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**TAPETORETINAL DEGENERATIONS
AND CNS GENETIC DISEASE**

TAPETORETINAL DEGENERATIONS IN SPINOCEREBELLAR DEGENERATIONS (HEREDOATAXIAS)

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The association of hereditary spino-ponto-cerebellar degenerations with tapetoretinal degenerations of varying types, and particularly with Stargardt's macular degeneration, is not rare, as at the present time more than 200 cases are known. Therefore the one-gene hypothesis seems to be the most plausible. The fact that there exist complex neuroophthalmological forms near purely neurological or purely retinal forms, is also in favour of one gene with polyphenic manifestation.

INTRODUCTION

There are many forms of hereditary spino-ponto-cerebellar degenerations with ataxia. These conditions show a great variety of signs and there are so many combinations and transitional forms, in which these signs occur, that it is sometimes really difficult to differentiate one type of ataxia from another, and that some authors consider each case of heredoataxia which does not fulfil the criteria of Friedreich's disease as a Pierre Marie type, that is to say, "per exclusionem".

On the other hand, many authors have modified the classical classification and used their own, so that still more confusion exists. So, for example, some authors separate the hereditary spastic ataxia of Sanger and Brown from the spastic paraplegia of Strümpell and Lorrain, although both are pure spinal degenerations.

Very often there exists an association of heredoataxia and ocular anomalies, such as ptosis, external ophthalmoplegia, optic atrophy, and particularly tapetoretinal degeneration. This association suggests that the same pathologic gene, determining, for instance, an in-born error of metabolism, might produce an abiotrophy in closely related tissues.

Moreover, there are cases of heredoataxia, associated not only with tapetoretinal degeneration, but also with deafness (Clauss 1924, Vitello 1939, Barré and Rohmer 1948). These cases might belong to Hallgren's syndrome (Becker 1966).

In all these cases, are we dealing with several pathologic genes or with only one gene, having a pleiotropic or polyphenic effect?

The theory of hereditary chains based on the linkage of genes supposes several mutations of the same gene, what is an extremely rare occurrence (Dureux 1955).

On the other hand, the association by chance of two different pathologic genes taken at random occurs only once in every fifty thousand million births.

Therefore the one-gene hypothesis seems to be the most plausible (Franceschetti and Klein

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1948 and 1950). There is, indeed, a striking parallelism between the spinocerebellar dystrophy and the retinal dystrophy: the homochronicity and the homoevolution are obvious.

On the other hand, the fact that there exists complex neuroophthalmological forms near purely neurological or purely retinal forms, is also in favour of one gene, which has a polyphenic effect and may vary in its clinical manifestations and localizations, so that some signs, such as ptosis or external ophthalmoplegia, may even occasionally be considered as equivalents.

The pleiotropic or polyphenic effect can be explained by the fact that the abnormalities are caused by a genic influence on the induction phenomena at the time when the organizing centres come into action. This has been demonstrated experimentally.

Furthermore, before the 4th month of embryonic life, both the retina and the brain, which have a common origin, are under the influence of the same organizing centre (Dureux 1955). Hence, the effect of a single gene in this phase of great sensitivity can be sufficient to cause diverse abiotrophic associations.

These facts explain why there is not only one spinocerebellar heredoatopia, but instead a group of different heredoatopias within wide limits and with overlapping (Botermans 1972), so that a more general term, such as neuroophthalmological abiotrophies or dystrophies, would be justified (Arnould et al. 1965).

Not only the great variety of spinocerebellar dystrophies and the dubious or unprecise diagnosis in many cases make the discussion of the relation between the neurological and the ophthalmological manifestations difficult, but also the fact that the ophthalmoscopic details are often inadequately described. Moreover, in older reported cases without electrophysiological data, it is also difficult to decide whether there is a tapetoretinal degeneration or not. One may have the clinical impression of optic atrophy, because the pigmentary anomalies are not obvious, or of chorioretinitis, which may be an atypical tapetoretinal degeneration.

All these considerations show that the discussion of spinocerebellar heredoatopias and of their retinal manifestations is complex.

The following diseases could be discussed here, as they all show ataxia:

1. *Refsum's disease* (1946), or heredopathia atactica hemeralopica polyneuritiformis, which is due to a deficiency of phytanic-acid alpha-hydroxylase and a resulting storage of phytanic acid.

2. *Hallgren's syndrome* (1959), characterized by pigmentary retinopathy, congenital deafness, mental and neurological abnormalities, such as vestibulo-cerebellar ataxia.

3. *Sjögren-Larsson syndrome* (1957), characterized by macular degeneration, oligophrenia, congenital ichthyosiform hyperkeratosis, spasticity, and ataxia.

4. *Bassen-Kornzweig syndrome* (1950), characterized by atypical pigmentary retinopathy with extinguished ERG, spinocerebellar ataxia of the Friedreich's type, celiac signs with steatorrhea, acanthocytosis and a-beta-lipoproteinemia.

5. *Louis-Bar syndrome* (1941), or ataxia-telangiectasia syndrome, characterized by symmetrical cutaneous and conjunctival capillary telangiectases and cerebellar symptoms including ataxia. This disease is due to a deficiency of gamma-1-A-globulin (IgA), which explains the immunologic incompetence of the patients.

Nevertheless, we will not discuss them, because they are not really heredoataxias, or because other reporters will discuss them. Notwithstanding, they are interesting, because they show that an enzymatic defect could be the cause of the heredoataxias.

We will study the tapetoretinal degeneration in the following spinocerebellar diseases:

1. Spinocerebellar heredoataxia of Pierre Marie
2. Spinal heredoataxia of Friedreich
3. Marinesco-Sjögren syndrome
4. Spastic paraplegia of Strümpell-Lorrain
5. Neural amyotrophy of Charcot-Marie-Tooth
6. Olivo-ponto-cerebellar atrophy of Déjérine-Thomas.

1. SPINOCEREBELLAR AND CEREBELLAR HEREDOATAXIA OF PIERRE MARIE

Pierre Marie disease combines a kinetic and static cerebellar syndrome and a pyramidal syndrome (paresis, contraction, tendinous hyperreflectivity, Babinski's sign, and clonus of the foot). The cerebellar signs are predominant. Its heredity is either autosomal recessive or autosomal dominant.

We know of at least 75 cases of Pierre Marie disease associated with a tapetoretinal degeneration (28 families).

1. Clauss (1924): 1 woman with atypical pigmentary retinopathy and deafness.
2. Zonca (1937): 1 mother and her 2 sons showed a typical pigmentary retinopathy.
3. Froment et al. (1937) reported a transitional form between Pierre Marie disease and spastic paraplegia. The grandmother showed a spastic paraplegia with cerebellar signs, a central and peripheral tapetoretinal degeneration with an areolar degeneration of the pigment epithelium in the macular region. The father showed also a spastic paraplegia with cerebellar signs and a macular degeneration. The son, 5 years of age, showed an intermediary form between Pierre Marie disease and Friedreich's disease. Ophthalmoscopically the optic disc was pale, the retinal vessels narrow, peripheral and peripapillary atrophy of the pigment epithelium, numerous yellowish grains around the disc, separated by pigmentary spots and a more marked pigmentation of the macular region (fig. 1). The heredity is autosomal dominant with anticipation and intrafamilial variability of the tapetoretinal degeneration.

