptoms are progressive or stationary. Previous reports of ophthalmological examination can be very helpful in establishing the previous visual acuity, visual fields, and so on. Based on history, a working diagnosis can be formulated. If the main complaint is night blindness, with loss of peripheral visual field, it points to a rod-predominant disorder. Whereas if the patient has early central vision loss with color vision loss and photophobia, then it would be a cone-predominant disorder.

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A history of consanguinity and a similarly affected family member should be specifically asked for. Sometimes, the examination of an affected family member might be contributory in diagnosing the condition. A pedigree involving at least three generations can reveal the inheritance pattern, such as X-linked inheritance in juvenile retinoschisis or an autosomal dominant pattern. Fig. 1 shows an example of a pedigree charting for a patient with IRD. Presence of systemic disorders in family members can also be important in diagnosing IRDs. For example, history of diabetes mellitus in the mother and hearing impairment in her sister can point to a mitochondrial inheritance. Consanguinity is often associated with autosomal recessive diseases.

Similarly, a history of systemic, nonocular symptoms is also important as many of the IRDs can be a part of a larger syndromic condition often involving multiple organ systems. For example, presence of hearing loss (HL) can point to Usher syndrome (USH). Presence of obesity, polydactyly, and mental retardation along with night blindness may be a part of Bardet–Biedl syndrome (BBS).

History of nonprogressive or stationary night blindness narrows down the possible diagnosis to a few stationary conditions such as congenital stationary night blindness (CSNB) if the fundus is normal. But if the fundus is abnormal, showing plenty of white flecks, it could be a fundus albipunctatus. The fundus typically shows large, uniformly distributed white, round flecks all over [Fig. 2]. In case of Oguchi's disease, the fundus shows a Mizuo phenomenon, wherein the fundus has a bright golden sheen in the light adapted state, which vanishes on prolonged dark adaptation.

Progressive night blindness can occur due to a variety of diseases which include RP [Fig. 3] and RP-related syndromes, choroidal degenerations such as choroideremia and gyrate atrophy, various vitreoretinopathies such as Stickler's syndrome, Wagner's syndrome, and so on. Some varieties of progressive night blindness could be due to acquired causes related to vitamin A deficiency or toxicity to drugs such as phenothiazines, hydroxychloroquine, pentosan polysulfate or due to autoimmune or carcinoma-related retinopathy.[6-10]
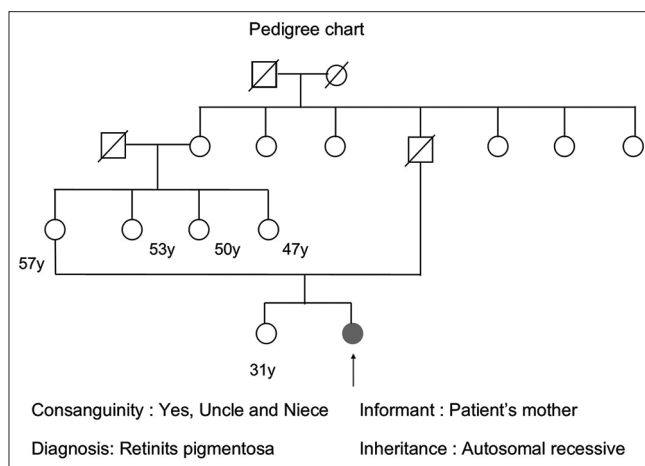
Figure 1: Pedigree chart of a female patient with retinitis pigmentosa, born of consanguineous marriage, shows autosomal recessive inheritance pattern

Determination of Visual Function

Visual function testing is an important part of the work-up of an IRD patient. It not only helps in further counseling of the patient, but also provides useful information regarding the differential diagnosis. Checking the visual acuity with Snellen's chart is a very basic test which is easily done in the adults, but can be challenging in very young children. Lea symbols or the Landolt rings can be used for checking of visual acuity in young preschool children. Refraction with and without cycloplegia can help in improving the patients' visual function. At the same time, it can be a valuable additional point toward strengthening of the differential diagnosis. Often, patients with Leber congenital amaurosis (LCA) are hyperopic, while patients with RP or CSNB are myopic. In patients with only mild impairment of visual acuity, it helps to check the color vision. Color vision defects along with subtle retinal changes can help differentiate between IRDs and optic neuritis. Other differential diagnoses which need to be ruled out, especially in young children, are delayed visual maturation, central visual disorders, and optic nerve hypoplasia. The role of ancillary tests including visual fields and elctrophysiological tests (electroretinography [ERG]) cannot be stressed more. A full-field ERG (ffERG) can accurately differentiate among these conditions. A normal ERG would point toward optic nerve pathology, whereas an abnormal ERG indicates retinal disease. Further, a pattern ERG (PERG) or multifocal ERG (mfERG) can help differentiate between macular pathology versus optic neuropathy.

Visual field testing can give valuable information about the central as well as the peripheral field defects, which not only help in characterizing the disease, but are also mandatory in follow-up examinations to document progression. Tubular fields in advanced RP are characteristic, but many patients may also have a central field defect due to macular atrophy. Whereas the diseases mainly affecting the macular area, such as Stargardt disease, will predominantly cause a central scotoma. The visual fields charting is also necessary to categorize the visual loss for certification of visual impairment and availing of facilities. Many workplaces will have specific requirement of vision and fields, and patient might be declared fit or unfit to work based on these tests.

