

CREATINURIA IN MÖBIUS' SYNDROME

BY

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Since the first description by Harlan (1881) of a patient with bilateral congenital facial palsy and external rectus palsy, several excellent reviews of the Möbius' syndrome have been published, in which various theories regarding the aetiology of the condition have been discussed.

Möbius (1892) believed that the mixture of cranial nerve lesions was due to a toxic or degenerative process. Heubner (1900) described the pathological findings in one case, in which the ganglion cells were absent from the motor nuclei of certain cranial nerves, with poor development of the formatio reticularis, olives and pyramidal tracts. Rainy and Fowler (1903) considered the primary pathology to be in the muscles, with secondary degenerative changes in the nuclei.

The bizarre combinations of cranial nerve lesions, and the associated somatic anomalies have intrigued later writers. Henderson (1939) reviewed the condition, describing the typical findings. Paralysis may be complete or incomplete, unilateral or bilateral and most commonly involves the muscles of the face especially in the upper half. External rectus palsy is common, while the muscles supplied by the third, fifth and twelfth cranial nerves are occasionally affected. Club-foot occurs in one third of the cases, and defect of the pectoralis major muscle with mammary hypoplasia is a common associated anomaly. Poor general muscle development may also occur. Deformities of one hand or arm and of the ears and nose, absence of the lacrymal caruncles and glands, micrognathos, a high arched palate, vasomotor disturbances and mental defect have all been recorded. This writer discussed the analogy of the Bonnevie-Ullrich syndrome as one mechanism to account for the widespread somatic defects, but could not associate this with agenesis of cranial nuclei. Evans (1955) pointed out that all the major defects are of structures which are differentiated at the end of the second month of intra-uterine life, and considered that the primary pathology was probably in muscle. Sproffkin and

Hillman (1956) discussed the similarity to Werdnig Hoffman and Oppenheimer's disease.

Two cases of Möbius' syndrome are presented in this paper. Biochemical investigations were carried out to see if any light could be thrown on the aetiology of the condition.

Case Reports

Case 1. R.W., a boy, was born at home to a healthy multigravida. The labour was normal and at term (he weighed 6 lb.), but as he failed to breathe normally he was transferred to the Sorrento Premature Baby Unit for resuscitation.

On admission he had infrequent gasping respirations, a poor colour, poor muscle tone and excessive pharyngeal mucus. An intracranial birth injury seemed the most likely diagnosis; his appearance was odd even at this stage with marked scaphocephaly, micrognathos, low set ears, an absent left nipple and bilateral talipes equinovarus. His expressionless face was thought to be part of the generalized hypotonía.

The baby survived, unexpectedly, and sub-dural taps and a lumbar puncture did not support the original diagnosis. He could not suck and feeding remained a formidable task throughout his life. It gradually became obvious that he had bilateral facial palsy, bilateral external rectus palsy and probably weakness of some of the external ocular muscles supplied by the third cranial nerve. The intrinsic ocular muscles and the superior oblique muscles were unaffected. The masseters, the pterygoid muscles and the palatal muscles were all weak and later developed contractures. His general muscle development was poor, and he developed a marked thoracic kyphoscoliosis. The left pectoralis major was absent. There were marked epicanthic folds and he did not secrete tears. There was a complete absence of facial expression and a severe dysarthria, so that a gurgle of laughter was indistinguishable from a cry of rage, apart from his change of colour. He did not learn to sit or stand or to speak, but this seemed to be due to muscle weakness rather than to mental defect.

He made slow progress until the age of 18 months (see Fig.), but the contracture of the masseters increased the feeding difficulties and led to frequent aspiration pneumonia. He died at the age of 22 months from a respiratory infection.



FIG.—R.W., Case 1, aged 18 months.

The serum electrolytes, calcium and phosphorus, urea and proteins were normal on several occasions. The urinary amino acid chromatogram was normal. Radiographs of the skeleton showed no defect apart from mandibular hypoplasia.