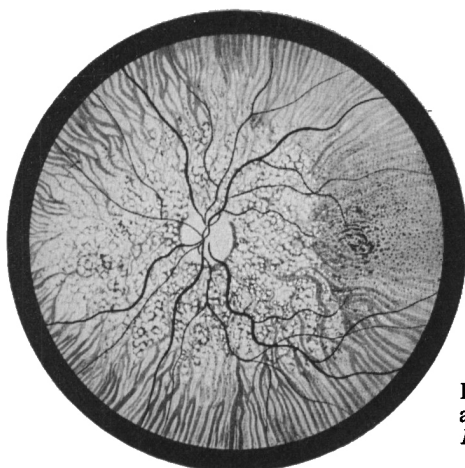


Fig. 1. Peripapillary pearly tapetoretinal degeneration in a case of Pierre Marie heredoataxia. [After Froment et al. 1937 and Renard 1946].

4. Piton and Tiffeneau (1939): 1 man showed a pigmentary retinopathy, whilst his half-sister showed an optic atrophy, which was probably the manifestation of a tapetoretinal degeneration "sine pigmento", so much the more that no ERG has been made and that in the early state the ophthalmoscopic lesions may be minimal, although the visual functions are already very diminished.
5. Vitello (1939): 2 siblings showed a pigmentary retinopathy "sine pigmento" and deafmutism.
6. Sjögren (1943): 1 man with Stargardt's disease.
7. Walsh (1947): 2 brothers with Stargardt's disease.
8. Barré and Rohmer (1948): 1 man with atypical pigmentary retinopathy, external ophthalmoplegia and partial deafness.
9. Havener (1951): 1 man with Stargardt's disease.
10. Boudin et al. (1952): 1 woman and her son.
11. Arnould et al. (1955): macular degeneration of Stargardt's type.
12. Björk et al. (1956): 5 cases (1 woman and her daughter, 2 women, and 1 man). The authors were the first to register an ERG. In one case the *b*-wave was nearly normal at the beginning, but 4 years later its amplitude dropped from 320 to 230 μ V. At the age of 12, the response was only scotopic, what indicates a selective lesion of the cones. In the other cases the results were similar. It was only in the late stage that the amplitude of the scotopic *b*-wave was diminished. It seems that firstly the cones are altered and that only later the rods are also progressively affected, whilst in true pigmentary retinopathy the receptors are diffusely affected from the beginning. In fact, we are dealing here with a progressive cone dysfunction.
13. Lombard (1956): 1 woman with retinopathia punctata albescens.
14. Van Bogaert (1957): 3 sisters with a macular degeneration (Stargardt?), diagnosed at the age of 10, slight mental retardation, and congenital incontinentia pigmenti of Block-Sulzberger. This association is really exceptional. The parents were consanguineous (uncle and niece).
15. Seltzer et al. (1959): 1 man.
16. Ledic and Van Bogaert (1960). In a first family there were 2 cases of spastic paraplegia and 1 case of Pierre Marie disease. Two of these patients showed a tapetoretinal degeneration predominantly macular. The same family included a case of Leber's congenital tapetoretinal degeneration. An intrafamilial variability here also exists. In a second family there were 2 sibs, both affected by spastic paraplegia and Stargardt's macular degeneration. One of them had also a cerebellar ataxia.
17. Jampel et al. (1961): 5 cases through 3 generations (fig. 2). Three of them were affected by heredoataxia and tapetoretinal degeneration and 2 by macular degeneration without ataxia (two girls, respectively 7 years and 12 years old).
18. Bessière et al. (1962): 1 man with Stargardt's disease.
19. Foster and Ingram (1962): macular dystrophy.
20. Bergstedt et al. (1962): 4 cases with central tapetoretinal degeneration through 3 generations. Two patients showed also a vestibular disturbance, what is really exceptional. There was also anticipation in the last generation.
21. Halsey et al. (1967): 11 affected members through 3 generations. Seven patients were blind by optic atrophy with pigment clumps in the macular region (tapetoretinal degeneration?).

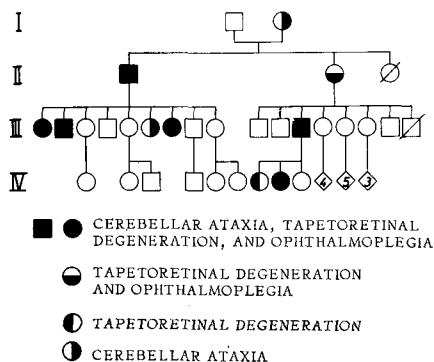


Fig. 2. Spinocerebellar ataxia associated with tapetoretinal degeneration and ophthalmoplegia. [After Jampel et al. 1961].

22. Hariga and Moutschen (1968): 1 man.
23. Furukawa et al. (1968): 10 affected members through 4 generations. They showed, in addition to Pierre Marie disease, a pigmentary retinopathy, a muscular atrophy, and a diabetes mellitus.
24. De Marco (1968): 1 case with peripheral and macular tapetoretinal degeneration and external ophthalmoplegia.
25. Boyazis et al. (1968): 1 woman with a macular degeneration: an area of yellow round spots surrounded by a pigment border.
26. Mainzer et al. (1970): 2 sibs showed a pigmentary retinopathy with extinguished ERG. The heredoataxia was associated with juvenile nephrophtisis (medullary kystic disease) and skeletal abnormality (disturbed endochondral ossification).
27. Stanescu et al. (1970): 1 man showed a retinopathia punctata albescens. At the right eye, near the macula, round white spots were found. In the inferior part of the retina there was a greyish area, surrounded by white spots. At the left eye numerous white spots were seen. There was hemeralopia. The ERG was electronegative. Four brothers and sisters were affected by Friedreich's disease.
28. Bigorgne et al. (1971): 5 cases through 2 generations. The father died blind and ataxic. His daughter showed optic atrophy, narrow retinal vessels and macular degeneration of the Stargardt's type (fine grey spots in the macular region). ERG: no scotopic activity, but normal photopic activity. A cousin was affected by a cerebellospasmodic syndrome with bilateral optic atrophy, narrow retinal vessels and macular changes.
29. Sykehus (1973) observed 58 cases of Pierre Marie disease. He found 1 case with hemeralopia, 2 cases with peripheral retinal degeneration, and 2 cases with optic atrophy.
30. *Personal observation* of some members of a family published by Verougstraete and Toussaint (1973). As seen in the pedigree (Fig. 3) I₁ and II₄ had disturbances of the equilibrium from the age of 60 years on.
- III₁ (40 years of age) showed disturbances of the equilibrium as well as a diminution of the vision at the left eye. R.E. macular peppering, L.E. lamellar hole. V.R.E. 9/10, L.E. 1/10. Bilateral acquired dyschromatopsia of red-green axis. Conclusion: atypical Stargardt's macular degeneration without other ocular abnormalities.
- III₂. The eyes are anatomically normal, but there is also a bilateral acquired dyschromatopsia of red-green axis.
- III₄ (32 years of age). Spastic paraplegia. Diminution of the vision since 7 years. Bilateral macular degeneration of the Stargardt's type (black and red peppering without foveal reflex). Sequels of uveitis at the R.E. V.R.E. 1/40, L.E. 1/20. Central scotoma. Normal limits of the visual fields. Nyctalopia. Acquired dyschromatopsia of red-green axis. ERG, R.E. b-wave 110 μV, L.E. b-wave 85 μV (subnormal). Three years later, in addition, bilateral optic atrophy.
- III₅ (41 years of age). Neural amyotrophy with cerebellar ataxia. The patient is bedridden. Diminution of vision since the age of 24 years. Ataxia and dysarthria appeared 4 years later. Bilateral macular degeneration of the Stargardt's type (pigmentation and snail slime) and optic atrophy. V.R. and L.E.: 1/50 (central scotoma of 10°). Normal limits of the visual fields.

