

## Syndrome of the month

Edited by D Donnai and R Winter

# Moebius syndrome

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Moebius syndrome consists of congenital complete or partial facial nerve palsy with or without paralysis of other cranial nerves (most commonly an abducens paralysis) and often associated with other malformations of the limbs and orofacial structures. The first description of congenital facial diplegia was given by von Graefe in 1880<sup>1</sup> and this was soon followed by other reports. Moebius<sup>2,3</sup> drew attention to the association of congenital facial diplegia with other malformations. Alternative terms<sup>4</sup> used to describe the syndrome include congenital facial diplegia, nuclear agenesis, congenital nuclear hypoplasia, congenital oculofacial paralysis, and congenital abducens-facial paralysis. There is considerable overlap with the hypoglossia-hypodactyly syndrome, the glossopalatine-ankylosis syndrome, and Charlie-M syndrome.<sup>4</sup> The criteria for diagnosis are difficult to define; however, based on previous published reviews,<sup>5-7</sup> the following guidelines should assist in making a diagnosis of Moebius syndrome.

### Criteria for diagnosis

- (1) Complete or partial facial nerve paralysis is essential for the diagnosis of Moebius syndrome.
- (2) Limb malformations (syndactyly, brachydactyly or absent digits, and talipes) are often present.
- (3) The following additional clinical features in association with complete or partial facial nerve (VII) paralysis may also be present and should be helpful in making a clinical diagnosis of Moebius syndrome: bilateral or unilateral ocular nerve palsies (commonly of the abducens (VI) and less commonly of the oculomotor (III) and trochlear (IV) nerves); hypoplasia of the tongue owing to hypoglossal (XII) nerve

paralysis; swallowing and speech difficulties owing to trigeminal (V), glossopharyngeal (IX), and vagus (X) nerve palsies; malformations of the orofacial structures (bifid uvula, micrognathia, and ear deformities); other anomalies of the musculoskeletal system, for example, Klippel-Feil anomaly, absence of the sternal head of the pectoralis major, rib defects, and brachial muscle defects.

### Clinical findings

The condition can usually be diagnosed soon after birth and manifests with incomplete closure of the eyelids during sleep, drooling of saliva, and difficulties in sucking. Later, it is noted that the child does not smile or move its facial muscles on crying, the so called 'mask-like facies' (fig 1). The seventh

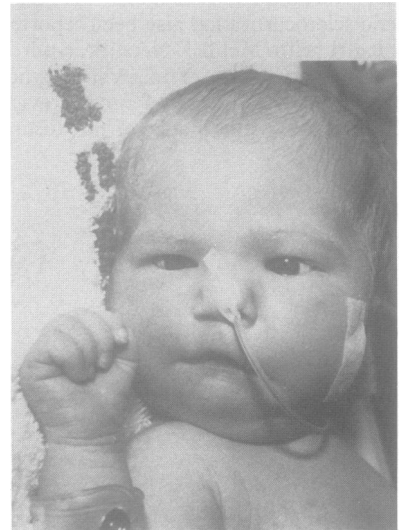


Figure 1 Seven day old female infant with Moebius syndrome. Note smooth, expressionless face, inner epicanthic folds, and convergent strabismus. This child also had talipes and small toes with syndactyly.

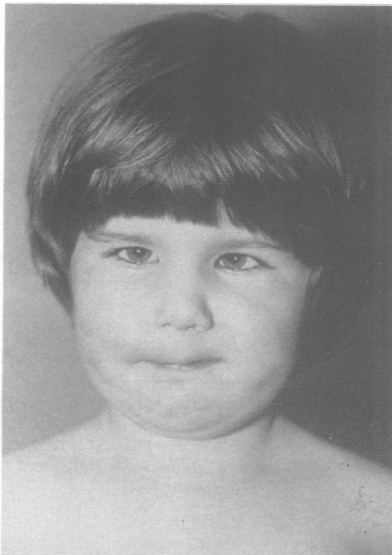
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nerve palsy is usually bilateral (fig 2) and incomplete (fig 3) and more commonly involves the upper face, which differentiates it from lower motor neurone facial nerve palsy, where both the upper and lower



*Figure 2 Ten year old girl with Moebius syndrome. Note expressionless face owing to bilateral facial nerve palsy with left convergent strabismus secondary to sixth nerve paralysis. She is mentally normal but is obese and the height is below the 3rd centile. She also has limb defects (see fig 4).*



*Figure 3 Female with Moebius syndrome aged 3 1/2 years. Note strabismus and partial seventh nerve palsy with some function on the left side.*

halves are involved, and from supranuclear lesions, which affect the lower face only.<sup>8</sup> Paralysis of the sixth cranial nerve with inability to abduct the eye is a frequently associated anomaly and tends to be bilateral and complete. The oculomotor and trigeminal nerves are occasionally involved. Conjugate horizontal eye movement is paralysed, but conjugate vertical movement is normal and convergence may be present to some degree.<sup>8</sup>

