Transient familial congenital hypothyroidism: About a sibling of three

Abstract :

INTRODUCTION:

Congenital hypothyroidism is one of the most common preventable causes of intellectual disability . It is classified into permanent and transient. The transient disorder refers to a temporary deficiency of thyroid hormones at birth but then recovering to normal thyroïd hormone production .

We will present a case of congenital hypothyroidism in a sibling of three.

CASE REPORT :

Symptomatology seems to date back to the age of 2 months in the first two siblings for which they were hospitalized in pediatrics for hypotonia and macroglossia associated to anemia.

Contrasting with the youngest sibling who was screened at day 7 of life .

Biological findings revealed hypothyroidism.

Supplemented by ultrasound showing a normal thyroid volume, while thyroid scintigraphy revealed a moderately reduced fixation.

They were all put on Levothyroxin. However, we noted a spontaneous improvement in the youngest brother leading to cessation of hormone replacement therapy at the age of 5.

DISCUSSION:

While thyroid dysgenesis remains the most common cause of congenital hypothyroïdism, the incidence of dyshormonogenesis has been increasing over the last few decades.

Transient hypothyroidism may be caused by mutations in the genes encoding essentialy for DUOX2/DUOXA2 suspected in our sibling due to the transient caracter in younger brother.

However, mutations in pendrine, sodium iodine symporter, thyroid peroxidade, thyroglobulin genes are often assoxiated with goiter and severe permanent hypothyroidism.

Finally, new born screening and effective treatment is a major achievement in preventive medicine.

Keywords: hypothyroidism, familial, transient

Introduction :

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. Thyroid hormone (TH) action for neurodevelopment is limited to a specific time window, and even a short period of deficiency of TH can cause irreversible brain damage, making CH one of the most common preventable causes of intellectual disability (1,2).

The clinical manifestations are often subtle or not present at birth, due to trans-placental passage of some maternal thyroid hormone while many infants have some thyroid production of their own (3).

CH may be caused by abnormal development or function of the thyroid gland, or of the hypothalamus and pituitary, but also to impaired TH action (4).

CH is classified into permanent and transient which refers to a temporary deficiency of thyroid hormone, discovered at birth, but then recovering to normal thyroid hormone production (3).

The immediate goals of treatment are to rapidly raise the serum T4 and normalize serum TSH levels, while frequent laboratory monitoring in infancy is essential to ensure optimal neurocognitive outcome (3).

With the advent of screening of newborn populations, the incidence was reported to be in the range of 1/3000 to 1/4000 (3).

Aims :

We will present a case of congenital hypothyroidism in a sibling of 3, in order to:

- Underline the importance of early detection of CH
- Explore the transient nature of congenital hypothyroidism
- Investigate the genetic causes of primary congenital thyroid dysfunction

- Highlight the benefits of frequent initial follow-up

Case report :

Symptomatology seems to date back to the age of 3 months in the first two siblings, for which they were hospitalized in pediatrics for hypotonia with macroglossia. The check-up revealed hypothyroidism with respective TSH at 400 ui/l and 100 ui/l for both elder sisters regarding low peripheral hormone levels T4 and T3 (< 0.1 pmol/l) all evolving in a context of anemia.

Contrasting with the youngest sibling who was screened at day 7 of life with lower TSH levels at 11 uui/l.

Cervical ultrasound revealed normal thyroid volume, while technetium-99 thyroid scintigraphy showed a thyroid gland of normal size and moderately reduced fixation.

Acutely complicated for the 2nd sister by 2.3cm auricular septal defect with pulmonary hypertension, and dilatation of the right cavities, with indication for urgent surgical closure. Successfully operated on one month later.

Unfortunately, the genetic analysis was not performed initially, but is currently underway.

They were all put on LT4 10 mcg/kg/d,with progressive adjustments.

However, the youngest sibling showed spontaneous improvement, leading to cessation of hormone replacement therapy at the age of 5.

Discussion :

Thyroid hormones, produced by the thyroid gland, are essential to the development, growth, and metabolism of practically all human tissues. TH production (T4 and T3) is regulated by the hypothalamic-pituitary-thyroid axis. A TH deficiency, at birth, or congenital hypothyroidism (CH) results in severe retardation of growth and neuropsychomotor

development in the absence of replacement therapy initiated quickly from the neonatal period (5).

Many of the classic features (large tongue, hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling, cold hands and feet and lethargy…), when present, are subtle. In addition to the aforementioned findings, nonspecific signs that suggest the diagnosis of neonatal hypothyroidism include: prolonged, unconjugated hyperbilirubinemia, gestation longer than 42 weeks, feeding difficulties, delayed passage of stools, hypothermia, or respiratory distress in an infant weighing over 2.5 kg (5).

To deal with these unexpressive clinical vignettes, several guidelines and expert opinions on congenital hypothyroidism (CH) are currently available, starting with requiring initial screening. On the same level also comes the need for fast, effective treatment to ensure proper global functions, better growth and, above all, optimal psycho-motor development (6,7,8).

