Eur J Pediatr
DOI 10.1007/s00431-016-2761-3

ORIGINAL ARTICLE

Natural history and life-threatening complications in Myhre syndrome and review of the literature

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Received: 18 December 2015 / Revised: 8 August 2016 / Accepted: 15 August 2016

Abstract Myhre syndrome (OMIM 139210) is a rare developmental disorder inherited as an autosomal dominant trait and caused by a narrow spectrum of missense mutations in the *SMAD4* gene. The condition features characteristic face, short stature, skeletal anomalies, muscle pseudohypertrophy, restricted joint mobility, stiff and thick skin, and variable intellectual disability. While most of the clinical features manifest during childhood, the diagnosis may be challenging during the first years of life. We report on the evolution of the clinical features of Myhre syndrome during childhood in a subject with molecularly confirmed diagnosis. The clinical records of 48 affected patients were retrospectively analysed to identify any early clinical signs characterizing this disorder and to better delineate its natural history. We also note that pericarditis and laryngotracheal involvement represent important life-threatening complications of Myhre syndrome that justify the recommendation for cardiological and ENT follow-up for these patients.

Conclusion: Short length/stature, short palpebral fissures, and brachydactyly with hyperconvex nails represent signs/features that might lead to the correct diagnosis in the first years of life and direct to the proper molecular analysis. We

Revisions received: 14 July 2016; 9 August 2016

Communicated by Beat Steinmann

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Published online: 25 August 2016

underline the clinical relevance of pericarditis and laryngotracheal stenosis as life-threatening complications of this disorder and the need for careful monitoring, in relation to their severity.

What is Known:
- *The clinical and radiological signs of the disease in children older than 7–8 years.*
- *Pericarditis, sometimes occurring with constrictive pericardium requiring pericardiectomy, has been reported as a recurrent feature but has not been adequately stressed in previous literature.*

What is New:
- *Short length/stature, short palpebral fissures, brachydactyly with hyperconvex nails represent clinical signs that might lead to diagnosis in the first years of life.*
- *Review of the literature showed that pericarditis and laryngotracheal complications represent major recurrent issues in patients with Myhre syndrome.*

Keywords Myhre syndrome · Pericarditis · Cardiac tamponade · Laryngotracheal stenosis

Abbreviations

BMI	Body mass index
CT	Computerized tomography
ENT	Ear nose throat
FISH	Fluorescence in situ hybridization
MRI	Magnetic resonance imaging
MYHRS	Myhre syndrome
SMAD4	SMA- and MAD-related protein 4

Introduction

Myhre syndrome (MYHRS) (OMIM 139210) is a rare developmental disorder inherited as an autosomal dominant trait and caused by a narrow spectrum of missense mutations in *SMAD4* [5, 11]. MYHRS was originally described 35 years ago [19]; since then, 69 individuals have been reported, 48 of whom with molecularly confirmed diagnosis [2, 4, 5, 7, 9, 11, 12, 18–20, 23]. MYHRS is characterized by a distinctive face characterized by short palpebral fissures, mid-face hypoplasia, short philtrum, prognathism, narrow mouth, and small ears. The other major clinical features include variable intellectual disability, short stature, limited joint mobility (with particular difficulty in fist-clenching and arm-raising), thickened skin, and muscular pseudohypertrophy [18]. Hearing loss, skeletal anomalies, and brachydactyly also recur in affected subjects. Patients with MYHRS can exhibit numerous long-term complications, including obesity, arterial hypertension, broncho-pulmonary insufficiency, laryngotracheal stenosis, pericarditis, and recurrent infections [12]. While MYHRS should be an easily recognizable disorder, the majority of patients reported in the literature are adults or adolescents. The poor delineation of the clinical "phenotype" of the disorder during childhood likely explains the relatively late diagnosis in a significant proportion of patients.

Here, we report on the evolution of clinical phenotype during childhood in a boy with molecularly confirmed diagnosis of MYHRS. Of note, the child exhibited pericarditis and cardiac tamponade as life-threatening complications. Retrospective analysis of the clinical records suggests that this feature has not been adequately stressed in previous literature, in relation to its severity and the necessity for careful monitoring.

