ABIOTROPHIC OPHTHALMOPLÉGIA EXTERNA*

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DYSTROPHIC NATURE OF PROGRESSIVE EXTERNAL OPHTHALMOPLÉGIA

THE various names given to the condition of ptosis and progressive ophthalmoplegia first described by von Graefe (1868), reflect views regarding the undecided aetiology of this condition, *e.g.* chronic progressive nuclear ophthalmoplegia, ocular myopathy, progressive muscular dystrophy involving the extra-ocular muscles, etc. Möbius (1900) had named the condition "progressive nuclear ophthalmoplegia", as he believed there was an absence of the nuclei of the ocular nerves, but Fuchs (1890), 10 years earlier, basing his opinion on biopsy material, had propounded a myopathic cause, as did Gourfein (1896). Langdon and Cadwalader (1928) and Jedlowski (1943) thought that the condition was due to degeneration of the nuclei, and McMullen and Hine (1921) suggested defective nuclear development. Trauma (Senita and Fisher, 1958) and autonomic dysfunction (Sunaga, 1927) have also been put forward. In recent years, however, several cases have been reported where biopsy material from the extra-ocular muscles has indicated that the condition is a myopathy (Sandifer, 1946; Beckett and Netsky, 1953; Schwarz and Liu, 1954; Kirschbaum and Holland, 1958) and most recently, on the basis of simultaneous biopsies from the extra-ocular and skeletal muscles, it has been suggested that the myopathy in the ocular muscles is a local manifestation of a generalized muscular dystrophy (Gartner and Billet, 1949; Kiloh and Nevin, 1951; McAuley, 1956; Nicolaissen and Brodal, 1959). Mention might be made at this point of a case reported by Elliot (1939) of generalized muscular wasting associated with ptosis and external ophthalmoplegia. Elliot considered this to be a myopathy though biopsy evidence was lacking. In general, the hereditary features of dystrophic ophthalmoplegia are weak and uncertain (Adams, Denny-Brown, and Pearson, 1953).

Holmes (1956) suggested that the pathology of this interesting condition might be elucidated by electromyography of the affected muscles, and recent

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electromyographic studies (Breinin, 1957; Esslen, Mertens, and Papst, 1958; Papst, Esslen, and Mertens, 1958) have strengthened the evidence indicating that the disease is a myopathy. Fig. 1 is an electromyogram obtained from the levator palpebrae superioris of a patient suffering from muscular dystrophy affecting the lower limbs. The extra-ocular muscles were normal on clinical examination. The potentials are of normal amplitude but their duration is abnormally short. Such a solitary observation must always be interpreted cautiously but appears to support the view that the extra-ocular muscles are involved in muscular dystrophy.

FIG. 1.—Electromyogram of levator palpebrae superioris on upward gaze. The sine-wave represents time and voltage, the wave length being equivalent to 10 m.sec. and the amplitude 100 μ v.

ASSOCIATION OF EXTERNAL OPHTHALMOPLÉGIA WITH RETINITIS PIGMENTOSA

Ptosis and external ophthalmoplegia are rarely associated with retinitis pigmentosa, and in fact only 18 cases have been described in the literature. This syndrome was first described by Barnard and Scholz (1944) who reported four cases. However, as they themselves remarked, it was not at all certain whether other factors were not responsible in their cases for the external ophthalmoplegia. Their first patient had had a thyroidectomy, after which proptosis of one eye had been observed and 3 years later there was "partial limitation of all movement of the right eye and limitation of downward movement of the left eye". No exophthalmos was noted, but the palpebral fissures were "abnormally wide and there was lid-lag". The second and third of their patients had syphilis when first observed, and later developed various neurological abnormalities. Their fourth patient was microcephalic, with bilateral nerve deafness, palatal palsy, and cerebellar ataxia. It would seem that the external ophthalmoplegia in three of these cases could be attributed to thyroid disorder and syphilis, and these should accordingly be excluded from reported cases of the syndrome. The fourth

case, microcephalic and showing various associated neurological abnormalities, should be regarded with suspicion.

Walsh (1957) described six cases of the syndrome, but the six include the fourth case (Case 269) reported by Barnard and Scholz (1944) and one (Case 267) reported by Ford (1952); as mentioned by Walsh himself, a third (Case 270) probably did not belong to the syndrome. Three cases have been reported by Chamlin and Billet (1950), one by Erdbrink (1957) in which there was a family history of ptosis, one by Alfano and Berger (1957) with an associated spastic quadriplegia, and two by Kearns and Sayre (1958) who confirmed the myopathic nature of the lesion by *post-mortem* examination. Thus the number of cases in the literature, in which the clinical authenticity is undoubted, is only eleven.

