An eight day old hyperthyroid neonate with a resistance to thyroid hormone

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SUMMARY :

A tunisian newborn girl presented for a systemic clinical control at the age of eight days with tachycardia. Holter electrocardiography showed sinus tachycardia, cardiac ultrasound was normal. Biochemical findings showed high levels of FT4 and TSH. The search for anti-TSH antibody receptors was negative, thyroxine binding globulin level was normal for age. Molecular analysis of the β-receptor for thyroid hormones gene has demonstrated the A268D mutation in exon 8 in the heterozygous state responsible for resistance to thyroid hormones. Her parents and her brother showed no mutation.
Betablocker treatment was inefficient on the tachycardia so it was discontinued after one month.
We did not put the infant on any treatment. During 5 years of follow-up, she had normal mental development, tachycardia disappeared, had recurrent media otitis. Thyroid hormones levels remained high, TSH level became normal at the age of one month.

BACKGROUND :

Resistance to thyroid hormone (RTH) is a rare genetic. It was first described by Refetoff and al in 1967 (1-2). Its incidence is estimated to 1 : 40000 live births(3). The patients with RTH have elevated serum levels of free thyroxine (FT4) and triiodothyronine (T3) in the absence of thyroid stimulating hormone (TSH) suppression. Mutations of thyroid hormone receptor ß gene (THRB) are responsible for 85% of the cases(1). Inheritance is autosomal dominant.There are de novo mutations in approximately 17 to 22% of the cases(2). Males and females are equally affected.
Clinical presentation of RTH is very heterogeneous : from subclinical to symptomatic (2, 4).
Signs of thyroid hormone deficiency, sufficiency, and excess may coexist in one patient such as tachycardia along with delayed growth or learning disabilities (5).
In this article, we describe a 5-year-old girl with RTH diagnosed in neonatal period with de novo mutation.

CASE PRESENTATION : Our patient is the second child of a non-consanguineous couple. Her mother was 29 years old, with a history of anemia. Her 36-year-old father was in good condition of health, as well as his three-year-old brother.
Pregnancy was complicated by pregnancy toxemia and intrauterine growth retardation. She was born at term with a birth weight 2100g, height of 48cm and head circumference of 31.5cm.
L. was hospitalized in neonatology due to materno-fetal infection treated with antibiotics. She did not have neonatal screening for congenital hypothyroidism because the program is not available, so far, in Tunisia.
On a systemic clinical control at the age of eight days, a tachycardia was noticed. A 24-hour holter electrocardiography showed a sinus tachycardia, cardiac ultrasound was normal.
The thyroid balance showed a high FT4 level at 41.63 pmol / mL (normal values between 9 and 20 pmol / mL) and a high TSH level at 6.92 µUI / mL (normal values between 0.25 and 5 µUI / mL).
The search for anti-TSH receptors antibodies and antithyroid peroxidase antibodies was negative, thyroxine binding globulin level was normal for age. The infant received betablocker with no effect on tachycardia, so the treatment was discontinued after one month.
L. walked at the age of 9 months, on the toes of the feet. The neurological examination has objectified a pyramidal syndrome. Cerebral MRI was normal.
L. was referred to our department at the age of 2 years. At admission, her weight and height were normal for her age, her cranial perimeter was -2DS for age. Her heart rate was 112 beats per minute, she had no goiter. Her osteotendinous reflexes were sharp. She was hyperactive.

INVESTIGATIONS :

Molecular analysis of the β-receptor gene has demonstrated the A268D mutation in exon 8 in the heterozygous state leading to the transition from alanine to aspartic acid. Her parents and her brother showed no mutation.

TREATMENT :

When the patient was referred to our department, she was asymptomatic. She received no treatment.

OUTCOME AND FOLLOW-UP :

During the follow-up, the tachycardia disappeared at rest. The child did not show any other clinical sign except recurrent otitis media, her mental development was normal, hyperactivity disappeared. The audiogram was normal. Biologically, the FT4 and FT3 levels remained high, the TSH level became normal at the age of one month as shown in figure 1.

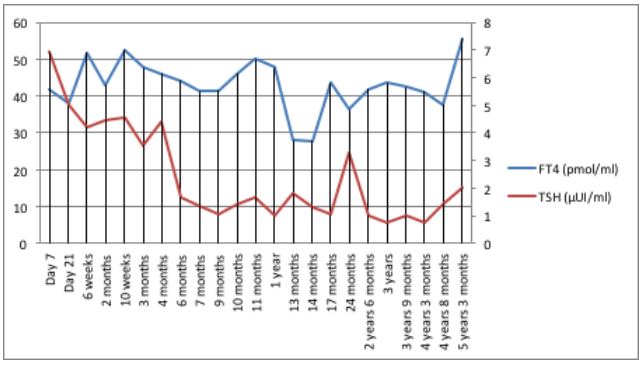

Figure 1 : Evolution of FT4 and TSH.

