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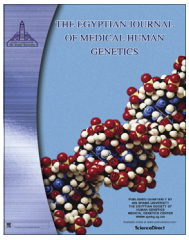

CASE REPORT

# Moebius syndrome with macular hyperpigmentation, skeletal anomalies, and hypoplasia of pectoralis major muscle in an Egyptian child

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**KEYWORDS**

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Ptosis;
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**Abstract** We report a 4 month old female infant, 3rd in order of birth of the first cousin consanguineous parents. The patient has congenital right facial nerve palsy, with asymmetry of facial expression during crying and difficulty in swallowing. Associated anomalies include abnormal facial features, bilateral finger anomalies, bilateral talipes equinovarus, kyphoscoliosis, hypotonia, high frequency hearing loss. Bilateral macular hyperpigmentation was detected in our patient on fundus examination which was not reported previously in Moebius syndrome cases. In addition there is hypoplasia of the right pectoralis major muscle.



## 1. Introduction

Moebius syndrome is a congenital, nonprogressive complete or partial facial nerve palsy, with limited abduction of one or both eyes [1]. Other associated features may include other cranial nerve dysfunction with deafness as well as orofacial, musculo-skeletal and neurodevelopmental problems [2–5], but they are not necessary for diagnosis, making the syndrome extremely variable in its clinical manifestations.

Although neither the etiology nor the pathogenesis of the syndrome have yet been elucidated, there are two theories: a developmental rhombomeric defect involving predominantly motor nuclei and axons as well as traversing long tracts due to a genetic cause [6], or an interruption in the vascular supply of the brainstem resulting in ischemia in the region of the facial cranial nerve nuclei owing to an environmental, mechanical or a genetic cause [7,8]. Moebius syndrome can also be considered as a complex regional developmental disorder of the brainstem [9].

We report a case with the typical features of Moebius syndrome who has in addition some unreported features after taking consent of the parents.

## 2. Case report

A 4 month old female, 3rd in the order of birth of 1st cousin consanguineous marriage. The patient was delivered at full

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term by cesarean delivery after uncomplicated pregnancy with no history of fever, drug intake or smoking by the mother. Her birth weight was 1.250 kg (< 5th percentile). The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of developmental delay and poor weight gain. Since birth the patient was admitted to neonatal intensive-care unit for 12 days due to poor suckling, difficulty in swallowing and low birth weight. There was no improvement of weight gain in spite of nutritional management. The mother noticed that her baby did not close her right eye completely during sleep with no blinking. The patient suffered drooling of saliva from the right side of the mouth. She also had developmental delay as she cannot support the neck. Family history was unremarkable. She had two healthy sibs. Both parents were normal.

On examination, her weight was 3.100 kg (below 5th percentile), her length was 53 cm (below 5th percentile), and her skull circumference was 35 cm (below 5th percentile). The patient had mask face, facial asymmetry, epicanthal folds, broad protruding flat low set ears more marked on the left side which had flat auricle and rudimentary ear lobule, microretrognathia, high arched palate, and tongue tie (Figs. 1 and 2). The patient had clenched fists, adducted thumbs, bilateral overlapping 2nd finger over thumb, bilateral flexion deformity of 4th and 5th proximal interphalangeal joints, left simian crease, dystrophic nails, and bilateral talipes equinovarus deformity (Figs. 3 and 4). There is kyphoscoliosis of the back more marked on thoracolumbar vertebrae. Abdominal, genital, and cardiac examinations were normal. Neurologic examination demonstrated mild hypotonia, normal pupil size and reactivity, convergent squint, limited abduction of the right and the left eye (6th nerve palsy), unilateral right facial palsy with no blinking, and the right eye was opened during sleep and crying (Fig. 5). She also had decreased response to loud voice. She had central uvula with normal tongue movement. Right pectoralis muscle is hypoplastic.

Abdomino-pelvic ultrasonography and ECHO cardiography were normal. Extended metabolic screen, serum lactate,

