NUCLEAR AGENESIS

MÖBIUS' SYNDROME : THE CONGENITAL FACIAL DIPLEGIA SYNDROME

BY

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> 'The immobility of this man's face is very striking; it is as smooth and expressionless as if carved out of wood. The passions and emotions of eighteen years have left no trace upon it, and time has changed only its size.'

Thus Harlan (1881) described the appearance of a patient with bilateral congenital facial and external rectus paralysis. Chisholm's account (1882) was equally clear. The collation of cases of congenital facial palsy combined with other cranial muscle weakness by Möbius (1892) led to more general recognition of nuclear degeneration (as he termed it), or agenesis, and to eponymous fame.

More recently Henderson (1939) and Danis (1945) have fully reviewed the condition. Paralysis may be total or partial, unilateral or bilateral. The face is practically always involved, the external rectus muscles rather commonly, those supplied by the twelfth, third and fifth nerves, and the palate, may be affected. The weakness or paralysis is assumed to be due to aplasia of the appropriate nuclei, but the pathological evidence is hard to interpret, and until it becomes decisive, ideas about the nature of the condition must depend partly on consideration of how the various cranial paralyses come to be associated. Further weight must be attached to the circumstantial evidence provided by other congenital anomalies found in these patients. Most of them have been seen and recorded in adolescence and adult life, but patients seen in early childhood may show additional features, for example, mandibular hypoplasia and laryngeal stridor, which do not appear in other lists such as Wilson's (1940): epicanthus, absence of lacrymal caruncles, microphthalmia, deformed ears, syndactyly, micromely, localized muscle defects and club foot.

The following account includes all the cases that I have seen. Those with solitary unilateral facial paralysis are omitted, for in them the common presence of deformity of the face and external ear suggests that simple pressure by the shoulder may have produced the deformation of adjacent structures during intra-uterine life (Browne, 1936).

Case 1. Unilateral External Rectus and Facial Palsy

C.P., a boy, was born in 1948. He was the second child of healthy parents not related by blood: there was no illness during pregnancy; he was born by normal labour, at term, and weighed 6 lb. Right facial weakness was noticed at once; he could not suck well but was breast fed for two months. Because gain in weight was slow he was brought to hospital at 3 months. Weakness of the right external rectus muscle was noted. At 5 months there was slight hypoplasia of the right side of the face, which was completely paralysed. At 9 months there was a right convergent squint, which was treated operatively when he was 23 months old.

Case 2. Bilateral External Rectus and Unilateral Facial Palsy and Symbrachydactyly of the Hands

C.A., a girl, was born in 1952. She was the second child of healthy parents not related by blood: there was no illness during pregnancy; she was born at term by normal labour. She was seen at 5 months; her general condition was good but she had bilateral sixth nerve palsy; facial movements were normal on the right, but on the left the brow was always smooth, the eyelids flickered but did not meet, there was a little movement of the upper lip (a recent development not present in the earlier months), the mouth was pulled down almost normally. The hands were small and symmetrical; the fifth digit was perhaps of normal size but the others were reduced to its length, and there was syndactyly with the middle three digits fused as far as the base of the nails while the thumb and the little finger were joined to the central mass up to the level of the base of the intermediate phalanx. The feet showed slight metatarsus varus with some reduction in size of the third digit on each side.

Case 3. Unilateral Facial and Bilateral Palatal Palsy

M.D., a girl, was born in 1944. She was the third of four children of healthy parents unrelated by blood, there was no illness during pregnancy; she was born at term by normal labour. Difficulty in swallowing was noticed in the maternity hospital; until she was 5 years old solids and fluids came down the nose and even when she was nearly 9, liquids occasionally did so. In most ways she developed well but speech was unintelligible for a long time and nocturnal enuresis is still

troublesome. Speech therapy was started at 6 years.

On examination at 8 years 11 months, she was seen to be a well grown healthy American child, with no abnormalities except severe but not complete symmetrical palatal paralysis, and weakness of the left labial muscles.

