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Myhre syndrome: new reports, review, and differential diagnosis

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Several conditions characterised by short fingers, reduced joint mobility, short stature, and muscular build with or without mental retardation have been delineated during the past 30 years: Moore-Federman syndrome, Myhre syndrome, acromicric dysplasia, geleophysic dysplasia, GOMBO syndrome, and LAPS (Laryngotracheal stenosis, Arthropathy, Prognathism and Short stature) syndrome. In 1980 Myhre *et al*[1] reported two unrelated males with mental retardation, facial dysmorphism (short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, small mouth), short stature, brachydactyly, muscle hypertrophy, decreased joint mobility, mixed hearing loss, and cleft lip and palate in one of them. *X* rays showed a thickened calvarium, hypoplastic iliac wings, broad ribs, and large, flattened vertebrae with large pedicles. Five further cases were reported. Mental retardation of variable severity was present in all patients. Three of the older patients had hypertension.

We report here four new unrelated patients who fit a diagnosis of Myhre syndrome, expanding the behavioural profile of the disorder, and discuss the differential diagnosis.

CASE REPORTS

Patient 1

Patient 1, a male, was the second child of healthy, non-consanguineous parents. The father was 181 cm tall and the mother was 165 cm tall. They were aged 40 and 34 years, respectively, at time of delivery. Birth weight was 2130 g, length 44.5 cm, and OFC 36 cm at 36 weeks' of gestation based on LMP (40 weeks based on morphological score of maturity). Recurrent hypoglycaemia requiring glucose infusion was recorded during the first weeks. Psychomotor development was normal, but dysarthria required long term speech therapy. He had bilateral deafness, with loss of 40 dB in low frequencies to 20 dB on the right side, and from 60 dB to 35 dB on the left side. MRI and CT showed bilateral dysplasia of the external semicircular canal. The stapedial footplate was bilaterally thick and, on the right side, fused with the oval window. This appearance was compatible with primary stapedial dysplasia or with otosclerosis. The absence of evolution of the hearing loss was considered as an argument for the dysplasia hypothesis. He wore a hearing aid. He had hypermetropia.

Progressive growth catch up occurred during the first year of life, reaching the 25th centile curve, then he slowly came back to the 3rd centile curve. OFC stayed around the 25th centile. Repeated bone age studies always showed skeletal maturation concordant with chronological age. Longitudinal skeletal survey showed generalised brachydactyly with brachyphalangy and brachymetacarpalia, large epiphyses (notably the femoral heads and proximal phalanges of fingers 2 and 3), and mild platyspondylic appearance of the vertebral

Key points

- Myhre syndrome is characterised by facial dysmorphism (short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, small mouth), short stature, brachydactyly, muscle hypertrophy, decreased joint mobility, hearing loss, and mental retardation.
- Radiological findings are a thickened calvarium, hypoplastic iliac wings, broad ribs and large, flattened vertebrae with large pedicles. Moore-Federman syndrome, acromicric dysplasia, geleophysic dysplasia and LAPS syndrome are the main differential diagnoses of Myhre syndrome.
- We report here four new unrelated patients who fit a diagnosis of Myhre syndrome. Absence of mental retardation was noted in one patient. Abnormal behaviour (impairment in social interactions and/or repetitive/stereotypic behaviour) was noted in 2/4 patients as in one previous report.
- Mixed hearing loss and hypertension (4/5 patients over 16 years old) seem constant in older patients. Thick skin was noted in three of our patients as in 3/7 previously reported patients and could be a major feature of Myhre syndrome.
- Paternal age was increased in half of the reported cases, suggesting a new mutation of an autosomal dominant gene. X linked transmission cannot be excluded since all reported cases (11/11) were males.

