Congenital ophthalmoplegia

A myopathic aetiology in two siblings

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The two members of a two sibship family, a boy aged 15 years and his sister aged 11 years, show a striking limitation of ocular gaze believed to have been present from birth. There are no other comparable cases in the family. Both patients were floppy infants and the boy has in recent years developed limb girdle weakness of myopathic type. There is also a familial abnormal aminoaciduria and the possible relationship between this, the ophthalmoplegia, the floppiness at birth, and the features of limb girdle myopathy is discussed in detail in another communication (Hurwitz, Carson, and Allen, 1968). In this paper evidence is given suggesting that the congenital ophthalmoplegia is due to a myopathic process.

CASE REPORTS

The parents of a non-consanguineous marriage show no abnormal signs and the mother was healthy during both pregnancies. The children were floppy at birth and in each a diagnosis of amyotonia congenita was made. There was convergent squint at birth and clinical notes from the Children's Hospital (Professor F. M. B. Allen) suggest that the ocular signs were maximal in the early years of life and probably from birth. Motor development was delayed. The boy had great difficulty in sucking in the first few months of life and had three episodes of pneumonia before the age of 2 years. On present examination both are of average intelligence and are normal in stature. They have rather expressionless faces and do not wrinkle the forehead when attempting to look upwards, but there is good movement of the facial

muscles on eyelid closure or when they are asked to whistle or blow out their cheeks or smile. The tendon reflexes are decreased and there is limb girdle weakness in the boy but not in the girl. The boy has mild talipes and the girl a high arched palate. There are no other significant deformities. The Wassermann test is negative in both parents and in the patients and routine laboratory tests showed no abnormality. The ocular and otological features are now given in more detail.

CASE 1 J.F., is a boy aged 15 yr. Visual acuity is 6/6 right and left eye. The refractive index after Mydrilate is $R. +2.00$ $\downarrow 90^\circ$ $L. +2.75$. The optic fundi and optic discs are normal in appearance. The pupils are equal, central and circular, and react briskly to light and on accommodation. Ptosis is not present. There is a manifest left convergent squint; corneal reflection and prism cover test measure Eso 50 Δ . Fixation in the primary position can be maintained by the left eye, with the consequent tripartite visual field. Figure 1 illustrates the ocular movements. Adduction in either eye is full. Abduction in either eye is restricted to the midline. There is neither retraction of the globe nor variation of the width of the palpebral fissure on horizontal movements. Elevation is absent in either eye, though the upper lid is retracted on attempted upward gaze. Bell's phenomenon is absent. Depression is limited in either eye. Reflex following or passive movements of the head do not increase ocular mobility. The major amblyscope shows alternate suppression. Absence of simultaneous perception prevents a Hess screen record. Diplopia is not elicited when the deviation is corrected with prisms or red and green goggles.

FIG. 1. The range of ocular movement in Case 1. Adduction of each eye is normal, while there is marked or complete limitation of movement in all other directions of gaze. (a) Looking right. (b) Looking left. (c) Looking up. (d) Looking down.

Case 1 was examined otologically by Mr. G. D. L. Smyth. There was mild perceptive hearing loss in the left ear. There was no positional nystagmus. On caloric testing by the method of Fitzgerald and Hallpike there was no response with water at 44°C in either ear, but with water at 10°C instilled in the left ear there was a wide amplitude slow beating nystagmus away from the stimulated ear which lasted for 110 sec. The patient complained of a 'drifting' sensation for as long as the nystagmus lasted and as the nystagmus ended he stated that the sensation ceased. There was no response with water at 10°C in the right ear.

CASE 2 K.F., is a girl aged 11 yr. Visual acuity is 6/6 right and left. The refraction, optic fundi, and optic discs are normal. There is no ptosis. A manifest alternating convergent squint for distance is present. The visual axes are aligned for near vision. Restriction of ocular movements is in all respects similar to Case 1, except that slight elevation is possible. Likewise there is no retraction of the globe or variation in the width of the palpebral fissure on horizontal eye movements. This girl was also examined by Mr. G. D. L. Smyth. There is mild left perceptive deafness. Left bone conduction threshold is elevated to 20 db at all frequencies and speech discrimination on the left is reduced to 80°. There is no positional nystagmus. Caloric testing (on two occasions) with water at 10°C produced no response in either ear and no subjective sensation.