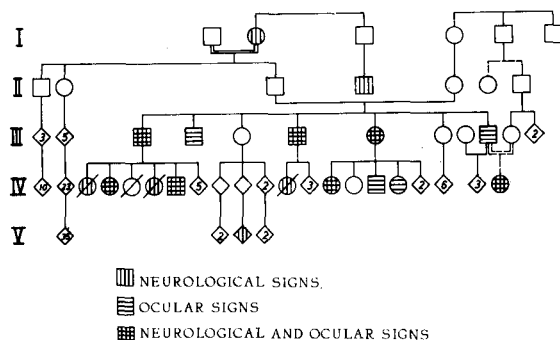


Fig. 3. Heredoataxia. [After Verougstraete and Toussaint 1973].

III₇. No neurological signs. Vision and fundus are normal, but there is an acquired dyschromatopsia of red-green axis.

IV₁ died at age 1½ from encephalitis (?).

IV₂. Diminution of vision since childhood. At age 15 albinoid fundus, macular and perimacular pigmentation, pale discs. V.R. and L.E. 1/10. Visual fields normal. At age 17 first signs of ataxia.

IV₃ died at 6 weeks (cardiac malformation).

IV₄ showed cerebellar ataxia at age 4 and died at age 7 (cerebellar atrophy).

IV₅ showed disturbance of the equilibrium at age 18. In the R.E. pigmentations of the macula. Bilateral acquired dyschromatopsia of red-green axis. Vision and visual field normal on both sides.

IV₁₀ died at age 7 (cerebellar atrophy).

IV₁₂. Disturbance of equilibrium. Bilateral macular alterations. V.R. and L.E. 1/20 (central scotoma). Normal limits of the visual fields. Bilateral acquired dyschromatopsia of tritan type.

IV₁₄ (14 years of age). Shagreen appearance of both maculas. Cicatricial chorioretinitis at the L.E. V.R. and L.E. 2/10. Enlargement of the blind spot.

IV₁₅ (11 years of age). Macular peppering on both eyes. V.R. and L.E. 9/10. Relative central scotoma of 5°. Bilateral acquired dyschromatopsia of red-green axis.

IV₁₉ (12 years of age). Grumous pigmentation of both maculas. V.R. and L.E. 4/10. Bilateral acquired dyschromatopsia of red-green axis. At the age of 15 cerebellar ataxia, the patient being bedridden.

Summarizing, we see that:

(1) There is an autosomal dominant inheritance with anticipation and aggravation of the manifestations in the IV generation.

(2) In this family we find pure neurological forms, pure ocular forms, and mixed forms, the ocular signs being always the first to appear.

(3) The neurological forms are various: spinocerebellar ataxia of Pierre Marie, as well as spastic paraplegia, neural amyotrophy, or cerebellar atrophy, are found. This fact proves the relationship between the different heredoataxias.

(4) In this family the most frequent ocular manifestation is a macular degeneration of the Stargardt's type, but optic atrophy was also found.

(5) An ERG was performed in only one case. It was subnormal. In tapetoretinal degeneration, associated with heredoataxia, the deterioration of the ERG is mostly progressive, in opposition with what is seen in true pigmentary retinopathy.

After this review of the literature, we may conclude:

(1) There are families, affected by Pierre Marie disease associated with a tapetoretinal degeneration, where some members show only a retinal dystrophy without neurologic signs (Ledic and Van Bogaert 1960, Hariga and Moutschen 1968, pers. obs.).

(2) In Pierre Marie disease various forms of tapetoretinal degeneration are found:

a. A typical or atypical pigmentary retinopathy associated or not with an optic atrophy.
b. An isolated macular degeneration of the Stargardt's type, which is the most frequent manifestation.

c. Retinopathia punctata albescens or other rare tapetoretinal degenerations, such as choroidal sclerosis or Leber's congenital tapetoretinal degeneration.

d. Mixed forms of tapetoretinal degeneration (peripheral and macular).

(3) It is quite likely that the cases with optic atrophy were in fact pigmentary degenerations sine pigmento, the optic atrophy being secondary. This conclusion is likely so much the more that no ERG was made in these cases.

2. FRIEDREICH'S SPINAL ATAXIA

Friedreich's disease combines a cerebellar syndrome, which is more static than kinetic, a posterior radiculo-cordonal syndrome (tendinous areflexia, ataxia, alteration of the deep sensitivity), a pyramidal syndrome (paresis of the flexors, Babinski's sign) and a trophic syndrome (club foot). The spinal signs are predominant. Its inheritance is autosomal recessive, as proven by its occurrence in one single sibship and by the frequent consanguinity of the parents.

A tapetoretinal degeneration has been observed in at least 25 sibships.

1. Rüttimeyer (1883, 1887). The pedigree of the Glaser family has been completed by Frey (1912), Hanhart (1923*b*, 1924, 1941), Franceschetti and Klein (1947*b*, 1948: Fig. 4). A Friedreich's heredoataxia is observed in several sibships of this family with many consanguineous marriages. The disease is associated in two sibships with juvenile macular degeneration, in another sibship with a pigmentary retinopathy and in a fourth sibship with a retinopathia punctata albescens. Franceschetti and Klein think that Friedreich's ataxia and tapetoretinal degeneration are manifestations of the same pathological gene. Becker (1966), on the contrary, thinks that the many consanguineous marriages were at the origin of various pathological genes, which became manifest in the homozygous subjects.

2. Lenoble and Aubineau (1901): 2 brothers, the parents of whom were consanguineous, were affected by an intermediary form between Pierre Marie and Friedreich's disease, associated with an atypical pigmentary degeneration.

3. Van Bogaert (1924, 1947): the retinal lesions resembled a healed choroiditis (pseudoinflammatory involvement of the choroid).

4. Giddings (1927).

5. Kapuscinski (1934): 1 brother and his 2 sisters, who showed a progressive and diffuse involvement of the choroid (choroidal sclerosis and atrophy: Fig. 5) and myopia, with ataxia, dementia, choreiform and athetotic disturbances. One of the sisters had no secondary sex characteristics and the brother had cryptorchidism.

6. Fialho Filho (1937): 1 man was affected by a Friedreich's disease, "atrophia gyrata chorioideae et retinae" and hypogenitalism.

7. De Mello (1943) examined the patient of Fialho Filho and found the same condition in 1 first cousin, a woman with oligophrenia and hypogenitalism. In fact, there was in both patients a peripapillary choroidal sclerosis with peripheral pigmentary retinopathy (Franceschetti et al. 1963).

8. François and Descamps (1949, 1951) observed complex neurological manifestations in a man, 44 years of age, who was affected by an intermediary form between Pierre Marie and Friedreich's disease with signs of olivo-ponto-cerebellar atrophy, endocrine disorders (obesity, acromegaloid appearance) and progressive deafness. He showed also a multipigmentary retinopathy of the classic type with hemeralopia and severe constriction of the visual fields (fig. 6).

9. Stadlin and Van Bogaert (1949): 2 sisters, the parents of whom were consanguineous, showed pseudoinflammatory lesions of the chorioretina, resembling cicatricial chorioretinitis (Fig. 7).

10. Montalban (1952): 2 sibs showed a pigmentary retinopathy with severe atrophy of the choroid (choroidal sclerosis). There was also hypogenitalism.

11. Winnik et al. (1953): 1 man, the parents of whom were consanguineous, was affected by a Friedreich's disease associated with a choroidal sclerosis as well as with progressive deafness, mental retardation, mild endocrine disturbances and paranoia.

