Chapter I

Introduction

BASIC CONSIDERATIONS OF RETINITIS PIGMENTOSA

I. DEFINITION, HISTORICAL REVIEW AND PREVALENCE OF RETINITIS PIGMENTOSA

DEFINITION:

Retinitis pigmentosa (RP) is the name commonly given to a group of heredofamilial diseases characterized by progressive visual field loss, night blindness and abnormal or nonrecordable electroretinogram (ERG).[1,2] This broad definition encompasses a large number of primary (ocular only) and secondary (other organ or systemic involvement) diseases.[3]

RP has been defined in a number of ways, one such definition is that it is a set of hereditary disorders that diffusely and primarily affect photoreceptor and pigment epithelial function.[4] Even this broad definition tends to exclude those frequently found RP patients in whom no family history can be found; it is commonly assumed, but not proven, that patients with a negative family history have genetically determined disease such as diseases transmitted by autosomal recessive inheritance.[4,5]

The name RP should not be used without qualification where a non-heritable causal factor (e.g. vascular disease, infection, inflammation, etc) is likely. Such cases have sometimes been described as "pseudo-RP"

or would be better described simply as "retinal pigmentary degeneration" associated with an underlying disease process.[6,7]

HISTORICAL REVIEW:

Donders is generally credited with first describing "retinitis pigmentosa" in 1855 and 1857, although there were early observations of familial complicated night blindness by Ovelgan (1944) as well as reports of poor vision and pigmented lesions in the retina by Schon (1828) and Von Ammon (1838). Subsequently, various authors have attempted to suggest, without great success, other names for the disease. The term retinitis, implying a primary inflammation as the etiology, is clearly erroneous. However, the term is so well established it probably warrants retention. Other terms which have been used for RP include tapeto-retinal degeneration, primary pigmentary degeneration, and dystrophia retinae pigmentosa.[7,8]

In 1858, Von Graefe demonstrated the hereditary nature of the disease to which he gave the name of pigmentary degeneration. Liebreich (1861) emphasized the importance of consanguinity in association with pigmentary retinopathy. The hereditary nature of RP was well documented by Nettleship in 1908 when he published the results of family studies in RP based on 976 families.[8]

In 1945, Karpe demonstrated that the ERG was absent in patients with RP.[9] The advent of indirect ophthalmoscopy allowed ophthalmologist to find early cases; the age of molecular genetics was heralded in 1984 with Bhattacharya and colleagues mapping the X-linked recessive retinitis pigmentosa to Xp11 on the short arm of the X-chromosome.[10,11]

PREVALENCE:

Retinitis pigmentosa represents a significant cause of visual loss to people from all over the world.[12]

RP may be an uncommon diagnosis among the patients in any one ophthalmologic practice, but in fact this group of disorders represents a relatively common form of genetic eye diseases. It is difficult to obtain accurate and comprehensive incidence figures, since many patients remain undiagnosed or are not ascertained in clinical studies.[13] The prevalence of this disease (Table I) has been reported to range from about 1 in 4,000 in Shanghai, China[14], to about 1 in 9,300 in Japan.[15] The incidence has been estimated to be 1 in 3,500 to 1 in 3,700 births in the United States[16,17] and 1 in 3,400 to 1 in 8,000 births in Japan.[15]

Table I: Prevalence of Retinitis Pigmentosa Around The World.[18]

Country	Prevalence
China	1 in 4,000
Israel	1 in 4,500
England	1 in 4,900
United States	1 in 5,200
Switzerland	1 in 7,000
Japan	1 in 9,300

RP is found to be much more common in communities with a high rate of consanguineous marriages. No race is known to be exempt or particularly prone to it.[3]

Males are more frequently affected than females owing to the occurrence of sex-linked cases.[19] The incidence in males being variously quoted as between 55 and 63% of all cases.[20]

The disease is almost invariably bilateral and usually both eyes are equally affected but exceptional cases of unilateral disease were reported.[21,22]

II. CLASSIFICATION OF RETINITIS PIGMENTOSA

A uniformly accepted classification of the many pigmented retinopathies has not been established. Researchers in the field of RP have been confronted with the problem of how to adequately diagnose and classify a group of patients who generally have the same symptomatology and clinical findings. Because there is no specific diagnostic biochemical or pathohistological marker for any type of primary RP, some researchers have chosen to "lump" RP patients together without a serious attempt to separate them by other means. However, unless there is an attempt to "split" the RP types, many biochemical and clinical studies of RP are not likely to make much sense, but incorrectly split, these studies also will be nonsense.[1,23]