DISCUSSION :

RTH is an inherited syndrome characterized by refractoriness of target tissues to thyroid hormone.
Thyroid hormone receptors (TRs) are ligand-dependent transcription factors that mediate the activity of T3. 2 genes encode tRs : α and β genes. Four different TRs have been described : α-1, α-2, β-1 and β-2. Each TR isoform has tissue specific expression. Thyroid hormone receptor alpha-1 (THRα1) is highly expressed in the heart, bone, and brain; THRβ1 is more abundant in the liver, kidney, and thyroid; and THRβ2 expression is limited to the pituitary, hypothalamus, and ear(6).
More than 100 mutations have been reported through the world. Familial occurrence of RTH has been documented in approximately 75% of cases. Inheritance is usually autosomal dominant (6-7), de novo mutations arise in approximately 20% of the cases(8).
RTH is classified into two phenotypes : general RTH (GRTH) and pituitary RTH (PRTH). Patients with GRTH are typically euthyroid or hypothyroid, whereas patients with PRTH are usually hypermetabolic (7). Recently, mutations in the THRα gene have been identified. These patients had with relatively low serum T4 and high serum T3 levels, growth and developmental retardation, delayed bone development, and constipation (6). Some patients can present with large goiter causing compressive symptoms requiring surgical intervention (9).
Greater than 20% of patients exhibit some form of hearing loss, often conductive. History of ear, nose, and throat infections were reported in up to 50% of resistance patients because it has been suggested that thyroid hormones and receptors participate in middle ear development and mesenchyme function (8, 10). During follow-up, auto immune diseases can occur. Anti thyroid peroxidase antibodies must be monitored.
The proposed treatment may consist of therapeutic abstention, symptomatic treatment such as beta-blocker or treatment with thyroid hormones (6). Some studies compared between the effect of treatment by D T4 and triiodoacetic in lowering heart rate and thyroid hormone levels (11). Triiodoacetic acid was used by Chiesa et al in three pediatric patients. It was successful in two of them as TSH levels diminished, but failed in the patient who had severe features (5). Fortunately, most of the patients do not require any treatment such as our patient but it is crucial not to misdiagnose them and subsequently avoid inappropriate antithyroid drug treatment or thyroid ablation.
In children, particular attention must be paid to growth, mental development and bone maturation.

LEARNING POINTS :

- RTH is a rare condition characterised by peripheral refractoriness to the high levels of thyroid hormones with non-suppressed TSH levels.
- In most cases, patients show no symptoms.
- This syndrome should not be misdiagnosed in order to ovoid inappropriate antithyroid drug treatment.
- In children, bone and mental development should be monitored.

RÉFÉRENCES :

[1] Refetoff S. Resistance to thyroid hormone : one of several defects causing reduced sensitivity to thyroid hormone. Nat Clin Pract End Met 2008;4:1-.

[2] Olateju TO, Vanderpump MP. Thyroid hormone resistance. Ann Clin Biochem 2006;43:431-40.

[3] Rivas AM, Lado-Abeal J. Thyroid hormone resistance and its management. Proceedings (Baylor University Medical Center) 2016;29:209-11.

[4] Ferrara AM, Onigata K, Ercan O, Woodhead H, Weiss RE, Refetoff S. Homozygous thyroid hormone receptor beta-gene mutations in resistance to thyroid hormone: three new cases and

review of the literature. J Clin Endocrinol Metab 2012;97:1328-36.

[5] Chiesa A, Olcese MC, Papendieck P, Martinez A, Vieites A, Bengolea S, et al. Variable clinical presentation and outcome in pediatric patients with resistance to thyroid hormone (RTH). Endocrine 2012;41:130-7.

[6] Lee JH, Kim EY. Resistance to thyroid hormone due to a novel mutation of thyroid hormone receptor beta gene. Ann Pediatr Endocrinol Metab 2014;19:229-31.

[7] Kammoun I, Bouzid C, Kandara H, Ben Salem L, Turki Z, Ben Slama C. A Case of Resistance to Thyroid Hormone with Chronic Thyroiditis: Discovery of a Novel Mutation (I54V). Case Rep Endocrinol 2011.

[8] Chantler D, Moran C, Schoenmakers E, Cleland S, Panarelli M. Resistance to thyroid hormone – an incidental finding. BMJ Case Reports 2012.

[9] Canadas KT, Rivkees SA, Udelsman R, Breuer CK. Resistance to thyroid hormone associated with a novel mutation of the thyroid β receptor gene in a four-year-old female. International Journal of Pediatric Endocrinology 2011;2011:3.

[10] Cordas EA, Ng L, Hernandez A, Kaneshige M, Cheng S-Y, Forrest D. Thyroid Hormone Receptors Control Developmental Maturation of the Middle Ear and the Size of the Ossicular Bones. Endocrinology 2012;153:1548-60.

[11] Guran T, Turan S, Bircan R, Bereket A. 9 years follow-up of a patient with pituitary form of resistance to thyroid hormones (PRTH): comparison of two treatment periods of D-thyroxine and triiodothyroacetic acid (TRIAC). J Pediatr Endocrinol Metab 2009;22:971-8.