TAPETORETINAL DEGENERATIONS AND DISORDERS OF LIPID METABOLISM

Part I: Clinical, Genetic, Pathological, and Therapeutic Aspects

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The clinical findings in a group of syndromes in which tapetoretinal degenerations are associated with systemic lipid disorders are described. This group includes abetalipoproteinemia (the syndrome of Bassen and Kornzweig), Refsum's syndrome, Neuronal Ceroid Lipofuscinosis, and Cockayne's syndrome. All four are transmitted by single autosomal recessive genes. The pathological findings are discussed. If diagnosed early enough, abetalipoproteinemia should be treated by administration of vitamin A, and Refsum's syndrome by restriction of intake of phytanic acid and phytol.

Retinis pigmentosa, or as it is now usually called, peripheral tapetoretinal degeneration, is not an uncommon hereditary disease in man (as well as in experimental animals). It is usually confined to the eye and in these cases its biochemical basis is virtually unknown. However, many of the tapetoretinal degenerations are just one expression of a generalized syndrome caused by a specific mutant gene. Although rare, these syndromes are important as they may present a clue to a better understanding of the basic genetic, pathological and biochemical aspects of retinitis pigmentosa. Such is the group of syndromes in which tapetoretinal degenerations are associated with systemic lipid disorders.

1. ABETALIPOPROTEINEMIA (BASSEN-KORNZWEIG SYNDROME)

The first description of this syndrome (Bassen and Kornzweig 1950) was in a patient with an atypical retinitis pigmentosa consisting of pigmentary stippling in the periphery, attenuated retinal vessels, and spots of pigmentation and depigmentation in the macular area. The visual fields showed an arcuate scotoma and tubular vision, as found in many cases of retinitis pigmentosa. There was a central scotoma as well, due to the macular involvement. The red blood cells were crenated in their appearance, and the child had malabsorption and neurological disturbances. Seven years later, the same authors (Kornzweig and Bassen 1957) reported on a brother of this patient with the same disease, indicating that it is genetic in origin.

At least 32 cases of abetalipoproteinemia have now been reported (Bohlman et al. 1972). I should like to summarize the clinical picture of this well defined syndrome on the basis of previously described cases, as well as two patients that I have seen.

Proc. 4th Int. Congr. Neurogenet. Neuroophthalmol. (1973)
Acta Genet. Med Gemellol. (*Roma*), 23: 25-31

The child is born normal, but during the first four months of life a steatorrhea appears which is usually misdiagnosed as coeliac syndrome. However, a jejunal biopsy will show, even at this age, a finding typical for this disease. Comparison of a normal jejunal biopsy (stained with hematoxylin-eosin) with tissue from a 1-year old child with abetalipoproteinemia shows that in the latter case, the cells of the villi are vacuolated and their nuclei are pressed down to the cell base. A sudan red stain shows that these vacuoles contain lipid substances.

Towards the end of the first year of life the child starts to show disturbances of the neuromuscular system, beginning with clumsiness, and progressing to obvious muscle weakness. Later cerebellar ataxia, nystagmus (often of the vertical type), and pyramidal signs, such as a positive Babinsky, appear. All of these signs progress throughout the following years.

The name acanthocytosis was originally given to this syndrome because of the peculiar crenation of the erythrocytes (Singer et al. 1952). This phenomenon is best seen in wet blood preparations but it is also apparent in routine smears. The erythrocytes have a normal life span and a normal osmotic fragility. Blood transfusions do not alter the hematological picture since the donor erythrocytes are soon transformed from their normal shape into acanthocytes.

The ocular signs consist basically of retinitis pigmentosa with its typical symptomatology. Vision is normal initially, but night blindness and visual field disturbances are usually noted by the beginning of the second decade of life. Later there is a progressive deterioration leading to blindness. Nystagmus is seen as part of the cerebellar disease, and strabismus may also be found. Although the fundus is initially normal, pigmentary stippling in the periphery and in the posterior pole is observed at later stages. By the second decade of life, the patients usually show the typical pigmentary bone-corpuscles, attenuated blood vessels and waxy pale discs (Jampel and Falls 1958). Whitish dots resembling those present in retinitis punctata albescens have been described in a few cases (Mier et al. 1960). Histological studies have revealed both a total absence of visual receptors and a defective pigment epithelium (von Sallmann et al. 1969). This is the picture usually seen in retinitis pigmentosa, but in addition lipid deposits between the nerve fibers in the optic nerve are prominent in abetalipoproteinemia.