CASE 1: ELECTROMYOGRAPHY

This examination was carried out by Mr. I. M. Strachan. A DISA machine was used, and the left lateral rectus, medial rectus, and inferior oblique muscles were separately sampled with concentric needle electrodes, 0.20 mm diameter, inserted subconjunctivally after local anaesthesia with 1% amethocaine. The recti muscles showed firing of motor unit potentials in the 'resting' position, but the amplitude of the potentials from the medial rectus was greater than those from the lateral rectus. Attempted abduction increased the number and amplitude of potentials in the lateral rectus and decreased those in the medial rectus, while adduction increased medial rectus motor activity and decreased lateral rectus motor activity. Thus the normal pattern of reciprocal innervation was preserved (Fig. 2). It is noteworthy that, although there is no clinical evidence of abduction beyond the midline, the amplitude and the number of motor unit potentials are increased during attempted abduction while motor potentials disappear on adduction. No electrical activity was recorded from the inferior oblique muscle. Electromyographic examination of the right frontalis muscle was within normal limits.

CASE 1: OPERATIVE FINDINGS

Under a general anaesthetic on 21 August 1967, forced duction tests showed a minor degree of restriction in all directions except abduction. When detached from the globe both the medial and lateral recti of the right eye could easily be extended by traction so that biopsy specimens were obtained from the muscle bellies. These muscles appeared normal in bulk and colour and in other

FIG. 2. J.F. Electromyography of left rectus muscle showing a normal pattern of reciprocal innervation. The left lateral rectus muscle shows motor units with the eye in the primary position. When the patient attempts abduction (no movement of the eyeball occurs) there is an increase in amplitude and in number of motor units firing. During adduction the muscle becomes electrically silent. The electromyogram is not the continuous recording more commonly studied by other workers but represents an interrupted sweep.

respects. Their insertions were normally sited and no abnormal muscular or fascial connexions were present. The right medial rectus was recessed 5 mm, and the right lateral rectus was resected 7 mm. Post-operatively, the residual manifest left convergent squint measured 12° by corneal reflections.

CASE 1: HISTOPATHOLOGY

MATERIALS AND METHODS Biopsies of the right medial and lateral recti were carried out under general anaesthesia at the time of the definitive operation to correct squint.

Light microscopy Tissue was fixed in Helly's fixative for approximately 12 hr. Longitudinal and transverse sections were cut at 3–5 μ and stained using the following stains: haematoxylin and eosin and Mallory's phosphotungstic acid-haematoxylin. The diameters of 100 fibres were measured using a calibrated micrometer eye-piece. Sections were cut at a distance from the tendinous parts of the muscle.

Electron microscopy Specimens were fixed for 2 hr at 4°C by immersion in 1% osmium tetroxide in mammalian Ringer solution buffered to pH 7.4 with veronal-acetate. After dehydration in ethanol, some portions were stained for 3 hr in 1% alcoholic phosphotungstic acid. The material was embedded in Epon and sections obtained with a Cambridge ultramicrotome, collected on carbon-coated grids and examined with AE1 EM6 electron microscope. Sections from the material not treated with phosphotungstic acid were stained on the grids either with 4% aqueous uranyl acetate followed by 0.3% lead citrate or by a combination of 1% aqueous uranyl acetate and 1% potassium permanganate.

LIGHT MICROSCOPY

Right medial rectus muscle There is a moderate variation in fibre diameter: the maximum diameter is 38 μ , the minimum 5 μ , and the average 16 μ . The outline of the fibres is in general rounded and centrally placed nuclei are apparent; some of these are pale and vesicular.

While no fibre necrosis is apparent, a few of the larger fibres show granular change in the sarcoplasm (Fig. 3). Fatty infiltration is not apparent but there is a slight increase in interstitial fibrous tissue. This is in contrast to the regular arrangements of muscle fibres seen in a control section from a patient of the same age.