Clinical report

The propositus was a child of healthy non-consanguineous parents. He was born at 37 gestation weeks by vaginal delivery after an uneventful pregnancy. At birth, his weight and length were 2225 g (<3rd centile) and 43 cm (<3rd centile), respectively, while Apgar scores were 1 min: 9, 5 min: 10. Aside from mild aortic coarctation, no other abnormalities were noticed. His early psychomotor development was recorded as normal, but he was subsequently found to have a delay in speech development. He was seen in our Clinical Genetics Unit at 9 months of age. Length, weight, and head circumference were below the 3rd centile. Facial features included slightly short palpebral fissures, down-turned mouth, and superiorly protruding ears (Fig. 1a–c). Brachydactyly and hyper-convex nails were also observed in both hands and feet (Fig. 1d–f). Clinodactyly of the 5th finger bilaterally was noted.

He had recurrent respiratory infections during the first 3 years of life, with otomastoiditis and pneumonia. Immunological tests showed selective IgA deficiency. He also had transient hypocalcaemia without seizures. At the age of 7 months, the ionized calcium was 0.85 mmol/l, and serum phosphorus was 6.6 mg/dl, which normalized without therapy. Calcemia was 10.6 mg/dl at the age of 1 year and 9.7 mg/dl at the age of 2 years. Serum phosphorus was 5.5 mg/dl at the age of 1 year and 4.8 mg/dl at the age of 2 years. 22q11.2 microdeletion was ruled out by FISH analysis and G-banded karyotype was normal. At 27 months of age, X-rays of hands showed short and large first metacarpals, large proximal phalanges, hypoplastic distal phalanges, and delayed bone age (1 year and 3 months for phalanges and <3 months for carpal bones; bone age was severely retarded with the Greulich-Pyle method) (Fig. 3a–b).

At 8 years of age, physical examination showed harmonic short stature (height:109 cm, <3rd centile; weight: 27.8 kg, 75th centile; Span:108 cm) and relative macrocephaly (head

