Isolated Congenital Central Hypothyroidism due to a Novel Mutation in TSH-Beta Subunit Gene

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Disclosure : The authors have nothing to disclose.

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Objective

Congenital isolated thyrotropin (TSH) deficiency is a rare condition due to autosomal recessive defects in *TBL1X* , *TRHR*, *TSHβ* genes. To date, seven different TSH- subunit mutations leading to CCH have been identified. These patients display the typical manifestations of severe untreated congenital hypothyroidism. Most patients are unrecognized, even in newborns screening settings due to unelevated TSH levels, which results in severe growth failure and intellectual disability. We describe a baby boy with isolated congenital central hypothyroidism (ICCH) due to a novel homozygous *TSHβ* gene mutation.

Case Report

A 53-day-old male was admitted for investigation of severe hypotonia, prolonged jaundice, and constipation which began around 4 weeks of age. Parents were third degree cousins. Following a normal delivery with birth weight of 4230 g (+3.4 SDS), he had been hospitalized for 8 days in a neonatal care unit for hypotonia and transient tachypnea of the newborn. There was no jaundice, umbilical hernia or macroglossia noted in the newborn period. At referral to our clinic, he was 5940 g in weight (+0.9 SDS), 60.5 cm in height (+1.29 SDS), and 40,5 cm (+0,89 SDS) in head circumference. He had severe hypotonia, jaundice, dry skin with , macroglossia, and coarse facial features. Anterior fontanelle was 2x2 cm, and posterior fontanelle was closed. His physical examination was otherwise unremarkable. On laboratory testing, free T4 was < 0.25 (normal range, 0,61-1,12 ng/dl); TSH was, 0.06 µIU/ml (0.34–5.6 µIU/ml).To rule out multiple pituitary hormone deficiencies, additional hormone tests were performed which revealed a spot GH level of 5.8 ng/dl (0-1 ng/ml), IGF-1 33.1 ng/ml (15-189 ng/ml), IGFBP-3 1.53 µg/ml (0.7-3.6 µg/ml), FSH: 2.65 mIU/ml, LH 1.75mIU/ml, total testosterone 0.93 ng/ml and PRL 26 ng/ml. Sufficient cortisol response detected in the low-dose ACTH stimulation test. An MRI of the head and pituitary was unremarkable. He was started on levothyroxine replacement. After 4 weeks of treatment, he was much more alert, active, and feeding better. We identified a novel homozygous mutation c.217 A>C (p.T73P) of the *TSHβ* gene responsible for a severe isolated TSH deficiency in male infant missed from neonatal screening.

	At the presentation	After treatment		
Age (weeks)	7	11	15	32
Body length (cm) and centile	60.5 (75 th)	62.5 (75 th)		76 (75-90 th)
Body weight (kg) and centile	5.940 (75 th)	6.8 (75 th)		9.8 (75 th)
LABORATORY				
TSH (µIU/l) (0.34 – 5.6)	0.06	<0.015	<0.015	<0.015
fT4 (ng/dL) (0.61-1.12)	< 0.25	3.3	0.78	0.82
GH (ng/mL) (0-1.0)	5.89			
IGF-1 (ng/mL) (15-189)	33.1		20.1	
IGF-BP3 (µg/mL) ((0.7-3.6)	1.53		2.1	
FSH (mIU/l) (1.27-19)	2.65		1.7	
LH (mIU/l)(1.7-8.6)	1.75		3.42	
T.Testosterone(ng/mL) (0.75-4)	0.93		1.1	
Prolactin (ng/mL)	143 (0-125)		26.5 (4-25)	
Low dose (1 mcg) ACTH test peak cortisol (µg/dl) 40'	25.3			
Pituitary MRI	Normal			
Extrathyroidal Abnormalities	None			
Neurodevelopment	Hypotonia	Active		
Haematological	None			

