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CHRONIC PROGRESSIVE OPHTHALMOPLEGIA EXTERNA, OR "INFANTILE NUCLEAR ATROPHY"* (Moebius)

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IN Volume I of "Neurology of the Eye," published in 1900, Wilbrand and Saenger grouped as a clinical entity certain cases of external ophthalmoplegia, which, in their opinion, had definite characteristics, which separated them, not only from the congenital cases of this affection, but also from the cases definitely due to some toxic cause, or to syphilis, or associated with wider spread manifestations of nervous disease.

These cases, according to these authors, have the following characteristics:

There is a gradual onset, generally in infancy or early childhood, more rarely in later life, of a bilateral, progressive paralysis of the external eye muscles, not associated with other signs of disorder of the nervous system, nor with fever. The disease may come to a standstill permanently, or for long periods, at any stage of its

* A paper read before the Sections of Neurology and Ophthalmology of the Royal Society of Medicine, on March 10 and 11, 1921.

development, but generally ends in complete, or nearly complete, external ophthalmoplegia. In most cases both sides are affected from the beginning, but sometimes it appears on one side long before the other; often the two sides are unequally affected in the early stages.

Ptosis is generally the first sign, and may be for a long time the only one. When the muscles of the eyeball become affected diplopia may be complained of, but this symptom is only rarely noted, principally because the paralysis develops gradually, and often symmetrically, on both sides, and because it frequently comes on in childhood before the function of binocular vision is fully developed.

The progress is often extremely slow, and thirty or forty years may elapse between the appearance of the first symptoms and the development of complete ophthalmoplegia.

The general health is not affected, and there is a noteworthy absence of signs indicating disease in other parts of the nervous system.

Since the 32 cases collected by Wilbrand and Saenger few similar cases have been reported.

In 1912 one of us (W. H. McM.), brought a case which seemed to be of this nature before the Ophthalmological Society, and recently the other (M.L.H.) has seen two similar cases, one of which was shown at a meeting of the Ophthalmological Section of the Royal Society of Medicine in 1919, while the other is recorded here for the first time.

We propose to describe these three cases together, and then to discuss their probable origin, and the various views that have been held as to their relationship with some other similar conditions, as it is by no means generally admitted that Wilbrand and Saenger are justified in regarding such cases in a separate group.

CASE 1.—Wm. L——, seen first in 1911, at the Royal Westminster Ophthalmic Hospital; he was then aged 32.

History.—There were no signs of paralysis in early childhood. When two years of age he had one fit of "convulsions," but no other illness of any importance until he was five or six years old. He then began to suffer from headaches, on account of which he had to be kept away from school a good deal. These headaches gradually became worse. The pain was usually on the left side of the forehead, but occasionally on the right. The attacks usually lasted about half a day, recurring three or four times a week. They were not accompanied by vomiting.

When eight years old he had left ptosis, lasting one month, and recovering spontaneously. According to his mother, he had diplopia for a time when he was 7-9 years old. When 9 years old (in May, 1888), a year after the first transient attack of

ptosis, the drooping of the left lid recurred. This time the paralysis was preceded by an aching pain in the left brow for two or three days. About a month later he was taken to St. Thomas's Hospital* where the following conditions were noted: Incomplete ptosis on the left side, and defective action of the L. internal rectus. On looking at a close object the L. eye diverged. No other defect of ocular movements. Pupil reactions normal. No fundus changes.

Eleven days later there was R. ptosis also, the right lid being slightly lower than the left; there was still much pain in the left temple.

Nine days later he was admitted (on June 27, 1888), under Mr. Nettleship. The right ptosis became much less while he was in hospital, and after five weeks it was very slight. Shortly after leaving the hospital he had an illness which was called "rheumatic fever." After this the ptosis became worse, so that he had to throw his head back in order to see.

Two years later, when 11 years old, he went to St. Thomas's Hospital again. By that time he had incomplete ptosis on both sides, rather more marked on the right side. Both eyes were almost immovable, the right more so than the left. There was hardly a trace of convergence. The pupils were normal, and he could read J.1. Patellar reflexes were normal.

Almost complete bilateral ophthalmoplegia externa had therefore developed in three years from the first onset of ptosis.

When 12 years old, he was seen by Mr. Johnson Taylor, who found no change in the condition of the ocular muscles, but noted that there was, in addition, slight weakness of the "lower" facial muscles, especially the right, and some weakness of accommodation.