Electrophysiological Tests

Electrophysiology has a pivotal role in characterizing the IRDs. It not only helps in identifying the site of damage in the visual pathway, but can also pinpoint the cell type involved in the degenerative process. These tests are noninvasive and include ffERG, mfERG, and PERG.[11] ffERG can differentiate between inner and outer retinal changes, which might not always be possible by retinal examination. In ffERG, the responses are dominated by the peripheral retina. For the evaluation of the macular function, PERG or mfERG is preferable. PERG is recoded using an alternating dark and light checkerboard pattern. The responses from PERG, namely, P50, a positive peak, indicates macular function and N95, a negative deflection, indicates retinal ganglion cell function. The overall response from PERG is also influenced by uncorrected refractive error and media opacities. The spatial localization of defects is better with mfERG. ERG is found useful in cases where fundus examination does not correlate with the visual function. For example, in sector RP, the fundus findings may not correlate
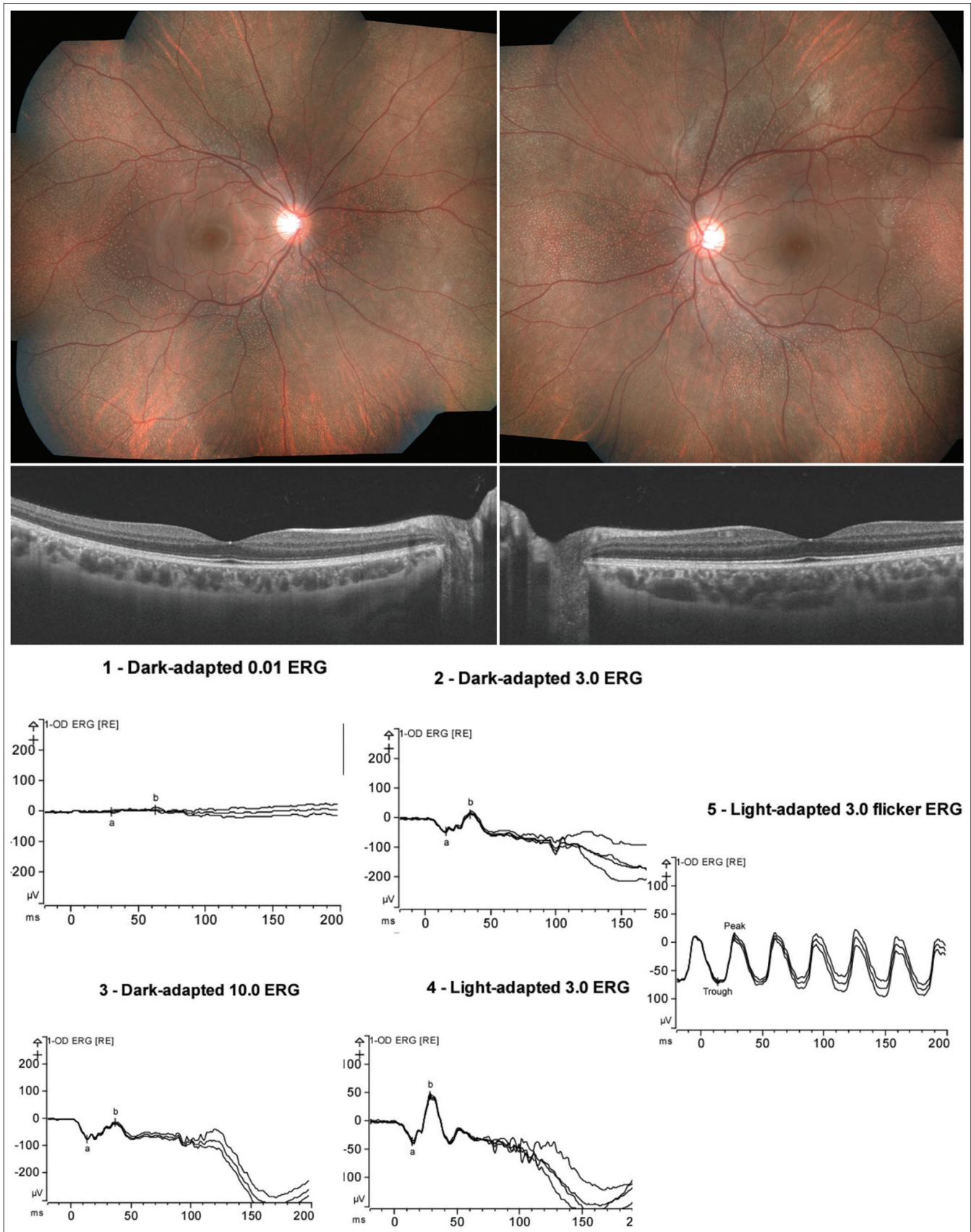
Figure 2: Fundus albipunctatus – a 16-year-old boy complained of delayed dark adaptation and stationary night blindness. His vision was 20/20; the retina had small, regular white spots distributed all over with normal vasculature and optic nerve head. The ERG showed reduced scotopic and normal photopic responses. ERG = electroretinography
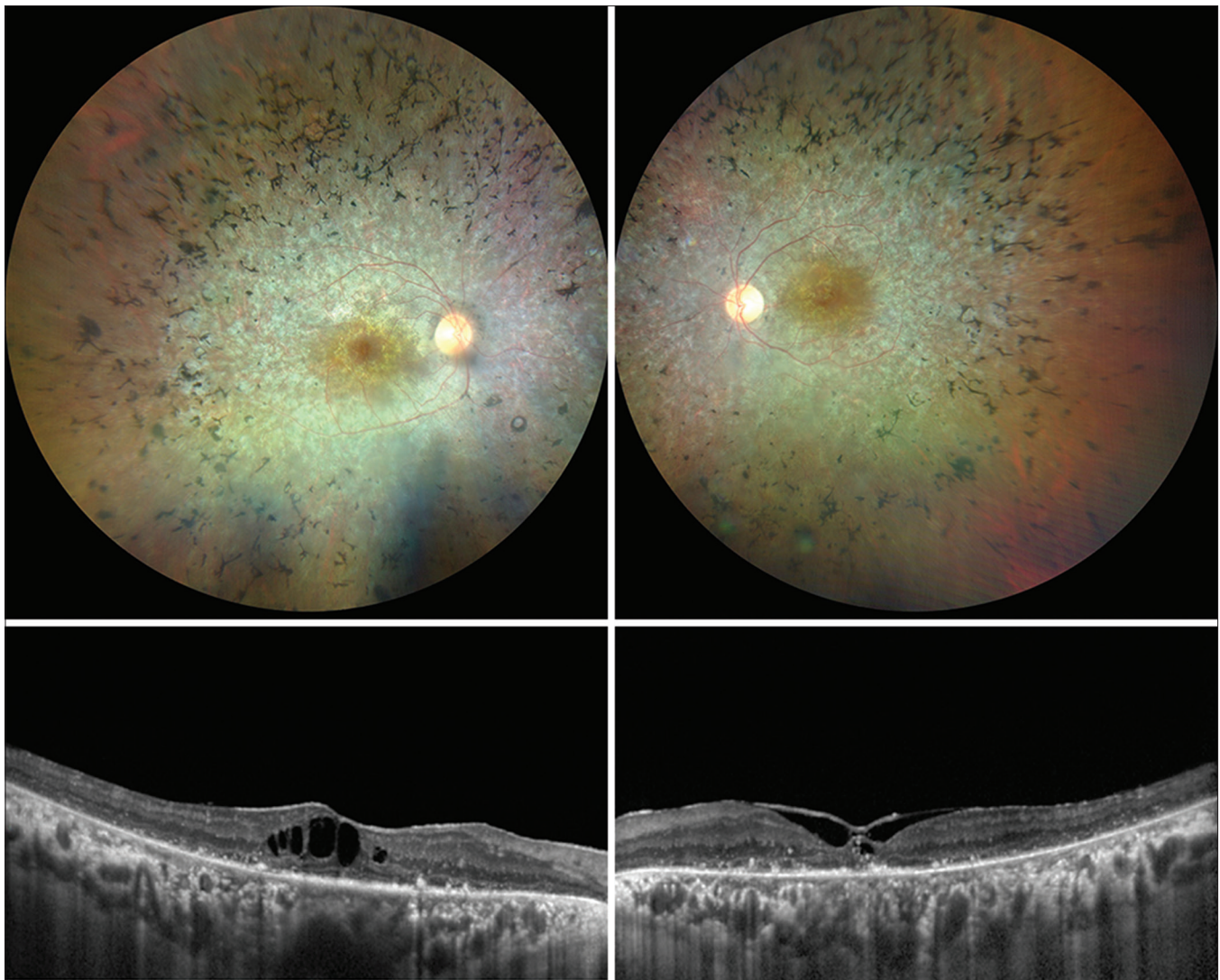
Figure 3: A 40-year-old woman had progressive night blindness and diminished side vision for 20 years. Retinal evaluation revealed typical retinitis pigmentosa with multiple whitish atrophic patches and bony spicule pigments in midperiphery. The vessels were attenuated, and the optic nerve head was pale. The ERG was extinguished. The OCT revealed outer retinal atrophy, thinning, high reflective spots, and shadowing below. Macular edema was seen in both the eyes with an epiretinal membrane in the left eye. ERG = electroretinography, OCT = optical coherence tomography