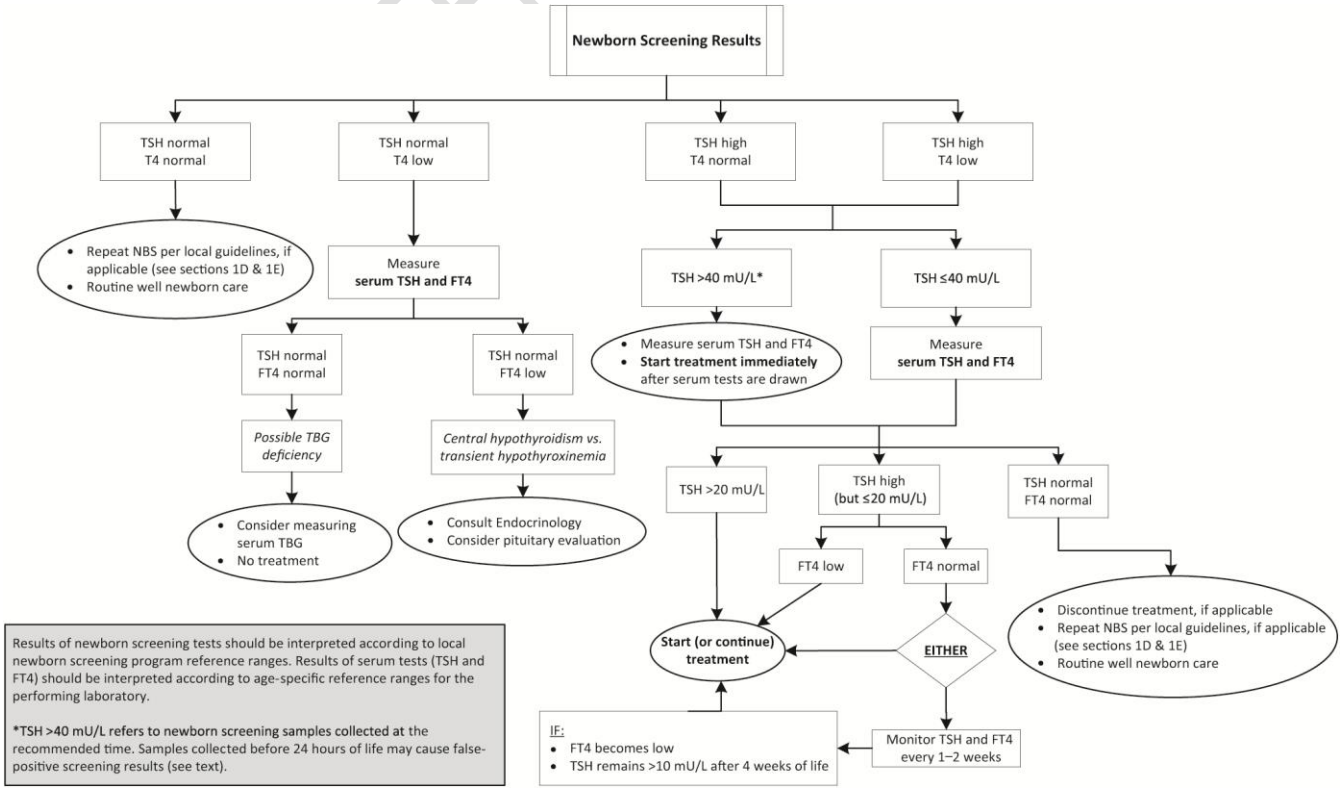


Figure N 1 : Screening recommandations (8)

There is now a well-established correlation between the occurrence of CH and the alteration of thyroid development. The Nkx2-1, Foxe1, Pax8, and HHex transcription factors are essential for the specification of the thyroid. Migration of the progenitor cells is a crucial stage for development and thyroid function. The markers of terminal differentiation are the TSH receptor (TSHR), the iodine transporter (NIS, sodium/iodine symporter coded by the SLC5A5 gene), thyroglobulin (TG), thyroperoxidase (TPO), DUOX2 and DUOXA2, involved in hormone synthesis . Iodine, drawn from the bloodstream, enters the thyrocyte through the iodine transporter (NIS). The iodine is then oxidized by TPO and the H_2O_2 DUOX2/DUOXA2 producer complex to TG, TH matrix protein, T4, and T3. Malformations at any stage of thyroid development (such as the specification, proliferation, migration, growth, organization, differentiation, and survival) can result in a congenital abnormality and/or an alteration to hormone synthesis leading to varying degrees of hypothyroidism (2,7).