R.V. 5/18. c. −0·75 sph. =5/6. c. +1=J.1.
L.V. 5/5 & J.6. c. +2=J.1.

The patient states that the ptosis became rather less marked when he was about 14-15 years old, since which time there has been no change. There is a history of some difficulty with micturition 3-4 years before 1911, lasting 3-4 weeks only, viz., some difficulty in starting.

Family History.—Father a "rackety" man, who drank. Died "paralysed." Mother died of "cancer" in 1914. Had following family: 1. Girl. Born 1876. Has some defect of vision. 2. Boy. Born 1877. No defect of vision. 3. Early miscarriage. 4. Patient. Born 1879. 5. Still-born at 8 months. 6. Boy. Died at 6 months from "convulsions."

Patient has following family: 1.—Girl. Born 1906. Has slight concomitant squint. She has been examined by W. H. McM. and

* We are indebted to Mr. A. C. Hudson, who in 1912 was Ophthalmic Registrar to St. Thomas' Hospital, for looking up the notes of this case, and sending an abstract.

found to have no palsy. 2. Boy. Born 1907. Has "infantile paralysis" (?) in R. forearm: onset aet. 8-9 months with "bad cold." 3. Boy. Born 1905. No defect. Patient knows of no deformity or defect of nervous system in any other relations.

Condition in 1912. Incomplete ptosis R. and L., rather more on R. side than on L. As a rule about half the cornea was covered in the right eye and a trifle less in the left. The ptosis varied in degree to quite a noticeable extent. It was least early in the day, and increased towards night. He was seen at 10 a.m. one morning with the whole of the pupillary area uncovered in both eyes. There was marked compensatory contraction of the frontalis on both sides. The skin of the lids was smooth, with no horizontal folds. When looking forwards horizontally the head was thrown very slightly backwards. The eyeballs were almost immobile. Measurements with the perimeter showed the following range of movement:

	R. eye		*L. eye.*	
Upwards ...	0°	18°	6°	24°
Downwards	18°		18°	
Outwards	2°	10°	6°	14°
Inwards	8°		8°	

No appreciable convergence occurred on looking at a near object. The left eye was then used for fixation. The pupils were equal and reacted to light, occasionally showing rather marked hippus. They also contracted when patient fixed a near object, although there was no appreciable convergence.

R.V.=6/60 −5 sph.=6/9.

L.V.=6/18 −2 sph. −1·5 cyl. ax. hor.= 6/6 pt.

With full correction he could read J1. at a distance of 8" with slight difficulty. His accommodation was, therefore, fairly efficient. He had no diplopia under normal circumstances, but Maddox rod test could be carried out with some difficulty, and showed exophoria of 15° in distant vision and of 7° at a distance of 12". Instillation of cocain caused dilatation of the pupils and slight elevation of the lids, with the appearance of fine transverse folds in the skin.

Ophthalmoscobic Appearances.—In both eyes there was a "large physiological cup," enough to raise a suspicion of glaucoma (but T.n. and V.n.). No other abnormality of fundus in either eye. In the left eye there was a peculiar kind of irregular lental astigmatism, apparently due to a change of form the inverse of lenticonus.

Visual fields, as examined on a McHardy perimeter, showed no defect.

Dr. Gordon Holmes examined him at this time, and was unable to detect any other signs of disease of the central nervous system.

Later History.—In February, 1918, this patient returned to hospital, and was found to have glaucoma in the right eye, with a sector scotoma in the upper nasal quadrant. A trephine operation was performed with very satisfactory result.

Present Condition (February 24, 1921): Pupils react to light; some hippus; contract well on accommodating. Ptosis is rather less marked than before, and is less in the right eye than the left. The whole of the pupil is uncovered in both eyes. Patient can voluntarily raise lids so as to uncover nearly all the right cornea and 4/5ths of the left. On asking him to look up quickly the lids are quite noticeably raised so that the sclera is exposed above the R. cornea and the L. cornea almost wholly uncovered. There are numerous fine transverse folds in both upper lids, more marked on the right side than on the left, and there is also a well marked tarso-orbital fold.

Range of Movement.		*R. eye.*		*L. eye.*	
Vertical	Upwards	6°	16°	7°	19°
	Downwards	10°		12°	
	Lateral	8°		10°	

There would therefore seem to be a definite increase in the range of upward movement in the right eye, but other movements are either stationary or, if anything, slightly diminished.

R.V. c. −6 sph. ⊂ −1·5 cyl. ax. hor. = 6/9 pt.