with the visual function. ERG can be used to localize the loss of photoreceptors.[12,13] In RP, progressive loss of rods can be monitored effectively with ERG. In case of cone–rod dystrophy (CRD), where there is a progressive loss of cone function followed by the rod function, the ERG shows abnormal cone responses with preserved rod responses during the initial stage of the disease, but further abnormal rod responses with the progression of the disease.[13-15] ERG can also help in identifying the genotype. For example, in cone dystrophy with mutation in *KCNV2* gene, a characteristic response of reduced cone response and supernormal rod response is seen.[16] In congenital X-linked retinoschisis (CXLR), the ffERG is usually negative with the preservation of the a-wave and reduction in b-wave amplitude.[17,18] mfERG can also be used in detection or screening for carriers of *CXLR* mutations. Kim *et al.*[19] reported that there is a reduction in macular response amplitude in carriers of *CXLR* gene when fundus examination appears to be normal. Fig. 4 shows some examples of the ERG responses in IRDs.

Optical Coherence Tomography

Optical coherence tomography (OCT) enables the cross-sectional visualization of tissues *in vivo*. It is superior to ophthalmoscopic examination and gives much more information about all the layers of the retina. It can demonstrate the outer retinal thinning and loss of photoreceptors. Inner retinal manifestations such as macular hole, cystoid macular edema, epiretinal membrane, foveal schisis, and so on can be easily detected and followed up with OCT.[20] The impact of outer retinal layers in visual outcome is higher.[21] Progressive worsening can be effectively and easily monitored using OCT.[22] Most patients with RP initially show peripheral thinning and atrophy of the outer retina due to predominant rod degeneration,[23] whereas patients with CRDs show mainly central atrophic changes in the outer retina. The progressive conditions can be easily differentiated from the stationary conditions such as CSNB or achromatopsia, where the OCT hardly shows any change.[24-26] In CXLR, the OCT shows schitic spaces predominantly involving the ganglion cell layer in the perifoveal
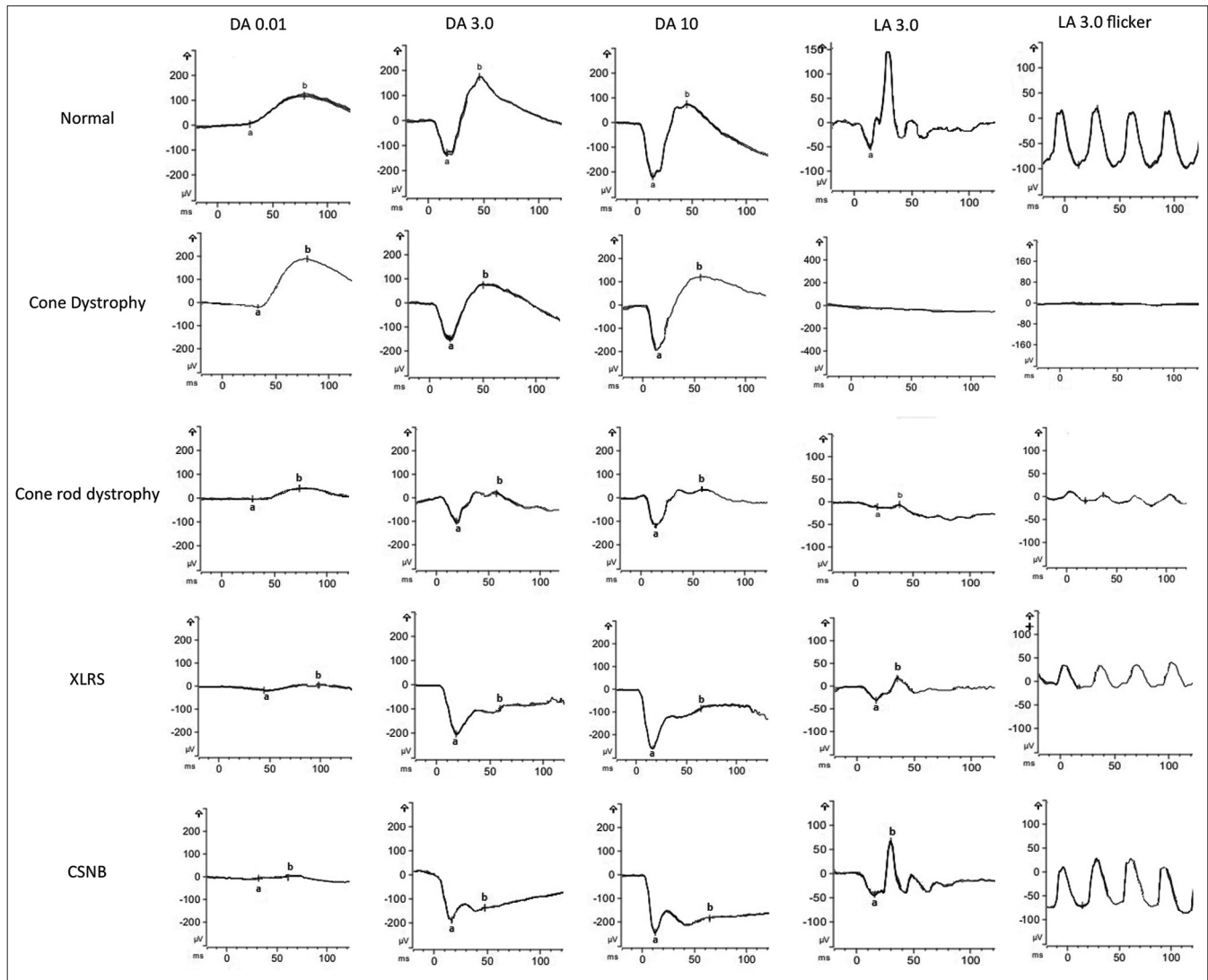
Figure 4: This chart shows examples of ERG changes in a few IRDs. ERG = electroretinography, IRD = inherited retinal disease

