REVIEW ARTICLE

Retinitis Pigmentosa and Allied Disorders

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Retinitis pigmentosa (RP) is a generic term for a group of disorders characterized by hereditary diffuse usually bilaterally symmetrical progressive dysfunction, cell loss and eventual atrophy of retina. Initially photoreceptors are involved and subsequently inner retina is damaged. Although both rods and cones are involved, damage to the rods is predominant. RP may be seen in isolation (Typical RP) or in association with systemic diseases. The reported prevalence of typical RP is approximately 1: 50000 worldwide. Most commonly 46% of the cases are sporadic with only one affected member in a given family. X- linked recessive inheritance is least common, amounting to 8%. Autosomal dominant inheritance is found in 19% and recessive in 19%. The age of onset and the natural history of the disease depend on the inheritance. Genetic heterogeneity exists within an inheritance pattern, for instance nine genetic loci exist on seven chromosomes for dominantly inherited RP and three genetic loci exist for x-linked RP. Therefore, RP is a group of diseases caused by abnormal genes at various loci within the human genome (1).

Typical Retinitis Pigmentosa

Clinical Features :-

***Night blindness (Nyctalopia)*:-** People with RP have constriction of the visual field in dark and visual disorientation in dim lit environments. Becoming accident prone especially at night is a highly suggestive symptom. Onset of night blindness occurs at median age of 10.7 years in autosomal recessive disease and 23.4 years in autosomal dominant disease. Nyctalopia can also be a feature of high myopia, congenital stationary night blindness and age related macular degeneration (2).

Visual field loss is insidious, progressive, peripheral and symmetric between two eyes (except x-linked RP which can have bizarre and asymmetric patterns). In the majority of patients the earliest defects are relative scotomas in the periphery between 30 and 50 degrees from fixation, which enlarge, deepen and coalesce to form a ring of visual field loss. As ring scotomas enlarge toward the far periphery, islands of relatively normal vision remain usually temporal but occasionally inferiorly. In typical RP the progression of visual loss is slow and relentless. Berson et al found that overall about 4.6% of remaining visual field was lost per year (3).

Central visual loss

This can occur early in typical RP while significant peripheral field remains cystoid macular edema, macular preretinal fibrosis and retinal pigment epithelial defects in macula can occur early in the disease process limiting the visual acuity. To considerable extent, the likelihood of retaining central acuity to a given age in life depends on the specific inheritance type of RP. Patients with autosomal dominant RP are more likely to loose central vision than autosomal recessive or x- linked RP, and are usually blind by 30-40 years of age (3).

Other Symptoms

Photopsia occur at sometime during the course in midperipheral field adjacent to areas of scotoma, which are generally stationary with in the field and continuous rather than episodic. Color vision is generally not affected until visual acuity is less than 6/12. Color vision may be lost early where central cones are abnormal from the beginning.

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Fundus findings

Classic description of RP fundus include attenuated retinal vessels, bone spicule intraretinal pigmentation, mottling and granularity of the retinal pigment epithelium and optic nerve head pallor, choroidal vessels become visible in advanced stages due to atrophy of RPE and choriocapillaris. Patients with early RP without fundus changes are often diagnosed as 'Retinitis pigmentosa sine pigmento'. This is no longer considered a specific subtype of RP but a stage of RP.

The earliest abnormality is attenuation of retinal vessels and appearance of fine mottling or granularity of RPE in the mid and far periphery. The macular region may show increased luster or wrinkling suggesting either macular edema or preretinal fibrosis. Intraretinal, bone spicule pigmentation represents migration of pigment into the retina from disintegrated RPE cells. Yellowish white metallic tapetal reflex or sheen can occasionally be observed in women who are carriers for the X-linked RP (4). Optic disc may be normal in early RP, show a waxy fullness with hyperemia or appear waxy and pale. A 'golden ring' or yellowish white halo can often be seen surrounding the disc in early RP. In advanced disease, dense optic nerve head pallor results, in part from optic atrophy and part from gliosis overlying the disc. Drusen may develop on the optic nerve or adjacent retina. Uncommonly peripheral retinal vasculopathy with lipid exudations and serous retinal elevation similar to coats disease occurs but it is usually bilateral, shows no sex predilection and usually occurs in old patients. In many cases of mild to moderate RP fluorescein angiography reveals transmission defects of the RPE with late diffuse leakage and few may show leakage of dye from perifoveal capillaries suggesting cystoid macular edema. Cataracts, most frequently posterior sub capsular lens opacities are seen in- patient of RP. Keratoconus and primary open angle glaucoma are more frequent in RP. High myopia and astigmatism are frequently associated with RP (4).

