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Short clinical report

Retinal involvement in two unrelated patients with Myhre syndrome

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ABSTRACT

Myhre syndrome is a very rare condition described thirty years ago and related to mutations in the *SMAD4* gene. It has been reported in 19 patients, including 13 males and 6 females before the recent finding of heterozygous mutations in the *SMAD4* gene in 19 patients. It is characterized by mental retardation, short stature, muscle hypertrophy, limitation of joints movements, deafness, skeletal anomalies, and facial dysmorphism. Ophthalmological involvement includes hypermetropia and congenital cataract. We report here the new finding of retinal involvement including retinitis pigmentosa and maculopathy in two unrelated patients with Myhre syndrome. The patient with retinitis pigmentosa carried the p.I500T mutation in *SMAD4*, but no mutation was found in the patient with the maculopathy.

1. Text

Myhre syndrome (MS; MIM 139210) is a rare disorder first reported in 1981 by Myhre et al. who described two unrelated male patients with the unique association of mental retardation, short stature, cryptorchidism, generalized muscular hypertrophy, limitation of joints movements, deafness, heart malformation, facial dysmorphism, and skeletal anomalies [1]. Major facial features were short palpebral fissures, maxillary hypoplasia, small mouth, short philtrum, and prognatism, while hypoplastic iliac wings, broad ribs, thickened calvarium, large, and flattened vertebral bodies with large pedicles were the main radiological findings. The report of eleven further male patients with MS added other clinical features to the description of this condition (Table 1) [2–7]. Because all patients reported before 2003 were male, sex-related inheritance was suspected. However, the report of six female patients thereafter [4,8–12] challenged this hypothesis. The recent finding of *de novo* dominant mutations in the *SMAD4* gene in 19 patients confirmed the sporadic dominant mode of inheritance of MS [13,14].

Most patients share the major clinical involvements reported by Myhre et al., and the clinical spectrum defined by these reports include ophthalmological features, i.e. congenital cataract and hypermetropia. Retinitis pigmentosa (RP) has never been reported however in MS. We report here on two patients with retinopathy and a diagnosis of MS, which opens a new ophthalmological entry in the diagnosis of MS and broadens the spectrum of differential diagnoses.

1.1. Clinical description

1.1.1. Patient #1

Patient #1 was a boy referred to our Unit of Medical Genetics for the diagnosis of learning difficulties. He was the third child of healthy, non consanguineous parents of Algerian origin. At the time of his birth, his father was 35 year-old, 170 cm tall, his mother was 32 year-old, 157 cm tall and obese. Both grandmothers had non-insulin dependent diabetes mellitus. He had two brothers; one was obese but had neither learning difficulties nor visual

Abbreviations: MS, Myhre syndrome; RP, retinitis pigmentosa; OFC, occipito-frontal circumference.

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Table 1
Clinical features of 21 patients with a diagnosis of Myhre syndrome.

