Cardiology in the Young

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Myhre syndrome: expanding its paediatric phenotypic spectrum

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Brief Report

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Abstract

Myhre syndrome is a rare disease secondary to pathogenic variants in *SMAD4* gene. It is a multisystem disease characterised by short stature, deafness, joint stiffness, craniofacial dysmorphism, and potential cardiac manifestations. Herein, we report two new paediatric cases of Myhre syndrome who, additionally, presented with mid-aortic syndrome. This confirms and extends the scarce reports describing the association between these two entities.

Myhre syndrome is a rare connective tissue disease caused by pathogenic variants in mothers against decapentaplegic homolog 4 (*SMAD4*) gene, located in 18q21.2, causing proliferation of abnormal fibrous tissues.[1,2] It has been reported in approximately 90 individuals with molecular confirmation in 70.[3] It is a multisystem disease characterised by short stature, deafness, neurodeveloppmental delay, joint stiffness, skeletal anomalies, and characteristic facial dysmorphism.[3] Besides, Myhre syndrome involves cardiovascular, respiratory, gastrointesintal and skin systems.[2,4] Herein, we report two new paediatric cases of Myhre syndrome caused by *de novo SMAD4* pathogenic variants associated with mid-aortic syndrome.

Case report

Patient 1

An 11-day-old male newborn from a non-consanguineous parents was referred for evaluation of a heart murmur (Table 1). He was the second pregnancy of a mother with lupus erythematosus. His prenatal brain magnetic resonance revealed mild bilateral ventriculomegaly and mild dysgenesis of the corpus callosum, confirmed shortly after birth. The amniocentesis showed normal karyotype. He was born by elective caesarean section for intrauterine growth retardation at 34 weeks of gestation with a birth weight of 1800 g (9^{th} centile, −1.4 SD) and length 41.5 cm (5^{th} centile, −1.9 SD). On examination, he presented hypertolorism, short philtrum, short neck and bilateral single palmar crease. His echocardiogram showed a thoracic aortic coarctation for which a percutaneous transluminal angioplasty was performed with amelioration of the aortic gradient. Two months later, he required a second percutaneous transluminal angioplasty for aortic recoarctation without significant improvement. Hence, surgical intervention with extended coartectomy with term-terminal anastomosis was performed. Despite initial success, he required three further percutaneous transluminal angioplasties of the thoracic aorta due to recoarctation with a stent placement at the level of the proximal descending aorta during the latter procedure. At the age of 1.7 years, he required another percutaneous transluminal angioplasty of the implanted stent and a stent within a stent implantation for stent stenosis. After his latter procedure, he presented biphasic stridor due to mild subglottic stenosis secondary to a synechia, which was resected without complications. At 2.3 years of age, he was diagnosed with mid-aortic syndrome after his CT angiography revealed diffuse narrowing of the descending thoracoabdominal aorta. Surgical intervention was excluded at that time for the high complexity of his arterial disease and his young age. He required two further percutaneous transluminal angioplasties for in-stent restenosis at the age of 7.0 and 8.5 years (Fig 1). He is currently on three antihypertensive agents with stage 1 hypertension 1.9 years after his last procedure.

Meanwhile, he presented epilepsy, bilateral conductive hearing loss, and neurodevelopmental delay. A clinical exome sequencing was performed and he was found to be heterozygous for a *de novo* pathogenic variant in *SMAD4* gene [p. Ile500Val (NM_005359.5:c.1498A>G)], consistent with Myhre syndrome.

Table 1. Clinical features of our two new children with Myhre syndrome.

	Patient 1	Patient 2
Sex	Male	Male
Age MS diagnosis, years	10.7	8.4
Follow-up, years	10.8	10.5
SMAD4-affected residue	Ile500Val	Ile500Val
Targeted gene/exome sequencing	Exome sequencing	Exome sequencing
Blood pressure control	Satge 1 hypertension	Satge 1 hypertension
Mid-aortic syndrome	+	+
Age diagnosis, years	2.2	2.9
Extent of the disease	Descending thoracic aorta, narrowed coeliac axis, superior and inferior mesenteric arteries, and renal and iliac arteries.	Descending thoracic aorta, narrowed coeliac axis, and narrowed left renal artery.
Treatment (n)	Surgery (1) PTA (8) with two stent implantation	Nil
Intellectual disability	+	+
Epilepsy	+	–
Altered puberty	+	+
Hearing loss	+	+
Pseudopapilledema	–	+
Short stature	+	+

MS = Myhre syndrome; PTA = percutaneous transluminal angioplasty.
+: present; –: absent.

Patient 2

A 2.9 year-old boy was referred for hypertension. Unfortunately, there was no available data regarding his prenatal history. On examination, he had broad nasal bridge and bilateral clynoadctily of the fifth finger. Moreover, he presented hearing loss, ocular pseudopapilledema, and short stature. His echocardiography showed isolated pericardial effusion without haemodynamic compromise which self-resolved over the following months. A CT angiography revealed narrowed thoracic and abdominal aorta consistent with mid-aortic syndrome diagnosis. He has not required any interventions to date. He is currently on angiotensin-converting enzyme inhibitor with stage 1 hypertension. He underwent a clinical exome sequencing and was found to carry a pathogenic variant in *SMAD4* gene [p. Ile500Val (NM_005359.5: c.1498A>G)] associated with Myhre syndrome.

Discussion

This study confirms and extends the previously reported association between Myhre syndrome and mid-aortic syndrome.