L.V. c. −4 sph. ⊂ −2 cyl. ax. 170° = 6/6 pt.

Sector scotoma R. eye, upper nasal, including blind spot.

Both discs deeply cupped. T.n. Left field normal.

CASE 2.—Rose B.——, aged 18 years, was brought to the Royal Westminster Ophthalmic Hospital on May 28, 1919, for an opinion as to whether anything could be done to improve her vision by raising the lids.

It was stated that four years previously both upper lids had begun to droop, and at the same time she was noticed not to be moving her eyes properly. The onset was very gradual, and did not occur after any particular illness. She was taken to Moorfields in September, 1915, where the condition of ptosis and external ophthalmoplegia was noted, but her fundus was not examined in that rather busy time. Her eyes had never previously been examined, and the father declared that her vision had always been good. She has always had a very violent temper and been very obstinate, and

her father states that he has sometimes been frightened that she would "go like her mother."

Family History.—Father alive and well. No specific history. Mother died in 1918, in an asylum, of "pulmonary tuberculosis," after being an inmate for seven years.

Her family was as under.

1st child.—Died at age of 4 months. 2nd child.—Miscarriage. 3rd child.—Brother, alive and well, aged 20. 4th child.—Patient, aged 18. 5th child.—Brother, alive and well, aged 17. 6th child.—Sister, alive and well, aged 15. 7th child.—Sister, alive and well, aged 13. 8th child.—Brother, alive and well, aged 11.

Present State.—Patient is a fairly well developed girl, with nearly total external ophthalmoplegia. Ptosis on the right side is almost complete, on the left it is slightly less. In both eyes the range of movement is extremely limited, as shown below.

Range of Movement.		*R. eye.*		*L. eye.*	
Vertical	Upwards	3°	5°	5°	9° (down and in)
	Downwards	2°		4°	
Lateral	Outwards	8°	13°	2°	12°
	Inwards	5°		10°	

To day there is even less movement than indicated by above measurements. The right eye is now almost fixed and inward movement of left eye is not more than 5°. Pupils are equal and active to light and accommodation. There is no weakness of accommodation. No diplopia is complained of. Patient fixes with left eye. There is no convergence. R.V. 6/18, under mydriatic c.+3 sph. ⊂ +1 cyl. ax. 90°=6/18. L.V. 6/12 c. +4 sph.=6/12. Post-mydriatic correction is +0.5 sph. less. With this, patient reads J.2. at 6″ with each eye. Both fundi show scattered fine pigmentary changes of old retino-choroiditis. No other stigmata of syphilis. Wassermann reaction is negative. Dr. Gordon Holmes, who kindly examined the patient in 1919, reported that her reflexes generally are diminished, but otherwise found no changes, apart from the ocular condition.

Treatment.—The patient has been given her correction, as above, fitted into a pair of "orbital ridge" spectacles, as recommended by Mr. Rayner Batten. These she has found very satisfactory, and does not like to be without them. The chief difficulty with them appears to be the equal adjustment of the pressure on the upper lids, and the retention of the curl of the side-pieces in exactly the right position. If this is altered in the slightest way, the pressure

of the "ridges" becomes unequal, and one lid may droop, and the other become sore.

CASE 3.—Was first seen in November, 1919, at a provincial school clinic, a girl aged 12, with the following history:—According to the mother, the eyes were "beautiful" until the child was 7 or 8 years of age, when she noticed that she seemed unable to open her eyes properly if tired or run down. She took her to see Mr. Hugh Thompson, who was then in charge of the clinic, in June, 1917, when she was aged 10. He noted "photophobia," but no affection of the ocular muscles at that time. The drooping has become more constant since then. The mother, had not herself noticed any loss of movement in the eyeballs, but said she had often noticed that the child moved her head round a good deal when looking at anything. The patient has suffered a lot from headache for a long time, but had never had any serious illness, though always rather delicate.

Family History.—Mother, aged 33, alive and healthy. Father, aged 31, killed in the war. Was a healthy man. First child, the patient. Second child, girl, aged 8. Has R. convergent concomitant strabismus, since infancy. No other affection of ocular muscles. No other relatives known to be affected in same way as patient.

Present State.—Patient is a fairly well developed, but somewhat anaemic girl, brought to the clinic on account of the drooping of the lids, above noted, and frequent severe headaches. She has almost complete ptosis, slightly greater right than left. On right side two-thirds of the pupillary area are covered. The movements of the globes are very restricted in all directions, the outward movement being the best in both eyes.