12. Walsh (1957) observed a partial choroideremia with pale optic discs and narrow retinal vessels.

13. Danis and Brihaye-Van Geertruyden (1962) observed 1 woman with an isolated macular degeneration (fig. 8). Histologically, the lesions were localized in the macular and paramacular region. There was a complete atrophy of the external retinal layers (pigment epithelium and neuroepithelium). The internal granular layer and the ganglion cell layer were nearly not altered. The choroid and the choriocapillaris were normal. The peripheral retina was unchanged (Figs. 9 and 10).

14. Heck (1963) found in the same family a Friedreich's ataxia with autosomal recessive heredity and a pigmentary retinopathy with macular degeneration, which showed an intermediate sex-linked heredity, the female carriers being fully or only partially affected.

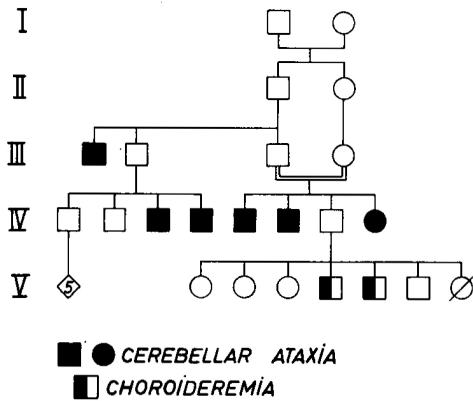


Fig. 4. Pigmentary retinopathy and heredo-ataxia in the same family. [After Franceschetti and Klein 1948].

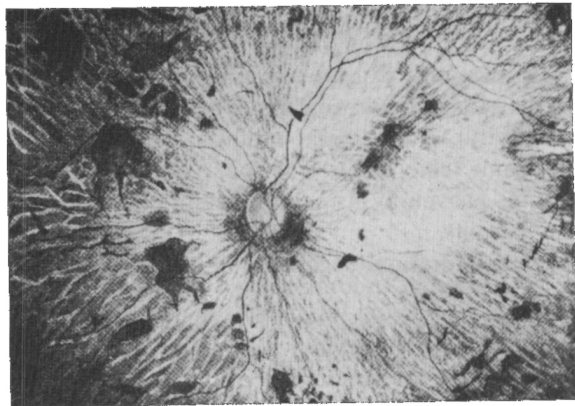


Fig. 5. Familial tapetoretinal degeneration with choroidal sclerosis in a girl 14 years of age. [After Kapuscinski 1934].

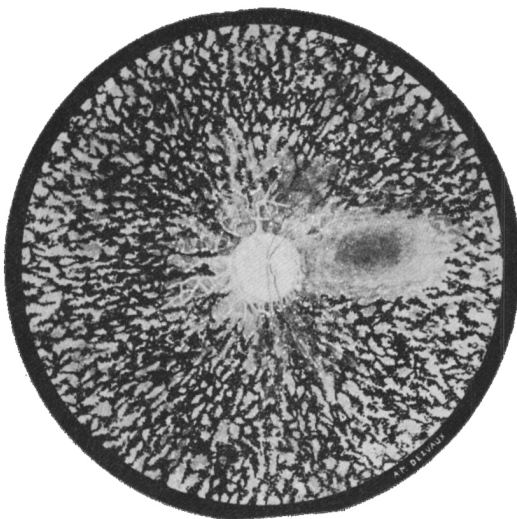


Fig. 6. Hyperpigmented tapetoretinal degeneration in a case of heredoataxia. [After François and Descamps 1949].

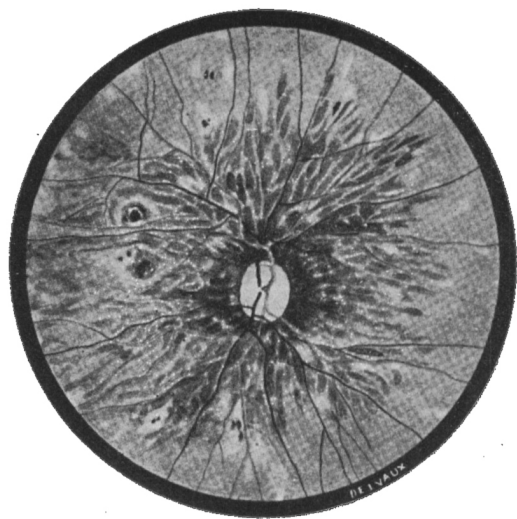


Fig. 7. Pseudoinflammatory chorioretinal degeneration in a case of Friedreich's heredoataxia. [After Stadlin and Van Bogaert 1949].

15. Arnould et al. (1965): 1 man.

16. Boyazis et al. (1968): 1 brother and his 2 sisters. First case: temporal pallor of the discs, macular degeneration, and pigment migration. Second case: pigment migration in the macular region. Third case: in the right eye macular degeneration. No ERG was made.

17. Lenz and Purgyi (1969): 1 boy showed, in addition to Friedreich's disease, a pigmentary retinopathy with optic atrophy and hypobetalipoproteinemia.

18. Boucher and Gibberd (1969): 2 sisters showed a retinal degeneration and hypogonadism.

19. Stanescu et al. (1970) observed 3 sisters and their 2 brothers. A girl, 6 years of age, was affected by a "fruste" form of Friedreich's disease. She showed a mixed form of retinopathia pun-

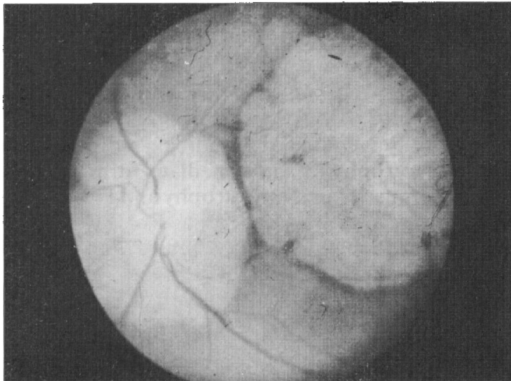


Fig. 8

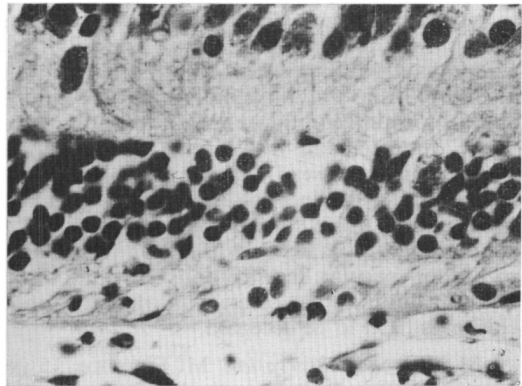


Fig. 9

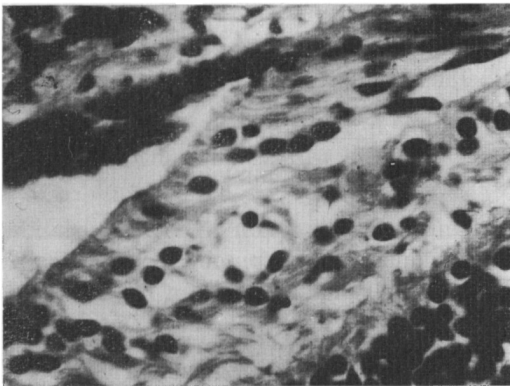


Fig. 10

Fig. 8. Macular degeneration in a case of Friedreich's heredoataxia. [After Danis and Brihaye-Van Geertruyden 1962].