Consistent with the majority of reported Myhre syndrome cases, our two patients were secondary to *de novo* heterozygous mutations in *SMAD4*.[8,9] *SMAD4* gene encodes the SMAD4 transducer protein necessary for either bone morphogenic proteins signalling and transforming growth factor-beta (TGF-β).[9] Although the natural history of Myhre syndrome remains uncertain, Lin et al hypothesised that the spectrum of cardiovascular diseases relates to the capability of the SMAD4 protein to integrate different signalling pathways such as the TGF-β and bone morphogenic proteins.[3,5] As TGF-β is a key factor of fibrotic disease, a pool of pro-fibrotic factors at the area of the injury could appear.[4] This might potentially explain the fact that Myhre syndrome patients are susceptible to post-intubation tracheal stenosis, likewise our first patient.[8] Hence, extreme caution with intubation has been recommended in Myhre syndrome patients.[8]

About 70% of Myhre syndrome patients present cardiovascular abnormalities, namely patent ductus arteriosus, pulmonary hypertension, aortic or mitral valve stenosis, and pericardial diseases.[4] In this regard, our second patient presented mild pericardial effusion which self-resolved. Moreover, Lin et al described that 5.6% (3/54) of the reported Myhre syndrome patients had mid-aortic syndrome, characterised by severe narrowing of the distal thoracic and abdominal aorta usually involving visceral and renal arteries.[5] In our institution, the two patients with Myhre syndrome diagnosis presented with mid-aortic syndrome. Besides, two out of the eight patients with mid-aortic syndrome (25%) followed up in our centre had Myhre syndrome. Due to the small sample size of our cohort, we could not determine whether patients with Myhre syndrome and mid-aortic syndrome have worst prognosis compared to patients with isolated mid-aortic syndrome.

Medical therapy represented the first-line treatment in our two patients, and none of them underwent surgery for mid-aortic syndrome. This could be related to the young age of both and the fact that some studies have proposed to postpone surgical intervetion until adolescence, when idiopathic mid-aortic syndrome seems to stabilise and best long-term results have been described.[6,7]

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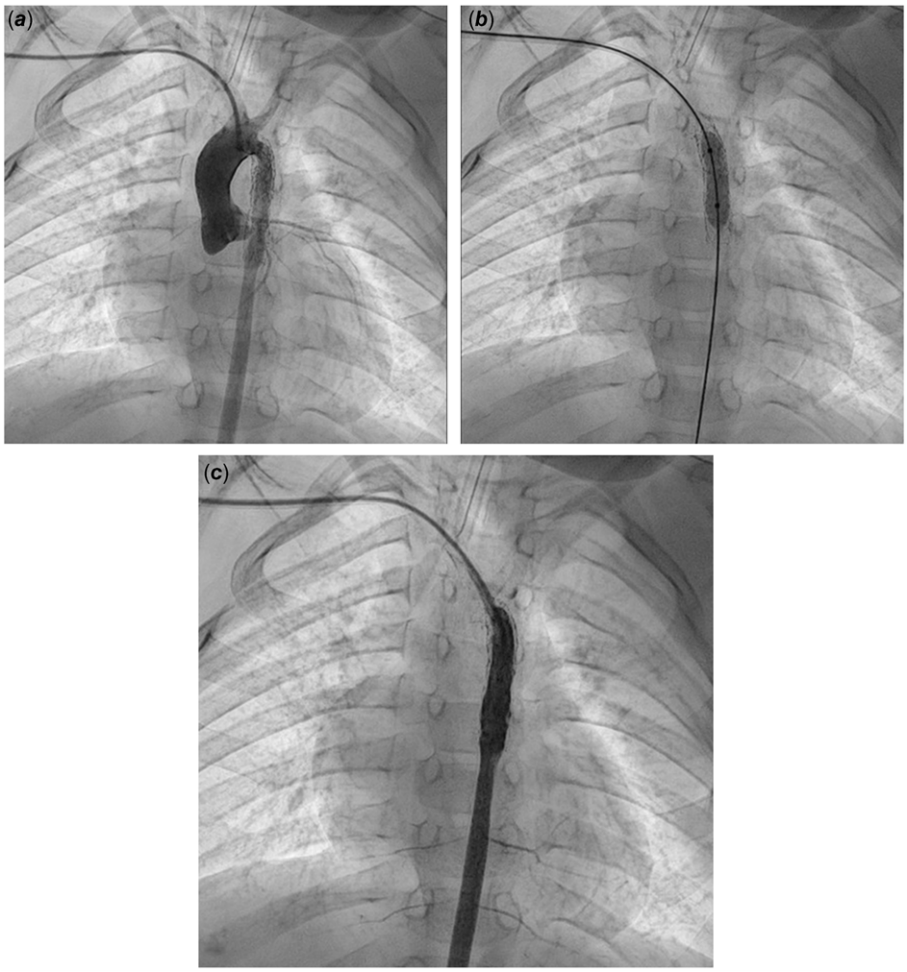

Figure 1. Catheterism angiography of patient 1. (*A*) Angiography taken before percutaneous transluminal angioplasty showing in-stent stenosis. (*B*) Percutaneous transluminal angioplasty. (*C*) Angiography after the percutaneous transluminal angioplasty with improvement of the in-stent stenosis (from 4.5 to 8 mm) with persistent hypoplastic thoracic aorta.

In conclusion, our findings highlight the importance of suspecting mid-aortic syndrome in patients with Myhre syndrome diagnosis and, therefore, how paramount regular cardiovascular surveillance is in Myhre syndrome patients. Further studies including larger cohorts and longer-term follow-up are required to better define risk stratification and treatment options of these patients.

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Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides and have been approved by the institutional committee of Hospital Sant Joan de Déu.

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