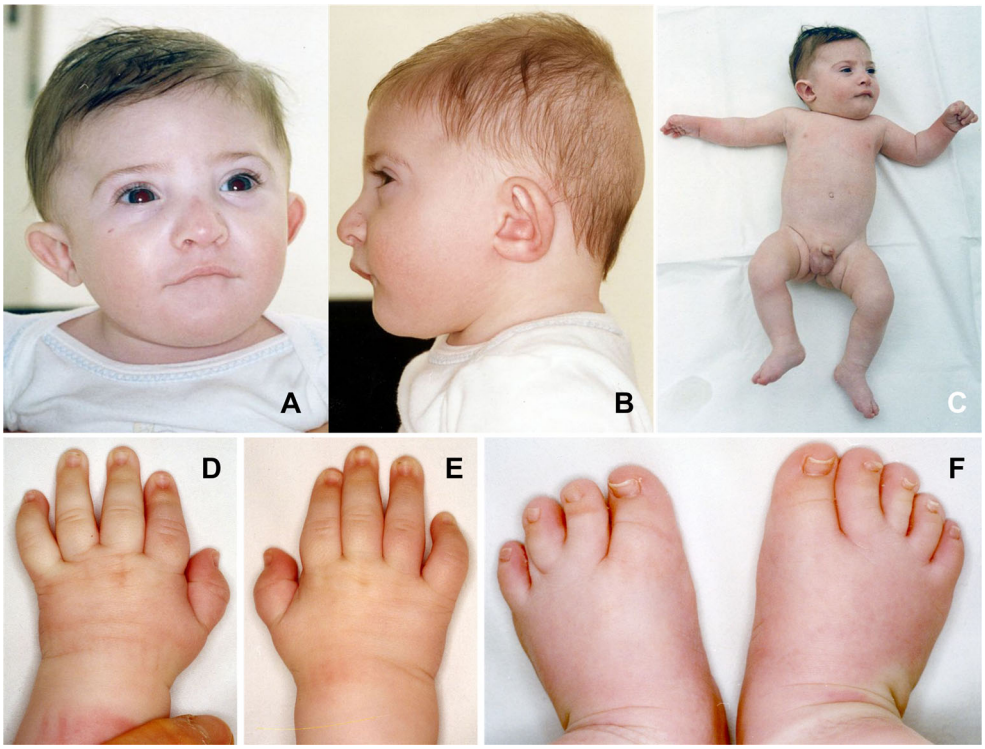

Fig. 1 Clinical features of the subject included in the study (9 months of age). **a**–**b** Facial features. Note the slightly short palpebral fissures, down-turned mouth, and sticking-out ears in the upper part. **c** Picture showing whole body. Length 63 cm (<3rd centile), weight 6650 g (<3rd centile), head circumference 42.5 cm (<3rd centile). **d**–**e** Brachydactyly, hyperconvex nails, clinodactyly at 5th finger bilaterally. **f** Brachydactyly, hypoplastic and hyper-convex nails

circumference: 53 cm, 90th centile) (Fig. 2c Fig. 4). Short palpebral fissures, mid-facial hypoplasia, and prognathism were noted (Fig. 2a–b). Brachydactyly (Fig. 2d–e), stiff and thick skin, muscular hypertrophy, and generalized joint

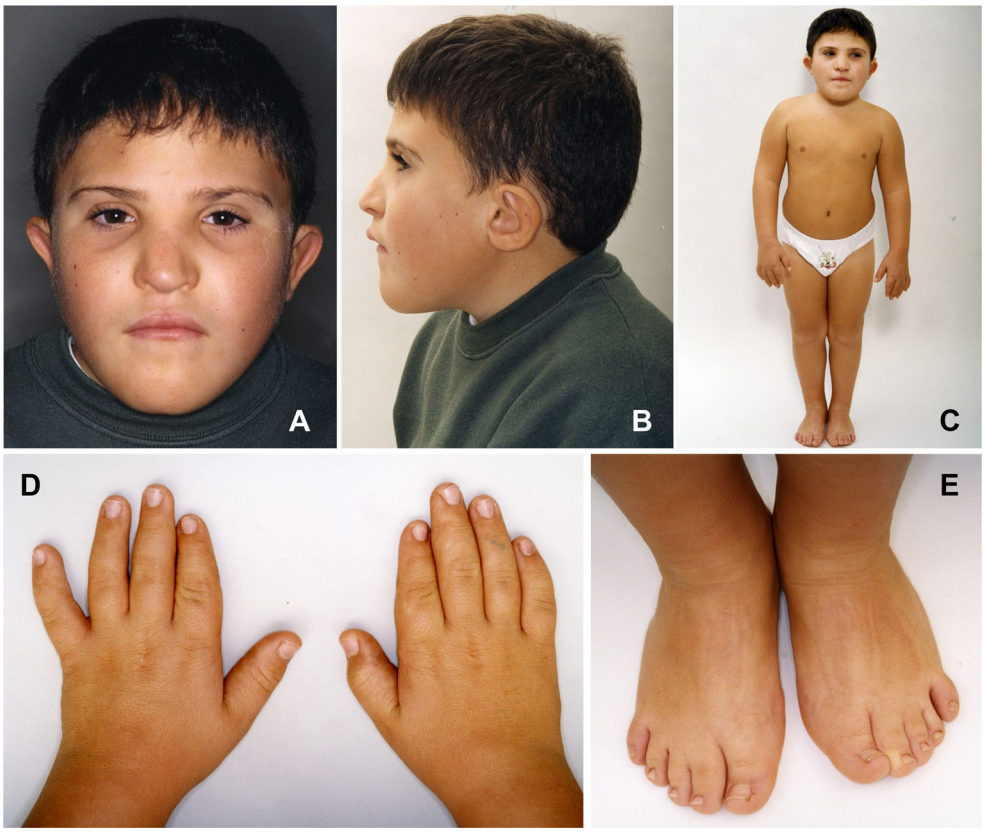

Fig. 2 Clinical features of the subject included in the study (8 years of age). a–b Facial features include short palpebral fissures, midfacial hypoplasia, prognathism, and slightly sticking-out ears. **c** Picture showing whole body. Height 109 cm (<3rd centile), weight 27.8 kg (75th centile), head circumference 53 cm (90th centile), pubertal stages: A0 B1 P1 testes 1–2 ml bilaterally. Stiff and thick skin, muscular hypertrophy, generalized joint stiffness. d–e Hands and feet brachydactyly

