Primary Congenital Hypothyroidism Associated with Additional Anomalies: Phenotypic Characterization and Therapeutic Approach

Iva Stoeva, Iliana Boneva, Radka Tincheva, Daniela Avdjieva, Liubomir Spassov, Radoslava Emilova

University Paediatric Hospital Sofia

SUMMARY To our knowledge, this is the first report of 46, XY, del (2) (q13-q21). Further investigations are needed, regarding the breaking points of the deletion with molecular- cytogenetic methods and the mechanisms of the retarded development. The complex phenotype in our patient, with the involvement of the thyroid gland, heart, central nervous system and kidneys on the background of a marked muscle weakness, poses many different problems. Our priority, after the establishment of the congenital hypothyroidism, was the prompt substitution with L-Thyroxin. However, despite successful management of the thyroid hypofunction, marked muscular hypotonia, absence of a catch-up growth and severe mental retardation limits the social adaptation of the boy and lay a heavy burden on his mother, who has to take care of him and his handicapped father at home.

table 1. Hormonal parameters on the 14 day of age, before treatment

Age (days)	Screening *(dried blood spot)*		Confirmation *(serum levels)*			
	NeoTSH (mU/l)	*NeoT4 (nmol/l)*	*TSH (mU/l)*	*T4 (nmol/l)*	*FT4 (pmol/l)*	*Tg (ng/ml)*
4	44.5 (Ref.<15 mU/l)	66.3				
14	19.4 (Ref.<8 mU/l)	76.8	34.9 (Ref.0. 5-8.7)	88.1 (Ref.130-243)	13.5 (Ref.11.2-29.6)	63

fig.3 Individualization of hormonal substitution with L-T4 focused on stable euthyroid state

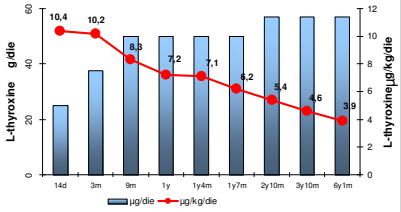


fig. 4 Auxological parameters fig.5 Head circumference up to 4 yrs of age

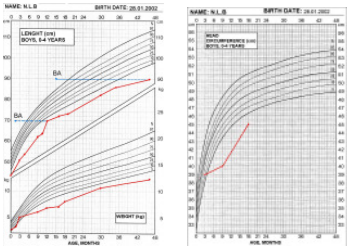
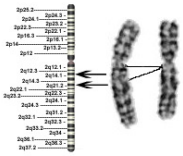


fig.8 Patient's Chromosomal aberration and chr2 idiogram



Case report

N.L.B. male;

Prenatal history: 3rd pregnancy (not monitored first 4 months, dental abscess treated with tetraolean, work with glues, paints, incipient placental abruption);

Delivery: BD 28.01.2002, 37 gestational weeks, BW 2400 g, BL 44 cm ***(SGA)***, normal mechanism, APGAR 8(1');

Family history: grandmothers with goiter, father with cerebral stroke before 50 years of age; healthy older brother and sister;

Postnatal findings:

A) Neonatal ward: morphological maturity corresponding to 34-35th gestational weeks; delayed cardio-pulmonal adaptation, muscle hypotonia and slow reflexes, marked jaundice, hyperviscosity, systolic heart murmur transfer to the Cardiology Clinic of the University Hospital Sofia;

B) Cardiology (day 6): hypotonia, acrocyanosis, jaundice (indirect hyperbilirubinemia 367 µmol/l), reduced subcutaneous fat, tachy-dyspnea, holosystolic heart murmur with transversal propagation; no liver and spleen enlargement; maximal milk suckling capacity 15-20 ml;

Investigations:

Transitory hypocalcemia; TORCH- negative; inflammatory markers-negative; ECG- right ventricular overload;

US of the heart: ASD, (no blood flow); VSD membranous type (5.5-6.0 mm, left-to-right shunt); peripheral stenosis of the left brunch of a. pulmonalis, next to the bifurcation.

Day 13: ***increased TSH*** from the neonatal screening;

Evaluation by a pediatric endocrinologist: lax skin, anterior fontanelle 40/40 mm, broadly opened sagittal suture, connected with an open posterior fontanelle > 5 mm, low position of the umbilicus, slow suckling.

Investigations: X-ray of the knee and foot- significantly delayed bone age, corresponding to 29-th gestational week. The blood tests confirmed the screening results (table 1);

Treatment: L-Thyroxin was started on the 14-th day at a dose 10.4 µg/kg/d (25 µg/d). Improved feeding, slightly better muscle tone and reduced icter were observed in the course of the treatment and rapid dynamics of T4 and slow decrease in TSH were registered (fig.1,2). At the same time signs of cardiac failure became manifested: increased thoraco-abdominal asynchrony, persistent tachypnea and aggravating hepatomegaly (3.0 cm below the costal margin). Treatment with diuretic, Captopril, KCL and Ceglunat was started, without reduction of the dose of L- Thyroxin.