Psychophysical findings

Perimetry :-

Techniques for two-color scotopic static perimetry have been developed to evaluate rod and cone retinal sensitivities in different regions of the retina. Using this technique Massof and Finkelstein (5) found that patients with RP could be divided into two groups. Type I RP, which is associated with early diffuse loss of rod sensitivity relative to cone sensitivity, childhood onset nyctalopia and type II RP, associated with focal and loss of both rod and cone retinal sensitivity and adult onset nyctalopia. An excess of type II over the type I form has been reported in simplex disease.

Dark adaptometry

Patients with RP when tested with dark adaptometry may show elevation of the cone segment, rod segment or both to varying degree. Also in some patients there may be delay in reaching what eventually for; them is relatively good final dark adaptation threshold (6).

Retinal densitometry (Fundus reflectometry)

It is a technique where by to deduce effective photoreceptor pigment density, measurements are made of the difference between light shone into the eye and light reflected out of the eye. From these data, estimates can be made of the rates of photo pigment regeneration. Rhodopsin levels have been found to be reduced in all patients, but rhodopsin bleaching and regeneration kinetics have been normal (7).

Electrophysiology

Patients with early RP could have subnormal but easily detectable a-wave and b-wave response. Responses are not only reduced in amplitude but also delayed in b-wave implicit times. In general more sizable responses are seen with younger patients or at earlier stages of disease. RP patients with scotopic ERG amplitudes of 100 v or greater have a 'delimited' form of the disease with a better visual prognosis (8). Other patients with advanced RP have undetectable responses (typically less than 10 v) to light flash. Berson *et al* (3) found that patients lost an average of 16% to 18.5% per year of remaining ERG amplitude to bright white flashes (a mixed rod-cone amplitudes). Massof and Finkelstein (9) found that the scotopic rod dominated ERG was affected to a much more severe degree than the photopic cone mediated ERG in type I RP, whereas the scotopic and

phtopic ERG's were equally abnormal in type II RP. The ERG can be used to identify not only which patients have widespread progressive forms of RP but also which patients are normal. Relatives of patients with RP, age 6 years or over can be observed to develop this disease at a later time (10, 11).

Differential Diagnosis

Pseudoretinitis pigmentosa is a heterogeneous group of disease with various etiologies in which the fundus appearance resembles retinitis pigmentosa. A careful history is important, since it will often elucidate the specific disorder. The ERG is single most important diagnostic test, since it will rarely be markedly abnormal or absent as is typical for retinitis pigmentosa. The differential diagnosis of RP is important because the prognostic implications of the disease are serious, and an error in diagnosis can be devastating in terms of psychological impact or failure to recognize a treatable entity. A bilateral pigmentary retinopathy may be due to variety of etiologies such as inflammation (syphilis, rubella) drugs (thioridazin, clofazimine, cloroquine) resolution of rhegmatogenous and exudative detachments, peripheral retinal degenerations, and other hereditary chorioretinal dystrophies (stargardt's disease, pigment paravenous chorioretinal atrophy). Uniocular pigmentary retinopathy (pseudo-retinitis pigmentosa) results from an acquired disease either inflammation (toxoplasmosis, DUS) or trauma (contusion, intraocular foreign body, ophthalmic artery occlusion). Unlike all the previous disorders, cancer associated retinopathy is not confused with retinitis pigmentosa because of a mimicking fundus appearance. In fact the retina appears normal. The confusion arises in these older patients because of the recent onset progressive night vision difficulties and profoundly abnormal ERG (8, 10).

Phenocopies of retinitis pigmentosa

There can be conditions confined to the retina or having associated systemic manifestations that may or may not have appeared at the time of examination. Detailed retinal investigations and survey for systemic signs in patients and relatives is required. Cone-rod dystrophy (CRD) is characterized by early loss of visual acuity and color vision, with subsequent progressive peripheral visual field loss. Macular pigmentation and atrophy precedes variable degrees of peripheral pigmentary abnormalities. Peripheral retinal bone spicule pigmentation, in later disease may resemble that seen in classical retinitis pigmentosa. With such potential for diagnostic confusion it has been suggested that a diagnosis of CRD should be based on the basis of marked reduction or absence of cone electroretinographic responses in the presence of quantitatively less reduction in rod response.

Lebers Congenital Amatlrosis is characterized by severe visual impairment before the age of 1 year with nystagmus, poor pupillary reflexes, either normal or abnormal fundus appearance or an autosomal recessive inheritance. Oculodigital sign 'eye rubbing' is a common association. These cases are often confused with early onset RP. Fundus abnormalities described in these include salt-pepper retinopathy, retinitis punctata albescence, macular pigmentation and macular coloboma. The other syndromic phenocopies of retinities pigmentosa include Alport syndrome, Alstrom's syndrome, Cockayne's syndrome and mucopolysachharidosis (4).

