

Myhre syndrome with facial paralysis and branch pulmonary stenosis

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List of key features

Branch pulmonary stenosis
Decreased joint mobility
Facial dysmorphism
Hearing loss
Hemivertebrae
Left facial paralysis
Recurrent respiratory infections
Short stature

Summary

Our patient is the first-born child of healthy non-consanguineous parents with three previous pregnancies, one ectopic pregnancy and two miscarriages at 8 weeks of gestation. Paternal age at birth was 38 years and maternal age 27 years. A 'twisted' spine was observed at the 20-week scan, but subsequent scans revealed no spinal abnormality. Pregnancy was otherwise uncomplicated and there was no intrauterine growth restriction. She was born at 41 weeks by an emergency Caesarean section, after failed ventouse and forceps deliveries, with a birth weight of 3.08 kg (9th centile). She remained in the postnatal ward for 1 week because of neonatal jaundice. Left facial nerve palsy was present at birth. This caused limited tongue movement and feeding difficulties during infancy. Cleft palate was excluded.

At 16 months of age, the child underwent chest radiography for a chest infection, which led to the identification of butterfly vertebrae at T9 and T10 with mild scoliosis. Failure to thrive, hearing loss with bilateral middle-ear effusions and recurrent chest infections are prevailing medical issues. A 2/6 systolic murmur was identified and confirmed by echocardiography as branch pulmonary stenosis. There are no behavioural concerns and no problems with fine nor gross motor development; the child walked independently at 12 months. She is undergoing speech and language therapy for poor articulation and delayed speech development.

On examination at 2 years and 5 months, her height was 75 cm (5.5 cm below the 0.4th centile), her weight was 10.7 kg (9th centile) and her head circumference was 48.5 cm (50th centile). She had facial dysmorphism

including a broad forehead, hypertelorism, a short philtrum and prognathism. Brachydactyly, mild clinodactyly of the fifth fingers, a sacral dimple, second and third toe syndactyly, tiptoe walking and left facial paralysis were also observed. She has a small strawberry naevus on her nose, which developed at 1 month of age.

Investigations

Investigations showed a normal female karyotype (46, XX) and array comparative genomic hybridisation analysis on an Agilent ISCA 60 K oligoarray (Agilent Technologies, Santa Clara, CA) detected no major imbalance. DNA analysis of JAG1 and NOTCH2, for the Alagille syndrome, did not detect any mutations. The diagnosis of Myhre syndrome was suspected because of the short stature and pulmonary stenosis and was confirmed by the identification of the SMAD4 mutation c.1499 T>C (p.Ile500Thr) in exon 13. This mutation was not identified in parental samples and, therefore, most likely arose *de novo*.

Discussion

Molecular testing for the Alagille syndrome was undertaken in our patient due to the facial features, pulmonary stenosis and butterfly vertebrae. This was negative and the diagnosis of Myhre syndrome was subsequently considered and confirmed on molecular analysis of SMAD4.

Myhre syndrome is a rare autosomal-dominant condition, with multisystem involvement. First described by Myhre *et al.* (1981), it is characterized by short stature, facial dysmorphism (short palpebral fissures, prognathism, midface hypoplasia and short philtrum), generalized muscle pseudohypertrophy, thickened skin and decreased joint mobility. Other commonly reported features include hearing loss (both sensorineural and conductive), developmental delay with intellectual disability, behavioural problems, skeletal dysplasia, cardiac defects, ocular anomalies and delayed puberty. Complications include pericarditis (Picco *et al.*, 2013), recurrent upper and lower respiratory tract infections (Michot *et al.*, 2014) and other respiratory complications such as tracheal stenosis (McGowan *et al.*, 2011).

Fig. 1



Two year old patient with Myhre syndrome and left facial paralysis.

Our patient (Figs 1 and 2) shows many of the common features listed above, but with the absence of any skin thickening or muscular pseudohypertrophy. At 2 years of age, our patient is, to our knowledge, the youngest reported case to date. The youngest patients previously reported were both 4 years and 5 months of age (Lopez-Cardona *et al.*, 2004; Caputo *et al.*, 2012). In a recent review of Myhre syndrome, 55 out of 56 patients were described as having muscular pseudohypertrophy or a muscular build, and all but four (with data not available on six patients) had thickened skin (Le Goff *et al.*, 2014).

In addition, this child has congenital left facial nerve palsy and branch pulmonary stenosis. Left facial paralysis has only been reported in the canonical description (Myhre *et al.*, 1981). Congenital cardiac defects are common in Myhre syndrome, including patent ductus arteriosus and aortic valve stenosis. Branch pulmonary stenosis, as diagnosed in our patient, has been reported only in one previous case (Whiteford *et al.*, 2001) – that is, in a boy who underwent pulmonary artery stenting at 9 years of age. Advanced paternal age has been noted in the majority of previously reported cases, and the paternal age was 38 years in our study.

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Fig. 2



Patient exhibiting absence of muscular pseudohypertrophy.

Conflicts of interest

There are no conflicts of interest.

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