At the age of 1 year the urinary creatine was 59 mg./100 ml. (approximately 34 mg./kg./day), and the urinary creatinine 38 mg./100 ml. (approximately 22 mg./kg./day), creatine : creatinine ratio, 1.55.

A post mortem examination showed death to be due to acute bronchitis. There was generalized hypoplasia of the muscles. There was no macroscopic abnormality of the central nervous system, and preliminary examination of celloidin blocks of various areas of brain, stained by the Nissl method, showed no anatomical abnormality.

This child had a paternal uncle who died at the age of 2 years and apparently 'he looked just like R.W.'.

Case 2. S.M., a boy, was born at St. Helier Hospital to a healthy multigravida at full term and weighed 7½ lb. There was hydramnios, but the delivery was straightforward. The baby was limp and respirations

were not established until 25 minutes after birth. An intracranial birth injury was suspected and he was nursed in oxygen for the first 12 days of life. He developed sclerema neonatorum. He required tube feeding for the first six weeks of life, but then sucked well and has been breast fed since.

The lack of facial expression and generalized hypotonia, noticed at birth, persisted and, when at the age of 4 months he developed a left talipes equino-varus, the diagnosis of Möbius' syndrome seemed established. There is now bilateral facial paralysis with some sparing of the orbicularis oris. The cry is strangely monotonous but the remaining muscles supplied by the cranial nerves do not appear to be affected. The muscles of the neck, trunk and legs are poorly developed, but his arm movements are normal for his present age of 6 months. He has a high arched palate, slight micrognathos and low set ears. The equinus deformity has been kept under control with Denis Browne splints, but the forefoot varus persists and as the tendons on the anterior aspect of the left ankle cannot be felt, the tibialis anterior muscle is probably absent.

Full biochemical investigations have not been undertaken. At 5 months of age the urinary creatine was 9.1 mg./kg./day and the creatinine 6.2 mg./kg./day, creatine : creatinine ratio, 1.48.

Discussion

Creatinine is normally produced in the body from creatine by enzymic action during muscular activity. This mechanism is more efficient in adult men than in women and children, in whom a degree of creatinuria is normal. However, the excretion of creatine should not exceed 30-40% that of creatinine. In normal infants the excretion of creatine is 0.7 mg./kg./day, and of creatinine is 11-14 mg./kg./day (Nitowsky, Gordon and Tyson Tildon, 1956). Creatinuria is found in myasthenia gravis, and in the muscular dystrophies in which levels of 8-11 mg./kg./day have been recorded (Wilkins, 1957).

The high levels of creatinuria found in the two infants recorded, seem to indicate some abnormality of muscle metabolism. The very high level in Case 1 may demonstrate the severity of the affection.

The clinical similarity of the Möbius' syndrome to amyotonia congenita has been noted, and this biochemical abnormality lends support to the opinion that the syndrome is a myopathy rather than a neurological defect. The absence of the pectoralis major and the nipple on one side and the micrognathos in Case 1, the high arched palate in Case 2, and the many associated somatic defects described in the syndrome show that this is not solely an enzyme abnormality.

Although all the structures affected in this

syndrome are differentiated at the end of the second month of intra-uterine life, it is unlikely that a permanent biochemical defect could be produced by an environmental 'insult' to the foetus at this stage of development. Thus it seems unlikely that the syndrome could follow damage by migrating myelencephalic blebs as in the Bonnevie-Ullrich syndrome. Possibly an abnormality of second month 'organizers' and an enzyme defect could be produced by a single genetic mutation. The occasional finding of a familial incidence would seem to support this view of the aetiology of the syndrome.

Summary

Two cases of Möbius' syndrome are described. The finding of marked creatinuria in both infants suggests that the muscle weakness is due to a myopathy rather than to nuclear agenesis. A single genetic mutation might produce an enzyme defect and abnormal second month 'organizers'.

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