Right lateral rectus muscle The appearances are similar to those seen in the medial rectus muscle. Fibre diameter ranged from a maximum of $24\ \mu$ to a minimum of $5\ \mu$ with an average of $13\ \mu$. Granular changes within the sarcoplasm are more frequently seen. 'Ribbons' of hyperchromatic, centrally-placed nuclei are noted in some longitudinally cut fibres. Mild interstitial fibrosis is noted between fibres, but fatty change is not a feature (Figs. 4 and 5).

ELECTRON MICROSCOPY Medial rectus The muscle fibres exhibit varying degrees of damage. Minor changes include variation in myofibril diameter and some splitting of fibrils. Elsewhere there is focal loss of fibrils including both myofilaments and Z-lines, sometimes extending over several sarcomeres (Fig. 6). In such areas the ground substance is increased in amount and is intensely granular. There is an increase in the number and size of mitochondria, many of which are abnormal in shape and show internal disarray. In some areas of more widespread degeneration the fragmented remains of myofilaments and Z-lines can be seen but the normal regular pattern of the sarcomeres is lost (Fig. 7). There are occasional small subsarcolemmal blebs with clear or particulate contents over which the sarcolemma is intact. In other areas,

FIG. 3. *Medial rectus. Medium power view of transverse section of muscle illustrating the variation in fibre diameter, the rounding of fibre outline, and patchy granular change in large fibres particularly (arrowed). Occasional small fibres contain central nuclei. H. and E. $\times 190$.*

FIG. 4. *Lateral rectus. High power view to demonstrate the granular change within the sarcoplasm, the variation in fibre diameter, and moderate interstitial fibrosis. H. and E. $\times 312$.*

mainly related to the perinuclear sarcoplasm, large electron-dense bodies are noted; these are probably lipid in nature and represent autophagic bodies (Fig. 8). Occasional vesicles with a single limiting membrane and clear or particulate contents have the features of lysosomes. Nuclear changes are minor in degree and consist of marked infolding of the nuclear membrane; central or eccentric nuclei are noted. The sarcolemma appears intact in the material examined and no obvious alteration is noted. Surrounding sheaves of collagen fibres are noted and appear abundant around some fibres.

DISCUSSION

Congenital ophthalmoplegia is closely associated with congenital facial diplegia. Thus Danis (1945) reported that bilateral congenital 'pure' paralysis of external ocular movement was associated in 46% of cases with facial palsy and in 40% with somatic malformations, while bilateral horizontal gaze paralysis was associated in 89% with facial weakness and 82% with gross malformations or paralysis of other cranial nerves. Similarly Henderson (1939) in his review of 61 cases with the congenital facial

diplegia syndrome reports 15 instances of severe external ophthalmoplegia and bilateral abducens paralysis in 29 others. The whole spectrum of involvement can be appreciated when it is realized that the facial weakness may be so slight as to be overlooked (Ingram, 1959), or congenital facial diplegia may be associated with unilateral lateral gaze paresis (Henderson, 1939), or congenital unilateral ocular paresis may be associated with facial paresis (Danis, 1945). Ptosis is not frequently described in the cases of Henderson (1939), Danis (1945), and Evans (1955). The eponym Möbius syndrome is generally applied to congenital facial diplegia, but it can be appreciated that it might be considered appropriate where oculomotor signs predominate, or even with paralysis of other muscles supplied by cranial nerves as in the cases of congenital flaccid bulbar palsy described by Graham (1964). Our present cases have severe congenital ophthalmoplegia without ptosis and only slight, if any, facial weakness. There are no significant

FIG. 6. *Medial rectus. Electron microscopy. There is an increase in the number of mitochondria (M), some of which are increased in size (M₁). The subsarcolemmal space is increased and fibrils show focal fragmentation. The fibrils are widely separated. S = normal sarcolemma. L = lysosome. × 11,000.*

FIG. 5. *Lateral rectus. The longitudinal fibres contain 'ribbons' of hyperchromatic nuclei both in the centre and beneath the sarcolemma. The presence of central nuclei within small atrophic fibres is noted and interstitial fibrosis is moderate. Granular change is evident within the sarcoplasm of many fibres. H. and E. × 367.*