region. However, in the extramacular region, the schitic spaces are present in the outer nuclear or inner nuclear layer[27] [Fig. 5]. Subtle changes such as small focal loss of photoreceptors are also picked up well by OCT when the retinal examination might be deceptively normal, failing to explain the reduced vision. Changes in the retinal pigment epithelium as well as the choriocapillaris are evident on OCT.[28] Thus, OCT has become indispensable in the evaluation and monitoring of IRDs. Apart from these, fundus autofluorescence (FAF) is also invaluable in detecting serial changes in the degenerative process, which might not always reflect in visual acuity changes. Large changes are needed to affect the visual acuity, but FAF can document even small changes, which are easily revealed on comparison of serial images.[24,29-31]

IRDs in the Pediatric Age Group

The list of major IRDs causing poor vision in the pediatric age group includes Stargardt disease [Fig. 6], Best disease/bestrophinopathies [Fig. 7], CXLR, familial exudative vitreoretinopathy (FEVR), cone dystrophy, LCA, achromatopsia, neuronal ceroid lipofuscinoses, Refsum disease, incontinentia pigmenti (IP), Norrie disease, and various syndromes such

as USH, BBS, Senior–Loken syndrome (SLN), and Joubert syndrome (JBTS). Table 1 gives a summary of some of the IRDs affecting children.

The initial clinical symptoms of IRD are generally recognized during the first year of life in the majority of children. Nystagmus (76%) is usually the first to be noticed (usually during the first 6 months of life), while abnormal visual behavior suggesting a visual loss (28%) is more frequently reported after 6 months of age.[32] A few children in the older age group may report visual field loss or bumping into objects (6%), night blindness (4%), or color vision problems (6%). It is important to differentiate sensory nystagmus from the primary infantile nystagmus. Clinically, sensory nystagmus worsens by fixing on objects. Abnormal visual behavior can represent a significant diagnostic challenge in young children. While this may be a sign of neurological or ophthalmological disorders, it can also represent a delayed visual maturation. Cortical visual impairment is a major differential in an infant presenting with visual loss. However, the diagnosis of cortical visual impairment would be a diagnosis of exclusion. Once all other causes are ruled out, the child can be labeled to have cortical visual impairment.
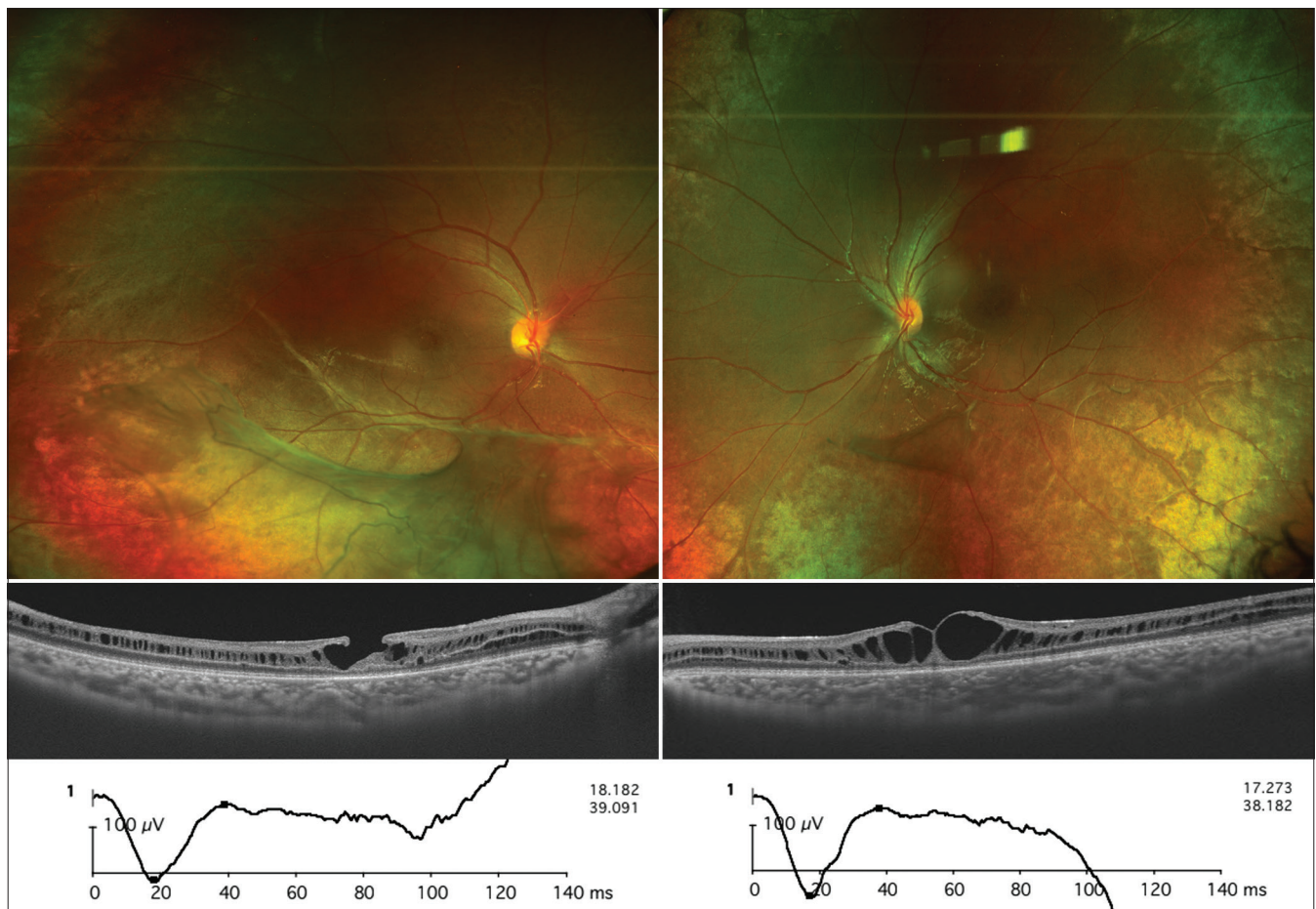
Figure 5: A 12-year-old young boy with congenital X-linked retinoschisis. Widefield, pseudo-color images show peripheral golden sheen, sclerosed vessels, vitreous veils, and retinoschisis in the inferotemporal quadrants. Swept source OCT clearly shows the schitic spaces in the inner nuclear layer and foveal area. ERG shows a reduced, negative b-wave. ERG = electroretinography, OCT = optical coherence tomography