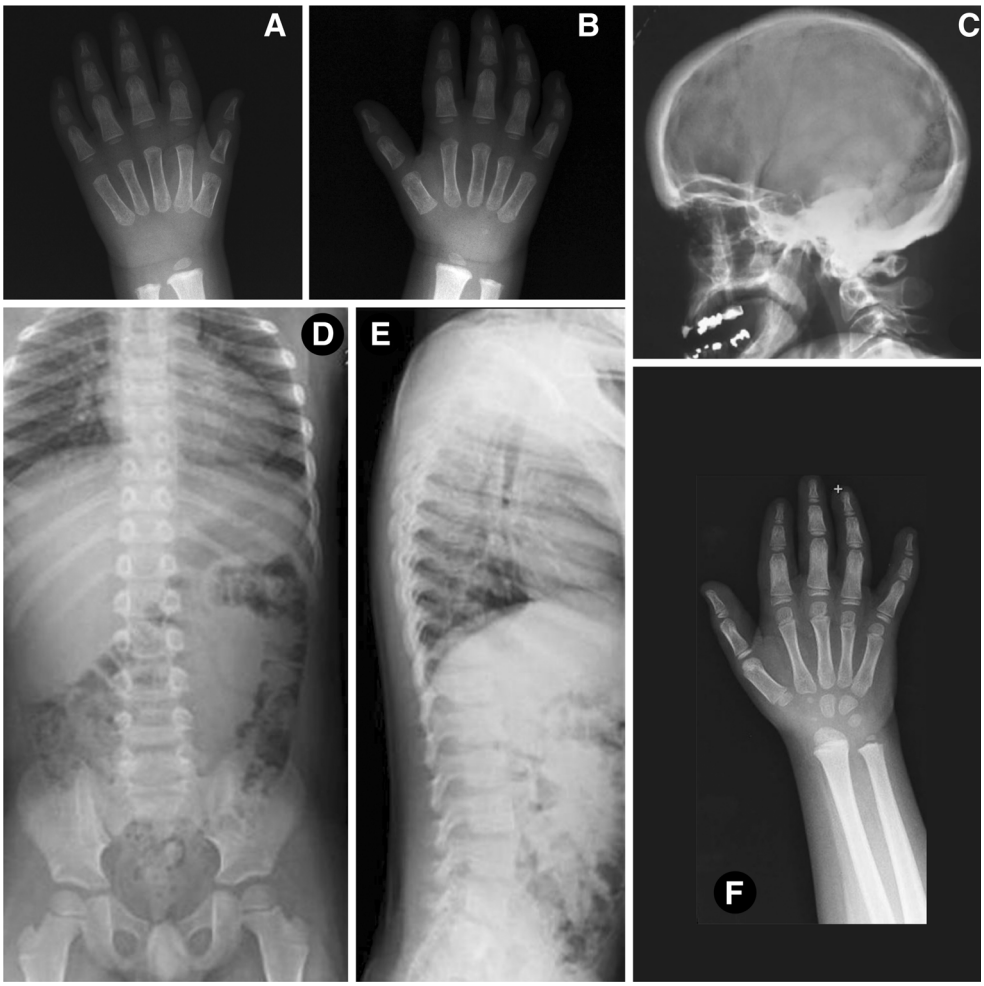

Fig. 3 X-ray evaluations at different ages. a–b Hands X-rays (2 years and 3 months): short and large first metacarpals, large proximal phalanges, hypoplastic distal phalanges, and delayed bone age (1 year and 3 months for phalanges and between newborn and 3 months for carpal bones according to the Greulich-Pyle method). **c** Skull X-rays (8 years): thick calvarium. d–e Spine and pelvis X-rays (8 years): broad ribs, large vertebral pedicles and hypoplastic iliac wings. **f** Hand X-rays (8 years and 7 months): clinodactyly of the 5th finger and bone age delay (4 years and 6 months with the Greulich-Pyle method)