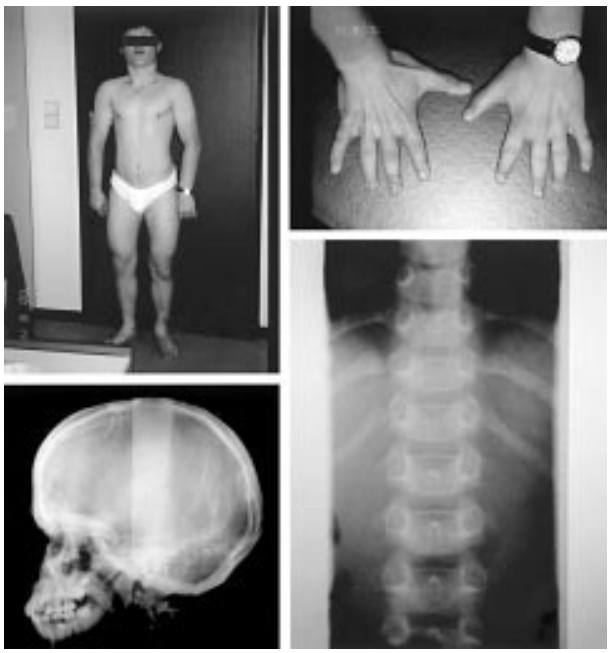

Figure 1 Patient 1. (A) Muscular build. (B) Brachydactyly. (C) Thickened calvarium. (D) Large vertebral pedicles.

bodies with irregular endplate (fig 1D). The pelvis was narrow. The calvarium and ribs were not thickened (fig 1C).

Bilateral cryptorchidism was surgically corrected at the age of 3. Puberty began at 13 years, but at the age of 17, pubertal development scored only Tanner stage P4 G4 with a subnormal testicular volume of 10/15 ml, which prompted endocrinological studies. These showed normal testosterone levels (5.61 ng/ml), high FSH levels (16.0 mUI/ml, normal <11), and normal LH level. This was compatible with primary (hypergonadotrophic) hypogonadism, possibly related to germinal cell aplasia (Sertoli cell only syndrome) or to another anomaly of spermatogenesis or anomalies of the FSH receptor.

When evaluated at the age of 20 he was a university student. He had difficult social relationships. He was 154 m tall and OFC was 56.5 cm (fig 1A). The facial dysmorphism included a square face, upward slanting eyebrows, short nose, very short philtrum, narrow mouth, and a large, prognathic chin. He had short hands with mild cutaneous syndactyly (fig 1B), and short feet with Y shaped syndactyly of toes 2 and 3. The skin was hard. There was generalised joint limitation, noted by the age of 10 and slowly worsening with time, and generalised muscular hypertrophy with extremely hard muscles. Neurological examination was normal, but osteotendinous reflexes were very weak. At the ages of 10 and 20, CK, EMG, and motor conduction velocity were normal. Muscle light microscopy at the age of 10 showed no abnormality. Hypertension (up to 170/100) was noted on different occasions during the last two years; no specific reason could be found. Echocardiography was normal. High resolution G banding and FISH with subtelomeric probes were normal.

Patient 2

This boy was the second child of healthy, non-consanguineous, young parents. Heights of the parents were 176 cm (father) and 160 cm (mother). The two sisters were healthy. At birth at 41 weeks' gestation, weight was 2130 g, length 42 cm, and OFC 32 cm. Neonatal examination showed left cryptorchidism, short hands, and slight facial dysmorphism. During the first year, growth was retarded and gluten allergy was suspected. A gluten free diet had no effect. Motor development was normal but later learning disabilities were noted at school. When he was 9 years old hearing loss was suspected and confirmed by audiogram. Hearing improved with bilateral hearing aids. He was admitted to an institution for deaf persons but poor school performances were noted. At the age of 9, height was 113 cm (less than the 3rd centile), regularly on this curve since birth. Endocrinological investigations showed normal GH, IGF1, T4, and TSH levels. Chromosomal analysis was normal, 46,XY. Bone age was 8 years. Echocardiography was normal. A diagnosis of acromicric dysplasia was suspected but facial dysmorphism was strikingly different. A few weeks later, growth velocity improved rapidly, and testis growth began. Endocrinological studies (testosterone and LH-RH test) confirmed central precocious puberty. Cerebral MRI was normal. Gonadotrophin releasing hormone agonist therapy was started and continued until the age of 14.

Clinical findings at 14 years showed short stature (136 cm, less than the 3rd centile), weight 44.5 kg (25th centile), and OFC 55.5 cm (50th centile). He had facial dysmorphism with small palpebral fissures, small round ears, a broad nasal bridge, short philtrum, small mouth, marked prognathism, and a short neck. The hands were short with brachydactyly. He had a striking muscular build. Moderate joint limitation was present in the elbows and the skin was very thick (fig 2). Ophthalmological examination showed hypermetropia and astigmatism. Longitudinal radiological findings were thick calvarium, platyspondyly with irregular endplate, very large vertebral pedicles, and large epiphyses (hands, femoral heads).