Case 4. Unilateral Facial and Lingual Palsy, Micrognathia, Laryngeal Stridor and Left Talipes

C.A., a boy, was born in 1950. He was the youngest of five children of healthy parents who were not related by blood: there was no illness during pregnancy: he was born by normal labour, at term, and weighed 8 lb. Left talipes equinovarus was noticed at birth. He slept for most of the first three days, then he became more active and stridor was noticed. The tongue was seen to be abnormal at 5 days; he could not suck well, and breast feeding was early abandoned; at 10 weeks he was admitted to hospital on account of undernourishment, vomiting, choking and going blue while being fed. He had a loud, high-pitched, inspiratory stridor unaffected by the position of the head or tongue. There was weakness of the whole of the face on the left, the mandible was small, the tongue was protruded to the left and its left side was small and wrinkled and showed fibrillation. The palate was not moving when he was first seen, but a week later it was moving well; he had been fed by gastric tube and was much stronger.

Feeding was difficult throughout the first year. When he was last seen, at 14 months, he could not sit quite steadily but he appeared to be moderately intelligent and was using two words. Stridor was still audible.

Case 5. Bilateral Facial and Lingual and Possibly Masseteric and Unilateral Palatal Palsy

M.R., a boy, was born in 1942. He was the youngest of three children of healthy parents; he was born by normal labour, at term, and weighed 9½ lb. There was no stridor. He sat and walked at the expected times, but at 2 years was not speaking, so a 'tongue-tie' was cut, with no improvement. The teeth were not carious. At 4 years he was still dribbling. His intelligence was tested next year, and was within the normal range (I.Q. 85). At 6 years he was seen by Dr. W. G. Wyllie, who noted weakness of the muscles of mastication on both sides and that the tongue could not be protruded but was not wasted; the palate moved up to the left; there was slight weakness of the face on the right but it was more severe on the left. The child guided food to his teeth with his fingers. In spite of his difficulties he did well at an ordinary school. At 9 years facial movement was scanty, but the only definite weakness was in firmness when closing the left eye. The right side of the palate was paralysed and the voice was nasal as well as indistinct, the tongue being still protruded only to the teeth. There was at this time no fifth nerve weakness, mastication being difficult only because the tongue did not guide food to the teeth. Facial sensation was normal, and there was no loss of taste on the anterior two-thirds of the tongue.

Case 6. Bilateral Facial, Palatal and Masseteric Palsy, Doubtful Wasting of Tongue and Micrognathia

F.C., a boy, was born in 1948. A detailed early history was not available, but it was known that he could not suck as a baby, and had to be admitted to hospital where he was tube fed and then spoon fed. Subsequently, he was treated for malocclusion of the teeth, and the tonsils and adenoids were removed. An intelligence test, performed because he 'looked vacant', placed him in the normal range (I.Q. 104) and he was found to be cooperative in speech therapy. When he was seen at 4¼ years he was a healthy blonde boy with blue eyes. The lower jaw was small, there was bilateral facial weakness, more pronounced on the left than the right, and the masseters were weak. The tongue was small and wrinkled but was protruded fairly well. The palate moved poorly, and when the post-nasal space was examined with a nasopharyngoscope 'the soft palate was seen to move very slightly in the mid-line and the post-nasal space was occluded'.

Case 7. Bilateral External Rectus and Facial and Unilateral Palatal Palsy, Micrognathia, Stridor, Imperfection of Primary Teeth, Klippel-Feil Syndrome

S.W., a girl, was born in 1947. She was the second child of parents who were not related by blood: the father was healthy: the mother was said to have congenital and rheumatic heart disease, and her mother had twin siblings, one of whom died at birth while the other was said to be 'double inside, with a double brain; very clever—an infant prodigy, but it was known that he would die, and when he was 5 he did'.

The mother was not ill during pregnancy, but her small size was a matter of comment and she had a stitch in her left side throughout; these features suggest oligamnios and increased pressure (Browne, 1936). Labour was one month premature but not otherwise abnormal; the baby weighed 4½ lb.

She was brought to hospital at 10 weeks with the complaints that she could not cry aloud, breathing was noisy, and she could not suck from the breast. The chin was very small and the tongue was bunched up to the palate, in the middle of which there was a small white nodule. The cry was hoarse and difficult; there was inspiratory stridor with suprasternal and lower costal recession. The neck was short. The left side of the chest, face and cranium were flattened anteriorly, and there was corresponding flattening on the right posteriorly, but this is so common a minor deformity that it was probably unrelated to the other abnormalities.

The symptoms were ascribed to the micrognathia, in which condition the falling back of the tongue may indeed produce noisy dyspnoea, but the character of the cry suggested that the stridor might be laryngeal, and in fact, it persisted for three years, long after the symptoms of micrognathia with 'tongue-swallowing' had gone. The voice is still hoarse at 4 years. Radiographs showed (at 10 weeks) adequate oral, nasal and pharyngeal airways, but the upper 5 mm. of the lumen of the larynx appeared to be only 1 mm. deep, enlarging in the next 7 mm. to a normal size. The trachea looked normal.