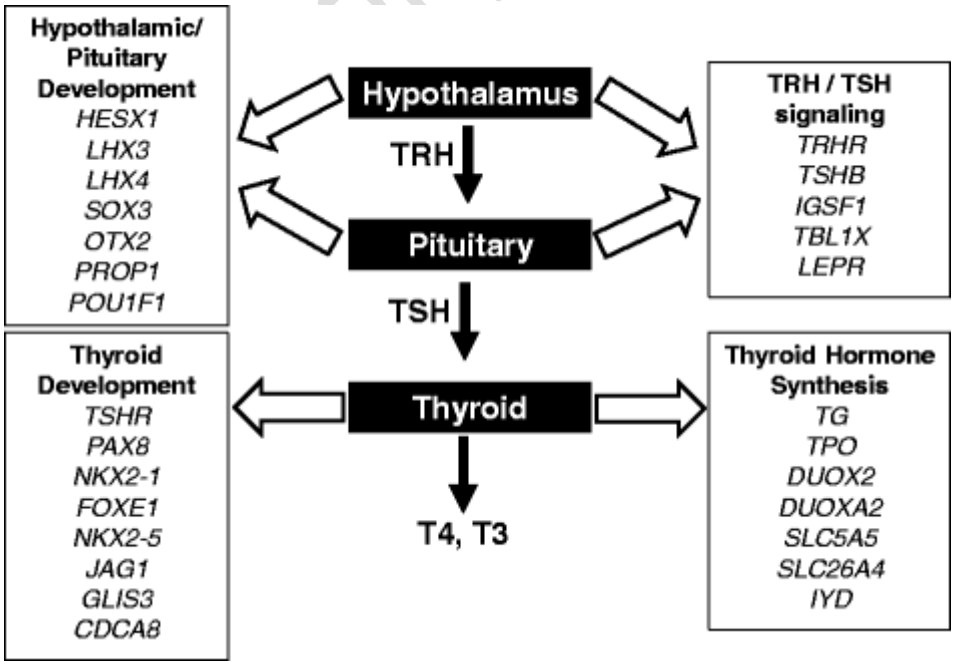
While ransient hypothyroidism may be caused by neonatal factors including : neonatal iodine deficiency or excess, congenital liver hemangiomas and mutations in the genes encoding for DUOX and DUOXA2, that we suspect in our sibling due to the transient caracter in younger brother.

In fact if only one copy of the *DUOX2 or THOX* gene is mutated, some hydrogen peroxide is produced. As a result, thyroid hormone levels are slightly reduced, causing mild congenital hypothyroidism. Sometimes, mild congenital hypothyroidism is temporary (transient), and thyroid hormone levels that are low during infancy increase with age (9,10).

	Gene locus	Inheritance
Monogenic forms of thyroid dysgenesis		
Thyroid stimulating hormone receptor (TSHR)		AR
NK2 1 (NK2-1, TTF1) brain-lung thyroid syndrome	14q13	AD
Paired box gene 8 (PAX8)	2q11.2	AD
Forkhead boxE1 (FOXE1, TTF2) (Bambforth-Lazarus syndrome)	9q22	AR
NK2 homeobox 5 (NKX2-5)		
New candidate genes		
Nertrin 1 (NTN-1)		
JAG1	20p.12.2	
Glis3	9p24.2	AR
Inborn errors of thyroid hormonogenesis		
Sodium/Iodide symporter (SLC5A5, NIS)	19p13.2	AR
Thyroid peroxidase (TPO)	2p25	AR
Pendred syndrome (SLC26A4, PDS)	7q31	AR
Thyroglobulin (TG)	8q24	AR
Iodothyrosine deiodinase (IYD, DEHAL1)	6q24-25	AR
Dual oxidase 2 (DUOX2)	15q15.3	AR/AD
Dual oxidase maturation factor 2 (DUOXA2)		AR/AD
CENTRAL HYPOTHYROIDISM		
Isolated TSH deficiency		

TRHR	14q31	AR
TSHB	1p13	AR
Isolated TSH deficiency or combined pituitary hormone deficiency		
Immunoglobulin superfamily member1 (IGSF1) gene defects	Xq26.1	X-Linked
Combined pituitary hormone deficiency		
POU1F1	3p11	AR, AD
PROP1	5q	AR
HESX1	3p21.2-21.2	AR/AD
LHX3	9q.34	AR
LHX4	1q25	AD
SOX3		X-linked
OTX2		AD

Figure N 2 : genetic causes of CH (5)



Figune N3 : gene causing congenital hypothyroidism

Levothyroxine (l-thyroxine) is the treatment of choice, and American academy of pediatrics and European society of pediatric endocrinology recommend 10-15µgm/kg/day as initial dose. The immediate goal of therapy is to normalize T4 within 2 weeks and TSH within one month. The overall goal of treatment is to ensure growth and neurodevelopmental outcomes as close as possible to their genetic potential(2). And this was indeed the case of the 2nd sibling, a levothyroxine treatment was started during the first weeks of life, which allowed good psychomotor development and growth.

Conclusion :

New born screening and effective treatment for congenital hypothyroidism has been included in neonatal programmes and is considered as a major achievement in preventive medicine. But still more efforts required to raise awareness of this importance in developing countries

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