Patient 3

This male patient was the second child of a 32 year old G2 P2 mother and a 38 year old father. The brother was healthy and family history was negative. During the pregnancy, ultrasonography showed short femora at 31 weeks' gestation. Fetal blood sampling was performed and karyotype was normal. Birth weight at 39 weeks' gestation was 2350 g, birth length 44 cm, and OFC 32 cm. Psychomotor development was normal in

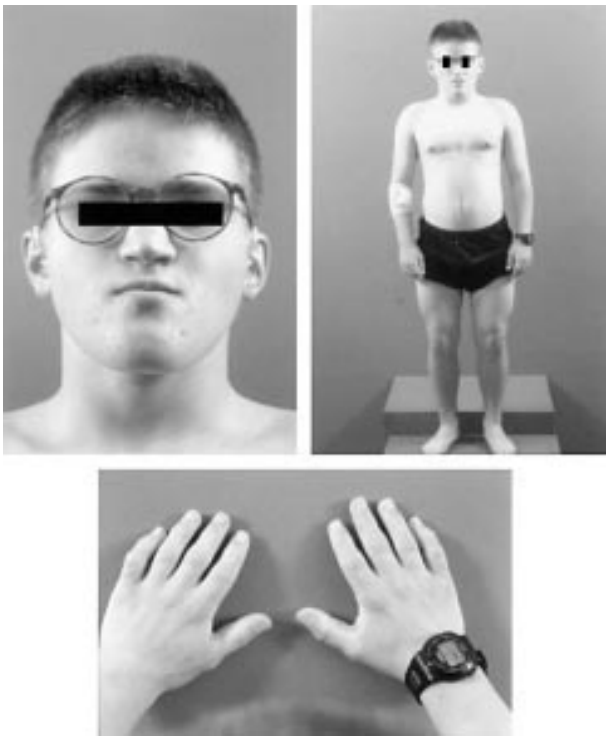

Figure 2 Patient 2. (A) Facial dysmorphism, short philtrum, thin lips. (B) Muscular build, joint limitation (elbows). (C) Brachydactyly.

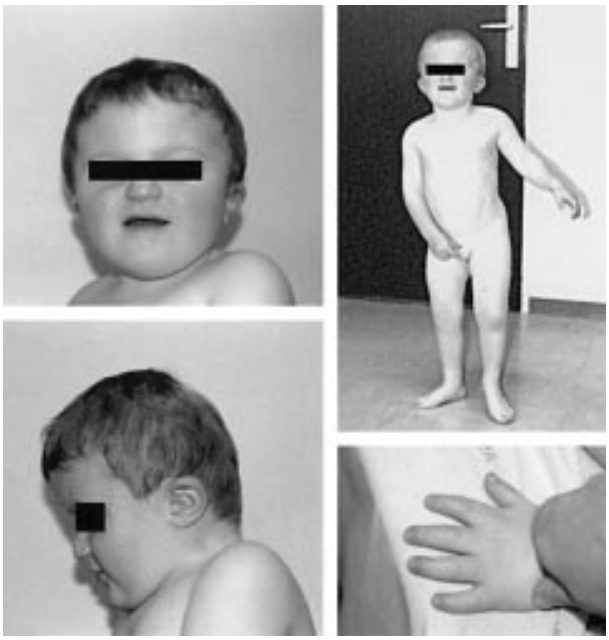

Figure 3 Patient 3. (A) Facial dysmorphism: short palpebral fissures, short philtrum, and thin lips. (B) Short neck and small ears. (C) Muscular build. (D) Brachydactyly.