stiffness, with particular difficulty in fist-clenching and arm-raising, were also observed. He had bilateral conductive hearing loss and mild intellectual disability. X-rays showed thick calvarium (Fig. 3C), broad ribs, large vertebral pedicles, and hypoplastic iliac wings (Fig. 3d–e); X-rays of hands confirmed clinodactyly of 5th finger bilaterally and delayed bone age (4 years and 6 months with the Greulich-Pyle method at the chronological age of 8 years and 7 months) (Fig. 3f); abdominal ultrasound was normal. Brain MRI demonstrated partial corpus callosum agenesis with rostrum hypoplasia, mild ventriculomegaly with square-shaped lateral ventricles, and periventricular frontal increased white matter signal bilaterally.

At 9 years of age, he had pericarditis with cardiac tamponade requiring pericardiocentesis. Approximately, 160 ml of fluid were removed. Neutrophils were prevalent in the effusion (74 %), but there was no evidence of viral or bacterial infection.

At the age of 12 years, CT and MRI of the middle and inner ear showed bilateral involvement of the epitympanic recess, aditus ad antrum, with chronic inflammatory aspects, thickened tympanic membrane, and mastoid sclerosis.

At the most recent physical examination (14 years and 6 months), height was 140 cm (<3rd centile), weight was 60 kg (75th–90th centile), head circumference was 57 cm (>97th centile), Span 139 cm and BMI was 37.5 kg/m^2. Figure 4 shows the growth curve of height, weight, and head circumference.

The clinical diagnosis of MYHRS was confirmed by Sanger sequencing, documenting the de novo presence of the recurrent c.1499 T > C missense change (p.Ile500Thr) in *SMAD4* in both circulating leukocytes and hair follicular epithelial cells [5].

Discussion

MYHRS is caused by heterozygous mutations in the tumour-suppressor gene *SMAD4* [5, 11, 12]. Analysis of 32 additional cases with a clinical diagnosis of MYHRS [18] confirmed previous findings indicating that a bunch of mutations in the gene underlies the vast majority of MYHRS. *SMAD4* encodes a protein acting as co-mediator of TGFβ/BMP signalling, and is required for transcriptionally active SMAD complexes. The