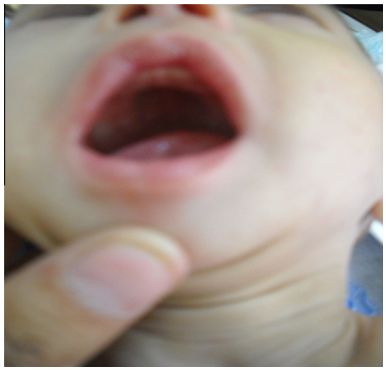

**Figure 2** High arched palate.

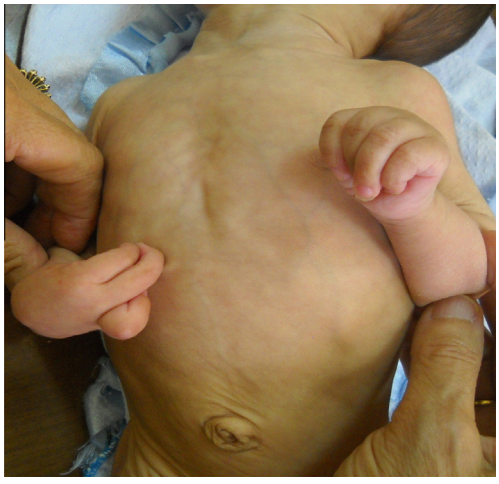

**Figure 3** Clenched fists, adducted thumbs, bilateral overlapping 2nd finger over thumbs, bilateral flexion deformity of 4th and 5th fingers.

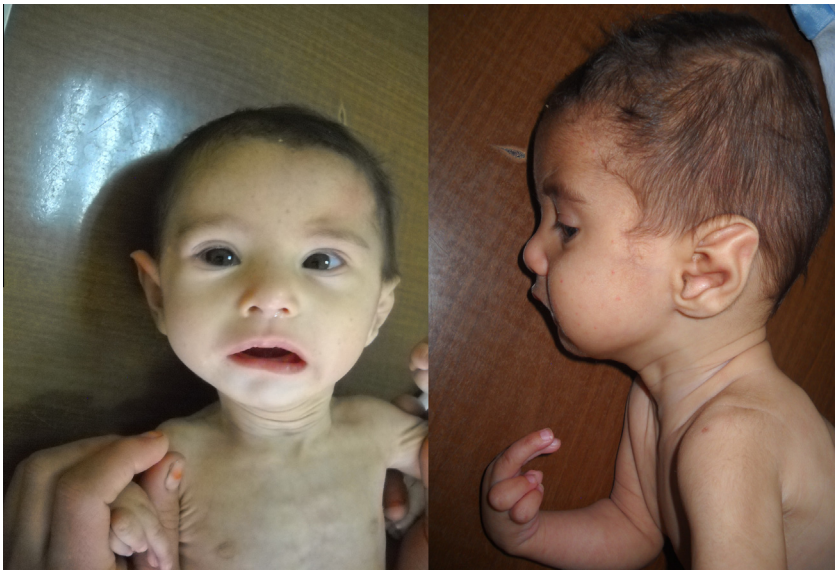

**Figure 1** Photo of the patient showing dysmorphic features, asymmetry of the masked face with loss of subcutaneous fat in neck and whole body.

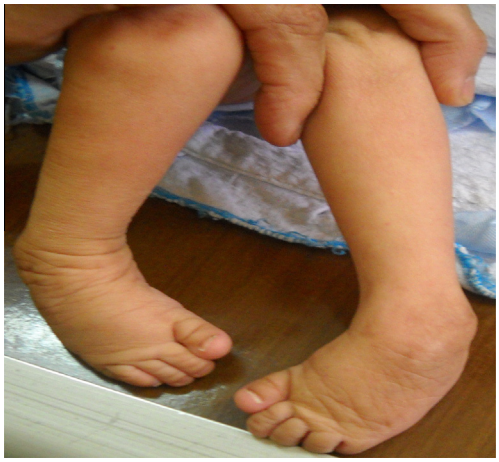

**Figure 4** Bilateral talipes equinovarus deformity.

**Figure 5** Right convergent squint of the opened right eye during crying.

serum ammonium and organic acids in urine were normal. Fundus examination revealed bilateral mild macular hyperpigmentation. Audiometry revealed right moderate and left severe high-frequency hearing loss due to conductive loss. Karyotype was normal. MRI revealed dilatation of the body and occipital horn of both lateral ventricles associated with the presence of cavum velum interpositum. The third ventricle is also dilated. Corpus callosum is uniformly thinned denoting hypoplasia (Fig. 6).

## 3. Discussion

The definition and diagnostic criteria for Moebius syndrome vary in different studies. In 1980 Von Graefe [10] and Moebius [11] accepted only cases with bilateral congenital facial diplegia and bilateral abducent nerve palsy. Dysfunction of other cranial nerves may also be present [4].

Later Henderson [12] broadened the definition and included cases with congenital unilateral facial palsy. Other studies are more restrictive and they require the presence of congenital musculoskeletal anomalies to make the diagnosis [13].

So it is evident that there is phenotypic variation in Moebius syndrome as reported also by Stabil et al. [6]. He presented a family with variable features of Moebius syndrome. One member had complete VI, VII palsy and mental retardation. His brother had left convergent strabismus and mental retardation, while his sister has only mental retardation.

