Extreme Short Stature and Severe Neurological Impairment in a 17-Year-Old Male With Untreated Combined Pituitary Hormone Deficiency Due to *POU1F1* Mutation

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BACKGROUND

POU1F1 is an essential transcription factor for the differentiation, proliferation and survival of somatotrophs, lactotrophs, and thyrotrophs. Mutations in the *POU1F1* gene are characterized by growth hormone (GH), thyrotropin, and prolactin deficiencies, commonly presenting with growth retardation and central hypothyroidism. Since the first report in 1992, more than 25 mutations have been identified in *POU1F1*.

CASE PRESENTATION

We describe a 17-year-old male who presented to our Pediatric Endocrinology clinic with extreme short stature (height 81.7 cm, −9.3 SD), cognitive impairment, deaf-mutism, and neurological disabilities.
L-thyroxine supplemental therapy, which had been initiated at the age of 6 months but ceased due to non-compliance, was reintroduced at presentation. GH therapy was initiated at 19 years of age, resulting in 42 cm linear growth, to a final height of 124 cm. Sequencing of *POU1F1* revealed a previously described homozygous insertion mutation —c.580_581insT, p (Thr194Ilefs*7)— in exon 4 causing a frameshift that introduces a stop codon 7 amino acids downstream, leading to a severely truncated protein lacking the homeodomain.

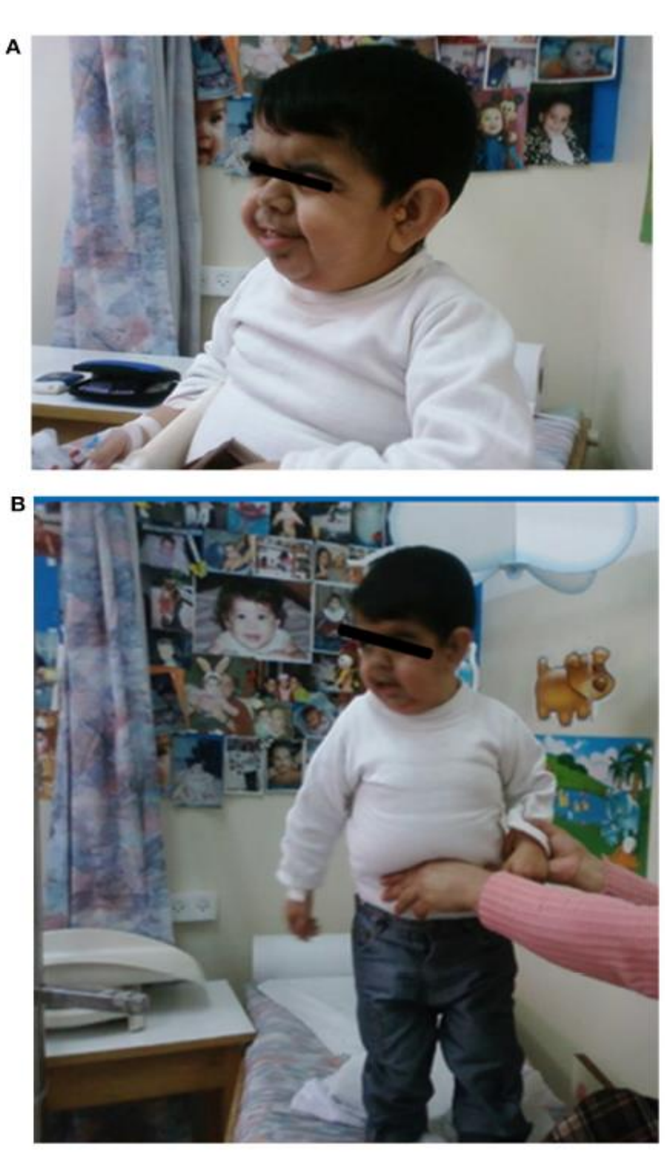

Figure 1. The patient at age 17 years. He had a deep nasal bridge, prominent forehead, micrognathia, flat nose, prominent and large auricles, multiple pre-auricular skin tags, and widely spaced teeth (With permission from the family).