Range of Movement.		*R. eye.*		*L. eye.*	
Vertical	Upwards	12°	17°	12°	19°
	Downwards	5°		7°	
Lateral	Outwards	20°	25°	15°	25°
	Inwards	5°		10°	

There are no fundus changes. R.V. c. +1 sph. ⊃+0.5 cyl. ax. 180°=6/6 and J.1 at 5". L.V. c. +0.75 sph. ⊃+0.75 cyl. ax. 180°=6/6 and J.1 at 5". There is no diplopia at 12". She fixes with left eye and has no convergence. Wassermann reaction negative. No stigmata of syphilis. Dr. Gordon Holmes has reported that he can find no evidence of other lesion of nervous system, apart from eye condition.

Referring again to the literature, in addition to those collected

by Wilbrand and Saenger, similar cases have been reported by Beaumont, Ayre and Altland. Beaumont's cases, twelve in number, are of considerable interest. They were characterized by being :—1. Familial; 2. Never congenital; 3. Slowly progressive; 4. Never fatal.

Ayre's patient was a boy, whose maternal grandfather had been similarly affected.

Altland's case is described in a paper entitled "A contribution to the study of Chronic Progressive Ophthalmoplegia." The onset was at the age of 22, with ptosis of the right upper lid. Twenty years later ptosis of the left upper lid occurred. When seen at the age of 51 there was complete ptosis of the right upper lid, incomplete ptosis of the left upper lid, and the globes were immovable. "There were no manifestations nor history of syphilis, and there were no marked anomalies in the rest of the nervous system."

In 38 of the cases mentioned above the age of onset has been recorded. In 20 cases it was before the age of 20 years, in 12 between 21 and 30, and in 6 only was it over 30.

As regards the question of syphilis, in none of our cases has the Wassermann reaction been positive, and none of the patients has shown any of the "Hutchinson triad" of signs of the inherited disease. In the second case, however, there are definite evidences of an old diffuse retino-choroiditis, which has affected the vision to some extent. This had been entirely overlooked, prior to her examination in 1919, and hence is probably of long standing. The patient's mentality also appears rather below normal, and she is subject to such violent fits of temper that some wider spread cerebral degenerative changes may be suspected.* In neither of the other cases was Dr. Gordon Holmes able to find other evidence of disease of the nervous system.

The question arises as to whether this class of case is to be considered in a separate group. There are cases of congenital ocular palsy presenting a similar clinical picture in which there is evidence that nuclear defects are the cause. Moebius grouped together, under the name of Infantile Nuclear Atrophy, some cases of ophthalmoplegia externa developing in childhood with a number of others of congenital origin.

Henry Cooper, in 1910, described a family in which several cases of congenital external ophthalmoplegia had occurred, attributing the condition to nuclear atrophy, but without giving reasons for so doing.

Bradburne, in 1912, described 16 cases of hereditary ophthalmoplegia externa, occurring in five generations, and while he ascribed

*See addendum at end of paper.

the condition to "arrested muscular development," Mr. Beaumont, on the other hand, pointed out that it was quite possible that these cases might be entirely analogous with those coming on later in life.

Then again Crigler, in 1914, described a case of ptosis and external ophthalmoplegia, without affection of the intraocular muscles, in a patient aged 60, in which the condition had, as far as could be ascertained, "always existed." This case he also attributed to lack of development of the nuclei supplying the ocular muscles.

In the absence of post-mortem examination, or of some operative interference with the orbital muscles for some reason or other, it may be impossible to say whether such congenital cases are due to imperfect muscular development, as in the case described by Heuck in 1879, or to imperfect nuclear development, but it would certainly seem probable that some, at least, are due to the latter cause. Few examinations have hitherto been made in such cases, but Siemerling, in a case of congenital ptosis, found an atrophic condition of the third nerve nucleus, and Heubner has also shown that this condition, in one case, was associated with an "aplasia" of the corresponding nuclear region.

Gowers, however, in his "Diseases of the Nervous System," does not very definitely dissociate "chronic progressive ophthalmoplegia" from other forms of ophthalmoplegia, caused by syphilis, etc. He does say, however, that "in some cases, and in younger subjects, the degenerations seem to be due to deficient vital endurance of the structures concerned, varying in degree so as to be manifested at birth or not till later life."