Retinities pigmentosa associated with systemic diseses (4) **:**

***Usher's Syndrome*:-** The most common RP association is with deafness seen in Usher's syndrome (AR). In type I there is total congenital deafness, mutism and abnormal vestibular function associated with early onset of retinitis pigmentosa. In type II, there is later onset of milder hearing loss, intelligible speech, normal vestibular function and a later onset of a mild form of retinitis pigmentosa. *Lawrence-Moon-Bardet-Biedl Syndrome* describes association of retinitis pigmentosa with mental retardation, hypogenitalism, and spastic paraplegia, polydactyly and congenital obesity. The retinal degeneration is atypical that the central receptors are affected early and visual acuity is diminished.

Bassen-Kornzweig disease (A-beta lipoproteinemia) hereditary acanthosis includes early onset of malabsorption syndrome with fat intolerance, neuromuscular dysfunction with ataxia, and spiny

malformed erythrocytes (acanthocytosis). Treatment with intramuscular vitamin A, raises serum vitamin A levels, normalizes the dark-adapted thresholds, and increases the previously diminished electroretino graphic responses. Vitamin E also has a therapeutic effect.

Refsum's disease (Autosomal recessive) has retinitis pigmentosa associated with peripheral polyneuritis with progressive paresis, ataxia and other cerebellar signs, nerve deafness, anosmia, dry skin (ichthyosis) and skeletal abnormalities. A deficiency in the enzyme phytanic acid oxidase results in abnormal accumulation of phytanic acid throughout the body. Treatment in directed toward severe dietary restriction of food with phytanic acid and its precursors.

***Kearns-Sayre syndrome*:-** A mitochondrial myopathy consisting of progressive external ophthalmoplegia and complete heart block in association with pigmentary retinopathy.

***Essential Gyrate atrophy*:** It is the only systemic metabolic disorder, which primarily affects the eye. Condition occurs as result of ornithine Amino-transference deficiency. Night blindness and distinctive fundus picture help in diagnosis but it can sometimes mimic RP. Arginine restricted diet is recommended.

Treatment

RP is incurable rather than untreatable. Patient can always be helped by careful refraction, cataract extraction when indicated, treatment of macular edema and referral for low visual aids. Genetic counseling can be useful to answer family concerns. Approximately 50% of patients with RP have 1 or more diopters of astigmatism. Uncorrected myopia can be cause of night blindness and therefore it is mandatory that patient has appropriate correction of refractive error and access to low visual aids. Reading vision should be tested and lenses prescribed as needed. Advance in electrooptical technology have resulted in night vision devices (night vision pocket scope) that function under scotopic or dim photopic conditions. Although such devices may be useful in specific circumstances, a wide angle, powerful flashlight is usually more effective and far less expensive than the night vision aid. Magnification LVA aids and vision closed circuit television devices can help the patient in near task. Periodic visual field examinations with compassionate examination of visual field defects can help patients appreciate the rate of progression and hence plan for future disability.

Cataract Extraction

Patients with RP develop visually significant cataracts. Cataract surgery should be recommended in many of these cases. RP patients do not seem predisposed to complications but some recommend usage of corticosteroids to prevent cystoid macular edema. Prior to surgery the patient must be explained that any improvement in central acuity will not be associated with improvement in central acuity will not be associated with improvement in visual field (12) and that cataract surgery will in no way affect the expected rate of progression of the disease (13).

Cystoid Macular Edema (CME)

CME can significantly reduce the visual acuity at later or even early, satisfactory results to date have been obtained using oral carbonic anhydrase inhibitor acetazolamide at a dose of 500mg/day (13). Visual acuity improvement by 2 to 1 lines have been noted in randomized prospective cross-over studies by Fishman *et al* (14). Along with improvement in visual acuity, an improvement in macular edema and extrafoveal retinal sensitivity has been seen but no effect on angiographic macular edema. Overall, the best way to monitor the effectiveness of acetazolamide treatment is though the subjective report of the patient rather than relying on visual acuity assessment or angiography. An induction dose of 500mg/day followed by maintenance dose of 250mg/day is recommended. A major limitation of this treatment is the side effects, which are common and limit the period over which the' patient will tolerate the drug (15).