Confirming the diagnosis may be particularly difficult in young children, since they are often unable to report sensory loss or cooperate with clinical and instrumental testing. Especially in infants, the clinical suspicion relies mostly on parental observation. There are three steps in the evaluation of IRDs in children. Clinical examination is the main step for the diagnosis; however, some IRDs, such as CSNB and RP sine pigmento, present with almost normal fundoscopy on initial examination. Genetic testing and electrophysiologic testing, ffERG and/or mfERG, and electrooculogram (EOG) are essential.[33,34] These tests are fundamental to understand their stable or progressive trend during follow-up. In uncooperative children, examination under anesthesia for a complete fundus examination, fundus photography, fluorescein angiography (FA), FAF, and ffERG can help narrow the differential diagnosis. Fig. 8 gives a simple algorithm for diagnosis of IRDs.

Systemic abnormalities such as HL, renal dysfunction, polydactyly, and neurologic dysfunction should definitely be looked for in these children, and they should be referred for appropriate screenings.[33-35]

Refsum disease is a peroxisomal storage disorder that presents with ichthyosis, ataxia, and RP. Dietary restriction of phytanic acid and plasmapheresis are standard treatments. Neuronal ceroid lipofuscinoses, such as juvenile CLN3, are progressive neurodegenerative disorders caused by abnormal accumulation of lipofuscin and lipid deposits. Retinal degeneration can predate the other manifestations. Unfortunately, patients develop neurologic decline and loss of motor coordination and die in their teens or 20s. Ocular mitochondrial disorders can affect the optic nerve or retinal ganglion cells or can lead to a pigmentary retinopathy. Those with retinal manifestations include chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, and others. These can be associated with ptosis, ophthalmoplegia, cardiac myopathy, and seizure.[35]

The biggest misperception on the part of both ophthalmologists and patients' families is that nothing can be done for these children, and so there is no reason for follow-up ophthalmologically. Yet, many children with retinal dystrophies need to be carefully followed to treat associated eye conditions. Correction of refraction, blue-filtering glasses (amber or brown sunglasses for Stargardt disease), and low vision aids (LVAs; closed circuit television or computer monitors) may help to improve their daily activities. Diseases like FEVR, CXLR, and IP can be treated with laser photocoagulation in early phases and with vitreoretinal surgery in late stages with satisfactory results.

Table 1: IRDs in pediatric age group

|	Age at diagnosis	Symptoms	Fundoscopy	Diagnostic test	Prognosis
Best disease	Any age	Moderate visual loss	Vitelliform lesion in macula	EOG, FAF, OCT	Good: one eye usually preserves a reading VA
Stargardt disease	First decade	Low vision in primary school years	Central beaten bronze atrophy with pisciform flecks, bull's eye maculopathy	FAF, OCT, FA	VA usually stabilizes around 20/400-20/200
Cone dystrophy (umbrella term for achromatopsia, incomplete achromatopsia, blue cone monochromatism)	Variable (infancy or late childhood)	Photophobia, low vision, color vision defect, nystagmus	Normal in the early phases	ERG, OCT, genetic testing	Variable prognosis. Stationary and progressive forms exist
LCA	Newborn	Nystagmus, low vision behavior	Normal or subtle changes	ERG, OCT, genetic testing	Blindness in infancy or during the first few years of life
Choroideremia	Early childhood Male	Night blindness, tunnel vision	Peripheral chorioretinal atrophy	ERG, OCT, genetic testing (X-linked recessive)	Central vision is usually preserved until late in life
Familial exudative vitreoretinopathy	First decade	Asymptomatic, nystagmus, strabismus, white pupil, phthisis bulbi	Bilateral, asymmetric disease, peripheral avascular retina, radial falciform retinal folds (mostly temporal), dragged disk and macula, TRD±RRD, exudation, vitreous hemorrhage	FA, genetic testing (autosomal dominant or recessive and X linked)	Patients with mild disease do well with laser Aggressive diseases starting in early childhood with retinal folds have guarded prognosis
Congenital X-Linked retinoschisis	5-10 years, male	Difficulty in scholastic tasks	Vitreous veils, bicycle wheel pattern in macula, macular atrophy, vitreous hemorrhage, TRD, RRD, bullous retinoschisis	OCT, negative ERG, genetic testing (X-linked recessive)	Variable depending on the complications Usually between 20/60 and 20/120
Norrie disease	Newborn male	Lack of eye contact	Leukocoria, TRD, NVG, buphthalmos	Genetic testing (X-linked recessive)	Very poor, incurable disease
Incontinentia pigmenti	Newborn female	Lack of eye contact, hypopigmented skin lesions, nail dysplasia, thin sparse hair, dental problems	Asymmetric involvement, leukocoria, retinal hypopigmentation, peripheral nonperfusion, neovascularization, TRD, microphthalmia, cataract, strabismus	Genetic testing (X-linked dominant)	Good if treated early with laser photocoagulation, poor if untreated