Excluding the doubtful cases mentioned previously, the features which appear to be most common in the syndrome are shown in the Table (opposite). The majority of cases have been reported in females (eight females as opposed to three males) with the onset of ptosis between "early childhood" and age 13, and that of external ophthalmoplegia between the ages of 12 and 27. (Erdbrink's case is not included, since the ptosis was hereditary and had been present since birth; also one of Walsh's cases is omitted as she had never had ptosis.) When recorded, the pupillary reactions were normal, with the exception of one case described by Chamlin and Billet (1950) where it was thought the child had had a retrobulbar neuritis, and that reported by Alfano and Berger (1957) where there was no perception of light. The visual fields were normal in four cases, not tested in one, showed peripheral contraction in two cases, marked enlargement of the blind spot in one, and the characteristic scotoma of retinitis pigmentosa in one. In the child who supposedly had a retrobulbar neuritis, the visual field of the left eye was normal whilst that of the affected eye showed a dense central scotoma with peripheral depression. In general, the pigmentary disturbance of the retina occurred throughout the fundus but was most marked in the periphery. In three cases the vessels were attenuated and only in one was there questionable pallor of the disc. It is interesting to note that the only patient showing pallor of the disc was also the only one in which the pigment was of the characteristic bone corpuscle type.

Summarizing the above review of previously reported cases, the syndrome characteristically occurs in females with the onset of ptosis in childhood and of external ophthalmoplegia in adolescence or early adult life. The pupils remain normal and an *atypical* retinitis pigmentosa is found with normal vessels and discs. The visual fields may show no defect, peripheral contraction, or the characteristic scotoma of retinitis pigmentosa.

It will now be evident that, in addition to the evidence of microcephaly, syphilis, or thyroid disorder, the cases reported by Barnard and Scholz (1944) did not show the syndrome as presented by cases later reported. Thus, in their first case, there was no ptosis, the onset of ophthalmoplegia occurred at

TABLE
ELEVEN CASES REPORTED BY PREVIOUS AUTHORS

Authors	Date	Sex	Age at Onset of		Pupils	Visual Fields	Fundi
			Ptosis	Ophthalmoplegia			
Chamlin and Billet	1950	Male	11	13	Reactions normal	Slight peripheral contraction	Discs and vessels normal Pigment at macula as well as periphery
		Female	12	14	Right: No reactions Left: Normal	Right: Dense central scotoma plus peripheral depression Left: Normal	Fine and coarse pigment deposits throughout fundi, especially at periphery
		Female	13	26	Not recorded	Normal	Pigmentary changes, fine deposits, mostly at periphery
Walsh	1957*	Female	No ptosis	18	Not recorded	Normal	Vessels normal Pigmentary deposits along vessels in periphery
		Female	8	12	Reactions normal	Normal	Vessels slightly narrowed and questionable pallor of discs Pronounced pigmentary changes (typical bone corpuscle) in periphery
		Female	11	13	Not recorded	Normal	Vessels normal Pigment mottling throughout fundus—no deposits along vessels
		Female	"Early age"	7	Not recorded	Not tested	Normal vessels and discs Atypical pigmentary degeneration of the retina
Erdbrink	1957	Female	"Since birth"	16	Reactions normal	Irregular concentric contraction to 30–35°	Peripapillary atrophy and attenuation of vessels Diffuse macular pigmentary disturbance; scattered clumps of pigment in periphery
Alfano and Berger	1957	Female	No ptosis	?	Semi-dilated and fixed	No perception of light	Discs not atrophic but arterioles markedly attenuated In places, pigment on vessels Salt and pepper appearance at macula Peripheral areas of bone-corpuscle pigment
Kearns and Sayre	1958	Male	20	20	Reactions normal	Huge enlargement of blind spots corresponding to most marked retinal disturbance	Discs good colour and vessels normal Peculiar stippled appearance of pigment epithelium around disc No actual pigment clumping even in periphery Choroidal vessels seen clearly around nerve head
		Male	3	"Shortly after ptosis"	Reactions normal	Characteristic defects of retinitis pigmentosa	Pigment epithelium mottled—most marked around disc but also extended to periphery where clumping occurred Discs fairly good colour and arterioles attenuated

* The first edition of Walsh's book appeared 1947.

age 37, and the fundi showed typical retinitis pigmentosa with narrow arteries and pale optic discs. In their second case, the onset of ophthalmoplegia occurred at age 31, the superior oblique muscles were spared, and only at the extreme periphery of the fundus were there corpuscular-like deposits of pigment. Their third case had abnormal pupillary reactions, bilateral optic atrophy with extreme attenuation of the vessels, and gross

macular degeneration in both eyes with a hole in the centre of each affected area. In their fourth case, ptosis became manifest at age 27, and, as mentioned before, there were cranial nerve palsies associated with cerebellar ataxia.