The head appeared to be resting on the shoulders, and the cervical vertebrae were fragmentary. The heart and lungs appeared normal but the cranial bones were very thin.

She grew fairly well and is at 4 years of normal size allowing for the prematurity. She sat, walked, and talked late, and was thought to be mentally defective, but it is not yet certain how much inability to move the eyes, face, or neck adequately has contributed to this impression.

As is usual in cases of congenital paralysis of the external recti, convergent squint developed at the age of 9 months. In infancy the face did not move, but at 4 years the upper eyelids move slightly when she tries to shut her eyes, and there is some lower facial movement especially on the left. The palate moves poorly on the right.

As the milk teeth erupted, it was noticed that each had black marks; the canines were sharply pointed; enamel had worn off the upper teeth when she was 3½ years old, and since then many upper and lower teeth have been extracted because of severe caries.

Case 8. Bilateral Oculomotor and Unilateral Facial and Lingual Nerve Palsy, Micrognathia, Stridor, Imperfect Primary Teeth

B.S., a boy, was born in 1947. He was the first child of healthy parents not related by blood; there was no illness during pregnancy; delivery was normal but three weeks premature; he weighed 6 lb. 9 oz. He had an umbilical infection which was treated in hospital. At 4 weeks he was again in hospital on account of difficulty in feeding, inspiratory stridor, and attacks of cyanosis. There was bilateral epicanthus; the mandible was very small.

At 3 years he was undersized but well. Dr. W. G. Wyllie saw him and noted right facial palsy and divergent squint; to look forward the boy turned his head to the right and used the left eye, in which there was a small subconjunctival cyst on the medial side. There was some hypermetropia.

He walked and talked late but did not appear by his actions to be mentally backward. At 5 years stridor was still quite loud when he had a cold. His face was expressionless, but when asked he would shut his left eye, and the left side of the mouth moved when he showed his teeth. When he cried the right side of the mouth moved, but not the upper facial musculature. There was right ptosis. The mandible was small but not truly micrognathic; its growth had been noted with pleasure and surprise. The tongue was protruded to the right. Gross dental caries developed in his fourth year, and most of the teeth were soon brown stumps.

Case 9. Bilateral External Rectus and Facial and Unilateral Oculomotor and Lingual Palsy, Micrognathia, Anomalies of Right First and Second Ribs

D.B., a boy, was born in 1939. He was the fourth child of healthy parents who were not related by blood; there was no illness during pregnancy; birth was difficult and long, but instruments were not used. Paralysis of the left side of the face was noticed soon after birth, but it lessened rapidly although slightly.

At five months he was seen by Dr. W. G. Wyllie who noted the small, underhung lower jaw, deficiency of facial movement, small size of the left side of the tongue, and weak cry. A convergent squint developed during the first year. It was later determined, by Mr. J. H. Doggart, to be due to paresis of both external recti with some weakness of the right internal rectus, and was treated surgically.

He was followed for years, and did well; at 13 years the face in repose is not unsightly, but the facial, oculomotor and left lingual paresis persist. There is no loss of sensation on the face, or of taste on the anterior two-thirds of the tongue. The mandible does not now appear small.

Clinical Features

The clinical features of facial diplegia have been reviewed in many previous publications, and will not be repeated here, but some points, illustrated by my cases, perhaps deserve more attention than they have received elsewhere. The first should be obvious, but in practice it has not been; it is that the lack of expression may suggest an unfounded diagnosis of mental defect. The infant who does not smile and laugh in response to his mother's endearments is thought to be dull, and if his apparent indifference is reinforced by failure to follow moving objects with his glance, the impression is strengthened. Later on weakness of the palate or tongue as well as the face may delay the acquisition of speech and add further weight. Dribbling is another unattractive feature in patients with oral paralysis. Case 5 (I.Q. 85), Case 6 (I.Q. 104), and perhaps Case 7 suffered in this way; in Case 9 the physician who referred the 5-month-old child from the welfare centre to the hospital noted that 'he follows the finger well and is quite bright, plays with his toys, etc.' but at 15 years he was still suffering at school from the nickname 'Dopey'.