Our patient has right sided facial paralysis (lower motor neuron, as both upper and lower halves are affected), bilateral convergent squint (bilateral 6th nerve palsy). There is mask like face on the right side of the face and bilateral convergent squint with inability to abduct both eyes.

Craniofacial abnormalities reported in Moebius syndrome include small palpebral fissures, epicanthic folds, hypertelorism, flat nasal bridge, external ear defects, microstomia, high arched palate, retromicrognathia, and external ear defects [4]. All these features are detected in our patient. Bifid uvula and cleft palate are described in some patients [14] and are not detected in our patient.

Hypoglossal nerve is affected with resulting tongue paralysis and hypoplasia is reported in some patients and is not detected in our patient [15]. Additional features include hearing loss and other cranial nerve dysfunction [5]. Our patient had bilateral conductive hearing loss.

A striking feature of Moebius syndrome is the high incidence of associated anomalies. These include dextrocardia[16], kidney and ileocaecal valve anomalies, club foot, arthrogryposis multiplex congenita [17], klippel-Feil anomaly, Poland anomaly [18], anosmia, and hypogonadotrophic hypogonadism (Kallmann syndrome) or hypogonadism alone [19].

The Poland sequence, characterized by ipsilateral hand malformation and partial or complete absence of pectoralis major muscle and breast, syndactyly, brachydactyly and hypoplasia of hands, is concurrent with Moebius syndrome in 15% of patients [18]. In our patient the pectoralis major muscle can be detected but it is hypoplastic.

Fundus examination of our patient detected bilateral macular hyperpigmentation which has not been reported previously in Moebius syndrome cases.

Our patient has hypotonia. Intrauterine growth retardation and hypotonia with delay in motor development have also been noted in some cases [20].

Limb malformations are frequently detected in these cases [16,21]. These include unilateral or bilateral club foot. Digital anomalies are also commonly seen and include syndactyly, brachydactyly, clinodactyly, ectrodactyly, terminal transverse defects, metacarpal abnormalities, stiffness of index fingers, bilateral valgus deformity of distal phalanges of big toes [4] and talipes equinovarus [16]. In our patient skeletal anomalies included kyphoscoliosis, bilateral flexion deformity of 4th, 5th proximal interphalangeal joints, and bilateral talipes equinovarus deformity.

Mental retardation is overdiagnosed in Moebius syndrome owing to the mask like face as well as speech difficulty. Mild to severe mental retardation occurs in about 10–50% in different studies [20,22].The mentality in our patient is normal as she is 4 months and she can recognize her mother.

Feeding problems at birth can be detected in 86% of Moebius syndrome cases [4]. Our patient suffered difficulty in sucking and swallowing at birth and till now she is suffering from difficulty in swallowing.

Associated syndromes included Poland syndrome [18,23]. Poland syndrome is characterized by unilateral absence of