ERG=Electroretinography, FA=Fluorescein angiography, FAF=Fundus autofluorescence, IRD=Inherited retinal disease, LCA=Leber congenital amaurosis, OCT=Optical coherence tomography, VA=Visual acuity, TRD=Tractional retinal detachment, RRD=Rhegmatogenous retinal detachment, NVG=Neovascular glaucoma

Disorders Associated with Syndromes (Syndromic IRDs)

If the IRD is present with both ocular and systemic manifestations, it is known as "syndromic IRD," for which more than 200 genes have been identified (Online Mendelian Inheritance in Man, https://www.ncbi.nlm.nih.gov/omim). Most of the syndromic IRDs can be broadly classified into two groups: inborn errors of metabolism (IEMs) and ciliopathies, and majority of them are inherited recessively.[34,36] IEMs present with neurological and ocular symptoms and include congenital disorders of glycosylation (CDG), neuronal ceroid lipofuscinosis (CLNs), mucopolysaccharidoses (MPSs), peroxisomal diseases, and so on. Ciliopathies are a group of genetic disorders that primarily affect the cilia, which is present in nearly every cell in the body including photoreceptors. In ciliopathies, several other organs – central nervous system, kidney, liver, skeleton, and inner ear – are commonly involved, besides ocular involvement. Commonly seen disorders are BBS, USH, SLN, Alstrøm syndrome (ALMS), and JBTS. Common ciliopathies are described here.

BBS has a prevalence of about 1/125,000. It comprises RP (rod–cone dystrophy, usually by age 6), polydactyly (fifth digit duplication in hands and/or feet), hypogonadism, renal disease, truncal obesity, intellectual disability, and ataxia.[37,38] Twenty-one causative BBS-related genes (*BBS1–BBS21*) have been identified. USH with RP and HL is found in about 3/100,000 persons. The most common variety, USH1, shows profound HL, absent vestibular function, onset by age 10, and progresses slowly. USH2 has moderate HL, normal vestibular function, onset by age 20, and no or slow progression. USH3 has
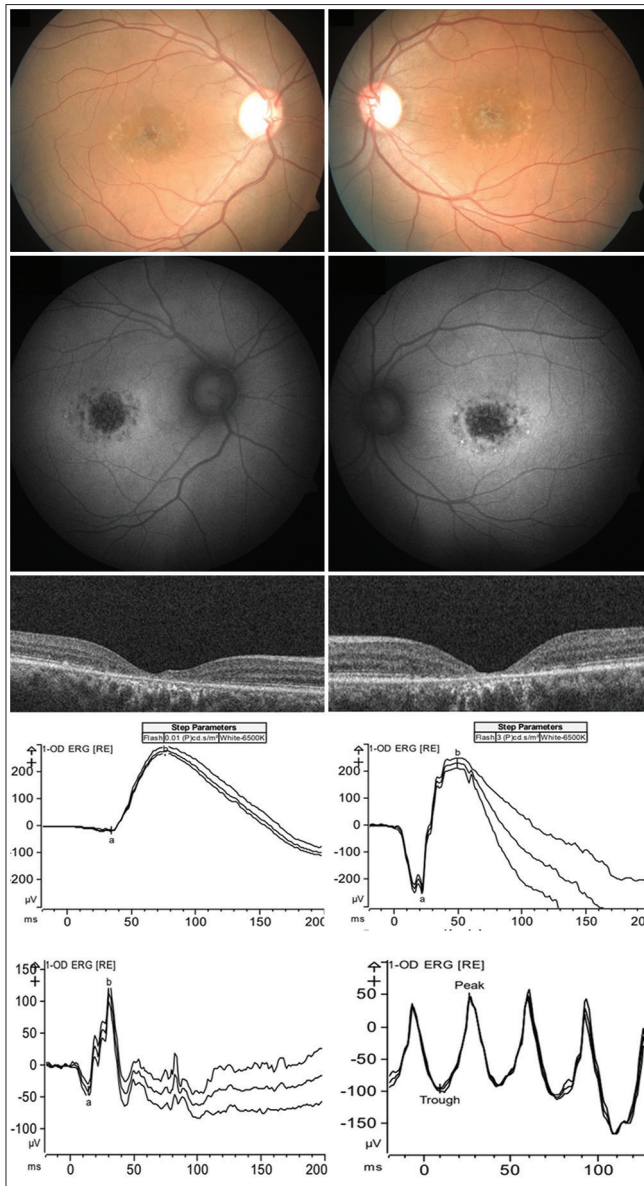
Figure 6: Stargardt disease reveals macular atrophy in a 15-year-old girl with central vision loss. A few flecks are seen around the atrophic area. Autofluorescence shows absent FAF at the fovea with hyper FAF around it. OCT shows gross thinning of fovea with absence of outer retinal layers. The full-field ERG is normal. ERG = electroretinography, FAF = fundus autofluorescence, OCT = optical coherence tomography