In discussion of these cases doubt has been expressed at the statement that there has been some improvement in the abnormalities, because they are congenital and thus are supposed to be fixed for ever. Yet development of an organ or tissue does not come to a standstill at birth, and there seems to be no reason why an abnormal tissue should not develop somewhat. Just after birth the facial muscles are limited in expression to the grimace associated with crying, and full animation is not achieved for several years, so it is not necessarily surprising that in Cases 2, 5, 7, and 9 some increase in mobility occurred. Eye movements are limited until the baby can "fix" with his eyes, but this is learnt at a comparatively early age and in my cases

no improvement in ocular mobility was noticed; on the contrary squint, absent at first, only became apparent as use of the eyes developed during the first year. Movement of the palate and tongue is imperfect in early life (for example, babies cannot separate them in order to breathe through the mouth for several weeks or months), and improvement in tongue or palate was seen in Cases 3 and 4, and might have been found in others if they had been observed closely when their feeding difficulties were being overcome.

Micrognathia (Cases 4, 6, 7, 8 and 9) is not recognized as a constituent of the facial diplegia syndrome, although it is apparent in some of the pictures of the younger patients (e.g., Spatz and Ullrich, 1931; Danis, 1945). Normally the proportions and shape of the mandible change greatly with age, so it is not surprising that mandibular hypoplasia becomes less obvious (e.g., Cases 8 and 9). A similar change occurs in Pierre Robin's syndrome of micrognathia and cleft palate (Pruzansky and Richmond, 1954; O'Brien, 1954). Stridor also is not commonly recognized as an associated feature and it too decreases with age (Cases 4, 7 and 8). It is difficult in these babies to decide quite certainly whether laryngeal deformity, displacement of the tongue or epiglottis produced by muscular weakness, or even defect of the intrinsic muscles of the larynx produces the stridor.

The Klippel-Feil deformity of the neck appears not to have been described hitherto as an associate of facial paresis.

Association of the Lesions

The bizarre association of the cranial nerve palsies are a challenge to the impulse to conjecture.

> ' Toute science physique résulte essentiellement de deux ordres de faits: les faits particuliers, que révèle l'observation; les faits généraux, que le raisonnement fait découvrir. Embrassés dans de communes études, ils se fécondent, se vivifient mutuellement.' (Saint-Hilaire, 1836.)

If the abnormalities of cranial musculature are produced by nuclear agenesis it is odd that the eleventh cranial nerve, and possibly also the fourth, are spared, as are the sensory nuclei also. The nuclei that are affected have no close embryological connexion for they arise in all three of the motor divisions—somatic, branchial and splanchnic. There may be some unknown metabolic connexion between them, but there is no consistent anatomical linkage, and their nerves also follow different paths. The type of paralysis is surprising; instead of the supranuclear lower facial paralysis, or the nuclear paralysis affecting both the upper and lower face, we find the upper part more affected than the lower. Again, it is an odd third nuclear palsy which consistently leaves the intrinsic muscles of the eye unaffected.

One can but wonder whether the nuclei are in the first place involved at all. The pathological investigation of three cases by Heubner (1900), Rainy and Fowler (1903) and Spatz and Ullrich (1931) showed that nuclei and nerves were hypoplastic or absent, but this need not be a primary abnormality. If muscle does not develop its nerve is atrophic; Dunnebacke (1953) regarded it as 'well established that the quantitative development of the first sensory or motor nerve centres is controlled by their peripheral fields'. She illustrated this by removing the primordium of the superior oblique muscle in chick embryos two and a half days before the trochlear fibres would be expected to grow, a procedure which was followed by gross reduction in the cells in the trochlear nucleus although the full number had already developed. Finally, there is no obvious reason why agenesis of certain cranial nuclei should be so often associated with abnormalities of hands, feet, chest wall (pectoralis major, ribs, breast) or jaw.

It is perhaps worth suggesting that the congenital facial diplegia syndrome is probably not due to nuclear agenesis, but the mere hesitant negative would be a dull conclusion. George Sand wrote that 'classification is Ariadne's clue through the labyrinth of nature' (Maurois, 1953) and we might reclassify Möbius' syndrome simply as a congenital defect of muscles.

The muscles concerned are those moving the eye, jaw, palate, face and tongue. With few exceptions (e.g., the external rectus) we do not know what individual muscles are defective, for we are concerned with clinical states such as almost complete ophthalmoplegia externa, asymmetrical movement of the palate, weakness of bite, lack of facial movement except for a little at the angle of the mouth, or wasting of the tongue with failure to protrude it. For example, our observations do not tell us whether defect of the levator or of the tensor palati is responsible for weakness of the palate on one side, yet the tensor is reported to develop in relation to the first branchial arch, the levator to the third and fourth.