It is ironic that the first cases which drew attention to the association of retinitis pigmentosa and external ophthalmoplegia should have to be excluded from the homogeneous group which can now be recognized as a syndrome.

Case Report

A boy aged 10 was referred because his parents had noticed drooping of the right lid during the preceding 12 months. There had been no variation in the degree of drooping of the lid nor had the child complained of diplopia. There was no family history of ptosis or of neurological or ocular abnormality.

General Examination.—He was a rather pale child with a myopathic facies and bilateral ptosis which was most marked in the right eye (Fig. 2).

Ophthalmological Examination.—The pupillary reactions were normal. The ocular movements were limited in all directions (Fig. 3) and there was no improvement after the injection of prostigmine.

FIG. 2.—Appearance at first examination.

FIG. 3.—Photographs taken after ptosis of right eyelid had been corrected. (Negative of photograph showing eyes on right lateral gaze has been mislaid.)

Both fundi showed a diffuse and widespread fine pigmentary disturbance which was most marked at the periphery and the macula. The discs were of normal colour and the retinal vessels of normal calibre (Fig. 4).

FIG. 4.—Fundus photograph of disc, macula, and periphery of right eye. The left fundus showed a similar appearance.

The visual fields showed bilateral annular scotomata (Fig. 5).

FIG. 5.—Visual fields.

The visual acuity in the right eye was 6/12 (6/9 with correction + 3 D sph., - 1.25 D cyl., axis 30°), and in the left eye 6/36 (not improved by + 3.5 D sph.).

Neurological Examination.—No abnormality.

Electrocardiogram.—Within normal limits.

Blood.—Red and white cell counts normal.

X-rays.—Chest, skull, and right carotid angiogram showed no abnormality.

Cerebrospinal Fluid.—Normal pressure and dynamics with protein 83 mg./100 ml., chlorides 766 mg./100 ml., glucose 72 mg./100 ml., Lange 0000001110.

Wassermann Reaction.—Both blood and cerebrospinal fluid negative.

Serum Proteins.—Albumin 5.4 g./100 ml., globulins 2.3 g./100 ml.; electrophoresis normal.

Serum Cholesterol.—160 mg. per cent.

Electromyography was performed on the right levator palpebrae superioris and the trace obtained (Fig. 6) showed potentials of normal amplitude but of abnormally short duration.

FIG. 6.—Electromyogram of right levator palpebrae superioris on upward gaze. Time and voltage scale as in Fig. 1.

Accordingly, the right ptosis was corrected surgically and the small piece of muscle thus obtained examined histologically (Dr. A. L. Woolf):

“The tissue shows a small piece of lacrimal gland and duct which appear normal, together with the levator palpebrae superioris. The muscle fibres which make up this muscle are much more slender than normal and the tendency to anastomose with one another is much more prominent, but this may simply be a result of the atrophy, so that a great number of fibres come into the plane of section. The sarcolemmal nuclei are enlarged, especially in the longitudinal axis of the muscle fibre. The cross striations have disappeared. The fasciculi are unduly separated from one another by loose connective tissue which contains an excess of histiocytes of the myophage type” (Fig. 7).

Progress.—The child has been followed for 14 months with no change in his condition.

FIG. 7.—Muscle excised on correction of ptosis. Haematoxylin and eosin. $\times 750$.

DISCUSSION

The heredo-degenerative diseases of the central nervous system may affect a single tract, such as spastic paraplegia, or a combination of tracts and nuclei, as in Friedreich's ataxia, giving rise in this way to the classical syndromes. Even these syndromes may not repeat themselves in a stereotyped manner within a particular family, and their genetic inter-relationship is demonstrated by the occasional occurrence of two of the hereditary disorders in the same family, *e.g.* spastic paraplegia and muscular dystrophy (Philip, 1886), Friedreich's ataxia and spastic ataxia (Bell and Carmichael, 1939), Friedreich's ataxia and Charcot-Marie-Tooth disease (Roth, 1948). It is not therefore surprising to find the occasional association with most of the various heredo-degenerative diseases of both retinitis pigmentosa and ophthalmoplegia: *e.g.* retinitis pigmentosa with Friedreich's ataxia (Zonca, 1938), spastic paraplegia (Clauss, 1924), and the Laurence-Moon-Biedl syndrome (Laurence and Moon, 1866), and ophthalmoplegia, partial or complete, with Sanger Brown's ataxia (Wilson, 1954), Friedreich's ataxia (Barrett, 1927) and Marie's ataxia (Franceschetti and Klein, 1949).