The hypoglossal nerve is the third most commonly affected cranial nerve (in about a quarter of cases) resulting in paralysis and hypoplasia of the tongue.<sup>8,9</sup> The eye muscles are always involved when the tongue is affected.<sup>5</sup> Speech may be defective because of involvement of the lips, tongue, palate, and occasionally the larynx.<sup>10</sup> Mental retardation is probably overdiagnosed owing to mask-like facies, drooling saliva, strabismus, and speech difficulties. Mild to moderate mental retardation has been estimated to occur in approximately 10% of cases in one study,<sup>11</sup> while in another moderate to severe mental deficiency was said to be present in at least half of the children with clinical features of Moebius syndrome.<sup>7</sup>

Limb malformations are frequently associated,<sup>12</sup> the most common of which is club foot (in about one third of cases) either bilateral or unilateral. Digital anomalies commonly seen are syndactyly or brachydactyly or both (fig 4). However, ectrodactyly (split hand) and terminal transverse defects are also seen. Other occasional anomalies include stiffness of the index fingers and marked bilateral valgus deformity of the distal phalanges of the big toes.<sup>8</sup> In approximately 15% of cases various muscle defects are present.<sup>6,11</sup> An absent sternal head of the pectoralis major (the second major component of the Poland anomaly) has been described associated with hand abnormalities in Moebius syndrome.<sup>5,13-15</sup>

Craniofacial abnormalities include small palpebral fissures, epicanthic folds, hypertelorism, external ear defects, microstomia, and micrognathia.<sup>16</sup> Bifid uvula and cleft palate have been described. Other less common anomalies are dextrocardia,<sup>14</sup> arthrogryposis multiplex congenita,<sup>17</sup> and Klippel-Feil anomaly.<sup>10</sup> Intrauterine growth retardation and hypotonia with delay in motor development have also been noted in some cases.<sup>11</sup> The association of Moebius syndrome with anosmia and hypogonadotrophic hypogonadism (Kallman's syndrome) and with hypogonadism alone has been noted.<sup>18</sup> The differential diagnosis includes neuromuscular conditions, for example facioscapulo-humoral muscular dystrophy,<sup>19</sup> infantile myotonic dystrophy,<sup>20</sup> and Charcot-Marie-Tooth disease,<sup>18</sup> that can have phenotypic features similar to Moebius syndrome; however, limb defects are not present.

### Pathology

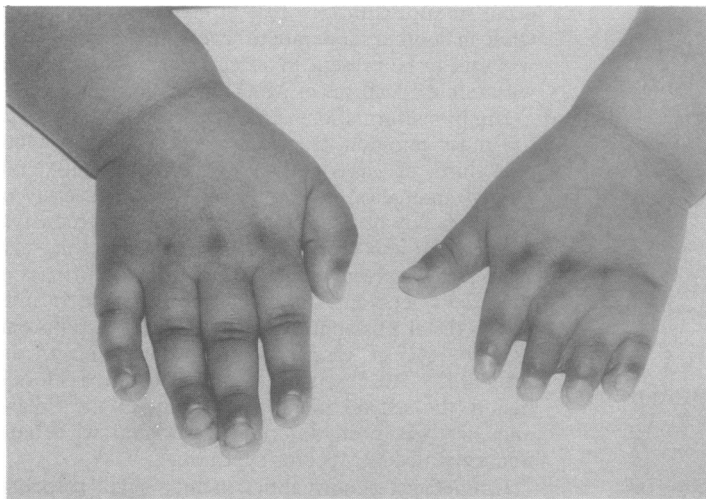
Moebius syndrome is unlikely to be a single entity as

pathologically different lesions have been described. A variety of pathological disturbances may produce a phenotype recognisable as Moebius syndrome.<sup>21</sup> The wide spectrum of congenital malformations points to some disturbance during early fetal development. Published reports suggest different pathogenetic mechanisms.<sup>22</sup>

Moebius, in his original description of the condition, postulated that the anomaly resulted from degeneration of the nuclei of the sixth and seventh cranial nerves.<sup>2,3</sup> On the basis of pathological changes noted in a 2 year old boy with congenital bilateral abducens and facial paralysis and atrophy of the left side of the tongue. Heubner<sup>23</sup> suggested nuclear agenesis or hypoplasia as the chief underlying cause of Moebius syndrome, which is supported by others.<sup>22</sup> However, a degenerative process rather than nuclear agenesis or hypoplasia has also been suggested.<sup>22</sup>

Apart from the cranial nerve nuclei, the site of the fundamental lesion within the nervous system may be cranial nerves or the muscles innervated by these or both. A supranuclear site has been suggested to explain the presence of conjugate gaze palsy in the absence of convergent strabismus.<sup>22</sup> Abnormal brain stem auditory evoked potentials in two of the three affected sibs with clinical features consistent with Moebius syndrome led to the suggestion of a supranuclear site (lateral lemniscus and inferior colliculus) for the acoustic lesion.<sup>24</sup> Neurophysiological studies, for example, nerve conduction studies, electromyography, and brain stem evoked potential abnormalities, may be helpful in locating the site of the lesion.