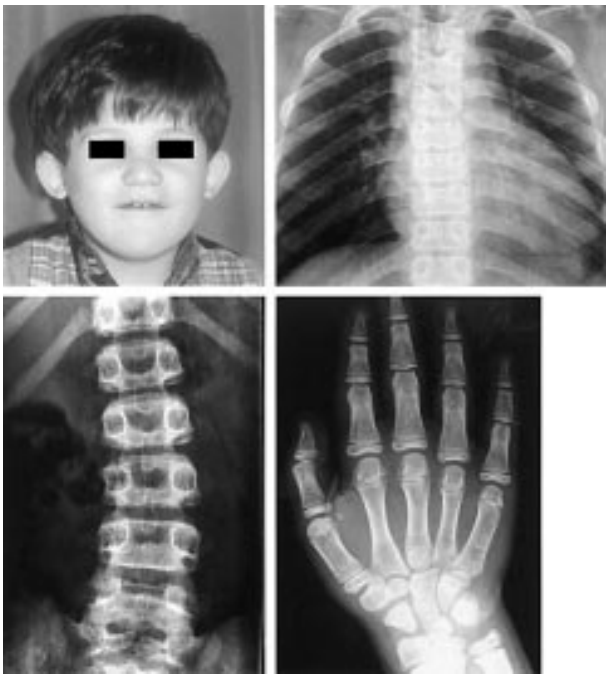

Figure 4 Patient 4. (A) Facial dysmorphism: short palpebral fissures, short philtrum, thin lips, and prominent mandible. (B) Broad ribs. (C) Large vertebral pedicles. (D) Brachydactyly.

the first months but language was delayed. At 2 years auditory evoked potentials showed hypoacusis. Hearing improved partially after transtympanic drains. Behaviour was abnormal. He had a severe impairment in social interaction (gaze and physical contact avoidance), abnormal communication (repetitive/stereotypic language), repetitive/stereotypic activities, difficulties with new situations, attention deficit, hyperactivity, and slight auto-aggressiveness. No standardised diagnosis of autism was available. These difficulties partially improved with time and psychotherapy. Growth was on the 20th centile in the first five years.

At 5 years, height was 1 m (5th centile), weight 19 kg (60th centile), and OFC 50 cm (25th centile). Clinical examination showed muscular hypertrophy and facial dysmorphism. He had brachycephaly, short palpebral fissures, deep set eyes, low set and small, round ears, a short philtrum, slightly convex profile of the nose, thin lips, and prognathism. The fingers were short with distal phalangeal hypoplasia. Extension of the elbows, knees, and ankles and pronosupination were limited. Achilles tendons were shortened but he had no spasticity or pyramidal signs. The skin was thick.

High resolution G band analyses, FISH with subtelomeric probes, cerebral CT scan, cardiac and renal ultrasound, and CK were normal. Ophthalmological examination showed hypermetropia, astigmatism, and strabismus. Skeletal *x* ray showed large vertebral pedicles and bone age was retarded (fig 3).

Patient 4

This male patient was born to healthy, non-consanguineous parents. He had a healthy older sister and three healthy half sibs from his mother and a healthy half sister from his father. The father was 168 cm tall and the mother was 153 cm tall. They were respectively aged 43 and 35 at the time of delivery. At birth weight was 2500 g, length was 47 cm, and OFC 32 cm at 38 weeks' of gestation. Global hypertonia and brachydactyly were noticed. Clinical findings at 5 years of age showed short stature (1 m, –2 SD) with normal OFC (53 cm, +1 SD), "muscular" habitus, and thick skin. A peculiar square face was observed with short palpebral fissures, short and broad nose, very short and marked philtrum, narrow mouth with thin lips, large, prognathic chin, and small, dysplastic, prominent ears. He had short hands with brachydactyly and short feet with slight II-III syndactyly. Osteotendinous reflexes were very weak. Psychomotor development was delayed and behaviour was abnormal with sleeping difficulties, frustration intolerance, hyperactivity, encopresis, and aggressiveness towards himself and others. Ophthalmological examination showed bilateral subcapsular cataract, which was surgically removed at the age of 6 years. Abdominal ultrasonographic scan