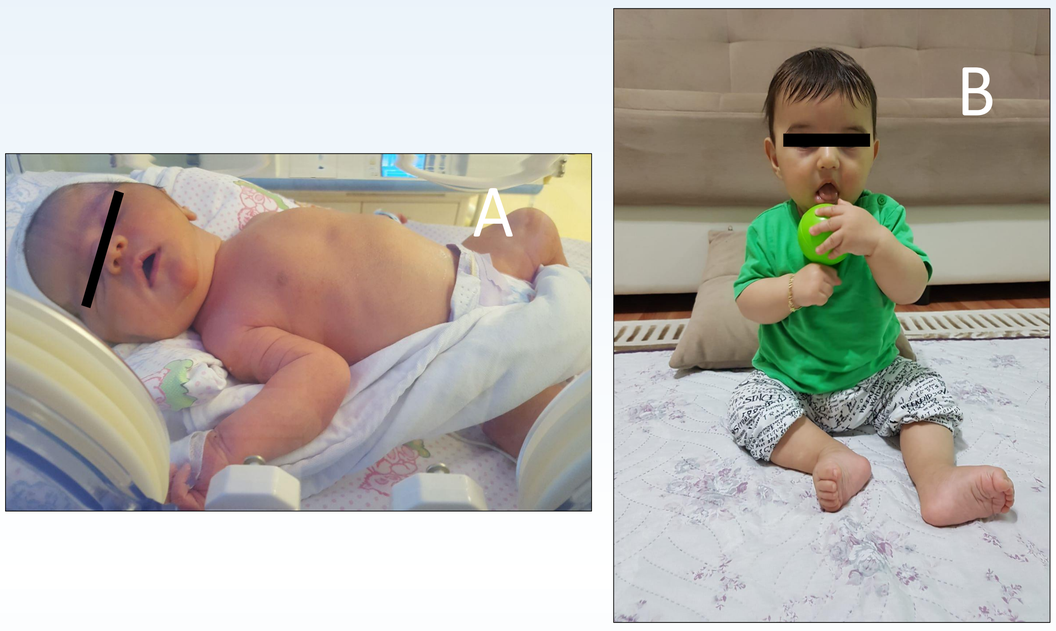

Figure 1. A) severe hypotonia **B)** Current state of patient

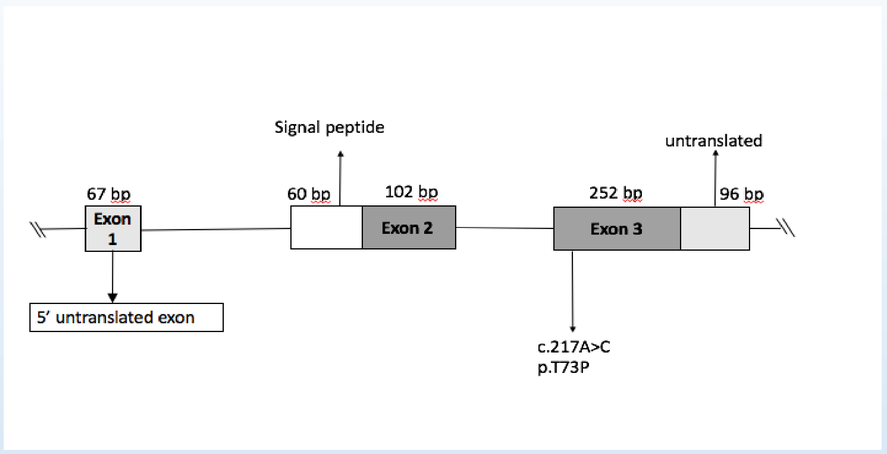

Figure 2. Thyrotropin *β* (TSH *β*) gene mutation in a patient with isolated congenital central hypothyroidisim .The TSH *β* gene iis located on chromose 1 and consist of one noncoding exon (exon 1), two coding exons and two introns. The approximate location of the reported TSH *β* gene mutation is indicated by the arrow.

Conclusion

It should be remembered that clinical features of hypothyroidism related to *TSHβ* mutations can be as severe as in cases with primary hypothyroidism.