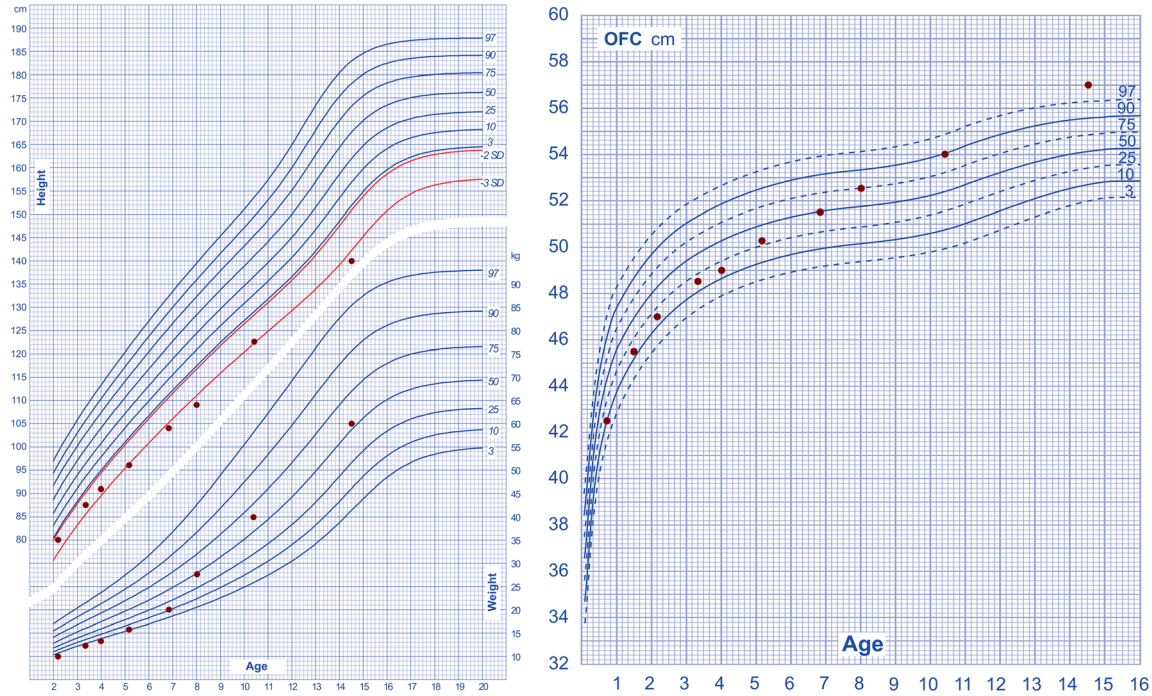

Fig. 4 Growth curve of height, weight, and head circumference

distinctive and narrow mutation spectrum of *SMAD4* lesions underlying MYHRS and the structural/biochemical/functional characterization of these mutations [4, 5, 10–12, 21, 22] strongly suggest that the MYHRS-causing SMAD4 amino acid substitutions do not engender loss-of-function. The absence of *SMAD4* mutation in a few affected subjects suggests that MYHRS may be genetically heterogeneous.

The available detailed photographic and radiologic documentation at various ages presented in this report illustrates the evolving phenotype characterizing MYHRS. In our patient, the diagnosis of MYHRS was only suspected at 8 years of age, when the distinctive features became evident. Retrospective analysis of the clinical record pointed out that most of the cardinal clinical features (i.e., prognathism, thick calvarium, broad ribs, large vertebral pedicles and hypoplastic iliac wings, stiff and thick skin, muscular hypertrophy, and generalized joint stiffness) were absent in the first years of life. Hearing loss was also diagnosed later during childhood. Brachydactyly with hyperconvex nails was the only characteristic noticed early. Consistent with these considerations, systematic review of the literature failed to identify any cases diagnosed within the first 2 years of life. Among the 69 subjects reported so far, only 8 subjects were diagnosed before 8 years of age [1, 3, 5–7, 12, 16, 17, 20]. Collected clinical data support the idea that the difficulty in reaching diagnosis in early childhood is attributable to the absence of any of the cardinal features characterizing this disorder generally used to make clinical diagnosis at older ages. Indeed, in our patient, who was observed from the first months of life to adolescence, the only evident clinical features identified during the first years of life were short length/stature, short palpebral fissures, brachydactyly with hyperconvex nails, congenital heart disease, and recurrent infections. These characteristics are not pathognomonic for MYHRS and occur commonly in several developmental disorders, including 22q11.2 microdeletion syndrome.

Pericarditis, sometimes occurring with constrictive pericardium requiring pericardiectomy, has been reported as a recurrent feature but has not been adequately stressed. Pericarditis has been reported in 6/48 (12.5 %) of subjects with molecularly confirmed MYHRS (Table 1). In the present case, pericarditis with cardiac tamponade represented a life-threatening complication. In 1998, Hopkin et al. [8] described one patient with clinical diagnosis of MYHRS with constricted pericarditis at the age of 10 years, leading to pericardiectomy at the age of 12 years. Pericardial histology showed fibrosis but without evidence of viral or bacterial infection. The same patient at the age of 23 years was subjected to tracheostomy for laryngotracheal stenosis. Two additional patients, who were diagnosed, presented with pericarditis [13–15]. The first subject developed pericardial effusion at the age of 14 years, with histological diagnosis of non-specific pericardial fibrosis, which required pericardiectomy in adolescence; the second individual, developed a constrictive pericardial sac requiring pericardiectomy. Both patients also required repeated procedures to address recurrent laryngotracheal stenosis. Another patient with MYHRS had an episode of pericarditis at the age of 6 years that apparently resolved spontaneously without complications [24]. More recently, Picco and

Table 1 Life-threatening complication in Myhre syndrome: Pericarditis and laryngotracheostenosis (review of the literature)