This belief, that the heredo-familial disorders are all different manifestations of a single basic defect (van Bogaert, van Leeuwen, Babel, Franceschetti, Klein, and Montandon, 1948), is further borne out by the case reported by Alfano and Berger (1957) where a spastic quadriplegia accompanied the syndrome of retinitis pigmentosa and ophthalmoplegia externa, and by the report of a family where retinitis pigmentosa was accompanied by cerebellar ataxia and spastic paraplegia (Froment, Bonnet, and Colrat, 1937). It is interesting in this context to note that the original cases of Laurence and Moon (1866) later developed spastic paraplegia (Hutchinson, 1882; Nettleship, 1907, 1908). Mention might be made at this point of a case reported by Reinberg (1950) where retinitis pigmentosa was associated with muscular dystrophy. (It is possible that electroretinography, as suggested by Björk, Lindblom, and Wadensten (1956), would reveal retinal degeneration in the hereditary ataxias long before it was clinically apparent as an atypical retinitis pigmentosa.) The family reported by Stephens, Hoover, and Denst (1958) is genetically significant: four members of one generation showed features of Friedreich's ataxia and Charcot-Marie-Tooth disease associated with external ophthalmoplegia, the ophthalmoplegia having been shown at autopsy to be due to dystrophy of the extra-ocular muscles.

It has long been known that heart failure is common in Friedreich's ataxia, and this would seem to be due to progressive degeneration of the heart muscle (Greenfield, 1954). The myocardium was involved in the case of progressive external ophthalmoplegia reported by Gartner and Billet (1949), and in the case reported by Sandifer (1946) there was bundle-branch block. Two cases of retinitis pigmentosa and external ophthalmoplegia have been reported where heart block was present and in fact caused the death of one patient

(Kearns and Sayre, 1958). Salleras and de Zárata (1950) have remarked on the association of myopia and external ophthalmoplegia, three of their cases having "cardiac malformations", and it is interesting to note the presence of —9 D myopia in the case reported by Gartner and Billet (1949), though this myopia was not familial.

Pupillary sparing in the syndrome of retinitis pigmentosa and external ophthalmoplegia has been emphasized (Walsh and Eisenlohr, 1959), and this fact is offered as evidence of a muscular abiotrophy by Mann (1957) since the sphincter and dilator pupillae are ectodermal in origin. When Gowers (1902) first suggested the term abiotrophy he included muscular dystrophy, Friedreich's ataxia, and heredo-cerebellar ataxia, attributing the process to "a degeneration or decay in consequence of a defect of vital endurance", but it has recently been suggested (Sorsby, 1955) that abiotrophy is in fact a congenital defect where the tissue has not developed fully, this failure of development becoming evident later in post-natal life, *e.g.* as retinitis pigmentosa. Cogan (1956) proposed the term "abiotrophic ophthalmoplegia externa" for the condition variously known as chronic progressive ophthalmoplegia externa, chronic nuclear ophthalmoplegia, etc., and, if the evidence of a dystrophic pathogenesis is accepted, there is certainly some justification for its use, however much new names are to be deprecated. It would seem, however, that on the evidence presented in this paper, greater benefit from the term would be obtained if it were applied to the syndrome of atypical retinitis pigmentosa and external ophthalmoplegia which has this striking link with the various heredo-degenerative abiotrophic disorders of the central nervous system. It would then of course be consistent to include within this group external ophthalmoplegia occurring in any *forme fruste* of the heredo-familial disorders.

SUMMARY

A case is reported in which external ophthalmoplegia is associated with atypical retinitis pigmentosa. The relevant literature is reviewed.

Since this syndrome provides a link between various abiotrophic disorders, it is suggested that the term "abiotrophic ophthalmoplegia externa" is apposite and should, moreover, also be applied to ophthalmoplegia occurring in any variant of the heredo-degenerative diseases.

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ADDENDUM

Since this paper was written a further case has been reported by Thorson and Bell (1959) whose patient showed dystrophic external ophthalmoplegia (confirmed by electromyography and biopsy), atypical retinitis pigmentosa, and a cardiac conduction defect. They concluded that the symptom complex was abiotrophic.