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BRIEF REPORT — CASE REPORT

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A severe case of Moebius syndrome with calcification on the fourth ventricular floor

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Abstract We report the case of a Japanese girl with a severe type of Moebius syndrome. Her morphological features were a mask-like face, limitation of horizontal eye movements, severe bulbar palsy, multiple and bilateral arthrogryposis including the elbow, knee, and ankle joints, and clubfeet. After birth, her general condition became worse because of repeated apneic spells and aspiration pneumonias due to dysphagia. She finally required tracheotomy. Computed tomography (CT) of the brain revealed minute calcifications on the fourth ventricle floor; this may have been due to severe damage to the brain stem. It is most likely that the various manifestations in our patient were due to disturbance of the blood supply to arteries perfusing the brain stem and to some other arteries, at a critical stage of fetal development.

Key words Moebius syndrome · Calcification · Arthrogryposis multiplex congenita · Blood supply disturbance

Introduction

Moebius syndrome is classified as a subclavian artery supply disruption sequence, and is characterized by congenital facial nerve palsy and malformations of limbs and the orofacial area (Kumar 1990). It has been suggested that the involvement of the brain is either caused by a defect of the brain stem cranial nerve nuclei due to disruption of blood supply from the primary trigeminal nerve artery, or is associated with an obstruction or hypoplasia of the basilar and vertebral arteries and their branches at around week 6 of gestation (Bavinck and Weaver 1986).

Although Moebius syndrome represents various clinical manifestations, it is usually not progressive and the prognosis is not poor. However, some patients with the syndrome die within one year of life, mainly due to respiratory insufficiency caused by aspiration pneumonias (Thakkar et al. 1977). The clinical severity will be dependent on the degree of the brain stem damage.

We report here the case of a Japanese girl with Moebius syndrome with severe respiratory disorder and other multiple anomalies.

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Clinical report

A girl was born with a birth weight of 2460g to a 24-year-old G0P0 woman at the 41st week of gestation. There were no problems during the pregnancy, except for polyhydramnios. Family history for malformations was negative. The parents were not consanguineous. The Apgar scores at 1min and 5min were 7 and 9, respectively. Her length was 48cm, and head circumference 34cm. Because of her dysmorphologic features, she was transferred to our hospital soon after birth. Physical examination revealed the following abnormalities: mask-like face, hypertelorism, epicanthus folds, a flattened nasal root, micrognathia, a closed small mouth, left auricular and antihelical abnormalities, narrow shoulder, extensive limitation of the elbow joints, loss of the left third distal phalanx, hypoplastic nails on the left second and third fingers, the left arm shorter than the right one, severe multiple arthrogryposis, and talipes equinovarus. Both major pectoral muscles seemed normal. Her tongue was not hypoplastic but fasciculation was seen on the left side. She sometimes kept her eyes open for a few hours without blinking (Fig. 1).

Neurological findings included lack of ocular horizontal movements, bilateral facial paraplegia, absence of corneal reflex, and severe bulbar palsy. Deep tendon reflex was normal, and muscular tonus was within the normal limits. She had neither abnormal lacrimation nor a congenital heart disease. The blood pressures in each of her limbs were similar. Her karyotype was 46,XX.

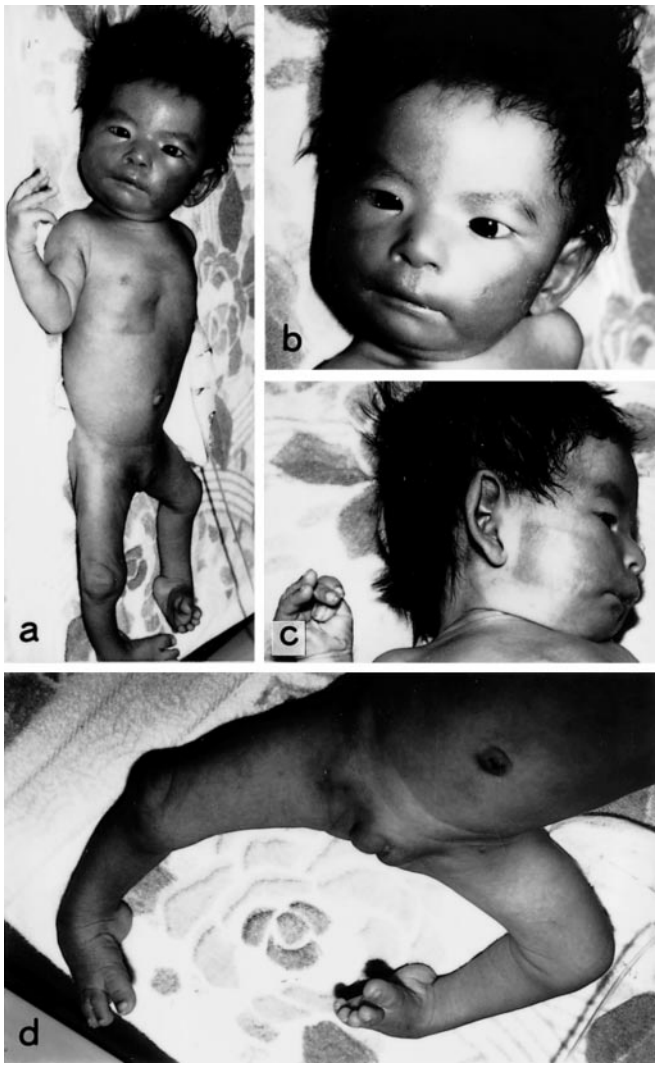

Fig. 1 Morphological features of the patient: the full-length figure with multiple arthrogryposis (**a**), mask-like face (**b**), auricular deformity (**c**), and club feet (**d**)