Table 1 Clinical data of Myhre syndrome patients

	Myhre *et al*[1]		Soljak *et al*[2]	Garcia-Cruz *et al*[3]		Whiteford *et al*[4]	Titomanlio *et al*[5]	This report				Total or mean*
	Patient 1	Patient 2	Patient 1	Patient 1	Patient 2	Patient 1	Patient 1	Patient 1	Patient 2	Patient 3	Patient 4	
Paternal age at birth	37	38	42	32	23	32	33	40	28	38	43	35*
Sex	M	M	M	M	M	M	M	M	M	M	M	11 M
General												
Birth weight (g)	2100	2900	3200	2200	2100	2870	2110	2100	2130	2.350	2.500	2.4*
Birth height	?	?	?	?	?	?	?	44.5	42	44	47	44.4*
Height in SD (adult height)	–5.5 (140 cm)	–4.5 (146 cm)	–4.5 (146 cm)	–6 (139 cm)	–3	<–2	–4	–2 (154 cm)	–3.6	–2	–2	–2/–6
Age at last observation	24	18	16	18	6	13	14	20	14	5	10	14.3*
Craniofacial features												
OFC (SD)	–1	–1.5	?	–1.5	M	+1.5	+1	–1	+0.5	–1	0	–1/+1.5
Ptosis	?	?	?	?	–	–	?	–	+	+	slight	3/6
Short palpebral fissures	+	+	+	+	+	+	+	+	+	+	+	11/11
Midface hypoplasia	+	+	+	–	+	+	?	+	+	+	+	9/10
Short philtrum	+	+	+	+	+	+	+	+	+	+	+	11/11
Narrow mouth	+	+	+	+	+	+	+	+	+	+	+	11/11
Thin upper lip	+	+	+	+	+	+	+	+	+	+	+	11/11
Prognathism	+	+	+	?	+	?	+	+	+	+	+	9/9
Cleft lip	+	–	–	–	–	–	–	–	–	–	–	1/11
Small ears	?	?	?	?	+	?	?	+	+	+	+	5/5
Skeletal anomalies												
Brachydactyly	+	+	+	+	+	+	+	+	+	+	+	11/11
Thick calvaria	+	+	+	+	+	+	+	–	+	?	+	9/11
Joint limitations	+	+	+	+	+	+	+	+	+	+	+	11/11
Broad ribs	+	+	+	+	+	+	?	–	+	?	+	8/9
Narrow pelvis	+	+	+	+	+	+	+	+	+	?	+	10/10
Thick femoral necks	–	–	+	+	–	+	?	–	?	?	+	4/8
Large epiphyses	?	?	?	?	?	?	?	+	+	?	+	3/3
Mild platyspondyly	+	+	–	+	+	+	?	+ (regress)	+	+	+	9/10
Large pedicles	+	+	+	?	?	+	+	–	+	+	+	8/9
Neuromuscular												
IQ	45	35–50	75	Low	Low	Low	Low	Normal	Low	50–60	55–60	
Behaviour	,	?	,	?	?	?	autistic	Difficult relationships	?	Repetitive/ stereotypic behavior, Hyperactivity	Hyperactivity encopresis	
Muscular hypertrophy	+	+	+	+	+	+	+	+	+	+	+	11/11
Muscle histology	?	?	Normal	Minor changes	?	Normal	Minor changes	Normal	?	?	?	
EMG/muscle ultrasound	?	?	EMG myopathic	Normal	?	Myopathic US changes	EMG neurogenic	EMGnNormal	?	?	?	
Miscellaneous												
Very thick skin	?	?	+	+	?	?	+	+	+	+	+	7/7
Deafness	+	+	+	–100dB	–	+	Mild	+	+	+	–	9/11
Abnormal inner ear	?	?	?	?	?	Ossicular fixation	?	+	?	?	?	
Ophthalmological anomalies	Hyperm	Hyperm	Hyperm	?	?	Cataract	?	Hyperm	Hyperm	Hyperm	Cataract	8/8
Heart malformation	+	ASD	–	–	–	PDA, PPS	Left atrium mild dilatation	–	–	–	Aortic and pulmonar valve stenosis	5/11
Kidney malformation	–	–	–	–	–	–	–	–	–	–	Right kidney agenesia	1/11
Hypertension	+	–	+	+	–	?	–	+	–	–	–	4/10
Inguinal hernia	+	–	–	–	–	–	+	–	–	–	–	2/11
Puberty	?	?	Normal	Delayed	?	?	?	Delayed	Precocious		Precocious	
Hypospadias	+	–	–	–	–	–	–	–	–	–	–	1/11
Cryptorchidism	+	+	–	?	–	–	+	+	+	–	–	5/10

ASD: atrial septal defect. PPS: peripheral pulmonary stenoses. PDA: patent ductus arteriosus. ?: not determined.