In 1960 and 1961 three independent teams of investigators discovered that in the syndrome described by Bassen and Kornzweig, there is an absence of betalipoproteins in the blood, with very low levels of carotenoids and vitamin A (Mabry et al. 1960, Salt et al. 1960, Lamy et al. 1961).

Genetically, the disease is most probably transmitted by an autosomal recessive gene (Kornzweig 1970). About half of the described patients are descendants of consanguineous marriages. Although heterozygotes with increased blood lipoproteins have been reported (Forsyth et al. 1965, Khachadurian et al. 1971), others have found that the plasma lipoprotein levels in parents of most patients so far examined are normal (Fredrickson et al. 1972).

The cases reported to date have stemmed from various ethnic groups, the largest number being of Jewish origin (Fredrickson et al. 1972, Kayden 1972).

The therapeutic aspects of this disease are very interesting. Both vitamin A (Wolff et al. 1964) and tocopherol (vitamin E) therapy (Wallis et al. 1971) have been suggested. Several investigators (Carr 1970, Gouras et al. 1971, Sperling et al. 1972) have found that vitamin A has a beneficial effect on the retinal disease. Improvements in both the visual fields and the dark adaptation curves were observed after administration of vitamin A. Gouras et al. (1971) showed that the drop in threshold occurs several hours after administration of vitamin A and is inversely proportional to the serum vitamin A level. This improvement is similarly re-

flected in the ERG, which may become normal 24 hours after the administration of vitamin A. Recently Sperling et al. (1972) indicated that a beneficial response to vitamin A is most likely to occur in younger, less involved, patients. They found that, while there was no response in an 11-year old patient, a moderately good ERG was noted in the 8-year old brother after oral administration of 200,000 I.U. of vitamin A palmitate.

2. REFSUM'S SYNDROME

In 1945 and 1946 Sigvald Refsum, a neurologist from Norway, described a syndrome which he called " Heredopathia atactica polyneuritiformis " (Refsum 1945 and 1946). The main features of the syndrome were: atypical retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia and albumino-cytological dissociation. The patients were not mentally retarded. The 28 proven cases described until 1965 (Richterich et al. 1965*a*), and the 50 or 60 known at the present time, fit well into this description.

The patient suffers from a polyneuropathy. There is initially muscle weakness which may progress to complete paralysis of all four limbs. Absence of tendon reflexes is practically always found. Cerebellar signs include cerebellar ataxia, nystagmus, positive Romberg, and other cerebellar signs.

Ocular symptoms begin with night blindness in early childhood progressing to severe deterioration of vision in adulthood. Richterich et al. (1965*a*) noted cataracts in 80% of the patients, an interesting fact stressing a close linkage between retinitis pigmentosa and early cataract formation. The ERG is extinct (Bider 1966) and miosis is a common finding.

Other senses, such as hearing and smelling, are usually affected, and sometimes the skin, bones, and heart are also affected.

There is little doubt that Refsum's syndrome is inherited as an autosomal recessive trait. In family A described by Refsum (1945, 1946), the two patients were siblings, descendants of a consanguineous marriage. In family B both pairs of parents were second cousins stemming from the same family. Additional families collected from the literature by Richterich et al. (1965*b*) also indicate autosomal recessive inheritance. It is interesting that most of the described cases have been in families originating from Norway or England.

Refsum's syndrome was shown to be a lipid disorder when Kahlke and coworkers (Klenk and Kahlke 1963, Kahlke and Richterich 1965) demonstrated an accumulation of phytanic acid in the tissues of an affected patient. In the one ocular pathologic description of Refsum's syndrome (Toussaint and Danis 1971) sudanophilic deposits were found mainly in the retinal pigment epithelium, but some were also present in the trabeculum and sclera. As expected in retinitis pigmentosa, the cones and rods were essentially missing. In the peripheral retina, the normal structure could not be recognized and macrophages, some laden with pigment, were found to have invaded the peripheral retina.

Regarding treatment, restriction of intake of phytanic acid and its precursor phytol has been suggested by several authors (Steinberg et al. 1967, Levy 1970, Steinberg et al. 1970).

3. BATTEN'S DISEASE (NEURONAL CEROID LIPOFUSCINOSIS)

I will try to summarize briefly the clinical aspects of this complex subject. A classification of some of the forms now recognized is given in an accompanying paper (Berman 1973). Here the discussion will be limited to the juvenile form, known for many years as the Spielmeyer-Vogt or Sjögren type of " juvenile amaurotic idiocy ".