	Hopkin et al. 1998			Lindor et al. 2002, 2009, 2012		Whiteford et al. 2001
Diagnosis[b]	LAPS/MYHRS	LAPS/MYHRS	LAPS/MYHRS	LAPS/MYHRS	LAPS/MYHRS	MYHRS
SMAD4 molecular analysis	?	?	?	Ile500Thr	Ile500Val	Ile500Met
Sex	F	F	M	F	F	M
Pericarditis	Constrictive pericarditis (10 years)			Pericardial fibrosis, non specific (14 years)	Constrictive pericarditis	
Life-threatening-complication				Pericardial effusion (180 cm^3)		
Resolution/Evolution	Pericardiectomy (12 years)			Aspiration pericardial effusion	Pericardiectomy	
Pericardial histology	Fibrosis; no evidence of viral or bacterial infection			a	n.a.	
Echocardiography	right ventricular hypertrophy			Thickened mitral valve		PDA, Peripheral pulmonary stenosis
Tracheal stenosis	Tracheal narrowing (23 years)	Tracheal narrowing (23 years)	Laryngotracheal stenosis (23 years)	Subglottic stenosis (30 years)	Tracheal stenosis (17 years)	Restrictive ventilatory defect (21 years)
Laryngotracheal broncoscopy or histological examination	n.a.	n.a.	n.a.	Hard tracheal texture	Subglottic region: inflammatory granulation, hyperkeratosis or dense fibrosis	n.a.
Resolution/Evolution	Tracheostomy	Permanent tracheostomy (25 years)	Permanent tracheostomy (23 years)	Tracheostomy	Permanent tracheostomy (20 years)	Death (chocking episode)

	Van Steensel et al. 2005	McGowan et al. 2011	Picco et al. 2013	Michot et al. 2014	Starr et al. 2015	Present patient (Caputo et al. 2012)
Diagnosis[b]	MYHRS	MYHRS	MYHRS	MYHRS	MYHRS	MYHRS
SMAD4 molecular analysis	?	Ile500	Ile500Thr	Ile500	Ile500Thr	Ile500Thr
Sex	F	M	M	F	F	M
Pericarditis	Simple pericar-ditis (6 years)		Recurrent pericarditis (7 years)	Progressive constrictive pericarditis	Pericarditis (12y)	Pericarditis (9y)
Life-threatening-complication			Pericardial effusion (200 cm^3), cardiac tamponade	?	Pericardial effusion	Cardiac tamponade
Resolution/Evolution	Sponta-neous		Pericardiocentesis pharmacological treatment: steroids, anti-inflammatory, recombinant interleukin-1 receptor agonist	Death	Pericardiocentesis	Pericardio-centesis
Pericardial histology			Pericardial fluid: lymphocytes 80 %	n.a.	n.a.	Pericardial fluid: neutrophils 74 %. No evidence of viral or bacterial infection

Table 1 (continued)

	Van Steensel et al. 2005	McGowan et al. 2011	Picco et al. 2013	Michot et al. 2014	Starr et al. 2015	Present patient (Caputo et al. 2012)
Diagnosis[b]	MYHRS	MYHRS	MYHRS	MYHRS	MYHRS	MYHRS
Echocardiography		Aortic coarctation		CHD	Dilated atria, small descending aorta	Aortic coarctation
Tracheal stenosis		Tracheal stenosis (27 years)		-	Subglottic stenosis (8 years)	-
Laryngotracheal broncoscopy or histological examination		thick short epiglottis, thick arytenoids, tracheal stenosis, laryngomalacia			Hypertrophic scar with complete soft tissue stenosis of the airway	
Resolution/Evolution		Tracheostomy (28 years)			Tracheostomy (13 years)	

aDense bundles of collagenous connective tissue containing thin-walled vessels not infrequently surrounded by round cells. No specific connective tissue degeneration, organisms, or granulomas

n.a. not available, *CHD* congenital heart defect, *PDA* patent ductus arteriosus

[b] Laryngotracheal stenosis, arthropathy, prognatism, and short stature (LAPS) is caused by heterozygous missense mutations in *SMAD4* and does not represent a distinct nosologic entity

co-workers described a boy of 7 years old with MYHRS who developed recurrent pericarditis with cardiac tamponade requiring pericardiocentesis [20]. The pericardial fluid was around 200 ml and lymphocytes were prevalent in the effusion. The patient required a long-term anti-inflammatory treatment with steroids and recombinant interleukin-1 receptor antagonist (anakinra). Another patient developed progressive constrictive pericarditis causing death [18].