There is no complete agreement about the origin of the cranial muscles (Hamilton, Boyd and Mossman, 1945; Keith, 1948). If we spread them as widely as possible we find eye muscles coming from pre-otic somites (at least in the shark), jaw muscles and tensor palati from the first arch, face muscles from the second, levator palati from the third and fourth, and tongue muscles from the three post-

occipital segments of the head. This leaves an awkward gap with the sternomastoid and trapezius arising from the second and third branchial segments but unaffected in Möbius' syndrome.

The adoption of some of the other theories permits much condensation; all the muscles affected might arise from only two branchial segments. It is accepted that the facial musculature arises in connexion with the second (hyoid) arch, and some assert that the external rectus muscle is derived from the facial, thus linking the two common pareses of Möbius' syndrome. Ignoring the levator palati, the rest can be linked to the muscle plates of the first (mandibular) arch and its premandibular process—the tensor palati and the jaw-closing muscles (the masseter and medial pterygoid; Last, 1954) as well as the oculomotor muscles supplied by the third nerve. This leaves only the lingual muscles which, 'according to most authorities appear in the mesenchyme of the developing tongue' (Hamilton *et al.*, 1945), itself a product mainly of the first arch, with contributions posteriorly from the second, later overlaid by the third.

Thus by selecting opinions to suit the case, one may argue that all the pareses found in the syndrome are due to interference with the development of the muscles of the mandibular and hyoid arches. These muscles are differentiated towards the end of the second month of intra-uterine life, and the sparing of the iridian and ciliary muscles is at once explicable, for they develop from the ectoderm and mesoderm of the optic cup much later, in the fourth month. The levator palpebrae is also a later differentiation, in the third month, but it is delaminated from the superior rectus (Keith, 1948) and it is deficient (or at least inactive) when there is complete opthalmoplegia as in the right eye in Case 8.

The associated abnormalities have still to be considered. Mandibular hypoplasia might be expected to occur with hypoplasia of muscle arising in connexion with the mandibular process; the cause of the stridor is obscure clinically and is perhaps sometimes produced by weakness of the tongue, but in Case 7 the long duration of the stridor and the observation of narrowing of the upper part of the larynx, with a normally active tongue, point to actual laryngeal abnormality which may possibly be due to deficient growth of the hyoid arch. The styloid process, a derivative of this arch, could not be seen radiographically when it was sought in this patient.

Other abnormalities were brachysyndactyly of the hands, deformity of the ribs, talipes equinovarus, epicanthus, and fragmentation of the cervical vertebrae. Talipes occurred in 37% of 62 cases surveyed by Danis (1945), and in 16% the hands were deformed. Defects of the chest wall were also common (18%), especially absence of the sternal head of the pectoralis major. This is the commonest of all congenital deficiencies of muscle (Bing, 1902) and cases of its association with brachysyndactyly have been noted by several writers (e.g., Poland, 1841; Bastian and Horsley, 1880; Schwalbe, 1906; Bing, 1939; Soderberg, 1949). Both are anomalies of development of the upper limb bud, one at its base and the other at its apex. Talipes might be produced by abnormality of growth of the lower limb bud.

To explain the coincidence of hypomandibulism, defective growth of cranial muscles and disturbance in different parts of the limb buds is not easy and will not here be attempted in detail. Some of the possibilities which need consideration are as follows:

Genetic. Genes being chemical units act chemically, so that there may be tissue-specific genes (Grüneberg, 1947) but in this condition muscle alone is not affected; cartilage and bone are also involved. The hereditary aspect has not been much studied but such an influence is not obvious, although Danis (1945) found a familial history in five out of 81 cases. The genetics of this condition might repay study, but even if inheritance were shown to be the governing factor we should still be left with the problem, physiological and anatomical, of how the abnormalities were produced by the genes.