In this syndrome the picture is one of an atypical retinitis pigmentosa. Visual disturbances are one of the earliest signs of the disease, starting with deterioration of central vision due to pigmentary changes in the macula. The tapetal reflex of retinitis pigmentosa can already be seen at this time. The arteries become thin, the disc atrophied, and only later, pigmentation in the form of bone corpuscles appears in the periphery. I have no explanation why the macula is more involved in this disease than in other types of retinitis pigmentosa. Histologically the retina shows loss of rods and cones, exactly as in any case of retinitis pigmentosa (Manschot 1968, Göttinger and Minauf 1971).

The first neurological signs are seizures, mainly of the grand mal type. Later spasticity becomes progressively more severe and this, together with pyramidal and cerebellar dysfunction, causes the patient to be bedridden. Mental symptoms include both mental retardation (which is usually progressive) and personality changes. In the late stages the patient is blind and demented.

Diagnostic signs include vacuolation of the circulating lymphocytes (Rayner 1962), ultrastructurally visible lymphocyte inclusions (Witzleben et al. 1971), and abnormal azurophilic hypergranulation of the polymorphonuclear cells (Strouth et al. 1966, Donahue et al. 1968). The disease is transmitted by a single autosomal recessive gene and these changes may sometimes be present in heterozygotes. The Spielmeyer-Vogt syndrome can be found anywhere, but the gene is probably more common in the Scandinavian countries. Sjögren (1931) collected 115 cases for his extensive study of this relatively rare disease. No treatment is available, although it has been suggested (Zeman and Dyken 1969) that good control of the seizures may arrest the progress of the disease.

4. COCKAYNE'S SYNDROME

Nearly 40 years ago, Cockayne (1936) described a condition in two siblings which he termed " dwarfism with retinal atrophy and deafness ". Ten years later he reported again on the same siblings (Cockayne 1946), indicating the progressive nature of the disorder. Cockayne's syndrome is relatively rare: only 38 cases have been described until now (Pearce 1972). Its main ocular feature is retinitis pigmentosa, and since hyperlipoproteinemia has been found in at least two cases to date (Fujimoto et al. 1969, Pfeiffer and Bachmann 1973), this syndrome has been included among the group of diseases under consideration in this survey.

COCKAYNE'S SYNDROME

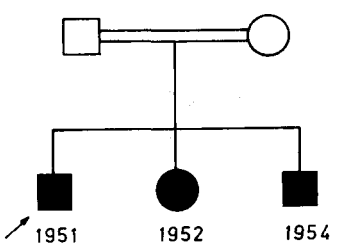

Figure. Pedigree of a family with Cockayne's syndrome. All three siblings were affected. The parents are first cousins.

https://doi.org/10.1017/S112096230002360X Published online by Cambridge University Press

The most striking feature of Cockayne's syndrome is the dwarfism. The face is peculiar and typical, triangular in shape, with sunken eyes and loss of subcutaneous fat. This gives the children a premature senile appearance. The condition is progressive, the child is born normal and develops normally for one to two years. Death usually occurs before the age of 30 due to some intercurrent infection.

An eye examination reveals a pigmentary retinopathy, with pigmentary stippling, narrow arteries and a waxy-pale disc. Cataracts are common, sometimes congenital, they often maturate in the third decade of life. Corneal opacities are very common and are, in my opinion, a result of the lack of tears often described (Lieberman et al. 1961, Coles 1969). The ERG was extinct in three cases that I have seen (Figure). These patients showed all the other features of the syndrome: dwarfism, severe mental retardation, deafness, and muscular weakness, but not the butterfly dermatitis sometimes described.

Genetically, there is little doubt that the disease is transmitted as a single autosomal recessive trait (MacDonald et al. 1960). Most reported patients have been of Anglo-Saxon origin (MacDonald et al. 1960, Paddison et al. 1963), but the family that I have observed are Jews of Egyptian origin.

Neurologically, upper motor neuron disease, cerebellar dysfunction, and muscular weakness, have been noted. Pathological studies have shown widespread mineralization of the cortex, basal ganglia and cerebellum, sometimes with a patchy demyelinization (Moossy 1967, Rowlatt 1969).

In summary, I have tried to highlight the clinical findings in all the tapeto-retinal degenerations known to be associated with disorders in lipid metabolism. There are however a number of isolated cases which I have not mentioned because the nature of the lipid involvement has not been elucidated. The biochemical aspects of these disorders are discussed separately (Berman 1973).

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