Fig. 9. Paramacular region in a case of Friedreich's heredoataxia. [After Danis and Brihaye-Van Geertruyden 1962].

Fig. 10. Paramacular region in a case of Friedreich's heredoataxia. [After Danis and Brihaye-Van Geertruyden 1962].

ctata albescens and atypical pigmentary degeneration (pepper and salt appearance). There was hemeralopia and an extinguished ERG. A sister, 9 years of age, was also affected by a "fruste" form of Friedreich's disease. The eye-fundus had a "pepper and salt" appearance. The *b*-wave of the ERG was subnormal. There was no hemeralopia. A brother, 11 years of age, was affected by a heredoataxia in the beginning stage. The eye-fundus had also a "pepper and salt" appearance. The *b*-wave of the ERG was subnormal. There was no hemeralopia. Another sister, 16 years of age, was affected by an intermediate form between Pierre Marie and Friedreich's disease. There was a peripapillary atrophy of the retina with accumulation of pigments in the posterior pole and white dots along the vessels of the lower temporal sector. The ERG was subnormal at the right side and electro-negative at the left. There was hemeralopia. Another brother, 19 years of age, was affected by a Pierre Marie disease. In the right eye white spots were found around the macula and in the lower nasal sector, as well as a grey area edged with white dots in the lower half of the retina. In the left eye numerous white spots were also found (retinopathia punctata albescens). The ERG was electronegative. There was night blindness. In conclusion, these 5 sibs were affected by various forms of tapetoretinal degeneration and of heredoataxia, although mixed forms of the ophthalmological and neurological conditions were found in the same patient.

20. Quarcoopome (1970) observed a Negro, 29 years of age, who was affected by ataxia, arachnodactyly, hypogenitalism, obesity confined to a slight spherical paunch, moonlike face, very narrow hips without flabby bags around the hips, and dwarfism. The posterior pole of the eyes was whitish

as in choroïderemia. The peripheral retina showed fine pigmentary deposits. The retinal vessels were narrow and the optic discs atrophic. The patient was nearly blind. As we will see later, we are probably dealing with a case of Laurence-Moon syndrome.

21. Sykehus (1973) found, among 31 cases of Friedreich's disease, one case with hemeralopia and one case with optic atrophy.

22. Stanescu and Wawernia (1973) examined 55 cases of heredoataxia: Friedreich's disease (26), Pierre Marie disease (5), spastic paraplegia (8), neural amyotrophy (5), intermediate form between Pierre Marie and Friedreich's disease (2), intermediate form between neural amyotrophy and Friedreich's disease (4), "fruste" forms of heredoataxia (2), and heredoataxia without diagnosis (3). The age of the patients was between 7 and 62 years. They showed either pigment migrations in the macular region, or macular degenerations, or optic atrophy, or pigmentary retinopathies, or also a normal fundus. But in all the cases, even when the fundus was normal, the ERG was subnormal. This conclusion is hard to be accepted.

23. *Personal observation.* M. Florence, 15 years of age. The vision is diminished since 4 years. The eyes are completely normal with the exception of the macula, which is dystrophic and covered by a pigmentary dust. The retinal vessels are a little narrow. The temporal sector of the disc is paler than the nasal sector. The fundus is albinoid and shows an irregularly distributed pigment dust. The fluorescein angiography shows no abnormality and no pathologic fluorescence. The macular region remains dark.

The vision is 0.3 at the right and 0.1 at the left. There is a central scotoma of 8-9°, but the peripheral limits of the visual field are normal. The adaptation curve is normal: threshold at the 15th min log asb 5.8. There is an acquired dyschromatopsia of the blue-yellow axis. The electroretinogram is completely normal (R.E. *a*-wave 175 μ V, *b*-wave 325 μ V; L.E. *a*-wave 180 μ V, *b*-wave 310 μ V).

In conclusion there is a macular degeneration without peripheral participation and without optic atrophy.

The marked choroidal involvement associated in some cases with mental retardation, minor endocrine disorders (hypogenitalism or hypogonadism) (Kapusinski 1934, Fialho Filho 1937, De Mello 1943, François and Descamps 1949, Stadlin and Van Bogaert 1949, Montalban 1952, Winnik et al. 1953, Walsh 1957, Boucher and Gibberd 1969, Quarcoopome 1970) remembers the cases of Laurence and Moon (1866), seen afterwards by Hutchinson (1882, 1900).

These cases have to be separated from Bardet (1920) and Biedl (1922*a, b*) cases, because Laurence-Moon syndrome must be regarded as a spinal ataxia of the Friedreich's type and as a spastic paraplegia associated not with a true pigmentary retinopathy, but with a progressive choroidal atrophy (Franceschetti and Klein 1948, Botermans 1972). There is no polydactyly or syndactyly and no significant obesity.

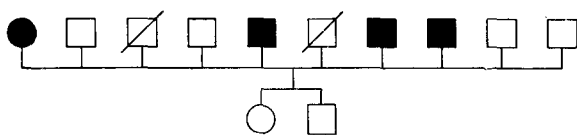


Fig. 11. Laurence and Moon family (1866).

It is worthwhile to remember the family of Laurence and Moon (1866). Four children out of 10 (3 boys and 1 girl) were affected (Fig. 11), from early childhood, by a paraplegia and a tapetoretinal degeneration, which was considered as an "atrophia gyrata chorioideae et retinae", but was rather a marked choroidal atrophy (Fig. 12). The 3 brothers showed, moreover, some degree of retardation in the physical development, as well as hypogenitalism and mammary hypertrophy. In 2 of them cryptorchidism was found.

In Bardet-Biedl syndrome there is typically polydactyly or syndactyly, marked obesity,

hypogenitalism or hypogonadism, mental deficiency, and pigmentary retinopathy with extinct ERG and flat EOG.

So, the Laurence-Moon cases do not belong to the Bardet-Biedl syndrome. Consequently the term "Laurence-Moon-Bardet-Biedl disease" is not correct. The Laurence-Moon syndrome is a peculiar type, which is allied to Friedreich's disease.

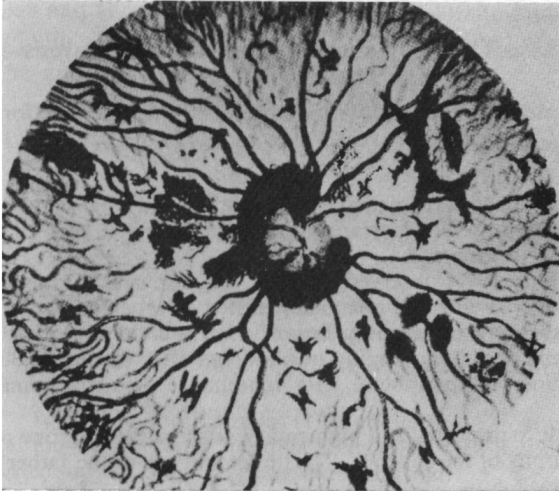


Fig. 12. Choroidal atrophy and retinal pigmentations in the youngest child of Laurence and Moon family. [After Hutchinson 1900].

In conclusion, true tapetoretinal degeneration is rare in Friedreich's disease. It is mostly of the peripheral type, the pigmentary retinopathy being often associated with a marked choroidal involvement. We know of only 2 cases of macular degeneration (Danis and Brihaye-Van Geertruyden 1962; pers. obs.).

When we separate the Laurence-Moon syndrome from Friedreich's disease associated with a tapetoretinal degeneration, only very few cases of the latter syndrome remain.

On the other hand, the cases, where deafness and mental retardation are associated with ataxia, such as the cases of François and Descamps (1949), Winnik et al. (1953), may belong to the group of Hallgren's syndrome (Becker 1966).