Table 2 Differential diagnosis of Myhre syndrome

	Myhre	LAPS	Geleophysic dysplasia	Acromicric dysplasia	Moore-Federman
Short stature	+	+	+	+	+
Brachydactyly	+	+	+	+	+
Joint limitation	+	+	+	+	+
Muscular hypertrophy	+	–	–	+/–	–
Mental retardation	Frequent	Learning difficulties	–	–	–
Deafness	+ 9/11	+ 3/5	–	–	–
Abnormal skin	+	+	+	–	+
Laryngotracheal stenosis	– (too young ?)	+ (severe adult onset)	+ (childhood onset)	+ (childhood onset)	–
Hepatomegaly	–	–	+	–	+
Cardiac disease	Congenital malformations	Pericarditis	Progressive cardiac valve disease	–	+/–
Transmission	AD? X linked? (11M/0F)	AD? (1M/4F)	AR	AD	AD

showed right kidney agenesis and cardiac ultrasonographic scan showed moderate aortic stenosis. Hearing was normal. Karyotype was normal 46,XY. Subsequently growth followed the –2 SD curve, behavioural difficulties persisted, but sleeping improved. Generalised muscular hypertrophy and "pugilistic" posture were more prominent. Progressive joint limitation was observed with enlargement of the big joints and limited extension of the elbows, knees, ankles, fingers, and limited pronosupination. At 10 years of age precocious central puberty occurred with advanced bone age. Cerebral MRI was normal (fig 4).

DISCUSSION

Myhre *et al*[1] reported two unrelated males with mental retardation, facial dysmorphism (short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, small mouth), short stature, brachydactyly, muscle hypertrophy, decreased joint mobility, mixed hearing loss, and cleft lip and palate in one of them. *X* rays showed a thickened calvarium, hypoplastic iliac wings, broad ribs, shortened tubular bones, and large, flattened vertebrae with large pedicles. Five further cases were reported.[2–5] The four patients reported here fit a diagnosis of Myhre syndrome.

Clinical data on Myhre syndrome patients are presented in table 1. The most important features are low birth weight (mean 2415 g), variable short stature, facial dysmorphism (midface hypoplasia, narrow palpebral fissures, short philtrum, and prognathism), short hands, muscular build, very peculiar thick skin, and joint limitation. Birth length was not previously reported but short stature was of prenatal onset in our four patients. Mental retardation is frequent but was absent in our patient 1. However, this patient had behavioural disturbances with difficult relationships. Abnormal behaviour was noted in the patient reported by Titomanlio *et al*[5] who was diagnosed as autistic. No standardised diagnosis of autism was available for our patient 3 but he had at least an "autistic-like condition". Further observations with a careful description of behaviour are needed in order to know if autistic or other behavioural disturbances are features of Myhre syndrome. Deafness is a frequently reported feature that seems constant in older patients, suggesting that hearing loss could be progressive. Hearing loss is mixed in most cases. One of our patients had cataracts, as did one previously reported patient.[4] Agenesis of one kidney is reported for the first time and could be a rare feature like cleft lip that was reported in one case. Thickness of the skin is present in 6/11 patients and is a major feature of Myhre syndrome. In patient 3, thickness of the skin was noted as early as 3 years old. No skin biopsy was performed in our patients. Titomanlio *et al*[5] reported dermis thickening with collagen infiltration in their patient. Four of 11 patients had hypertension. All were between 16 and 20 years old. This feature is possibly not present in younger children. Blood pressure had to be regularly measured in patients with Myhre syndrome. One hypothesis could be abnormal arterial stiffness but this remains to be confirmed by specific studies. Another clinical feature of interest is the abnormal onset of puberty observed in three of our cases, two showing early onset (before the age of 9 years) and another one showing delayed puberty with hypergonadotrophic hypogonadism. Although these phenotypic manifestations are discordant, they may point to a disturbance in the hypothalamo-hypophyso-gonadal axis that should be investigated in further cases.

Several syndromes were transiently considered in the differential diagnosis of our patients. OSMED syndrome shows megaepiphyses, irregular vertebral bodies, and deafness, but can be distinguished by a different facial dysmorphism (micrognathia), metaphyseal involvement, and progressive carpal fusion.[6] Phenotypic similarities were noted between Myhre syndrome and GOMBO syndrome,[7 8] but the latter has been shown to result from a cryptic translocation between chromosomes 3p and 22q.[9] Telomeric FISH analyses performed in two of our patients detected no cryptic rearrangement. Moore-Federman syndrome,[10] acromicric dysplasia,[11 12] geleophysic dysplasia,[13 14] and LAPS syndrome[15 16] are the main differential diagnoses of Myhre syndrome. Table 2 summarises the similarities and differences between these entities.

