NKX2-1 p.Asp266Argfs142X de novo mutation in a girl with congenital hypothyroidism (CH): phenotypic description

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Background: Ttf1-/-mice had complete absence of follicular and parafollicular cells, agenesis of lung parenchyma, ventral forebrain, pituitary[1]. CH patients with chromosomal deletions encompassing the TTF-1 locus[2] and point mutations in the *TTF-1* gene[3,4] confirmed its implication in the phenotype: CH with a thyroid gland in place, associated with respiratory distress syndrome, neonatal hypotonia followed by choreoathetosis or ataxia.

Objective : Description of the phenotype in a patient with NKX2-1 mutation from the Bulgarian thyroid screening cohort.

Methods: *Case report* and direct sequencing of NKX2-1.

Perinatal history: A girl, born from first pathologic pregnancy (toxicosis), 23 days after term, traumatic delivery with rupture of m. sternocleidomastoideus. Birthweight- 2500 (3rd percentile), birthlenght- 50 cm (50th percentile).

Family history: Unremarkable. Target height – 153 cm, SDS-MPH (Prader) - (-2.23).

Diagnosis: Congenital hypothyroidism was detected by the neonatal TSH screening (Table 1). Initial L-T4 dosage: 12 mcg/kg/d at day 53. At 2.5 years of age reevaluation was carried out and permanent hypothyroidism was established, due to thyroid dysgenesis – hypoplasia of the left lob, aplasia of the right lob (Fig.1).

Age (d)	NTSH mU/l	TSH mU/l	T4 nmol/l
3	31.4		
35	77.3		
53	97.8	145	77.9
2.5 yrs	76.3	137	57

Table 1- Thyroid function

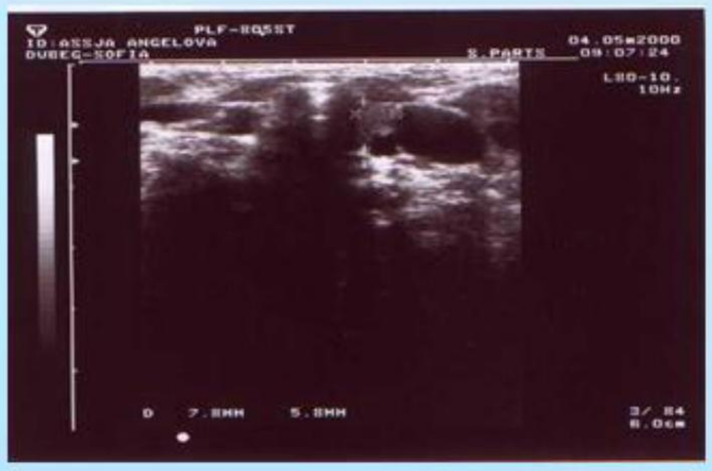

Fig. 1 US of the thyroid

Growth and development: Despite normal TSH and (f)T4 under substitution she developed persistent hypotonia from early infancy. Developmental delay - walking at 3 years, talking –after 2 years, IQ at 5 years - 50, 6 years of age – 66. Catch down (Fig. 2) of linear growth (SDS_h -3.6 at 2 yrs), mild bone age retardation during adrenarche. Until the age of 6 she had frequent respiratory infections (asthma, CF, chronic pneumonias were excluded). After start of walking, movement affection resembles choreoathetosis.

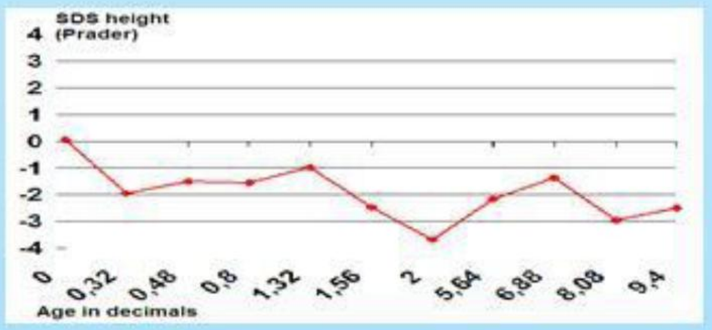

Fig. 2 SDS_h from birth to 10 years

Molecular analysis: According to the triad of thyroid, neurological and respiratory involvement the family was sequenced for NKX2-1 after informed consent. A small deletion c.796delGA leading at protein level to Asp266ArgfsX142 in the NK2-specific domain in exon 3 was found only in the patient (Fig. 3).

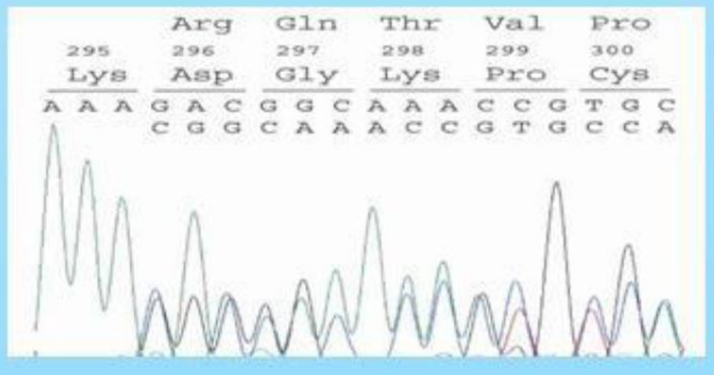

Fig. 3 c.796delGA

Conclusion: Monogenic CH is heterogeneous and belongs to rare diseases. Hypotonia despite sufficient L-T4 treatment is an early sign which can guide to the suspicion of underlying NKX2-1 mutations in primary CH.

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Pituitary

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