The role of heredity is widely acknowledged as a significant determinant, and most studies have attempted to divide RP populations by inheritance. RP patients are classified by genetic type into: autosomal dominant (AD); autosomal recessive (AR) and X-linked. Patients with no known family history are termed isolated or simplex.[24]

RP, as well as other hereditary retinal and choroidal diseases, have been classified and diagnosed using a number of different approaches. Usually, the fundus pattern (morphological appearance) and inheritance

pattern are correlated with the results of electrophysiologic/psycho-physiologic tests such as the electroretinogram (ERG), electrooculogram (EOG), dark adaptation test, and visual field. These results are compared to the patterns seen in established disease entities for the most accurate diagnosis. It may be necessary to observe the clinical course of the disease over many years and to examine other affected family members in order to finalize the diagnosis.[25]

The pigmented retinopathies can be divided into two large groups: The first includes those RP types in which the disease process is confined to the eye alone (Table II); and the second grouping includes those in which a pigmented retinal degeneration is associated with single or multiple organ system disease.[1]

ELECTRORETINOGRAPHIC CLASSIFICATION OF RP:

It is known from histopathology that in typical RP, rods are affected more than cones.[26] This preferential loss can also be demonstrated on electroretinographic testing. In these patients, the rod-mediated ERG is much more severely affected than the cone-mediated ERG and has been termed a "rod-cone" degenerative pattern (Type I).[1]

Some patients present with progressive visual field loss and a history of no or late onset night blindness. However, they have recordable ERGs in which the cone-mediated ERG is more severely affected than the

rod-mediated ERG. This has been termed a "cone-rod response" (Type II).[1] Psycho-physically, rod-cone degeneration patients demonstrate diffuse rod loss, while cone-rod patients usually show areas of preservation of rod and cone function.[18]

Table II lists those pigmentary retinopathies by inheritance type and subdivision which are confined to the eye alone, often using the pattern on the ERG as the basis for the classification. This list is evolving and as a knowledge of these diseases increases, this list will change and grow. In general, morphological retinal appearance cannot be used to classify the entities in table II because of non specificity of the patterns seen in the pigmented retinopathies and problems of secondary gene expression which may alter the fundus appearance in patients with the same genetic type of pigmented retinopathy. This means that with categories such as autosomal dominant and recessive degenerations, there are likely to be multiple types found.[1,4,18]

III. GENETIC ASPECTS OF RETINITIS PIGMENTOSA

In the past 20 years, great strides have been made in genetics. As genetic factors are proved responsible for more and more diseases, it becomes increasingly important to understand the principles of genetic

Table (II): Primary Forms of RP (Ocular Involvement Only).

AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA:

Rod-cone degeneration.

Cone-rod degeneration.

Leber's amaurosis congenital (rare).

AUTOSOMAL RECESSIVE RETINITIS PIGMENTOSA:

Rod cone degeneration.

Cone rod degeneration.

Leber's amaurosis congenital (rare)

Retinitis punctata albescens.

X-LINKED RECESSIVE RETINITIS PIGMENTOSA

Rod-cone degeneration.

Cone-rod degeneration.

SIMPLEX/MULTIPLEX RETINITIS PIGMENTOSA

Rod-cone degeneration.

Cone-rod degeneration.

transmission. Much of the background work in clinical medical genetics has been done in ophthalmology, since the eye seems unusually prone to genetically determined diseases.[27] Also, as larger numbers of patients with genetic ocular diseases are identified, public demands for prevention, treatment and counselling increase. Consequently, ophthalmologists, like other medical specialists, are expected to be familiar with the clinical manifestations, transmission patterns and therapeutic modalities of heritable disorders in their specialties.[5]

The importance of heredity in ophthalmology is emphasized by the fact that 50% of blindness occurring before the age of six and at least 33% of that in the general population is genetically determined.[28]

In this section, some basic material necessary for an understanding of the subject will be covered.

TERMINOLOGY[29,30]:

Some terms used in genetics may be confusing to the non geneticist, but their comprehension is valuable in the understanding and detection of heritable disorders.

Alleles:

Genes occupying the same position on each chromosome of an identical pair are called alleles.

Homozygous:

When both genes at the same locus on a pair of homologous chromosome are alike, a person is said to be homozygous.

Heterozygous:

When the two genes differ, the person is said to be heterozygous.

Hemizygous:

When a male is carrying a gene on his X-chromosome since he only has no opposing normal gene.

Designation	No. of alleles for trait	No. of opposing or normal alleles
Homozygote	2	0
Heterozygote	1	1
Hemizygote	1	0

Genotype:

This refers to the genetic makeup of an individual.

Phenotype:

This refers to the actual characteristics of the individual which are determined by his or her genotype.