3. MARINESCO-SJÖGREN SYNDROME

Marinesco (1931) - Sjögren (1950) syndrome is characterized by spinocerebellar ataxia, congenital cataract and oligophrenia.

Ocular manifestations. Besides the congenital cataract (Marinesco et al. 1931, Sjögren 1950, Hariga 1965, Géraud et al. 1965, Papp et al. 1971) and ocular paralyzes (Géraud et al. 1965), a pigmentary retinopathy has been reported twice:

1. Richards (1950).
2. Hagen et al. (1951: 1 case). Histologically, the pigmentary retinopathy involved chiefly the peripheral and equatorial region of the retina, where all the cell layers, including the ganglion cell layer, were destroyed.

Géraud et al. (1965) observed a family with 11 cases through 4 generations. Two of these cases showed optic atrophy, but no ERG was performed.

Papp et al. (1971) observed a woman, 25 years of age, with macular degeneration.

Sykehus (1973) examined 38 cases and found 1 case with diffuse retinal degeneration, 1 case with macular degeneration, and 3 cases with optic atrophy.

4. SPASTIC PARAPLEGIA OF STRUMPELL-LORRAIN

This disease is characterized by a spastic gait with pyramidal contraction and paresis of the inferior limbs.

We know at least 30 cases of spastic paraplegia associated with a tapetoretinal degeneration. There are 23 cases with pigmentary retinopathy.

1. Stewart (1937): 2 sisters with spastic paraplegia, pigmentary retinopathy, and oligophrenia.
2. Froment et al. (1937) and Renard (1946) observed a transitional form between cerebellar ataxia and spastic paraplegia with tapetoretinal degeneration.

3. Jéquier et al. (1945) and Jéquier and Streiff (1947) observed a family where spastic paraplegia (18 affected members) and pigmentary retinopathy (7 affected members) existed as separate diseases in different branches. In one branch the pigmentary retinopathy began in early childhood at the level of the macula and spread afterwards to the periphery, ending in blindness after the age of 30. In another branch the tapetoretinal degeneration was peripheral. Its inheritance was autosomal recessive.

4. Evans (1954): 2 brothers showed spastic paraplegia and pigmentary retinopathy. In one of them this was associated with a pronounced atrophy of the choroid. The father and one of the father's aunts were also affected.

5. Dureux (1955): 1 woman with spastic paraplegia and diffuse tapetoretinal degeneration.

6. Walsh (1957): 3 sisters with spastic paraplegia or quadriplegia and pigmentary retinopathy, one of them showing also an external ophthalmoplegia.

7. Alfano and Berger (1957): 1 man with spastic paraplegia, diffuse tapetoretinal degeneration and progressive external ophthalmoplegia.

8. Perrin (1958): 1 woman with spastic paraplegia and diffuse tapetoretinal degeneration.

9. Mahloudij and Chuke (1968): 3 siblings, affected by spastic paraplegia, 2 of whom with retinal degeneration.

10. Gordon and Capute (1973): 2 brothers affected by spastic diplegia and deafness. Both showed a diffuse bilateral pigmentary degeneration of the retina with coarsely granular pigment, pale and small optic discs, and subnormal ERG.

11. Sykehus (1973) found 5 cases of peripheral retinal degeneration among 48 cases of spastic paraplegia, that is to say, 10%. There were also 4 cases of optic atrophy.

There are 9 cases of spastic paraplegia with macular degeneration:

1. Louis-Bar and Pirot (1945): 1 case.

2. Landau and Gift (1951): the patient with macular degeneration belonged to a family in which the paraplegia was transmitted dominantly through 5 generations.

3. Kjellin (1949) observed 4 cases (2 sibships of 2 brothers) with a transitional form between spastic paraplegia and neural amyotrophy. The 4 patients were affected by a macular degeneration, characterized by the presence of atrophic foci with pigment migration. The vision was rather good. In one sibship the ERG was electronegative, in the other supranormal (increased *a*-wave, normal *b*-wave).

4. Ledic and Van Bogaert (1960) observed 2 sibs affected by spastic paraplegia and tapetoretinal degeneration of a predominantly macular type. In 1 case there was a cerebellar ataxia.

5. Sykehus (1973) found 1 macular degeneration among 48 cases of spastic paraplegia.

6. Macrae et al. (1973) observed a sibship of 11, 5 of whom were affected by spastic paraplegia

and retinal degeneration, which was most likely a fundus flavimaculatus, when the morphological, fluoro-angiographical and functional symptoms are taken into account. This family is the same as the one of Mahloudji and Chuke (1968).

Spastic paraplegia (associated with central or peripheral tapetoretinal degeneration) may show either an autosomal recessive or an autosomal dominant inheritance:

(a) An autosomal recessive heredity was likely in the cases of Stewart (1937), Louis-Bar and Pirot (1945), Dureux (1955), Alfano and Berger (1957), Walsh (1957), Perrin (1958), Kjellin (1959), Mahloudji and Chuke (1968), Gordon and Capute (1973, consanguinity of the ancestors in the fifth generation).

(b) An autosomal dominant heredity was likely in the families of Froment et al. (1937, 3 generations), Landau and Gift (1951), Evans (1954, 4 cases in 2 generations).

5. NEURAL AMYOTROPHY OF CHARCOT-MARIE-TOOTH

Neural amyotrophy, which shows an autosomal recessive inheritance and was first described by Charcot-Marie (1886) and Tooth (1886), is essentially characterized by a progressive muscular atrophy of the limbs with jerks and painful cramps of the muscles.

Three observations mention a retinal manifestation.

1. De Vic and Kapsalas (1930) described 1 boy, who showed an intermediary form between neural amyotrophy and Friedreich's disease. He had also a pigmentary retinopathy, whilst his elder sister showed only the neurologic affection.

2. Massion-Verniory et al. (1946) observed also 1 man with neural amyotrophy and pigmentary retinopathy. One sister showed also a pigmentary retinopathy and another sister a bilateral "cho-roiditis", but none of them had neurologic anomalies.

3. Boyazis et al. (1968) described 3 brothers with neural amyotrophy: all 3 showed a few pigmentary clumps in the macular region; in 2 of them, these pigmentations were bilateral and in 1 unilateral.

6. OLIVO-PONTO-CEREBELLAR ATROPHY OF DEJERINE-THOMAS

Olivoponto-cerebellar atrophy is essentially characterized by ataxia, incoordination of the hands, rest tremors, slurred speech, and writing athetosis (cerebellar, pyramidal, and extrapyramidal signs). Its inheritance is mostly autosomal dominant, sometimes autosomal recessive.

The disease may be associated with a peculiar retinopathy. We know of 29 cases, of which 24 with pigmentary changes of the retina, 16 with optic atrophy and 10 with external ophthalmoplegia: Woodworth et al. (1959: 4 cases), Carpenter and Schumacher (1966: 4 cases, father and 3 children), Weiner et al. (1967: 14 cases out of 27 affected members through 5 generations of the same family), Ryan and Smith (1971: 3 cases), Ravalico and Stanig (1972: 2 cases), Konigsmark (1973: 2 sibs).

1. Woodworth et al. (1959) observed 1 man and 3 of his 5 sons affected by olivoponto-cerebellar atrophy. One showed spotty areas of retinal degeneration, with optic atrophy and poor vision. The second showed bands of pigment around the disc and also optic atrophy. The third showed patchy pigmentary degeneration of the retina with optic atrophy and the fourth only optic atrophy. Histologically there was a destruction of the ganglion cells, the bipolar cells and the photoreceptors of the retina. The histological findings were similar to those of Weiner et al. (1967): Fig. 13.

