Two Sibling Cases with Growth Hormone Receptor Mutation: Variable Clinical Expressivity in Laron Syndrome

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INTRODUCTION

Laron syndrome (LS) is defined as primary growth hormone resistance caused by genetic defects in growth hormone (GH) and insulin-like growth factor 1 (IGF-1) axis. Varying degrees of severe or moderate growth failure and additional phenotypic features may be seen in patients, depending on mutations.

AIM

We present the variable clinical spectrum in two sibling cases of Iraqi Arab origin with growth hormone receptor (GHR) mutation.

RESULTS

- Birth week and birth weight were normal in both cases
- There was a first degree cousin marriage between the parents
- **Missense c.344A>C (p.Asn115Thr)** variant was detected in exon 5 in both siblings.
- The clinical features and laboratory findings of the patients at diagnosis are presented in Table 1.
- The clinical characteristics of the patients at the last evaluation are presented in Table 2.
- Dysmorphic findings of siblings are shown in figure 1.
- Growth curve for height with Laron syndrome in figure 2.

RESULTS

Table 1. Clinical and laboratory findings of the two siblings at diagnosis

At diagnosis	Case 1,Female	Case 2,Male
Chronological age(Year)	11,9	14,10
Height(cm)/SDS	**127,5 /-3,86**	**139/-4,27**
Weight(kg)/SDS	31,5/-1,89	35,9/-3,2
BMI(kg/m²)/SDS	19,3/0,16	18,58/-0,97
Puberty stage	2	2
Bone age (Years)	12	13
Basal GH (ng/mL)	1,28	**26,6**
Peak GH (ng/mL)	**27,8**	8,96
Basal IGF-1 (ng/mL)/SDS	**82/ <-2**	**97,7/ <-2**
Basal IGFBP-3(µg/mL)/SDS	**2,586/ <-2**	**2,06/ <-2**
Post generation test		
IGF-1(ng/mL)/SD	108/ <-2	213/ (-2/-1)
IGFBP-3 µg/mL/SD	2,429/<-2	4,802/(-1/mean)
Response to generation test(%)	**31**	**118**

Table 2: Clinical findings of the two siblings at last evaluation

Last Evaluation	Case 1,Female	Case 2,Male
Chronological age (years)	14,3	17,10
Target height (cm) /SDS	160 cm/ -0,53 SDS	173 cm/ -0,52 SDS
Height (cm) /SDS	138,3/-3,92	156,3/-3,17
Weight (kg) /SDS	50,3/-0,67	48,6/-2,98
BMI (kg/m²) / SDS	26,3/1,75	19,89/-1,27
Weight by height (%)	154	99

CONCLUSIONS

In the literature, there are three reported cases harboring the same mutation as in our cases, all being of Arab origin, suggesting a probable “founder effect” for the identified mutation. These three previously reported patients all had severe LS phenotype and lower final height SDS values and lower IGF-1 levels than our cases (-4.5 SDS in a female case, and -6.8 and -6.9 SDS in two male cases)(Table 3). The milder phenotype in our patients despite the same genotype suggests, a variable GHR activity potentially due to other modifiers such as downstream variants in other genes in the GH/IGF1 pathway.

Table 3. Clinical data of 5 LS patients with the same GHR mutation

	Gender	Consaanguinity/ ethnicity	Age at presentation years	Height SDS	BMI SDS	GH basal µg/L	GH level after stimulation ng/mL	IGF-1 after stimulation ng/mL	IGF-1 SDS	IGFB-3, mg/L
1	F	+/Arabic-Syrian	3.1	-4.5	-1.2	3.3	75.0	-	-7.3	-
2	M	+/Saudi Arabian	1.25	-6.9	-	-	213	<3	-	< 0.5
3	M	+/Saudi Arabian	3.0	-6.8	-2.77	-	50	<3	-	0.6
4 Case 1	F	+/Arabic-Iraqi	11 .9	-3.86	0.16	1.28	27.8	108	< -2	2.42
5 Case 2	M	+/Arabic-Iraqi	14.10	-4.27	-0.97	26.6	8.96	213	< -2	2.06

Figure 1: Dysmorphic findings of siblings with Laron syndrome

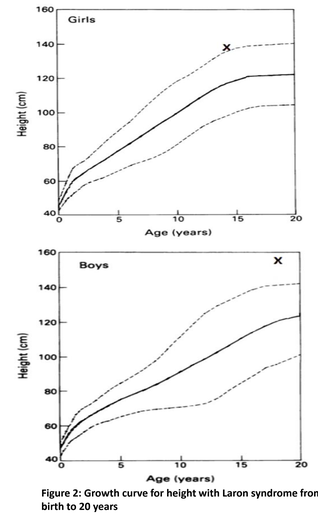

Figure 2: Growth curve for height with Laron syndrome from birth to 20 years

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