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CLINICAL FEATURES AND EFFECT OF GROWTH HORMONE TREATMENT IN 3-M SYNDROME CASES WITH SEVERE GROWTH RETARDATION

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Background: 3-M syndrome is an autosomal recessive growth disorder characterised by severe prenatal and postnatal growth retardation caused by mutations in CUL7, OBSL1 or CCDC8. Clinical characteristics include dysmorphic facial features and skeletal abnormalities.

Aim: Evaluation of clinical and molecular findings and the effect of growth hormone (GH) therapy in seven patients with 3-M syndrome from five different families.

Patients and Methods: Clinical and laboratory findings of seven patients (4males, 3females) from 5 different families [Family(F)I(Patient(P)1, P2), FII (P3, P4), FIII(P5), FIV(P6), FV(P7)] were evaluated retrospectively. Pituitary function, GH stimulation and IGF generation tests were recorded. Growth and pubertal features were evaluated . Five patients were started GH treatment.

Results: Median (range) age of the patients was 6.5(0.5-16.6) years, 4 males (P1, P2, P6, P7), 3 females (P3, P4, P5). There was consanguinity in 3 families (FI, FII, FIV). Six cases (85.7%) had low birth-weight SDS , -3.1[(-1.4) -(-5.1)]. All patients presented with severe growth-retardation; median (range) height SDS was -5.3[(-3.9)– (-7.9)], BMI SDS was -0.8[(-2.4)– (1.5)], head-circumference SDS was 1.4[(-0.17)– (-2.5)]. All patients had dysmorphic features related to 3-M syndrome. All patients' bone-ages were delayed. *CUL7* gene mutations were found in FI (homozygous; p.731insGlufs) and FV (novel, compound heterozygous; p. Pro1511Ser/p. Arg1528Ter), *OBSL1* gene mutations (homozygous; p. Thr425Asp) were found in FII and FIII. Family IV's molecular analysis has not been completed yet. GH response in stimulation tests were normal in P4, P5, P7, high in P1, P2, P3 and low in P6. Five patients were started GH treatment. Median of GH treatment duration was 1.9 years (0.1-4.3). Response to GH treatment was insufficient in all five patients. Patient 1 was 16.6 years-old at presentation while his pubertal-stage was Tanner-II and delayed. At recent evaluation he is 18.6 years-old and pubertal-stage is Tanner-III and puberty has not completed yet. Patient 6's puberty started at age 13.5 and progressing slowly; evaluation at age 17.1 his pubertal stage was Tanner-III and hormone levels were indicating partial primary hypogonadism. Recently, all female patients and P7 are below ten years of age and prepubertal. P2 is 13.1 years-old and prepubertal.

Table. Clinical and laboratory findings of the patients

	Family I		Family II		Family III	Family IV	Family V
	P1	P2	P3	P4	P5	P6	P7
At presentation							
Age (years)	16.6	8.5	0.75	2.5	6.5	12.04	0.55
Sex	M	M	F	F	F	M	M
Consanguineous marriage	1°		3°		-	2°	-
Birth weight SDS	-3.8	-3.1	-3.3	-1.4	-2.9	-5.05	-2.2
Birth length SDS	-	-4.0	-4.4	-4.8	-4.4	-	-2.4
Gestational age (weeks)	40	40	40	37	40	40	40
Weight SDS	-6.8	-4.7	-4.9	-4.4	-4.44	-0.93	-2
Height SDS	-7.2	-5.2	-7.9	-5.3	-6.28	-4.14	-3.9
SH/Height	0.53	0.55	0.65	-	0.56	0.55	0.66
BMI SDS	-2.4	-1.0	-1.8	-0.8	-0.2	+1.51	+0.23
HC SDS	-1.4	-1.8	-2.5	-	-	-	-0.4
Pubertal stage (Tanner)	2	1	1	1	1	1	1
(Testes volumes-Prader)	(6 / 6 ml)	(0.5-1/ 0.5-1 ml)	-	-	-	(2ml/2ml)	(1ml/1ml)
Bone age (years)	12.5	6	-	2.5	3.5	10	-
Target height SDS	-0.4	-1.9			-1.62	+0.68	-0.11
Typical dysmorphic features	+	+	+	+	+	+	+
Mutation	CUL7 Homozygous p.731insGlufs (Exon 8)		OBSL1 Homozygous p.Thr425Asp (Exon 3)			-	CUL7 Compound heterozygous p.Pro1511Ser (Exon 24) p.Arg1528Ter (Exon 25) Novel mutation
Laboratory results							
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	13.9 and 9.7	3.1 and 1.5	13.7 and 4.2
IGF generation tests							
Basal / Stimulated IGF-1 (ng/ml)	419 / 705	58.4 / 207	65.7 / 118	113/161	121/169	149 /-	70.1-
Basal / Stimulated IGFBP-3 (ng/ml)	4580 / 6190	1470 / 3940	3040 / 5080	2420/3420	4350/5100	3030/-	2430-
Onset of rhGH treatment							
Age (years)	-	11	4.8	4.1	9.6	12.1	-
Weight SDS	-	-4.6	-3.7	-3	-3.75	-1.03	-
Height SDS	-	-5.2	-4.6	-4.88	-4.55	-4.34	-
BMI SDS	-	-1.8	-0.6	-0.9	-1.43	1.6	-
SH / Height	-	0.55	0.59	-	0.54	0.55	-
Pubertal stage	-	1	1	1	1	1	-
Bone age (years)	-	7	2-$2^{6/12}$	2 $^{6/12}$	-	10	-
At recent evaluation							
Age (years)	18.6	13.1	7.9	5.8	9.67	17.1	1.44
Weight SDS	-6.7	-3.9	-0.94	-0.32	-3.75	-1.6	-2.63
Height SDS	-6.5	-5.0	-3.56	-4.48	-4.55	-4.84	-4.61
BMI SDS	-2.5	-1.9	1.26	2.8	-1.43	1.21	1.28
HC SDS	-1.5	-1.6	0.27	0.3	-0.47	-1.36	-0.78
SH / Height	0.54	0.53	0.55	0.57	0.54	0.54	0.64
Pubertal stage	3	1	1	1	1	3	1
(Testes volumes-Prader)	(10 / 10 ml)	(2-3 /2-3 ml)	-	-	-	(10 ml/ 10 ml)	(1ml/1ml)
Bone age (years)	16	8	6 $^{9/12}$	3	-	14	$2^{6/12}$

SDS: Standard Deviation Score,; SH: Sitting height, BMI: Body mass index, HC: Head circumference

Conclusions:

- 3-M syndrome should be considered in differential diagnosis of patients with severe prenatal and postnatal growth retardation.
- Children with 3-M syndrome are treated with GH but there is lack of evidence of efficacy in literature.
- Insufficient response to GH treatment and high levels of GH in tests might indicate GH resistance and IGF1 receptor resistance.
- 3M syndrome might cause slowly progressive puberty and partial primary gonadal insufficiency in boys.

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