Day 18 The child was discharged in an improved state; weight 2.640 g.

Next hospitalization (4 months of age):

Symptoms of gastroesophageal reflux; treated with Coordinax ;Correction of the diuretic and cardiotonic therapy

Follow- up (pediatric endocrinologist) during the first year:

Thyroid function

Stable euthyroid state (fig.1,2); Individualized L-T4 treatment (fig 3);

Thyroid gland on normal location (US), Mother's thyroid- normal structure and function

Development

Progressing retardation in growth and development (weight and height continuously <3-th p) (fig.4); Microcephaly (head circumference < 3-th p) at 3 month of age (fig.5); Decreased muscle tone (fig.7); Delay in the neuropsychological development; Dysmorphic face (fig.6)

Further diagnostic evaluation (Department for Clinical Genetics)

Dysmorphic syndrome

flat supraorbital arches, broad alveolar ridges, high forehead, epicanthic folds, low set ears,

skin sinus of the coccygeal zone, syndactyly of the 2-nd - 3-th toes of the right foot.

Neurological evaluation

Decreased muscle tone; no damages at the level of the central or peripheral motor neuron; normal brain structures (US)

Other problems

Recurrent laryngitis and otitis media; Inflammatory activity and microcytic anemia (FBC);

Transitory hematuria; Reduced size of the kidneys, especially of the left (US)

Karyotype (fig.8)

The karyotype (G-banding) (metaphase plates, produced by phytochemaglutinin stimulated lymphocytes from peripheral blood) revealed a de novo structural mutation: 46, XY, del, (2) (q 13-q21).

Follow- up (pediatric cardiologist) up to the fourth year:

Persisting VSD without signs of cardiac failure; Closing of the ASD.

Follow- up (pediatric endocrinologist) up to the sixth year:

Progressive retardation in the neuropsychologic, growth and bone development, despite euthyroid state; Aggressive behavior; Difficult contacts and adaptation to unknown environment; Speech development: pronounces specific sounds, interpreted only by the mother, no distinguishable words

fig.1 TSH dynamics depending on L-T4 dosage

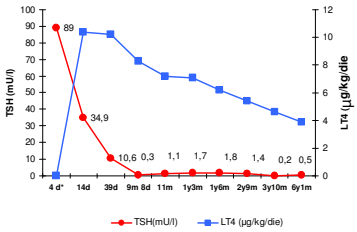


fig.2 T4 dynamics depending on L-T4 dosage

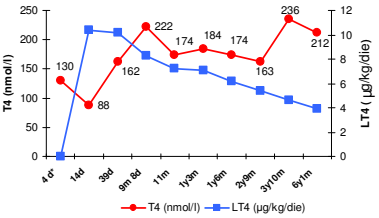
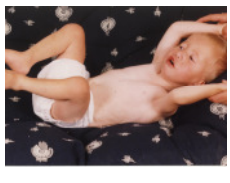


Table2. Developmental score (Manova-Tomova) changes by age

AGE	DS (Manova-Tomova)
3m	120
9m	72
1y4m	75
1y7m	77

fig.6 N.L.B at age 2 yrs 6 months

fig.7 N.L.B at age 2 yrs 6 months



Discussion 46, XY, del (2) (q13-q21) is not described in humans by now. The de novo deletion, established in our patient in one of the long arms of the second chromosome by GTG banding, involves the points, where some known genes: of PAX8 (2q12-q14), PROC (protein C- inactivator of the coagulation factors Va and VIIIa, 2q13-q14), CMD1H (2q14-q22, dilated cardiomyopathy 1H), BIN (1) q14, centronuclear myopathy, AR form), HMN1A (distal hereditary motor neuropathy type VII A with paralysis of the voice cords, 2q14), IL1A and IL1B (2q14, interleukines alfa and beta) are located, and many others, with partly elucidated or completely unknown function. In our patient there is a haploinsufficiency of all these genes, some of which code transcription factors.

Normal growth and development are characteristic for more than 90% of the children, diagnosed by the NTS on adequate hormonal substitution. Despite the prompt postnatal establishment of euthyroid state and the successful management of the cardiac problems, our patient failed to show the expected catch up growth and development.

Conclusions

- The presented patient represents a rare condition associated with CH in whom, despite early diagnosis and treatment, a substantial growth and development delay is evident
- Such patients should be characterized thoroughly in respect of phenotype-genotype relations
- Their optimal integration needs extensive integrative efforts of the society: medical, social, educational

Future goals in our patient:

It is of great importance to locate the precise breaking points of the deletion of chromosome 2 with molecular-cytogenetic methods;

More investigations are needed in relation to the developmental delay;

The patient poses many unsolved problems, related to **the etiology** (is the established structural chromosomal aberration satisfactory enough?), **the pathogenesis** and **the therapeutic approach**, and of utmost importance – **the possibility for future integration.**