Acromicric dysplasia is characterised by short stature below 3 SD noted after the age of 2 years, short and stubby hands and feet, and mild dysmorphic signs, including narrow palpebral fissures, full cheeks, and a short and anteverted nose. Radiological anomalies include short metacarpals (especially 2-5) with an internal notch on the second one, short and broad proximal and medial phalanges, cone shaped epiphyses, internal notch on the femoral necks, and delayed bone maturation. Hoarse voice, generalised joint limitation, and muscular build have recently been added to the clinical picture of acromicric dysplasia.[12] Microscopically, there is disorganised cartilage, abnormal organisation of collagen, and accumulation of glycogen in most chondrocytes. The distinction between acromicric dysplasia and the Moore-Federman syndrome, which are both dominantly inherited, is still a disputed issue, with both lumping and splitting suggested.[12 17] There is now convincing evidence to reject lumping with the recessively inherited geleophysic dysplasia as previously suggested.[18] There are obvious similarities between acromicric dysplasia and Myhre syndrome. Nevertheless, Myhre syndrome can be distinguished on the basis of facial features, IUGR, mental retardation, and on the severity of muscular and cutaneous involvement. Geleophysic dysplasia[13] is characterised by short stature with a "happy looking" facial appearance, short hands, joint contractures, thickened skin, hepatomegaly, and cardiac valve dysplasia. This is considered to be a storage disease with progressive worsening and a poor prognosis. Storage vacuoles are present in hepatocytes, chondrocytes, and fibroblasts.[14] Myhre syndrome and geleophysic dysplasia share some features but hepatomegaly and

cardiac valve dysplasia have never been reported in patients with Myhre syndrome even in older subjects. Facial dysmorphism is different with a short philtrum, small mouth, and frequent prognathism in Myhre syndrome. Additionally, short stature is postnatal in geleophysic dysplasia but was of prenatal onset in all our Myhre patients. Figuera[19] suggested that the patient reported by Rosser *et al* as having geleophysic dysplasia had Myhre syndrome. Nevertheless, as pointed out by McGaughran and Donnai[20] geleophysic dysplasia seems a more convincing diagnosis for this patient who had hepatomegaly, thickened mitral valve, and "geleophysic dysplasia facial dysmorphism".

Hopkin *et al*[15] described three patients with a disorder characterised by short stature, joint limitation, and progressive adult onset laryngotracheal stenosis. Lindor *et al*[16] reported two further patients and coined the acronym LAPS syndrome for Laryngotracheal stenosis, Arthropathy, Prognathism, and Short stature. Short stature, brachydactyly, joint limitation, prognathism, small, round ears, short palpebral fissures, abnormal skin, thick calvaria, and deafness are observed in Myhre and LAPS syndromes. A disturbance in the hypothalamo-hypophyso-gonadal axis may be another common feature. Abnormal onset of puberty was observed in three Myhre patients; among LAPS patients, one had precocious puberty, three had irregular menses, and one secondary amenorrhoea. Progressive laryngotracheal stenosis apparently clearly distinguishes LAPS syndrome from Myhre syndrome, but this could perhaps be explained by insufficient follow up, as the older Myhre patient was only aged 24 whereas onset of obstructive symptoms was between 17 and 30 in LAPS cases. Despite these similarities, some major differences exist. The impressive muscular hypertrophy, which is a cardinal feature of Myhre syndrome, was never reported in LAPS patients. Finally, the sex ratio is strikingly dissimilar, 11 M:0 F in Myhre versus 1 M:4 F in LAPS. These two latter arguments make lumping of LAPS and Myhre hazardous at this point. Further reports and longer follow up of Myhre cases would probably help to solve this nosological issue in the future.

The pattern of inheritance of Myhre syndrome remains unknown. All reported patients were sporadic and paternal age was increased in half of the cases (7/11) suggesting dominant new mutations. However all cases have been males (11/11) and X linked transmission cannot be excluded to date.

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