2. Carpenter and Schumacher (1966) observed 1 man and 3 of his 5 sons affected by olivoponto-

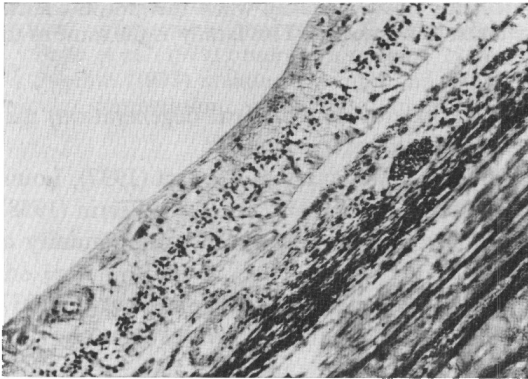


Fig. 13. Diffuse tapetoretinal degeneration in a case of olivo-ponto-cerebellar atrophy. Nearly total atrophy of the external layers of the retina and the neuro-epithelium. Normal choroid. [After Woodworth *et al.* 1959].

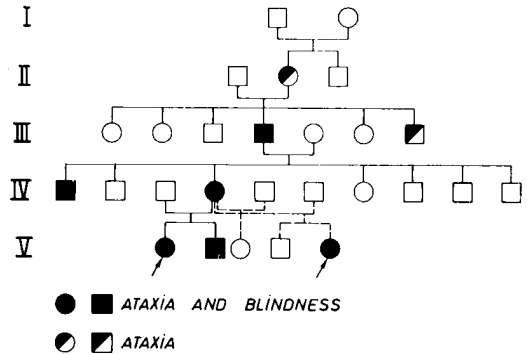


Fig. 14. Olivo-ponto-cerebellar atrophy. Autosomal dominant inheritance. [After Ravalico and Stanig 1972].

cerebellar atrophy. The father showed only optic atrophy with poor vision. The oldest son had pale fundi with scattered pigment. The second son showed a retinal degeneration of the “pepper and salt” type with pale discs and poor vision. The third son had pale retinas with punctate pigmentary changes in the periphery.

3. Weiner *et al.* (1967). In this large family 14 members over 5 generations were affected by olivo-ponto-cerebellar atrophy and pigmentary retinopathy with blindness, and 13 by olivo-ponto-cerebellar atrophy alone. Two new affected members are now known (Konigsmark 1973). The proband showed, in both eyes, peculiar atrophic round pale areas involving the entire macular region and sprinkled with brownish black pigment granules. There was a pigment peppering throughout the whole retina. Many round lesions resembling chorioretinitis were found in the periphery. Histologically, there was an almost total loss of the ganglion cells. Many of those remaining were vacuolated. The bipolar cells were greatly reduced in number. The outer nuclear layer was devoid of cells. The rod and cones were totally absent. There existed multiple areas of adhesions between the retina

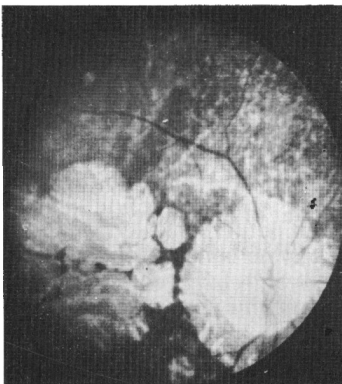


Fig. 15. Tapetoretinal degeneration with polycyclic chorioretinal atrophy of the macular region. [After Ravalico and Stanig 1972].

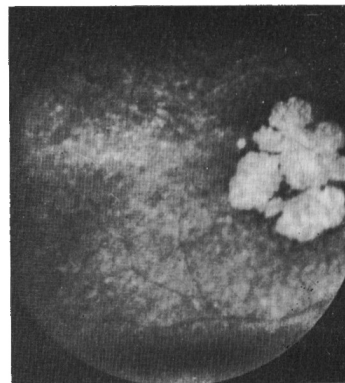


Fig. 16. Tapetoretinal degeneration with polycyclic chorioretinal atrophy of the macular region. [After Ravalico and Stanig 1972].

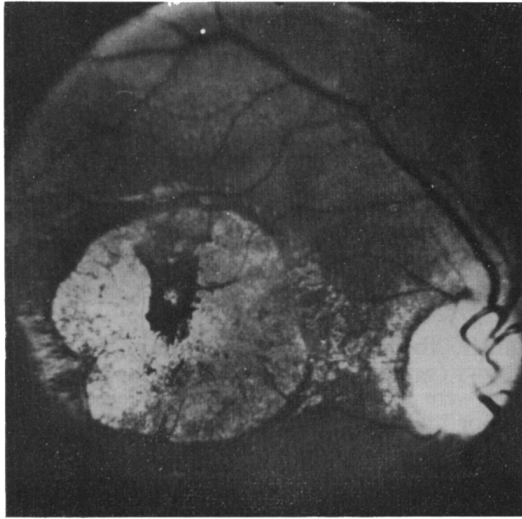


Fig. 17. Macular degeneration in olivo-ponto-cerebellar atrophy. [After Konigsmark 1973].

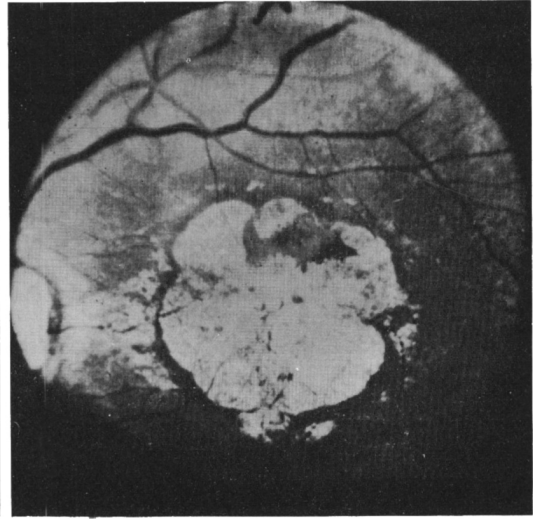


Fig. 18. Macular degeneration in olivo-ponto-cerebellar atrophy. [After Konigsmark 1973].

and the pigment epithelium in association with a patchy disappearance of pigment epithelial cells and some migration of pigment laden cells into the retina. There was also a marked loss of optic nerve fibers with demyelination. It is not impossible that the demyelination of the optic nerve was the first change and that it was followed by the degeneration of the retina.

4. Ryan and Smith (1971) observed a man, who showed a sharply circumscribed macular degeneration of 2 DD with pigment migration and a thin gliotic membrane, giving a shagreen aspect. The choriocapillaris was absent in the macular region, as proven by fluorescein angiography. The ERG and the EOG were subnormal. A sister and a niece showed, moreover, a marked migration of pigment in the whole retina and areas of choroidal sclerosis with extinguished ERG. They became blind.

5. Ravalico and Stanig (1972) observed 2 sisters, 18 and 26 years of age, belonging to a family in which the olivo-ponto-cerebellar atrophy was dominantly transmitted (Fig. 14). One sister showed an albinoid fundus with small, yellowish spots. There was a polycyclic chorioretinal atrophy of the macular region (Fig. 15). The discs were pale and the retinal vessels narrow. The ERG was extinct. The other sister showed an aspect of choroidal sclerosis of the posterior pole, which was more marked around the disc and at the level of the macular atrophy (Fig. 16). Here also the discs were pale, the retinal vessels narrow and the ERG extinct.