The pathogenesis of cranial nerve palsies associated with limb anomalies is difficult to explain. An ischaemic process resulting from an interruption in



*Figure 4 Hands of the girl in fig 2. Note short hands, brachydactyly, and syndactyly. She also had bilateral talipes equinovarus deformity and small toes with syndactyly.*



*Figure 5 Section of pons showing nodular calcifications, gliosis, and vascular prominences in the region of the tegmentum from a child with bilateral cranial nerve palsies (V and VII), cleft palate, adducted thumbs, and club feet. (Haematoxylin.)*

the vascular supply during early fetal development, probably around four to six weeks of gestation, may result in facial and limb anomalies characteristic of Moebius syndrome. This hypothesis is supported by the report of Moebius-like facies resulting from damage to the tegmentum of the mid brain secondary to basilar artery thrombosis, possibly related to birth trauma.<sup>25</sup> Pathologically, an ischaemic process may result in gliosis or calcification or both in and around cranial nerve nuclei in the region of the tegmentum (fig 5).

Another explanation for cranial nerve dysfunction and limb anomalies may be a primary metamerism defect in the brain stem nuclei and somite mesoderm of the limb buds.<sup>24</sup> The occurrence of Poland's anomaly in Moebius syndrome is probably related to a common pathogenetic mechanism.<sup>15</sup> Poland's anomaly is believed to result from a restricted defect in the metamerism process of the somite mesoderm.<sup>24</sup>

### Genetics

Most of the reported cases have been sporadic and both sexes are affected with equal frequency. There are no prevalence figures and the exact population incidence is not known. Pedigrees with an autosomal dominant, autosomal recessive, and X linked recessive inheritance pattern have been described.<sup>26</sup> Associated skeletal malformations, a frequent finding in Moebius syndrome, may be helpful in distinguishing the condition from monogenic primary muscle or anterior horn cell disorders for which appropriate neurophysiological tests are available.<sup>7</sup>

In one pedigree, suggesting an autosomal recessive inheritance pattern, the affected sibs had facial diplegia with deafness and mental retardation, but without skeletal abnormalities.<sup>24</sup> In a series of 15 children from two kindreds, with clinical features consistent with Moebius syndrome, more than one affected sib was found in two families; however, the parents were clinically normal and non-consanguineous. Skeletal anomalies were present in the affected subjects from these two kindreds.<sup>7</sup> A dominantly inherited syndrome with clinical features similar to Moebius syndrome with club foot, digital anomalies, and arthrogyrosis has been described in a family with 15 affected subjects in two generations.<sup>27</sup> Autosomal dominant inheritance has been suggested for congenital facial paralysis without the other malformations of Moebius syndrome.<sup>28</sup> An association of arthrogyrosis with Moebius syndrome was suggested in a family in which a patient had a sib affected with only arthrogyrosis.<sup>17</sup> Two black monozygotic twins with features suggestive of Moebius syndrome have been described with joint contractures and visceral anomalies involving the kidneys and ileocaecal valve.<sup>29</sup>

The majority of the published reports on Moebius syndrome refer to sporadic cases without any evidence of a known environmental aetiological factor.<sup>5-8 14</sup> Although there is not enough evidence to support an autosomal dominant mode of inheritance, it may be that in some instances the syndrome results from a new dominant mutation. There is a report of a 'Moebius syndrome variant' cosegregating with a reciprocal translocation between chromosomes 1 and 13, t(1p34;13q13), in at least seven members of a family over three generations.<sup>30</sup> The affected members showed congenital facial diplegia, finger flexion deformities, and mild intellectual impairment. The ocular and other cranial nerve musculature was normal and a primary muscle pathology was excluded by a normal EMG.

It is difficult to offer precise risk estimates in genetic counselling. Recurrence risks to sibs of 'classical' isolated cases is 2%.<sup>6</sup> Risks to offspring are still uncertain, but may be similar, since there is no firm evidence that classical Moebius syndrome is autosomal dominant.