FIG. 7. *Medial rectus. Electron microscopy. The myofibrils show obvious focal degeneration and fragmented Z-lines are present (Z). Small vesicles are apparent in this region (V). Mitochondria (M) vary in size. N = nucleus. S = sarcolemma. × 6,875.*

deformities, although there is some talipes in Case 1 and a high arched palate in Case 2 and both cases have mild hearing loss as occurs in a few of the patients described by Henderson (1939). For the purpose of this discussion the cases we describe will be considered descriptively allied to the oculofacial signs of the classical Möbius syndrome (Möbius, 1892).

NATURE OF THE EYE SIGNS IN THE PRESENT CASES
(a) Electromyography The ocular electromyogram (EMG) shows preservation of the normal reciprocal innervation. This is in contrast to the EMG in the detailed study in a man aged 26 with ocular paresis reported by Van Allen and Blodi (1960). These workers found motor action potentials in all muscles tested and a striking violation of normal reciprocal innervation. The electrical pattern and their finding of normal histology on subsequent biopsy of the left external rectus led them to postulate a supranuclear (brain-stem) lesion to account for the ocular weakness. Krüger and Friedrich (1963)—in a study (which included electromyography) of five patients with congenital oculo-facial ophthalmoplegia occurring in three generations of one family—also considered a supranuclear lesion to be present as well as peripheral neurogenic and muscular features. Strachan (personal communication) considers the finding of increased

motor unit firing on attempted abduction without actual movement of the eye being effected, to be compatible with a myopathy if it can be assumed that the eye is not tethered by adhesions. In Case 1, although there was at operation limitation of movement with forced duction, this was not sufficiently marked to account for the immobility of voluntary ocular gaze. Apart from Van Allen and Blodi's case (1960) there have been relatively few reports of electromyography in congenital ocular palsies. Breinin (1957) examined an infant aged 18 months with abductor gaze paresis. Only one area of the lateral rectus showed some regular motor unit activity of low amplitude and frequency. A curious gritty sensation was encountered during electrode insertion, suggesting fibrosis. Sampling of the orbiculares oculi and oris muscles showed almost complete silence except for a few insertion potentials from the orbicularis oris. Breinin considered his findings compatible with nuclear agenesis and a supranuclear involvement but felt that a primary muscle aplasia could not be ruled out. Hellström (1949) did electromyography of the right lower facial muscle in an infant with congenital facial diplegia and bilateral lateral rectus weakness and found some voluntary activity consistent, he thought, with denervated or never innervated muscle. Summarizing the EMG findings in cases of adult ocular myopathy, Breinin (1962) states that an action potential of diminished amplitude and shortened duration results. The retention of the motor unit but loss of individual muscle fibres (in myopathy) permits an intense interference pattern to be developed upon effort. In some patients exhibiting severe loss of mobility the electric pattern appears quite normal with good or even increased amplitude and an abundance of potentials. The EMG of the recti muscles in the present Case 1 suggests myopathy and not nuclear or supranuclear ocular muscle weakness.

(b) Histopathology There have been few comprehensive pathological studies in patients with congenital oculo-facial palsy. Pitner, Edwards, and McCormick (1965) give an authoritative review of pathological studies in Möbius syndrome and add a detailed report of the necropsy of a white male infant who died aged 48 days. This infant was said to have had on clinical examination facial diplegia, inability to abduct either eye, and atrophy of the right side of the tongue. The extraocular muscles were normal but there was severe alteration of facial musculature with marked adipose replacement of muscle. All the cranial nerve nuclei and fibres appeared preserved. Pitner and his colleagues (1965) felt that the lesion primarily involved the affected muscles, though they did not comment on their

FIG. 8. Medial rectus. Electron microscopy. There is a considerable increase in number of the subsarcolemmal mitochondria (M), some of which are irregular in outline. Numerous small electron-dense bodies (B) are probably lipid in nature. S = sarcolemma. $\times 8,250$.

finding of histologically normal extraocular muscles despite the clinical abduction weakness. A most useful Table in their communication gives previous necropsy findings in Möbius syndrome in relation to examination of the central nervous system, the peripheral nerve, and the involved muscles. Apart from their own case, only in the case of Heubner (1900) were all these three 'tissues' examined at necropsy and in that latter report the tongue alone of affected muscles—that is, including ocular and facial muscles—was studied. Again, the necropsy report of a 5-year-old boy with congenital bilateral abductor palsy described by Philips, Dirion, and Graves (1932) makes no mention of the histology of the ocular muscles.