6. Konigsmark (1973) observed with Capute and Gordon 2 children with olivo-ponto-cerebellar atrophy and macular degeneration (Figs. 17 and 18).

It seems that in olivo-ponto-cerebellar atrophy the retinopathy starts as a macular degeneration with involvement of the sensory retina, pigment epithelium and choriocapillaris (Ryan and Smith 1971). Afterwards, the pigment disturbance (clumps of pigment) spreads peripherally to involve the remaining retina (pigmentary retinopathy) and to cause blindness.

INTRAFAMILIAL ALTERNATION OF HEREDOATAXIAS AND TAPETORETINAL DEGENERATIONS

The association of heredoataxia and tapetoretinal degeneration in the same patients, is, as we have seen, rather frequent. But there are also families where an alternation of the two diseases is found. The question arises if one disease may be replaced by the other and constitutes the only manifestation of the neuroretinal heredodegeneration. It is not impossible.

1. Franceschetti and Klein (1941*b*, 1947) observed a family of 21 members with several consanguineous marriages (Glaser family). In some sibships Friedreich's ataxia was found, in 2 sibships a juvenile macular degeneration, in another sibship a pigmentary retinopathy, and in a fourth sibship a retinopathia punctata albescens.

2. Jéquier et al. (1944) and Jéquier and Streiff (1947) observed a family of 12 members affected by spastic paraplegia with disturbances of the sensitivity (neuritis) and skeletal abnormalities (coxa vara, spina bifida). In one collateral branch 7 members were affected by a tapetoretinal degeneration, which began as a macular degeneration at the age of 5 or 7 years to end in nearly complete blindness at the age of 30 or 35 years. In another branch there was a tapetoretinal degeneration of the peripheral type with normal adaptation to darkness. All these conditions (neurological and ocular) were transmitted in recessivity. Were they due to a single or to different genes?

3. Amman et al. (1961) found in the same family 2 cases of pigmentary retinopathy and 2 cases of Friedreich's disease.

4. Jampel et al. (1961) observed a spinocerebellar ataxia through 4 generations. Of 10 affected members 8 showed a macular degeneration. In 2 of these the macular degeneration was associated with a peripheral tapetoretinal degeneration. There were also 2 cases of macular degeneration without ataxia. In one of these 2 cases there was a paralysis of the convergence and the upward gaze.

These families show that it is possible that heredoataxia and tapetoretinal degeneration may be the manifestation of the same pathological gene (Franceschetti and Klein 1948).

We must, nevertheless, be cautious before concluding so. So, for example, Werthemann (1927) observed 7 cases of Pierre Marie disease in the same family. In one branch 2 brothers and 1 sister, the parents of whom were consanguineous, were affected. The only healthy brother had 2 sons affected by choroideremia. This is not a phenotypical alternation, as the choroideremia is sex-linked and must have been transmitted by the mother, but a coincidence.

HERODATAIXIA, OPHTHALMOPLÉGIA, AND TAPETORETINAL DEGENERATION

We know the association of one or another form of heredoataxia with a central or peripheral tapetoretinal degeneration as well as with an external ophthalmoplegia or a paralysis of the gaze, mostly of the upward gaze:

Piton and Tiffeneau (1939, 1940), Sjögren (1943), Barnard and Scholz (1944: case 4), Walsh (1947), Barré and Rohmer (1948), Boudin et al. (1952: cases 1 and 2), Alfano and Berger (1957), Woodworth et al. (1959), Jager et al. (1960), Jampel et al. (1961).

May the external ophthalmoplegia or the gaze paralysis be an equivalent of tapetoretinal degeneration? In any case there are numerous examples of association of heredoataxia with ophthalmoplegia or gaze paralysis without tapeto-retinal degeneration:

Magnus (1899: 2 brothers with Friedreich's disease and ophthalmoplegia); Schob (1921: Friedreich's disease with choroiditis, ophthalmoplegia, kyphoscoliosis, and mental deficiency); Lelong et al. (1941: spinocerebellar ataxia, ophthalmoplegia, chorioretinitis, and optic atrophy); Franceschetti

et al. (1945: 4 sibs with spinocerebellar ataxia and progressive external ophthalmoplegia); Schutt (1950: similar cases); Fanconi and Türler (1951: spinocerebellar ataxia with congenital ophthalmoplegia); Stephens et al. (1958: 4 sibs with Friedreich's disease and progressive external ophthalmoplegia); Fotopulos and Schulz (1962: spinocerebellar ataxia and progressive external ophthalmoplegia); Fignini et al. (1963: 3 brothers with ataxia, areflexia, analgesia, hypotonia, and congenital external ophthalmoplegia).

Rimbaud et al. (1932), Hallervorden (1937), Mollaret (1939), Sjögren (1943), Richter (1950), Fanconi and Türler (1951), Euzière et al. (1952), Barraquer-Bordas et al. (1954), published heredoataxias associated with a paralysis of the gaze, particularly of the upward gaze.

ADDENDUM

Finally and to be complete we will mention that a tapetoretinal degeneration has also been seen in some other nervous heredodegenerations with ataxia:

1. *Myotonic cerebellar dysgenesis*: 1 case published by Vercelli (1938) and Alabastro (1947).
2. *Progressive pallidal degeneration*: 2 brothers observed by Dercum (1925).
3. *Calcification of the ganglia of the brain basis*. Strobos et al. (1957) observed 2 brothers, affected by this disease, who showed a pigmented macular degeneration. A sister, who had no cerebral calcifications, showed ataxia and also a pigmented macular degeneration. Two cases of muscular atrophy were found in the same family (Fig. 19).

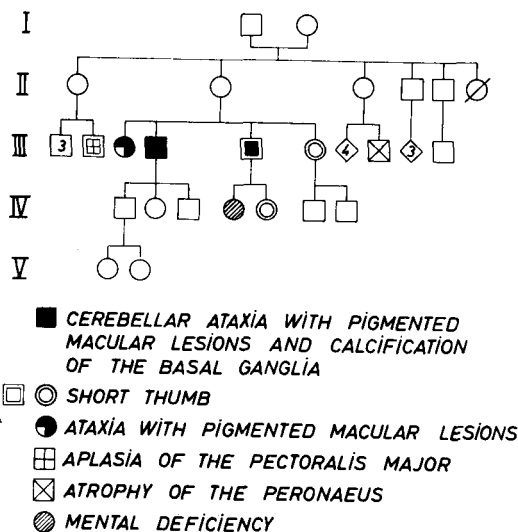


Fig. 19. Cerebellar ataxia with macular lesions and calcification of the basal ganglia. [After Strobos et al. 1957].

CONCLUSION

There are many different forms of hereditary spino-ponto-cerebellar degenerations with many transitional forms, so that it is justified to consider them as a whole, when we discuss their association with a tapetoretinal degeneration.

This association is not rare, as at the present time we know of more than 200 cases. Therefore the one-gene hypothesis seems to be the most plausible. On the other hand, the fact that there exists complex neuroophthalmological forms near purely neurological or purely

retinal forms is also in favour of one gene, which has a polyphenic effect and may vary in its clinical manifestations.

Various forms of tapetoretinal degeneration may be found:

1. Typical or atypical pigmentary retinopathy with or without optic atrophy.
2. An isolated macular degeneration of the Stargardt's type, which is the most frequent manifestation.
3. Mixed forms of tapetoretinal degeneration (central and peripheral).
4. Retinopathia punctata albescens, choroidal sclerosis, and Leber's congenital tapetoretinal degeneration are rare.
5. There may be equivalents, such as ptosis or external ophthalmoplegia.

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