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- 1 von Graefe A. In: von Graefe A, Saemisch T, eds. *Handbuch der gerammten Augenheilkunde*. Vol 6. Leipzig: W Engelmann, 1880.
- 2 Moebius PJ. Uber angeborene doppelseitige Abducens-Facialis Lahmung. *Munch Med Wochenschr* 1888;35:91-4.
- 3 Moebius PJ. Uber infantilen Kernschwund. *Munch Med Wochenschr* 1892;39:17,41,55.
- 4 Jones KL. In: Smith DW, ed. *Recognizable patterns of human malformations*. 4th ed. Philadelphia: Saunders, 1988.
- 5 Hendersen JL. The congenital facial diplegia syndrome. *Brain* 1939;62:381-403.
- 6 Richards RN. The Moebius syndrome. *J Bone Joint Surg [Am]* 1953;35:437-44.
- 7 Baraitser M. Genetics of Moebius syndrome. *J Med Genet* 1977;14:415-7.
- 8 Walsh FB, Hoyt WF. *Clinical neuro-ophthalmology*. 3rd ed. Baltimore: Williams and Wilkins, 1969.
- 9 Van Allen MW, Blodi FC. Neurologic aspects of the Moebius syndrome. *Neurology (Minneapolis)* 1960;10:249-59.
- 10 Evans PR. Nuclear agenesis-Moebius syndrome. *Arch Dis Child* 1939;30:237-43.
- 11 Hellstrom B. Congenital facial diplegia. *Acta Paediatr* 1949;37:464-73.
- 12 Temtamy S, McKusick V. *The genetics of hand malformations*. New York: Alan R Liss, 1978.
- 13 Jorgenson RJ. Möbius syndrome, ectrodactyly, hypoplasia of bone and pectoral muscles. In: *Orofacial structures*. New York: The National Foundation, 1974:283-94.
- 14 Sugarman GI, Stark HH. Möbius syndrome with Poland's anomaly. *J Med Genet* 1973;10:192-6.
- 15 Sudrashan A, Goldie WD. The spectrum of congenital facial diplegia (Moebius syndrome). *Pediatr Neurol* 1985;1:180-4.
- 16 Gorlin RJ, Pindborg JJ. *Syndromes of the head and neck*. New York: McGraw-Hill, 1986.
- 17 Sproffkin BE, Hillman JW. Moebius syndrome: congenital oculo-facial paralysis. *Neurology (Minneapolis)* 1956;6:50-4.

- 18 Rubinstein AE, Lovelace RE, Beherens MM, Weisking LA. Moebius syndrome in Kallman syndrome. *Arch Neurol* 1975;32:480-2.
- 19 Hansen PA, Rowland LP. Mobius syndrome and facioscapulo-humeral muscular dystrophy. *Arch Neurol* 1971;24:31-9.
- 20 Harper PS, Dyken PR. Early onset dystrophia myotonica. *Lancet* 1972;ii:53-4.
- 21 Pitner SE, Edwards JE, McCormick FW. Observations on the pathology of Moebius syndrome. *J Neurol Neurosurg Psychiatry* 1965;28:362-74.
- 22 Mellinger JF, Gomez MR. Agenesis of cranial nerves. In: Myrianthopoulos NC, ed. *Malformations. Handbook of clinical neurology*. Vol 50. Amsterdam: North Holland Publishing Co, 1987:211-23.
- 23 Huebner O. *Über Angeborenen Kernmangel (infantile Kernschwund, Moebius)*. Charite Ann 1900:211.
- 24 Stabile M, Cavaliere NL, Scarano G, Fels A, Valiani R, Ventruto V. Abnormal BAEP in a family with Moebius syndrome: evidence for supranuclear lesion. *Clin Genet* 1984;25:459-63.
- 25 Baraitser M. Moebius syndrome. In: Myrianthopoulos NC, ed. *Neurogenetic directory part 1. Handbook of clinical neurology*. Vol 42. Amsterdam: North Holland Publishing Co, 1981:324-5.
- 26 McKusick VA. *Mendelian inheritance in man. Catalog of autosomal dominant, autosomal recessive and X-linked disorders*. 8th ed. Baltimore: Johns Hopkins University Press, 1988.
- 27 Wishnick MM, Nelson L, Reich EW, Hubbard L. Moebius syndrome with dominant inheritance. *Am J Hum Genet* 1981;33:96A.
- 28 Van der Wiel HJ. Hereditary congenital facial paralysis. *Acta Genet Statist Med* 1957;7:348.
- 29 Hanissian AS, Fuste F, Hayes WT, Duncan JM. Moebius syndrome in twins. *Am J Dis Child* 1970;120:472-5.
- 30 Ziter FA, Wiser WC, Robinson A. Three generation pedigree of a Moebius syndrome variant with chromosome translocation. *Arch Neurol* 1977;34:437-42.