Table 2: Genes that are common to various IRDs after the analysis of genes from Retnet database using Venn diagram for overlapping genes for various diseases
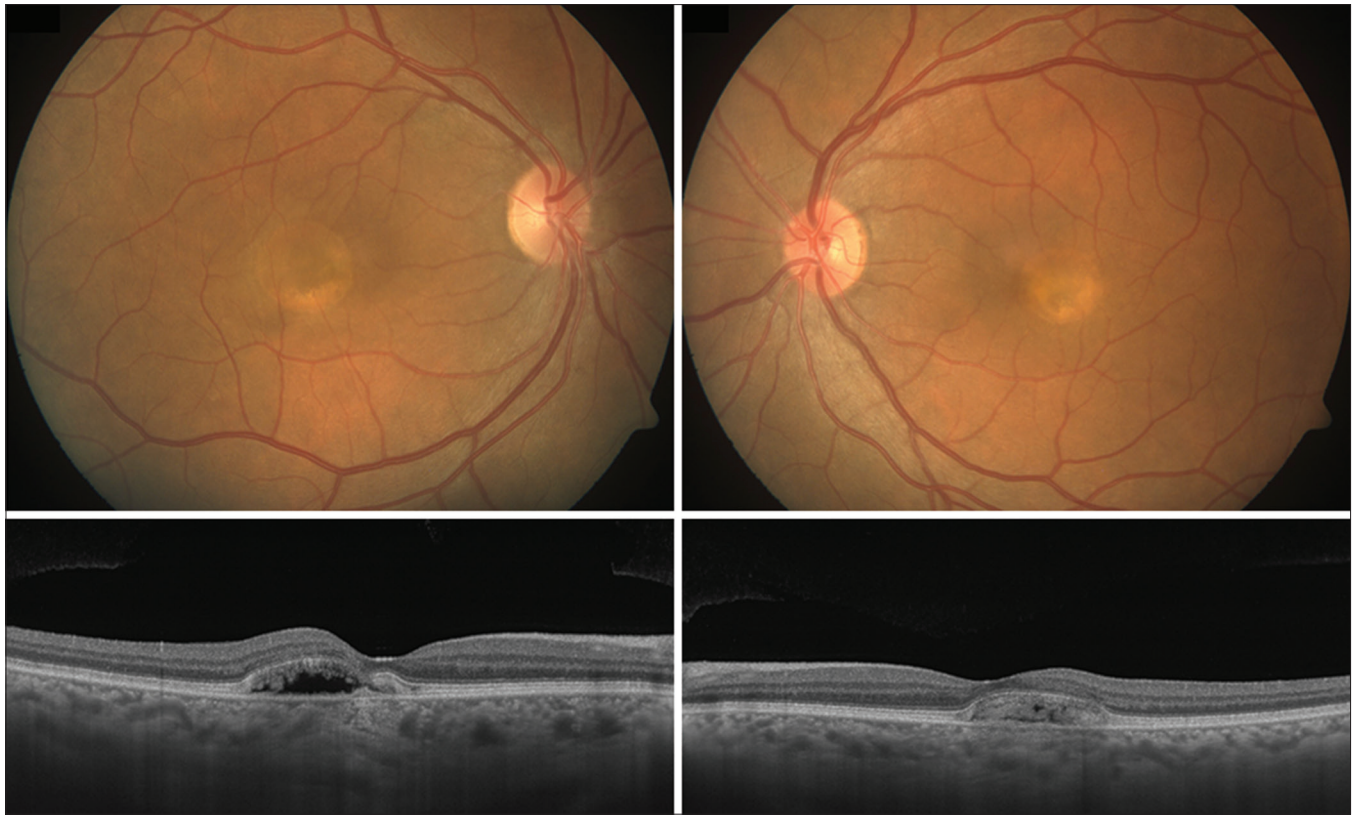
IRDs	Common genes
RP and macular degeneration	BEST1, FSCN2, GUCA1B, IMPG1, ABCA4, PROM1, RP1L1
RP and LCA	CRX, IMPDH1, RDH12, RPE65, CRB1, IFT140, LRAT, SPATA7, TULP1
RP, LCA, and MD	PRPH2
LCA and MD	OTX2
US and other retinopathy	ADGRV1, ARSG, CDH23, CEP250, CEP78, CIB2, DFNB31, ESPN, MYO7A, PCDH15, USH1C, USH1G
SDR, US, retinopathy	ABHD12, HARS
RP, SDR	ADIPOR1, CWC27, HGSNAT, IFT140, TRNT1, OFD1
RP and retinopathy	BEST1, KIF3B, NR2E3, CRB1, CYP4V2, MVK, RGR, PLBP1, ZNF408
RP, US, retinopathy	CLRN1, USH2A
RP and BBS	ADIPOR1, ARL6, BBS1, BBS2, IFT172, TTC8
RP and CCRD	SEMA4A, ABCA4, CERKL, PROM1
RP, CCRD, CSNB	CRX, PRPH2
RP, CSNB	RDH12, RPE65, SAG, CRB1, IFT140, LRAT, SPATA7, TULP1
RP, BBS, and CCRD	C8orf37
BBS, CSNB	KCNJ13

BBS=Bardet–Biedl syndrome, autosomal recessive, CCRD=cone or cone–rod dystrophy, CSNB=congenital stationary night blindness, IRD=inherited retinal disease, LCA=Leber congenital amaurosis, MD=macular degeneration, RP=retinitis pigmentosa, SD=syndromic/systemic diseases with retinopathy, US=Usher syndrome

Genetic Testing and Counseling in IRDs

Identifying the genetic cause of the disease should become a part of the clinical care of IRDs. The molecular diagnosis can help characterize the disease better in terms of the inheritance and progression. In very early or very late stage of the IRDs, the clinical picture can be confusing. Getting an accurate molecular diagnosis can uncover the correct diagnosis, which can guide in further investigations, for example, audiometry for HL, tests for cardiomyopathy or renal dysfunction, and so on. Nearly 280 disease-causing genes have been identified in IRDs. This has not only led to better understanding of the pathophysiology of these disorders, but has also led to discovery of novel therapeutic targets. With the apparent success of the first gene therapy, voretigene neparvovec for *RPE65*, many candidate genes are being evaluated for possible therapeutic interventions. RP is the most common IRD, with the highest number of identified genes found in the Retnet database (https://sph.uth.edu/retnet/; last accessed January 2022). There are several overlapping disease-causing genes between different IRDs [Table 2]. For example, *USH2A* gene mutation can cause both USH and non-syndromic disease.[36,39] Inheritance could be Mendelian, biallelic, multiallelic, and mitochondrial. It could result in transmission in either autosomal dominant, autosomal recessive, or X-linked fashion. Therefore, it is vital to study causative genes in large

progressive HL and late onset by two to four decades. Eleven USH genes have been identified. SNL has a prevalence of about 1/1,000,000. Its onset is during the first few years of life, like LCA. It is associated with photophobia, nystagmus, hyperopia, and renal disease – nephronophthisis or cystic kidney, which may progress to end-stage renal disease. ALMS, seen in around 1/1,000,000, has RP, HL, type 2 diabetes, obesity, and dilated cardiomegaly. The causative gene is *ALMS1*. JBTS with ataxia, developmental delay, abnormal eye movements, and molar tooth sign on magnetic resonance imaging (MRI) due to deep interpeduncular fossa, thickened superior cerebellar peduncles, and hypoplastic cerebellar vermis is seen in about one in 1,000,000 cases. Around 36 causative genes have been found.