From age 1 month, sudden apneic spells of unknown origin appeared. A variety of manifestations seemed to be associated with the onset of the apnea: hiccup-like movements, stretching herself with a flushed face, and upper gazing. As these apneic episodes continued, resulting in cyanosis, she required intubation and artificial ventilation at the age of 1 month. At 2 months, she was free from the respirator. However, episodes of apnea of short duration and accompanied by bradycardia persisted even after extubation, and she needed the respirator again. At age 4 months, a tracheotomy was done for easier respiratory management and tube feeding. To ascertain the cause of the respiratory arrest, electroencephalography was performed twice, but no abnormality was shown. Computed tomography (CT) of the brain demonstrated minute calcifications on the fourth ventricular floor, suggesting tegmental necrosis of the brain stem (Fig. 2). There was neither perifocal edema nor an enlargement of the subdural space. A main trunk of the basilar artery was able to be identified.

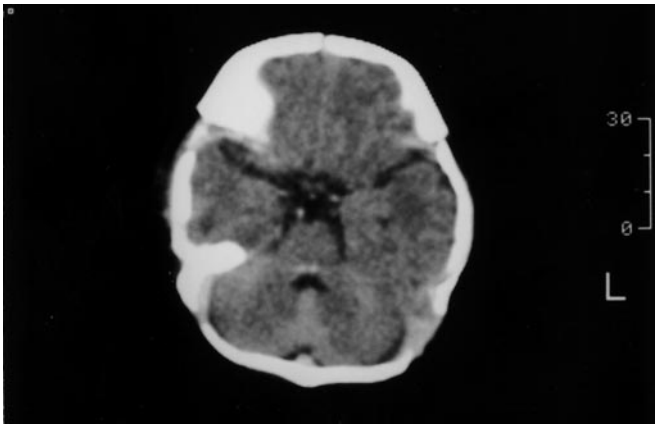

Fig. 2 Computed tomography (CT) scan of a pontine section at 1 month of age. Minute calcifications are seen on the fourth ventricle floor

Because of her bulbar palsy, she could not swallow adequately. Increasing the volume of feeding milk, an increasing frequency of aspiration pneumonia was noted. This was probably due to gastroesophageal regurgitation even if tube nutrition was performed. She is now 4 months old, and her weight is 2550 g.

Discussion

The clinical severity of Moebius syndrome may depend on the degree of the brain stem defect. Clinically, our patient had V,VI,VII,IX,X, and XII cranial nerve disturbances and respiratory control insufficiency. Calcification of the brain stem causing central respiratory dysfunction has been reported in some Moebius syndrome patients (D' Cruz et al. 1993; Charles et al. 1993). Govaert et al. (1989) reported a patient with severe symptoms, whose clinical course was similar to that in our patient. As minute calcifications on the fourth ventricle floor in both cases were detected by brain CT scanning, this diagnostic aid helps in the judgment of the clinical severity. The microcalcification on the fourth ventricular floor was explained as a consequence of damage to the tegmentum of the mid brain that was secondary to a blood flow disruption. The ischemic process may result in gliosis/calcification in and around the cranial nerve nuclei in the tegmentum (Thakkar et al. 1977).

During the 4th to 8th week of gestation, the remodeling of the blood circulation pattern in the brain stem and the differentiation of cranial nerve nuclei occur along with limb bud differentiation (Bavinck and Weaver 1986). At approximately 37–40 days of gestational age, the source of blood supply to the basilar artery changes from the primitive trigeminal artery to the vertebral/subclavian artery resulting from the regression of the former , and this causes the change of blood flow direction in the basilar artery from a rostocaudal to a caudal-to-rostral pattern (D'Cruz et al. 1993). If the sequential transition of blood supply to the

basilar artery is impaired, brain stem ischemia is likely to occur during this stage.

The limb defects associated with a brain stem lesion are also possibly due to vascular underperfusion. Although our patient had normal major pectoral muscles and the blood pressure of each limb was almost same, she had hypoplastic anomalies in the left upper extremity. This suggested a transient blood supply disturbance to the left upper extremity via the left subclavian/humeral artery. Therefore, the blood supply interruption in our case might have occurred at the basilar and/or bilateral vertebral arteries and the left humeral artery at around the 6th gestational week.

In addition to the left upper limb anomaly, our patient had clubfeet and multiple arthrogryposis. Arthrogryposis is sometimes present with Moebius syndrome, Poland anomaly, intestinal atresia, and/or gastroschisis, and these anomalies are assumed to be caused by vascular disruption. Based on the embryogenic development of vessels, Robertson et al. (1992) suggested that a simultaneous vascular disruption or a cluster of disruptive events occurred at around 6–8 weeks after conception in such disorders.

Anterior horn cells also differentiate at weeks 4–6 of gestation (Bayer et al. 1995), and developing anterior horn cells are affected easily by anoxia/hypoxia, resulting in the death of anterior horn cells or the failure of normal neuronal maturation (Horoupian and Yoon 1988). The loss of normal function of anterior horn cells leads to akinesis of the fetus, resulting in contractures of the involved joints (Hall 1996). Clubfoot is seen in one-third of Moebius syndrome patients (Henderson 1938; Baraitser 1977; Kumar 1990), and this is also assumed to be associated with vascular defects (Hootnick et al. 1982). Although it is not known in the present case whether arthrogryposis and clubfoot had been caused by direct disturbance of the blood supply to the anterior horn cells or by anoxic injury secondary to the general hypoxia, it is assumed that some hypoxic episodes occurred affecting these cells governing limb joints. Various manifestations in our patient are thus thought to be caused mainly by hypoxic injury due to blood supply disturbances in some organs at a critical stage of fetal development around the 6th week of gestation.

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