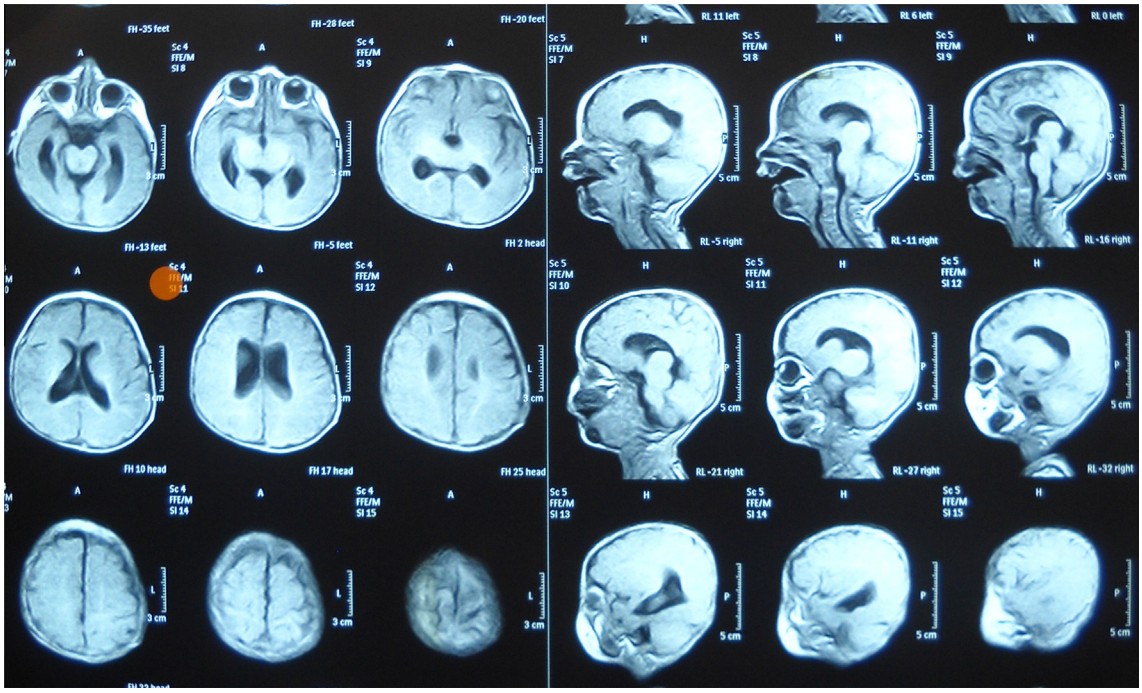

**Figure 6** MRI brain.

pectoralis major muscle and ipsilateral syndactyly. Our patient has hypoplastic right pectoralis major muscle.

As in our case, a large Italian case series demonstrated that nearly half of the patients had strabismus, most of whom were esotropic [24].

Our patient had bilateral conductive hearing loss. In cases with Moebius syndrome, conductive (due to serous otitis media) or sensorineural hearing loss may be noted [15]. Our patient MRI revealed dilatation of the body and occipital horn of both lateral ventricles associated with the presence of cavum velum interpositum. The third ventricle is also dilated. Corpus callosum is uniformly thinned denoting hypoplasia. Neuroimaging (CT and MRI) findings of Moebius syndrome include hypoplasia of the pons or medulla with corresponding CN6 and CN7 hypoplasia, absence of the medial colliculus at the level of the pons, absence of the hypoglossal prominence suggestive of CN12 nuclei hypoplasia, cerebellar hypoplasia or absence of middle cerebellar peduncles, depression of the 4th ventricle, and calcification in the pons in the region of the CN6 nuclei [25–30].

Inheritances in most cases are sporadic and both sexes are equally affected [31]. However pedigrees with autosomal dominant, autosomal recessive and x-linked pattern have been described [32]. Graziadio et al. [33], described a familial case suggestive of autosomal dominant inheritance presenting with skeletal anomalies. Our patient most probably is a sporadic case although parents are consanguineous. It is to be not that consanguinity is high in our society [34].

As regards the pathogenesis of Moebius syndrome neuropathologic findings demonstrated four categories. These included hypoplasia of cranial nerve nuclei due to maldevelopment, neuronal loss, and neuronal degeneration secondary to a defect in the facial peripheral nerve, decreased neurons as well as degeneration, focal necrosis, gliosis and calcification in the brain stem nuclei due to vascular insufficiency or infections or primary myopathic changes [35].

Verzijl demonstrated a spectrum of electrophysiologic abnormalities in Moebius syndrome patients which suggest defects at the supranuclear, nuclear or peripheral levels which denotes that the syndrome is a complex regional developmental disorder of the brainstem [9].

Slee et al. [36], observed deletion of 13q12.2 in a girl with Moebius syndrome, which suggested that a gene responsible for Moebius syndrome is located in the region 13q12.2-q13. On the other hand Nishikawa et al. reported a boy with a Moebius-like syndrome associated with a 1;2 chromosome reciprocal translocation: t(1;2)(p22.3;q21.1). Also, Donahue [37] et al. described a Moebius syndrome patient with Poland syndrome with a reciprocal translocation between chromosomes 1 and 11: t(1;11)(p22;p13) and he suggested that a disrupted gene at 1p22 may be the cause of the syndrome. So with the exception of the rare HOXA1 or TUBB3 mutations that cause atypical Moebius syndrome, its genetics remain unidentified [38].

The pathogenesis of cranial nerve palsies associated with limb anomalies is difficult to explain. An ischemic process resulting from interruption of vascular supply during the 4th–6th week of gestation may result in facial and limb anomalies [39]. There is also some evidence of a toxic origin of Moebius syndrome in some cases. A strong association between the syndrome and early prenatal use of misoprostol [40], ergotamine [7], cocaine [41] and zonisamide [42] has been implicated to cause ischemia or vasoconstriction of the embryo and result in the syndrome.

To conclude: It is evident that Moebius syndrome is variable in its clinical manifestations. We reported a patient with

the typical features of the syndrome who has in addition hypoplasia of pectoralis major muscle, skeletal anomalies as well as macular hyperpigmentation which was not reported before in this syndrome.

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