Figure 7: A 36-year-old lady with Best disease. Retina has a typical egg yolk-shaped, round, yellow lesion at the fovea, which shows high reflective deposition of material underneath. The Electrooculography (EOG) showed abnormal Arden's ratio
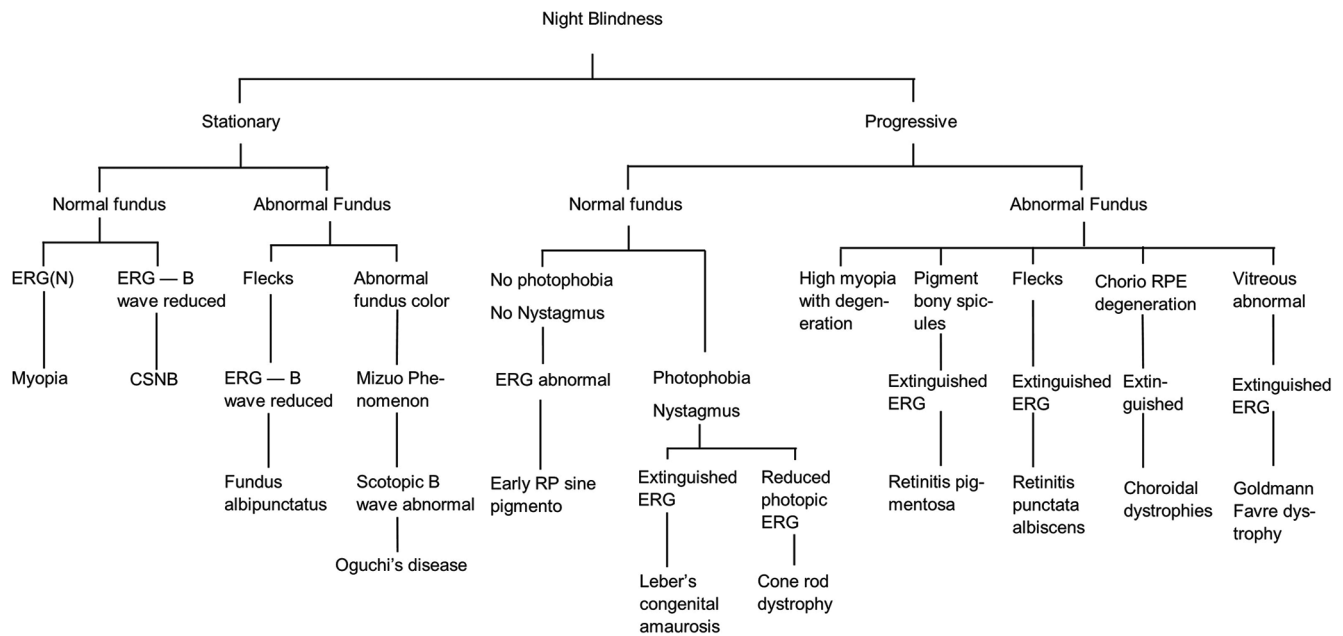
Figure 8: A simple diagnostic algorithm for IRDs. IRD = inherited retinal disease

families and analyze pedigrees for genotype–phenotype correlations.[40-45]

Presently, with the available technologies, it is possible to have a diagnostic accuracy of 56%–76%.[46] Targeted retinal gene mutation identification by Sanger sequencing, comparative genome sequencing (CGS) arrays, and next generation sequencing are popular methods used in genetic testing based on the type of the disease, cost factors, and complexity of the disease.[47,48] For more complicated diseases, a panel of genes is used. Whole genome sequencing is used if the disease is

caused by mutations in the regulatory regions and introns, for example, *ABCA4* gene in Stargardt disease.

Once the gene mutation has been identified, an interdisciplinary re-evaluation and phenotypic interpretation is needed. A comprehensive genetic counseling should be offered to the patient and his family, taking into consideration the emotional and psychological aspects of the results.

Visual Rehabilitation

It is important to attempt visual rehabilitation in patients with IRD even in the presence of severe dysfunction. Often, the treatment of associated conditions such as a posterior subcapsular cataract can result in restoring some useful vision in such eyes. It is frequently associated with open angle glaucoma. Timely recognition and treatment can prevent further vision loss. In the absence of any curative treatments, visual rehabilitation using LVAs is the only support that can be offered to them. Rehabilitation can be often difficult and involves thorough assessment of the residual visual function, which includes distance and near visual acuities, contrast sensitivity, central and peripheral fields, binocularity, and stereopsis. Evaluation of color vision, contrast, glare, daytime and nighttime vision, ocular motor function, and patient's visual requirements is also important. Various LVAs, ranging from simple magnifying lenses, half eye glasses, telescopic lenses, hand held or stand magnifiers to more complicated virtual reality cameras, closed circuit TVs, can be given to improve the distance or near visual function. Simple devices fitting the patients' requirements are well accepted, and nearly 100% of patients with IRDs can be rehabilitated, despite a poor baseline acuity.[49] Even in children, significant improvement can occur with the use of such low vision devices.[50] Several factors such as the baseline visual acuity, age of the patient, stage of the disease, and the patient's occupation influence the choice of an LVA.[51] The LVAs need to be periodically re-evaluated since the requirement might change as the disease progresses. It has a positive influence on the social functioning and improves the quality of life.

Future Direction

Till very recently, IRDs were considered untreatable. However, due to advances in genetic testing in establishing a molecular diagnosis, clinicians are now able to characterize IRDs both phenotypically and genetically. These advances led to the approval of voretigene neparvovec (Luxturna) by the Food and Drug Administration (FDA), the first gene therapy to treat *RPE65*-associated LCA. With genetic testing, it is possible to identify the causative gene in around two-thirds of patients with IRDs. Future research will focus on exploring identifiable mutations by studying whole genome sequencing. Despite an axial resolution of 5 μm with currently available OCT system, it is not possible to visualize individual photoreceptors. Adaptive optics scanning laser ophthalmoscopy (AOSLO), a promising imaging technique, might provide an insight into survival of photoreceptors as an outcome measure in future clinical trials. Advances in induced pluripotent stem cell (iPSC) research have the potential to study IRDs that do not have a relevant animal model – use of iPSC for gene augmentation for choroideremia. Role of regenerative medicine is also expanding. Some studies have transplanted photoreceptor precursors into animal models of retinal degenerative disease. Another approach could be to use iPSC-derived organoids to enhance the possibility of autologous transplants. As we make progress in the field of imaging, genetic testing, gene therapy, and regenerative medicine, the time is just right for marching toward what is known as PRECISION MEDICINE or personalized medicine, tailoring the therapy and delivery methods based on the severity of a disease.

Conclusion

This article provides broad guidelines for easy characterization and diagnosis of a patient with an inherited retinal disorder. Systematic approach with the help of diagnostic tests such as ERG are vital in diagnosis. Molecular diagnosis is essential as it often helps in prognostication. A multidisciplinary approach is required when dealing with some complex syndromic IRDs. The future holds promise as newer regenerative therapies are being evaluated.

Conflicts of interest
There are no conflicts of interest.

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