Vitamin A supplements

Berson *et al* undertook a randomized double-marked prospective study between 1984 and 1991 to determine the effects of oral vitamin A (retinyl palmitate) and E (dl-a-tocopherol) on the course of the more common form of RP (16). Although no significant difference occurred for the slow loss of visual field with time, the authors found that two groups receiving 15,000 IU/day of vitamin A had an

average, slightly slower rate of decline of cone ERG amplitudes. They also found that groups receiving 400 IU/day of vitamin E were found to be 42% more likely to have a decline in amplitude of 50% or more from baseline. The authors recommended that most adult RP patients take vitamin A (retinyl palmitate) in 15,000 IU/day supplements under supervision. Although no serious problems of safety in the recommended dose were encountered in the above-mentioned study, the long-term safety of taking high dose vitamin A supplements for many decades is uncertain. Side effects such as increased intracranial pressure; hepatomegaly, bone disease in the young and elevated blood lipid can however occur with this dose of vitamin A and are considered teratogenic. The study and its recommendations are controversial and an argument was made that greater benefit needed to be proven before recommending the use of vitamin A in RP (16).

Genetic Counseling

A diagnosis of RP always implies genetic disease. The first steps in the management of a patient with RP are to establish the mode of inheritance. Complete detailed pedigree is an essential part of the workup before genetic counseling can begin. The examination of other family members is essential for better appreciation of the range and extent of manifestation shown by other family members and the expected rate of progression. Two major issues to be addressed are the rate of progression of the disease and the risk of the patient's children. A major principle of genetic counseling has been that it should be nondirective and supportive. Variable expressing and incomplete penetrance particularly in autosomal dominant disease can influence predictions of severity: If RP in dominantly inherited (i.e. three consecutive generations with father to son transmission) each affected patient has a 1 in 2 chance with each childbirth of having a child of either sex having RP. If RP is inherited by an autosomal recessive mode (i.e. at least two comparably affected female siblings or male and female siblings comparably with normal parents, or an isolate case with a family history of consanguinity) each child has a 25% chance of being affected irrespective of the number of children already affected. An affected individual with an autosomal recessive disease has a small risk of having an affected offspring, depending on the frequency of carrier state in population. Inheritance of autosomal recessive traits is influenced by tradition of consanguinity in the community. A male with x-linked RP has all his sons normal all his daughters as carriers. A woman who is a carrier of x-linked RP has 50% chance of affected male and 50% chance of having carrier daughter with each childbirth. Patients with isolate (simples) RP (i.e. no known affected family members) can be considered to be autosomal recessive, although exceptions exist. All offspring of males or females with autosomal recessive RP are carriers of this condition. Carriers enjoy normal vision but have small =5%) risk of offspring unless the marriage in consanguineous. If a pedigree with multiple affected members is inconclusive as whether the disease is transmitted by a recessive or a dominant mode a digenic mode of inheritance should be considered. In digenic transmission two unrelated mutations (neither of which results in RP) causes this disease in patients with both mutations. Affected individuals can have asymptomatic parents but 25% chances of having an affected child with each birth. By the age of 30 years more than 90% of patients can be diagnosed with ophthalmoscope, but under age30 years, ERG testing is indicated if the patient wants to be certain whether any relatives are affected.

Retinal Transplantation

Li and Turner (l7) in 1988 showed that transplanting normal RPE cells into the sub retinal space of rats rescued photoreceptors in the immediate vicinity of the transplant. Human fetal neural retina has been shown to survive in the sub retinal space of the light damaged rats (18). More recently a small number of humans with RP have undergone fetal neural retinal transplants (19). The number of patients was small, functional improvement was minimal and untreated eyes also regained vision. The further advancements in this field are awaited, till then transplanting retina remains investigational.

Photoreceptor transplantation

All the structural and functional derangements in RP are initiated by disease in rod photoreceptors. Recent clinical trial using adult human cadaver allogeneic photoreceptor sheets harvested with the excimer laser with in 24 hours of death of the donor has evaluated the role of photoreceptor transplantation (20). In this study no beneficial effect on visual functions was seen but

procedure was found to be safe and well tolerated. Photoreceptors have been found to remain viable for prolonged periods in various species (21). Although viability of photo receptors does not establish their functional capabilities.

Retinal prosthesis (ASR)

The artificial silicone retina (ASR) is a 2 mm diameter silicone chip, which is implanted, in sub retinal space (22). It electrically stimulates the contacting retinal cells upon exposure to light (23). The pilot clinical trial has shown that chips are well tolerated (24) and lead to some improvement in visual function.

Intravitreal or sub retinal gene therapy

* Gene therapy is under investigation.
* The idea is to use an adenovirus or lentivirus vector to replace the defect in identified forms of RP. However, no current investigational protocols exist in humans.
* Because of the wide heterogeneity of defects in RP, gene therapy must be targeted specifically to each mutation.

It is not known which, if any, of the RP forms will show reversibility (even with a nondestructive reinsertion of the appropriate gene in the appropriate locus with appropriate regulation). Some promise has been shown in a mouse model of RP.

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