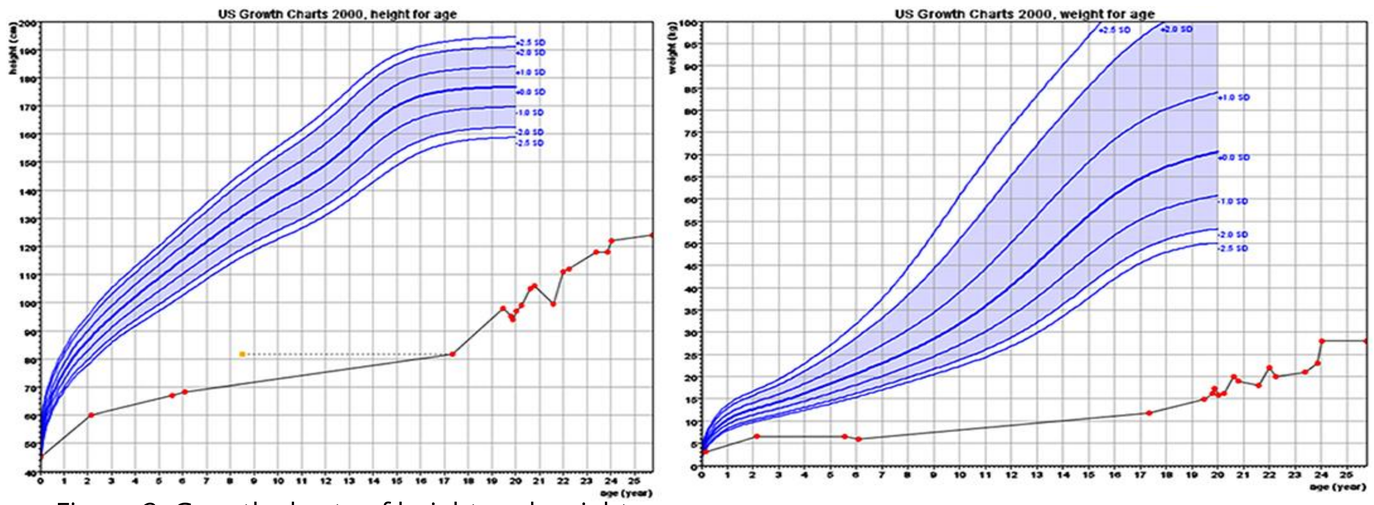

Figure 2. Growth charts of height and weight.

Table 1. Summary of hormonal results.

Test	Age (years)	0.5	5	17.5	25.10	Normal range
	TSH (mIU/L)	0.08	0.011	<0.015	<0.015	0.4–4.2
	Prolactin (mIU/L)		<44	<0.8	< 3.0	45–375
	FT4 (pmol/L)	5.4	1.34	9.5	20.8	10–20
	FT3 (pmol/L)		<0.044		7.4	3.5–6.3
TRH	Peak TSH		0.014	<0.015		
	Peak prolactin (mIU/L)		<44	<0.8		
	IGF-I (ng/mL)		<0.04	<3.25	<3.0	93–250
	IGFBP-3 (ng/mL)		<200	<500		2,700–8,900
Arginine	Basal GH (ng/mL)		<0.5			
	Peak GH /(ng/mL)		<0.5			>7.5
Clonidine	Basal GH (ng/mL)			<0.05		
	Peak GH (ng/mL)			<0.05		>7.5
Glucagon	Basal GH (ng/mL)			<0.05		
	Peak GH (ng/mL)			<0.05		
ACTH	Basal cortisol (nmol/L)		361	238	480	200–700
	Peak cortisol (nmol/L)		1,405			>550
	Basal ACTH (pmol/L)			2.53		0–10
GnRH	Basal LH (mIU/L)		<0.5	1.0	5.4	1.9–12.5
	Peak LH (mIU/L)		3.6			
	Basal FSH (mIU/L)		1.2	4.8	19.8	2.5–10.2
	Peak FSH (mIU/L)		9.5			
	Tesosterone (nmol/L)				22.0	8.4–28.8

DISCUSSION

Descriptions of patients with CH before the widespread implementation of neonatal screening in the 1980s, as well as reports of children with endemic cretinism due to iodine deficiency, describe clinical phenotypes with severe cognitive and neurological impairment including spasticity, particularly in the lower extremities, shuffling gait, discoordination, jerky movements, tremor, hypotonia, and extrapyramidal disorders. In addition, deaf-mutism, hearing loss, dysarthria, and extreme short stature are reported. It is therefore likely that the cognitive impairment, hypotonia, neurological deficits, and deaf-mutism seen in this case are consequences of delayed diagnosis and poor compliance with LT_4 treatment. Mental retardation, microcephaly, sensorineural deafness, and severe prenatal and postnatal growth failure were described in patients with IGF-1 mutation but not in patients with IGF-1 deficiency secondary to GH deficiency despite the occurrence of recurrent hypoglycemic events in infancy. This may indicate that the severe mental retardation in our case is attributable primarily to prolonged untreated hypothyroidism rather than unrecognized hypoglycemic events in infancy. Early diagnosis and initiation of LT_4 therapy as well as GH treatment might have prevented neurodevelopmental deterioration and improved final height. No previous descriptions of *POU1F1* mutations describe the untreated natural history of this condition. This case therefore extends the phenotypic spectrum associated with *POU1F1* mutations, highlighting the importance of appropriate treatment and follow-up.

CONCLUSIONS

This case report sheds light on the natural history of untreated patients with *POU1F1* mutations and raises awareness for early diagnosis and adequate treatment of central congenital hypothyroidism and GH deficiency.

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