It must be conceded that the classical view of nuclear agenesis as the lesion in Möbius syndrome would not apply to every patient. The evidence for myopathy in our Case 1 is, of course, not based on a complete pathological examination and so is not proven. There is presumption from a clinical point of view in relating the aetiology of the ocular features to the limb girdle weakness in Case 1 which is almost certainly myopathic. Also our Cases 1 and 2 were floppy babies (similar to the two cases described by Graham, 1964), a condition which might be considered due to a myopathic origin. The strongest argument in favour of a myopathic basis for the congenital ophthalmoplegia in the present cases lies in the pathological changes in the medial and lateral rectus muscles biopsied at operation. The variation in fibre diameter, the lack of grouping of atrophic fibres which would be expected in a neurogenic atrophy and the presence of granular degeneration in the sarcoplasm all point to a primary myopathy. In addition, the finding on electron microscopy of focal fibril degeneration, myofilament loss, alterations in mitochondrial morphology, and subsarcolemmal damage favours the diagnosis of myopathy. Wechsler (1966) has described the ultra-microscopic changes in various kinds of muscle atrophy and his findings do not coincide with those in the present case. The light microscopy findings are also similar to those described by Kiloh and Nevin (1951) who favour a myopathic process in progressive external ophthalmoplegia. Among cases in the literature where biopsy of the external ocular muscles has been performed, Yasuna and Schlezinger (1955) describe two patients in whom exploratory eye operations revealed grossly normal lateral rectus muscles with free movement of the eyes in response to forced duction manoeuvres. Muscle biopsy was said to show some abnormality with loss of striation and peripheral migration of the nuclei in some fibres. These changes were considered by the authors as not consistent with dystrophy

(which, however, might be questioned by some pathologists) and probably consistent with a relatively slight degree of muscle atrophy. In Case 3 of Reed and Grant (1957) no muscle fibres were seen in fascicles of dense fibrous tissue. Sprofskin and Hillman (1956) record that in a boy with Möbius syndrome and limb evidence of arthrogryposis multiplex, an operation to correct strabismus revealed a few strands of lateral rectus muscle and an inelastic left medial rectus.

While in general supporting the idea that Möbius syndrome may, on analogy with arthrogryposis multiplex (Pitner *et al.*, 1965), have nuclear, peripheral nerve, or a primary muscular basis or even a combination of the three, it is considered that in the present cases the cause of the ocular weakness is myopathy. The frequent association of deformities in congenital oculo-facial palsy also points to involvement of structures of more than one embryological layer at about the second month of foetal life (Evans, 1955) and when fully manifested gives the multiple features found in status Ullrich-Bonnaville (Ullrich, 1949). In our cases, the involvement of muscle predominates, but the very mild somatic deformities and possibly the impaired caloric responses—similar to those reported by Yasuna and Schlezinger (1955) and Van Allen and Blodi (1960)—and mild deafness may represent elements of a more widespread effect.

SUMMARY

Two siblings with congenital ophthalmoplegia of a clinical type similar to that found in Möbius syndrome are described. Both were floppy babies, and the boy, now aged 15 years, has features of limb girdle muscular dystrophy. Electromyographic and histopathological evidence is put forward that in these cases the ophthalmoplegia is myopathic in type.

We are particularly grateful to Mr. I. M. Strachan of the University of St. Andrews for the ocular electromyography and to Mr. G. D. L. Smyth for the otological investigation. Miss Rankin kindly let us use the details of her orthoptic examination. Dr. Michael Swallow allowed us to examine the patients when they were under his care.

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