Phenocopy:

This refers to a clinical picture in an individual produced entirely by an environmental factor, but nevertheless closely resembles, or is even identical with a phenotype.

The terms "hereditary", "genetic" and "heritable" can be considered nearly synonymous. A "congenital" condition is manifest at birth, but is not necessarily inherited. However, "congenital" does not imply or exclude a genetic basis for the condition.(31)

PEDIGREE ANALYSIS:

The study of heritable human diseases and their prevention through genetic counselling is based primarily upon pedigree analysis. It is important, therefore, to understand how pedigrees are constructed and the type of information they can provide. Family data can be summarized in a pedigree chart, which is merely a shorthand method of classifying the data for ready reference.

The affected individual who first brings a family to the attention of the physician is the "proband" (propositus or index case).(29)

The genetic aspects of RP is very important to the diagnosis, evaluation and provision of service for patients. RP is a heterogeneous group of disorders, with multiple genetic forms having been described within the three main Mendelian inheritance patterns. Although RP patients are considered by definition to have a genetic disorder, the mode of inheritance often is not easily recognized.[31]

The classification of patients by genetic type is essential not only for appropriate counselling, but also for identification of homogeneous groups of RP patients since it is difficult to determine pathophysiologic mechanisms when looking at a mixture of different diseases.[32]

Principles of classic Mendelian genetics should be followed in properly evaluating patients with hereditary retinal degenerations. Patients and their families should be carefully questioned and examined in a search for other affected family members. A pedigree should be drawn with each family member identified and considered for the possibility of having the disease.[31]

MENDELIAN GENETICS:

1. Autosomal dominant inheritance (AD):

Genetic traits are transmitted from generation to generation by genes, or groups of base pairs on DNA strands, which express themselves

through various mechanisms as body components or functions. Autosomal dominant genes may show full expression of the trait or disease with only one copy of the gene present.[29] There is a 50% chance of that particular dominant gene being passed to any offspring of the individual.[33] A summary of the criteria for autosomal dominant inheritance can be found in Table III.

Table III: Characteristics of Autosomal Dominant Inheritance with Complete Penetrance.[29,30,33-36]

1. *Trait appears in multiple generations (vertical transmission).*
2. *Trait is transmitted by affected person to 50% of the offspring.*
3. *Each affected individual has an affected parent, unless the condition arose by new mutation in the given individual.*
4. *Males and females are affected in equal proportions.*
5. *Affected males and females are equally likely to transmit the trait to male and female offspring. Thus, male-to-male transmission occurs.*
6. *Unaffected persons do not transmit the trait to their children.*
7. *The trait is expressed in the heterozygote, but more severely in the homozygote.*
8. *Variability in expression of the trait from generation to generation and between individuals in the same generation is expected.*

AD diseases may have variable expressivity, that is some affected patients may show milder signs of the disease or trait. Occasionally, a person with the gene may not show the disease at all, which is called nonpenetrance.[29] Conclusive evidence of autosomal dominant inheritance (AD) requires the demonstration of the disease in three successive generations, with both sexes showing equal effects of the disease. Male-to-male transmission is further proof that the pedigree is AD and not an X-linked recessive family in which carriers are affected.[30,34]

2. Autosomal recessive inheritance (AR):

In AR inheritance, two copies of an identical gene must be present (in a double dose) in order for the trait or disease to manifest itself.[29,30] AR carriers are asymptomatic.[30] Matings between relatives (consanguinity) is more commonly noted among parents of individuals with AR disease than in the general population. Consanguinity increases the probability that two individuals carry the same recessive gene.[34,37]

When two carriers of an AR trait mate, there is a 25% chance for each offspring to inherit two copies of the recessive gene and thereby exhibit the associated disease or trait, there is a 50% chance at each mating that the offspring will be a carrier, while there is a 25% chance that the offspring will not inherit the recessive gene.[29,38] A summary of the criteria for AR inheritance is presented in Table IV.

Table IV: Criteria for Autosomal Recessive Inheritance.[29,30,34-38]

1. Individuals inheriting both the genes (homozygote) of defective type express the disorder.
2. Mutant gene does not cause disease in the heterozygote (recession).
3. When both parents carry the gene, there is a 25% chance for any child to inherit the disease.
4. Sexes are equally affected.
5. Parents of the affected person may be genetically related (consanguinity) increasingly likely the rarer trait.

