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Case report

Möbius syndrome in a male with XX/XY mosaicism

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ABSTRACT

We report the case of a 2-year-old male with congenital symmetric facial diplegia, and bilateral paralysis of abduction of the eyes. Findings were compatible with a diagnosis of Möbius syndrome. Routine G-banded chromosome analysis revealed a mosaic karyotype with 40 cells showing normal 46,XX and 10 cells showing normal 46,XY. An XX male attributed to XX/XY mosaicism was diagnosed. The phenotype of our patient did not coincide with any described form of XX reversal syndrome, but and was a unique combination of both syndromes. The disorder of this patient is likely to represent a genetic condition with pleiotropic effects on brain development and sex determination, providing adding further evidence for the heterogeneity of Möbius syndrome and sex reversal syndromes.

1. Introduction

Möbius syndrome has been defined as congenital paresis or paralysis of the facial nerve that can be accompanied by paralysis or dysfunction of other cranial nerves, either unilaterally or bilaterally. The abducens nerves are most frequently involved, with concomitant paralysis of the hypoglossal nerve and hemiatrophy of the tongue present in one-third of cases. Most have congenital dysphagia, drooling, malocclusion, velopharyngeal incompetence, dysarthria, and delayed speech. Trigeminal nerve involvement with trismus is less frequent. Talipes equinovarus, malformations of the hands and fingers, and Poland anomaly may be associated.

Multiple factors are probably involved in pathogenesis, which is understandable in view of the many sites of pathology. Although often caused by environmental effects during pregnancy [1], a few cases have been familial with autosomal dominant and perhaps autosomal recessive inheritance. A pedigree has been described with seven affected members and a reciprocal translocation between chromosomes 1 and 13, demonstrable by banding techniques, which suggests that cytogenetic investigation is appropriate in the evaluation of

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affected patients [2]. We report the case of a Möbius syndrome patient with 46,XX/46,XY mosaicism.

2. Case report

The patient, the first son born to a 34-year-old mother and 35-year-old father, was conceived by *in vitro* fertilization because of his mother's fallopian tube obstruction. There was no family history of cranial nerve palsy. Pregnancy was uncomplicated, delivery was normal at 39 weeks, birth weight was 2550 g, and Apgar scores were unknown. He had feeding problems owing to inefficient sucking and swallowing due to paresis of the facial muscles as a newborn.

On physical examination at age 18 months, the child had a height of 84 cm (50–75 percentile), weight of 11 kg (25–50 percentile), and head circumference of 47.2 cm (25–50 percentile). A characteristic craniofacial appearance included epicanthic folds, a flattened nasal bridge, micrognathia, a high arched palate, hypertelorism, a small mouth with down-turned corners, and mild ptosis. Neurologic examination noted bilateral facial diplegia and abducens nerve palsy with conjugated horizontal gaze palsies. There was a palsy of the upper face with a relative sparing of the lower half of the face, including the perioral muscles and platysma. Sucking remained slow, but no aspiration or respiratory distress occurred. The eyes could not be totally closed. No other abnormal physical signs were noted, including talipes equinovarus or hypoplasia of the pectoralis muscle. The genitalia were normal for age, with both testes descended. At age 24 months, the Bayley Scales of Infant Development (BSID-II) showed a mental developmental age of 20 months, motor developmental age of 24 months, and language developmental age of 19 months. Brainstem auditory evoked response showed no sensorineural hearing loss. Echocardiogram was normal. Magnetic resonance imaging of the head including the brainstem was normal. He received speech therapy for his dysarthria. At age 3.5 years, electromyography revealed bilateral facial neuropathy. Routine G-banded chromosome analysis revealed a mosaic karyotype with 40 cells showing normal 46,XX and 10 cells showing normal 46,XY. An XX male attributed to XX/XY mosaicism was diagnosed. Abdominal CT scan revealed no female genital organ. At age 7 years, no significant abnormality was found in psychomotor development and the child had good performance at school. The Wechsler Intelligence Scale for Children, Third Edition (WISC-III) showed a verbal IQ of 83 and a performance IQ of 106. The patient showed the typical facial picture of Möbius syndrome.

3. Discussion

The exact etiology and pathogenesis of Möbius syndrome remain unknown, with two causes proposed: primary genetic [3] and primary ischemic [4]. Teratogenicity is suggested as a pivotal etiologic factor in both [5], but postulated etiologic mechanisms are based on limited pathologic observation. While the essential features of the syndrome are somewhat limited, it can be accompanied by neuromuscular and other abnormalities [6–8]. Various craniofacial, musculoskeletal, and cardiac malformations, as well as mental retardation, may be associated, giving rise to the term Möbius-like syndrome [9]. The disorder is usually sporadic, although a few cases have been familial. Ziter et al [2] observed congenital facial diplegia in seven members of three generations of a family with reciprocal translocation between chromosomes 1 and 13. Slee et al [10] observed deletion of 13q12.2 in a female patient. Kremer et al [11], by linkage analysis in a Möbius syndrome family, excluded chromosome 13q as a candidate region and found linkage markers at 3q21–q22. Localization of the present gene argues for genetic heterogeneity. Genetic heterogeneity has been suggested before, based on the clinical variability of the syndrome and segregation of the disorder in families [12].

Human males with a 46,XX karyotype were first described in 1964 by three different groups of investigators [13–15]. The frequency of this syndrome is estimated at 1 in 20,000 newborn males, although there are considerable geographic variations [16]. Most patients (85%) have a normal male phenotype at birth and are usually diagnosed after puberty when consulting a physician due to hypogonadism, gynecomastia, and/or infertility [17]. Although the clinical and endocrinologic features of XX males resemble those of 47, XXY Klinefelter's syndrome, XX males present normal or even low height and do not differ from the general population with regard to intelligence [18]. Our case is a XX male with XX/XY mosaicism. Mosaicism including a second cell line with a Y chromosome has been claimed as the origin of some cases of XX males.

The unique feature in this patient is a XX male with Möbius syndrome, and although numerous cases have been reported, no previous cases with sex reversal have been described. Möbius syndrome is a rare disorder, with incidence in the population not determined. The incidence of XX maleness is 1/20,000. Certainly a rare occurrence of both disorders in one patient raises the possibility of two phenotypes etiologically related. While sex-reversal syndromes are not usually associated with any neurologic abnormality, several multiple malformation syndromes can cause genital ambiguity and also result in neurologic involvement. In our reviews, sex-reversal patients with chromosomal deletion, such as deletion of 9p, 10q, or 18p, have development delay and neurologic signs [19–21]. This case of Möbius and XX sex-reversal syndrome is likely to represent a genetic condition with pleiotropic effects on brain development and sex determination, providing evidence of heterogeneity in Möbius and sex-reversal syndromes.

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