The Time Factor. Stockard (1921) showed that interference with the metabolism of fish eggs produced various abnormalities, depending on the time of the interference; this was elegantly demonstrated by Duraiswami (1950) in his experiments on the injection of insulin into hen's eggs. Interference with growth of the limb buds for a short time at the end of the second month might produce symbrachydactyly, pectoral defect and abnormality of the feet. This is just the time when the muscles of the visceral arches become differentiated, and the mandible begins to ossify. Here indeed is a connexion, but it is hard to see why other things which are then developing rapidly are not also affected. The clavicle starts to ossify at the same time as the mandible but grows normally; the cornea, anterior chamber and pupillary membrane form then but are in these patients normal, and so on. Lack of symmetry of the abnormalities which are found is less objectionable, for the position of the embryo may alter the degree of malnutrition of similar tissues on either side.

Multipotent Tissue. The neural crest (Hörstadius, 1950) contributes to the formation of a remarkable variety of organs, and a case could be made for supposing that interference with the growth of the cranial part (of which the human development was described by Bartelmez and Evans in 1926) would produce defects of the mandible, larynx and cranial muscles, and possibly the vertebral anomalies seen in Case 7. This would, however, leave the limb deformities unexplained, and they are so common that they cannot be ignored. Nevertheless, it is interesting to note the resemblance between examples of slight otocephaly, which alone would be viable, and the micrognathia of the congenital facial diplegia syndrome. In otocephaly (Saint-Hilaire, 1836) which occurs in several species including man, the mandible does not develop so that (broadly speaking) the ears subside to a place under the face instead of behind it; in severe cases there is a cyclops eye or even an absent head with a solitary ear in its place (O brave new world, that had such voters in't). The mildest degree shows only 'more or less reduction of the size of the lower jaw', in others there are abnormalities of the tongue and eye muscles, there is hypoplasia of jaw muscles, and in many strains (of guinea-pigs) club foot is common (Wright and Wagner, 1934). The basic factor may be inhibition of the anterior medullary plate and associated ectodermal placodes, which would interfere with the formation and migration of cells from the neural crest. Nevertheless, Wright and Wagner point out that in otocephaly the primary effect is on cartilage, secondary on muscle, whereas it appears that in the congenital facial diplegia syndrome muscle may be affected without gross change in structures which originate in cartilage.

The Bonnevie-Ullrich Syndrome. Having embarked on the dangerous waters of analogy we must face this concept. The story of its evolution may be compressed. Bagg and Little (1924) found in the offspring of *x*-irradiated mice some which showed abnormalities of paws, eyes, hair and kidneys; Bagg (1929) examined such mice *in utero* and found that the diverse deformities of the paws depended on interference with the blood supply by subcutaneous blebs; Bonnevie (1934) showed that the blebs arose where cerebrospinal fluid first escaped from the fourth ventricle (Weed, 1917) and, presumably because of over-production or under-absorption of fluid, travelled along lines of least subcutaneous resistance to limbs, back, etc. Unhappily Jost (1953) has cast a shadow of doubt over Bonnevie's observations, but has shown that in rats amputation of limbs and micrognathia may follow the development of blebs, into which bleeding occurs, produced by treating the mother with pitressin or adrenalin between the 15th and 18th days of pregnancy. This work opens a new vista.

Ullrich, in 1930, described a child with cranial nerve palsies and other abnormalities; in 1938 he adapted Bonnevie's concept to explain this and similar conditions, including pectoral defect and symbrachydactyly (Ullrich, 1949). Henderson (1939) rejected this explanation of agenesis of cranial nuclei, but if it is the muscles and not the nuclei which are primarily affected, his argument is irrelevant. One must admit that myelencephalic blebs might travel subcutaneously to the branchial arches and the limb buds after the seventh week of intra-uterine life, when the choroid plexuses are formed. It happens in the mouse, it might happen in man.

Summary

Nine cases of the congenital facial diplegia syndrome are described. In addition to facial paresis, they showed weakness of ocular, mandibular, palatal and lingual muscles, as well as micrognathia, stridor, epicanthus and abnormalities of the hands and feet.

Some of the abnormalities may decrease with age.

The particular association of the abnormalities is difficult to explain if the pareses are due to nuclear agenesis; congenital deficiency of muscles developing in connexion with the first two branchial arches is more probable.

All the major defects are of structures which are differentiated at the end of the second month of intra-uterine life. How they become malformed is unknown; Ullrich's suggestion that the migration of myelencephalic blebs (described in mice by Bonnevie) does the damage cannot be directly proved in man but might be true.

Dr. W. G. Wyllie first interested me in this condition. He introduced me to several of the patients, Mr. Denis Browne to another. Professor T. B. Johnston pointed out some mistakes but is not responsible for any that remain; Dr. P. E. Polani's suggestions have been helpful.

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