It may be pointed out here that, while Wilbrand and Saenger excluded all congenital cases from this group, differentiating these from the fact that they are non-progressive, it is difficult to get accurate records of the range of movement in such cases, which one can compare with another record taken after a sufficiently long interval. It may well be the case that if such patients were seen at the earliest age at which the range of movement could be noted on an arc perimeter, and were then kept under observation for twenty or thirty years, in many cases some increase in the defect would be noticed. The cases could then definitely be included in the group under consideration.

Oppenheim has pointed out that there is a closely allied rare condition, which is known as "The Infantile Form of Progressive Bulbar Paralysis," which is characterized by its hereditary and familial tendencies, and has been found to occur in brothers and sisters whose parents are closely related. In this disease the nuclei of the various cranial nerves are progressively, though slowly, affected, first those of the ocular muscles, and later those of the pharynx and larynx.

On the whole it would appear then that there is no very sharp dividing line between many cases of congenital ophthalmoplegia externa and some of those developing later in life, or between the latter and the condition of "hereditary progressive bulbar paralysis" mentioned above. All may be due to an "abiotrophy" or "lack of inherent vitality" of the specialized cells of the cranial nerve nuclei involved, the time of onset depending on the degree of vitality with which these cells were originally endowed.

Though Siemerling states that this affection may be entirely localized, there appears to have been no pathological examination of any uncomplicated case of the condition under consideration. Oppenheim, in his textbook published in 1911, says that in none of the cases of chronic external ophthalmoplegia, up to then examined post-mortem, had the affection been limited to the nuclei of the ocular nerve, as stated by Siemerling. Clinical experience also shows, he states, that in the majority of cases the chronic ophthalmoplegia is mainly the precursor or the local symptom of a complicated disease of the central nervous system, such as tabes, general paralysis, combined column disease of the spinal cord, disseminated sclerosis, an atypical form of progressive bulbar paralysis, and even progressive muscular atrophy or chronic anterior poliomyelitis. But in view of the series of cases recorded by Willbrand and Saenger, and those of Beaumont, Altland, etc., it is important, from the point of view of prognosis, in the interest of the patient and his or her relatives, to realize that in quite a number of these rare cases there may be no threat to life, and no development of further serious organic disease, and to lay stress on this fact, even though there may be no good pathological ground for separating such cases from those in which the degenerative changes in the nervous system are wider spread, it may be useful to regard them in a separate group, though we may also class with them some, at any rate, of the congenital cases.

The diagnosis of this group can, in the first place, be only a tentative one, dependent on the finding of no wider spread lesions.

The most useful form of treatment is the palliative one indicated in the report on Case 2 above, viz., by some form of lid-raising spectacles.

Addendum.—Since the above was written, Dr. Gordon Holmes has kindly re-examined Case 2, and reports that, in addition to the affection of intraocular muscles, "there is definite weakness of various muscles of limbs and face." Hence, this case does not really come into the group under consideration, but definitely belongs to the group in which there are wide-spread manifestations of disease of the central nervous system.

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DISCUSSION ON OCULAR PALSIES*

R. FOSTER MOORE said " I have a few words only to say upon two somewhat uncommon causes of ocular palsy.

First Graves's disease, and secondly spinal anaesthesia.

As regards the first, there can be no doubt, I take it, that the extreme pushing forward of the eyeball which occurs in some cases, is responsible mechanically for some restriction of the complete amplitude of movement of the eyes; it is, however, clear that in some cases another factor or other factors come into play. Cases in which a definite muscular weakness appeared to be present are reported by:—

Lang and Pringle (*Trans. Ophthal. Soc., U.K.*, Vol. VI, p. 105)
West (*Trans. Ophthal. Soc., U.K.*, Vol. VI, p. 76)
Ballet (*Rec. d'Ophtal.*, 1888, p. 321)
Bristowe (*Brain*, 1886, p. 313)
Warner (*Med. Times and Gaz.*, 1882, p. 540)
Maude (*St. Bartholomew's Hospital Reports*, 1892, Vol. XXVIII)
Voss (*Deutsch. med. Wochenschr.*, August 13, 1903)
and others.

In none of these cases has there been involvement of the internal branches of the third nerve.

I have recently had occasion to explore the orbit, in the case of a woman with Graves's disease, in whom there was general limitation of eye movements, and in whom the eyes were so proptosed that the eyelids on one side could by no means be brought together over the cornea, even under a general anaesthetic, and it was evident that if nothing were done, this eye in particular would be lost from corneal sloughing.

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