3. X-linked recessive inheritance:

A trait or disease determined by a recessive gene carried on the X-chromosome is unique in its familial pattern. Males have only one X-chromosome, so if they inherit the X-linked recessive gene from their mother, they will be affected. If they are affected, they will give the X-linked gene to all daughters, who then have a 50% chance of passing the recessive gene to each offspring. Female carriers' daughters are, therefore, at a risk of being carriers, and sons have a 50% chance of being affected (Table V).[29,30,35]

The story is complicated further, since early in embryogenesis, one X-chromosome is inactivated in every cell of a female. This inactivation, called "lyonization"[76], is random, so the X-linked recessive gene may be inactivated in some cells and the normal gene in the others. In practical terms, this means that a few carriers will appear completely normal and some will appear to be affected to varying degrees with the disease or trait.[29,38]

Table (V): Characteristics of X-linked Recessive Inheritance.[29,30,35,38]

1. Only males in a pedigree are severely affected.
2. An affected male gives the gene to all his daughters (obligata carrier) and to none of his sons (no history ofmale-to-male transmission.
3. All (even phenotypically normal) daughters of affected males are carriers (heterozygous females) who give the trait to half of their sons (on the average).
4. Affected males in a family are either brothers or related to one another through carrier females, e.g. maternal uncles.
5. If married to a carrier female, affected males will have daughters, half of whom are homozygous and affected, half of whom are heterozygous and carriers.
6. Some heterozygous females may be affected (manifesting heterozygotes) because of Lyonization.

4. Simplex and multiplex families:

A high percentage of RP patients present initially with no family history of RP.[27] Surveys in Europe and the USA have found that from 18% to 58% of patients have undefined or "sporadic" inheritance.[38] When there is only one affected member in a pedigree, the descriptive term "simplex" is used, while the term "sporadic" is generally avoided unless a mutational or environmental event is hypothesized.[29] A genetically determined trait may be isolated in the pedigree either because of small pedigree size, the full expression of the disease has not been sought in other relatives, the disorder represents a new genetic mutation, or the disorder is recessive and there is not an adequate investigation to determine that the parents are carriers.[31]

"Multiplex" refers to families in whom more than one sibling is affected. If other relatives are affected, other inheritance patterns must be considered. Although multiplex sibships do not all represent a single inheritance pattern, most are probably autosomal recessive (AR).[29,31] Several affected males and no affected females in a sibship, however, would be an indication to examine their mother, who may have carrier signs which would establish the diagnosis of X-linked recessive inheritance.[30] A fascinating aspect of multiplex inheritance is that in a number of multiplex pedigrees the segregation ratio does not follow Mendelian rules in that frequently more than 25% of the siblings are

affected.[29,31] This higher percentage suggests that additional genetic factors may be operating.

PERCENTAGE OF GENETIC FORMS OF RP:

Application of genetic methods has permitted estimation of the proportion of the various genetic forms of RP. Some of these recent studies are summarized in Table VI. Differences may be in part be accounted for by selection procedures as well as methods of analysis. The distribution across studies is surprisingly similar, although the proportion of X-linked cases in the United Kingdom population is higher. The analytic methods used the 1980 study were different, the proportion of "simplex" being lower because it includes only the excess proportion of cases that could not be accounted for by recessive inheritance.

Table VI: Distribution (in percent) of Genetic Types of RP.

Investigators	Year	Population	Simplex	AR	AD	X-linked
Pearlman[39]	1979	USA (CA)*	63	21	11	5
Boughman et al[16]	1980	USA	15	69	10	6
Hu[14]	1982	China	48.3	33.1	11	7.7
Jay M[3]	1982	England	42.1	15.5	24.4	18
Heckenlively[4]	1987	USA (CA)	42.2	30.8	16.9	10

*CA = State of California.

*USA = United States of America.

IV. PATHOLOGICAL ASPECTS OF RETINITIS PIGMENTOSA

Laboratory studies of RP have been severely handicapped by two major constraints:

1. A general lack of availability of tissue for study.
2. The little tissue that has been obtained, with few exceptions were from elderly blind eyes with advanced stages of the disease.[40]

For the reasons previously stated, with few exceptions, histopathological reports are based on inadequately preserved material and describe structural changes in advanced stages of retinal degeneration. It is, therefore, not surprising that the histological appearances of advanced cases of RP are remarkably similar regardless of the genotype of the disease.[41] It is hard to see how any cures can be derived without examining diseased tissue.[42]

In RP the primary abnormality with virtually 100% incidence in pathologic specimens, is the focal disappearance or loss of both rods and cones. The next most common findings are anomalies within the RPE, these may be depigmentation, atrophy, degeneration, or proliferation and generally when present are more pronounced in the midperipheral retina.[43] In the inner retina, the histological appearance in any given eye may vary widely between the two extremes of total loss of all retinal