In addition to pericarditis, review of the literature also revealed recurrent laryngotracheal complications in 4/48 patients with molecular confirmation (8.3 %) or 8/69 (11.6 %) if we consider all the patients, with and without molecular confirmation. McGowan et al. [17] reported one patient with MYHRS who developed sleep apnoea and a restrictive ventilatory defect leading to death following a choking episode. An affected individual reported by Whiteford et al. [25] developed progressive proximal tracheal stenosis at the age of 21 years, requiring partial tracheal resection, laser treatment, and tracheotomy. Previously, Hopkin et al. [8] reported on two 23-year-old patients exhibiting severe tracheal narrowing requiring permanent tracheostomy. Recently, Starr et al. described five previously unreported patients, two of whom died (age 8 and age 12) as a result of post-transplant complications (heart and lung). Another of their patients died at the age of 26 after a valvuloplasty for aortic valve stenosis.

In conclusion, available records indicate that the majority of MYHRS cardinal features are missing in the first years of life, making early diagnosis of this disorder challenging. During this period, useful clinical signs that might direct to MYHRS include reduced growth, short palpebral fissures, brachydactyly with hyperconvex nails, congenital heart disease, and recurrent infections. Most of the major features and signs usually emerge later during childhood and by 7–8 years; the disorder is easily recognizable. Above all, skin and joint signs must be taken into account, along with the radiological signs such as large pedicles and thick calvarium, which are really typical.

The present report and analysis of the available clinical records also indicate that pericarditis and laryngotracheal stenosis are life-threatening complications of this syndrome. The pathogenesis of recurrent fibrotic pericarditis and laryngotracheal stenosis remains unclear but further highlights the relevance of connective tissue involvement in MYHRS. The high recurrence of pericardial and laryngotracheal involvement cannot be considered accidental, and while it has not been adequately stressed in the past, it requires careful monitoring thus cardiac and ENT follow-up should always be offered to these patients.

Acknowledgments The authors wish to thank the co-operating family members for the necessary medical data and photographs for publication, Dr.Viviana Caputo Dr. Alessandro De Fanti, Dr. Chiara Gelmini, and Dr. Anita Wischmeijer for their cooperation and their valuable help in the study of this clinical case, as well as the photographers Marco Bonazzi and Luca Valcavi. The technical assistance of Dorothea Bornholdt is gratefully acknowledged.

Author's contribution Livia Garavelli[1] made the clinical diagnosis of Myhre syndrome, and conceived, and wrote the manuscript;

Ilenia Maini[1], examined the child in the follow-up, wrote the manuscript, and contributed to data collection and analysis;

Federica Baccilieri[1], examined the child in the follow-up and contributed to the manuscript;

Ivan Ivanovski[1,2], examined the child in the follow-up and contributed to the manuscript, and data collection and analysis;

Marzia Pollazzon[1], examined the child in the follow-up in the last 2 years for the connective tissue problems and carried out the genetic counselling for the parents;

Simonetta Rosato[1] collected all the auxological data;

Lorenzo Iughetti[3] examined the child in the follow-up for growth retardation;

Sheila Unger[4] confirmed the clinical diagnosis on the basis of the clinical and radiological features and contributed to the manuscript and data analysis;

Andrea Superti-Furga[5] confirmed the clinical diagnosis on the basis of the clinical and radiological features and contributed to the manuscript and data analysis;

Marco Tartaglia[6] carried out the molecular analysis together with his group, discussed the case with clinicians, and contributed to the manuscript and data analysis.

Compliance with ethical standards

Funding This study was supported in part by intramural funding by Ospedale Pediatrico Bambino Gesù (GeneRare to M.T.) and by Fondazione Cassa di Risparmio di Reggio Emilia Pietro Manodori.

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate All procedures performed in study involving the patient were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent to publish the photographs was obtained from the parents.

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