	Males Patients											
	Myhre et al		Soljak et al	Garcia-Cruz et al		Whiteford et al	Titomanlio et al	Burglen et al				McGowan et al
	P1	P2	P1	P1	P2	P1	P1	P1	P2	P3	P4	P1
Paternal age at birth	37	38	42	32	23	32	33	40	28	38	43	46
Birth weight (g)	2100	2900	3200	2200	2100	2870	2110	2100	2130	2350	2500	3600
Birth length (cm)	NA	NA	NA	NA	NA	NA	NA	44.5	42	44	47	NA
Birth OFC (cm)	NA	NA	NA	NA	NA	NA	NA	36	32	32	32	NA
Age at last observation (years)	24	18	16	18	6	13	14	20	14	5	10	14
Short stature	+	+	+	+	+	+	+	+	+	+	+	−
Height in SD	−5.5	−4.5	−4.5	−6	−3	<-2	−4	−2	−3.6	−2	−2	0
Height (cm)	NA	NA	NA	NA	NA	NA	135.5	NA	136	100	NA	160.5
Weight (kg)	NA	NA	NA	NA	NA	NA	58.5	NA	44.5	19	NA	82.5
Body Mass Index[a]	NA	NA	NA	NA	NA	NA	31.9 sev. obes.	NA	24.1 mod. obes.	19 mod. obes.	NA	32 sev. obes
OFC in SD	−1	−1.5	NA	−1.5	0	+1.5	+1	−1	+0.5	−1	0	0
Short palpebral fissures	+	+	+	+	+	+	+	+	+	+	+	+
Deep-set eyes	+	+	+	+	+	NA	NA	NA	NA	NA	NA	+
Mid-face hypoplasia	+	+	+	−	+	+	NA	+	+	+	+	+
Short philtrum	+	+	+	+	+	+	+	+	+	+	+	+
Narrow mouth	+	+	+	+	+	+	+	+	+	+	+	+
Thin upper lip	+	+	+	+	+	+	+	+	+	+	+	+
Prognathism	+	+	+	NA	+	NA	+	+	+	+	+	+
Small ears	NA	NA	NA	NA	+	NA	NA	+	+	+	+	−
Brachydactyly	+	+	+	+	+	+	+	+	+	+	+	+
Thick calvaria	+	+	+	+	+	+	+	−	+	NA	+	−
Joints limitations	+	+	+	+	+	+	+	+	+	+	+	+
Broad ribs	+	+	+	+	+	+	NA	−	+	NA	+	+
Narrow pelvis	+	+	+	+	+	+	+	+	+	NA	+	−
Mild platyspondyly	+	+	−	+	+	+	?	+	+	+	+	−
Large pedicles	+	+	+	NA	NA	+	+	−	+	+	+	−
Mental retardation	+	+	+	+	+	+	+	−	+	+	+	+
Behavior disturbance	NA	NA	NA	NA	NA	NA	+	+	NA	+	+	−
Muscular hypertrophy	+	+	+	+	+	+	+	+	+	+	+	+
Thick skin	NA	NA	+	+	NA	NA	+	+	+	+	+	+
Hearing loss	+	+	+	+	−	+	mild	+	+	+	−	+
Retinopathy	−	−	−	−	−	−	−	−	−	−	−	−
Cataract	−	−	−	−	−	+	−	−	−	−	+	−
Refractive error	hyperm.	hyper.m.	hyperm.	NA	NA	−	NA	hyperm.	hyperm.	hyperm.	−	−
Heart malformation	+	ASD	−	−	−	PDA, PPS	LAD	−	−	−	AVS, PVS	−
Arterial hypertension	+	−	+	+	−	NA	−	+	−	−	−	−
Puberty	NA	NA	N	del.	NA	NA	NA	del.	prec.	prec.	prec.	N
Cryptorchidism	+	+	−	NA	−	−	+	+	+	−	−	+

P: patient, M: median; N: normal; NA: not available or not applicable; OFC: occipital-frontal circumference; sev. obes.: severe obesity; mod. obes.: moderate obesity; perc.: percentile; hyperm: hypermetropia; myop.: myopia; ASD: atrial septal defect; PDA: patent ductus arteriosus; PPS: peripheral pulmonary stenosis; LAD: left atrium dilatation; AVS: aortic valve stenosis; del. : delayed; prec.: precocious.
[a] Body Mass Index according to the French charts.

impairment. He was born at 41 weeks of gestation after uneventful pregnancy with normal Apgar score and growth parameters: birth weight 3070 g (20th centile), length 49 cm (40th centile), occipitofrontal circumference (OFC) 34 cm (25th centile). His development during the first two years of life was normal except for delayed language acquisition. A mild unilateral hearing loss was then detected requiring a tympanostomy tube.

He was first referred to a pediatric nutritionist at the age of seven years for the exploration and management of polyphagia and obesity. Accelerated weight gain due to increased appetite had started after the age of two years and mental retardation was suspected because of learning difficulties at school. Hormonal studies revealed no abnormality except insulin resistance. Diet control was planned and the patient was referred to our Clinical