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THE 3M SYNDROME: A CAUSE OF PRE- AND POST-NATAL SEVERE GROWTH RETARDATION

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Background: 3-M syndrome is an autosomal recessive growth disorder characterised by severe pre- and post-natal growth retardation caused by mutations in *CUL7, OBSL1* or *CCDC8*. Clinical characteristics include dysmorphic facial features and fleshy prominent heels with variable degree of radiological abnormalities.

Aim: Evaluation of clinical findings and growth status of four new patients from two different families.

Patients and Methods: Some clinical and laboratory findings of patients are shown in the Table and the Figure. All of the patients had intrauterine growth retardation.

Family-1/Patients- 1,2

Two brothers (16.6 (Patient 1) and 8.5 (Patient 2) years-old) were referred for marked short stature. Their parents were first degree cousins. Physical examination revealed severe short stature and dysmorphic features. Pubertal stages were Tanner-2 and Tanner-1, respectively. Motor and mental development, endocrine work-up were normal. Sequencing analysis showed a homozygous frameshift mutation in the *CUL7* (insertion of glutamine in exon 8, causing a change of the aminoacid sequence from position 731 onwards). They had a high/normal response to growth hormone (GH) stimulation tests (Clonidine and L-dopa). Adequate rise was noted in insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) levelson IGF-1 generation test. rhGH treatment was started at 11 years of age (Patient 2). The treatment was discontiuned at 13 years of age because growth response was poor. Pubertal stage of Patient-2 is Tanner I at 13 years of age.

Family-2/Patients-3,4

Two sisters [Elder one (Patient 3) at 0.75 years-old, younger one (Patient 4) at 2.5 years old] were referred for marked short stature. Their parents were third degree-cousins. Pedigree analysis showed three similarly affected patients in the family. Physical examination revealed severe short stature and dysmorphic features. Motor and mental development, endocrine work-up were normal. Sequencing analysis showed a homozygous frameshift mutation in the *OBSL1* (involving insertion of an adenine base in exon 3, causing the aminoacid position 425 to change from threonine to asparagine). They had a normal response to GH stimulation and IGF generation test. rhGH treatment was started at 4.8 years-of age (Patient 3). She had a good response to rhGH treatment during first nine months.

Table. Some clinical and laboratory findings of the patients

	Family-1		Family-2	
	Patient 1	Patient 2	Patient 3	Patient 4
At presentation				
Age (years)	16.6	8.5	0.75	2.5
Gender	M	M	F	F
Birth weight (g) / SDS	2000 /-3.8	2250 /-3.1	2150 /-3.3	2310 /-1.4
Birth length (cm) /SDS	-	43 /-4.0	42 /-4.4	39 /-4.8
Gestational age (weeks)	40	40	40	37
Weight (kg) /SDS	28.2 /-6.8	15 /-4.7	4.5 /-4.9	7.5 /-4.4
Height (cm) /SDS	128.3/-7.2	101.1 /-5.2	55.5 /-7.9	71.3 /-5.3
SH/Height	0.53	0.55	0.65	-
BMI SDS	-2.4	-1.0	-1.8	-0.8
HC (cm) / SDS	55.4 /-1.4	50.2 /-1.8	41.3 /-2.5	-
Pubertal stage (Tanner) (Testes volumes- Prader)	2 (6 / 6 ml)	1 (0.5-1 / 0.5-1 ml)	1	1
Bone age (years)	12.5	6	-	2.5
Target height (cm) / SDS	174 /-0.4		151.8 /-1.9	
Dysmorphic features				
Typical facies	+	+	+	+
Clinodactyly	-	+	+	+
Prominent heels	+	+	+	+
Joint laxity	-	-	+	+
Hyperlordosis	+	+	+	+
Tall vertebral bodies	+	+	+	+
Small pelvis	+	+	+	+
Slender tubular bones	+	+	+	+
Laboratory findings				
GH stimulation tests (Clonidine and L-dopa)				
Peak GH (ng/ml)	>40 and >40	17.2 and 15.6	28.9 and 11.6	9.7 and 10.7
IGF generation tests				
Basal / Stimulated IGF-1 (ng/ml)	419 / 705	58.4 / 207	65.7 / 118	
Basal / Stimulated IGFBP-3 (ng/ml)	4580 / 6190	1470 / 3940	3040 / 5080	
Onset of rhGH treatment				
Age (years)		**11**	**4.8**	
Weight (kg) /SDS		17.4 /-4.6	10.8 /-3.7	
Height (cm) / SDS		**110.1 /-5.2**	**86.1 /-4.6**	
BMI SDS		-1.8	-0.6	
SH / height		0.55	0.59	
Pubertal stage		1	1	
Bone age (years)		7	2-2 $^{6/12}$	
At recent evaluation				
Age (years)	**18.6**	**13.1**	**5.5**	**3.4**
Weight (kg) /SDS	32.8 /-6.7	21.4 /-3.9	16.9 /-1.0	9.7 /-3.4
Height (cm) / SDS	136 /-6.5	**118.6 /-5.0**	**93.5 /-3.95**	75.1 /-3.4
BMI SDS	-2.5	-1.9	1.8	1.1
HC (cm) / SDS	55.5 /-1.5	52.9 /-1.6	51.3 /0.3	50.0 /0.3
SH / Height	0.54	0.53	0.57	0.56
Pubertal stage (Testes volumes-Prader)	3 (10 / 10 ml)	1 (2-3 / 2-3 ml)	1	1
Bone age (years)	16	8	-	2 $^{6/12}$-3

BMI: Body mass index; HC: Head circumference; SH:Sitting height

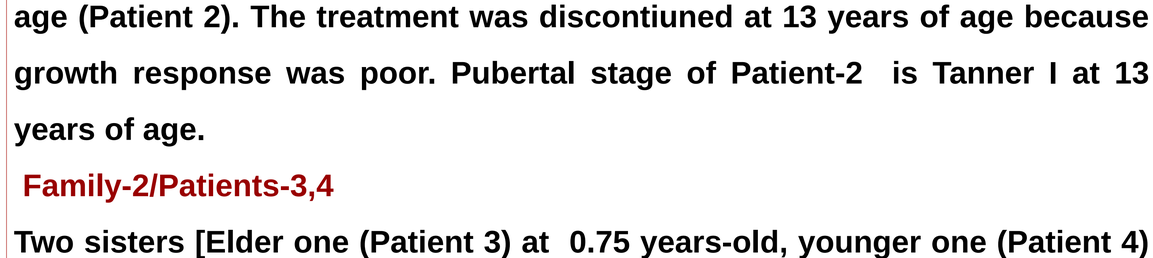

Figure. Clinical findings of 3-M syndrome children

Conclusions

- 3M syndrome should always be considered in the differential diagnosis of short patients with intrauterine growth retardation.
- Children are often treated by GH but there is no obvious demonstration of its efficacy.
- 3M syndrome might cause delayed puberty in boys.

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