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Case Report

Resistant Graves' Disease in Childhood, A Rare but Complicated Situation, through a Clinical Case

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Abstract

Graves' disease is by far the most common cause of hyperthyroidism in children [1]. In this specific population, the hyperthyroidism is willingly biochemically overt and clinically severe [2]. Childhood hyperthyroidism may also cause accelerated growth and bone maturation, and eventually deterioration in academic performance, hence the need for a good screening and a better management. children with GD require prompt treatment, for the most of cases it's initially medical. But once this fails or is not possible, a definitive treatment should be considered [3]. For the antithyroid drugs use, we currently consider no difference in biochemical control between DT and BR [2,4], unlike previous approaches which argue in favor of the use of bloc-replace method in children [5-6]. However, for a curative treatment, total thyroidectomy is the preferred option for GD patients younger than 10 years [3]. We report the case of a girl who was 2 and a half years old in the moment of diagnose, and whom we followed for Graves' disease for 1 and a half years.

Ethical considerations: In accordance with the regulations in force, informed consent, written and verbal, was provided to the parents of the child before the publication of this work.

Keywords: Graves' disease - TSHRAb - Antithyroid drugs- total thyroidectomy-radioiodine.

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INTRODUCTION

Graves' disease (GD) is an autoimmune disease that primarily affects the thyroid gland. It is the most common cause of hyperthyroidism; and occurs at all ages but especially in women of reproductive age [7]. Hyperthyroidism occurs in approximately 1 per 5000 children and adolescents, and Graves' disease accounts for the vast majority of these cases [8]. In childhood, most cases of hyperthyroidism are caused by underlying thyroid disease; with high serum free T4 (FT4) and/or free T3 (FT3) concentrations coupled with a collapsed thyrotropin (TSH; <0.1 mIU/L) [2, 9]. The expression of thyrotoxicosis in children dose not differ too much compared to adults, the main signs are changes in behavior, attention span, decline of school performance, anxiety, disturbed sleep, fatigue, palpitations, heat intolerance, tremor, diarrhea, sweating, and weight loss; while the objective signs on physical examination are symmetrical thyroid enlargement; sometimes accelerated growth and bone maturation [3]. The antithyroid molecules authorized to tread GD in childhood are the Thionamide Carbimazole (CBZ) or its active metabolite methimazole (AKA thiamazole), while PTU is prohibited due to its liver toxicity [10]. In addition of ATD, the use of beta-adrenergic blockade helps to better counteract the sympathetic effects of thyrotoxicosis and prevent an acute thyrotoxic storm [11]. The recommended optimal treatment duration is longer than in adults given the risk of relapse [03]. Given the poor response to medical treatment in children, as well as treatment intolerances and the severity of the disease, the discussion of radical treatment is a crucial time in the management of GD in childhood. This discussion is the aim of our work which relates the case of a child who was resistant to treatment with some phases of intolerance.

Aim: Narrative review in the treatment modalities of GD in children through a case report.

OBSERVATION

At the first consultation, she was only 2 years and 06 months old, the youngest of three siblings from a non-consanguineous marriage. Born at full term and with good stature and motor development; except for a speech delay. The first symptoms were dominated by simple turbulence and motor agitation. The most remarkable symptoms subsequently appeared for the parents; weight

loss paradoxically associated with hyperphagia, profuse sweating, diarrhea, and more marked behavioral problems such as insomnia and irritability. The clinical examination finds a very dynamic child, tachycardia at 195 bpm, with warm extremities. Examination of the neck reveals a large goiter with obvious vascular character and vascular thrill. The rest of examination finds a remarkable height advancement estimated at +2 SD with a BMI = 18.3 kg/m² (Figure 1). Otherwise, no orbitopathy or dermopathy specific to GD was observed. The results of the first assessment showed an erased TSH <0,001, and FT4 levels more than 5 times normal out of dosage range > 120 pmol/L (N: 12-22 pmol/L). FT3 > 30 pmol/L (N: 3.2-6.4 pmol/L). TRAbs = 62 m.IU/L (N: < 2.9). Anti-TPO = 123 UI/L (N: <32). Thyroglobulin = 385 ng/mL (excluding any exogenous T4 intake). Ultrasounds reveals a thyroid gland enlarged = 12 mL, hypervascularized on color Doppler with systolic velocities measured at 53 m/s, and high diffuse vascular resistances (Figure 2). Greulich and Pyle bony age method reveals a bone advance of 2 years compared to chronological age. She was put on Carbimazol at a dose of 0.5 mg/kg/day and beta blocker type Propanolol at a progressive titration. The evolution was marked by an initial reduction in FT4 levels from >5 to 3 times normal, and T3 to 4 times the normal. Except that the tolerance assessment showing a reduction in neutrophil levels at 1100, a close monitoring of WBC was carried out then, showing a worsening of leukopenia reaching 870 elements per mL. Leading to the substitution of CMZ by Thiamazole MMI after leukocyte levels return to normal rates. Further monitoring shows good tolerance to Thiamazol unlike carbimazole, but with persistent hyperthyroidism around levels of FT4 around 1.5 to 2 times the normal, and FT3 around 2 times normal despite good titration: the final dosage was 0.6 mg/Kg/day of MMI after a year and a half of treatment. This resistance to medical treatment led us to choose a definitive treatment. our patient underwent a total thyroidectomy, the postoperative course of which was simple without anatomical complications nor hypocalcemia.

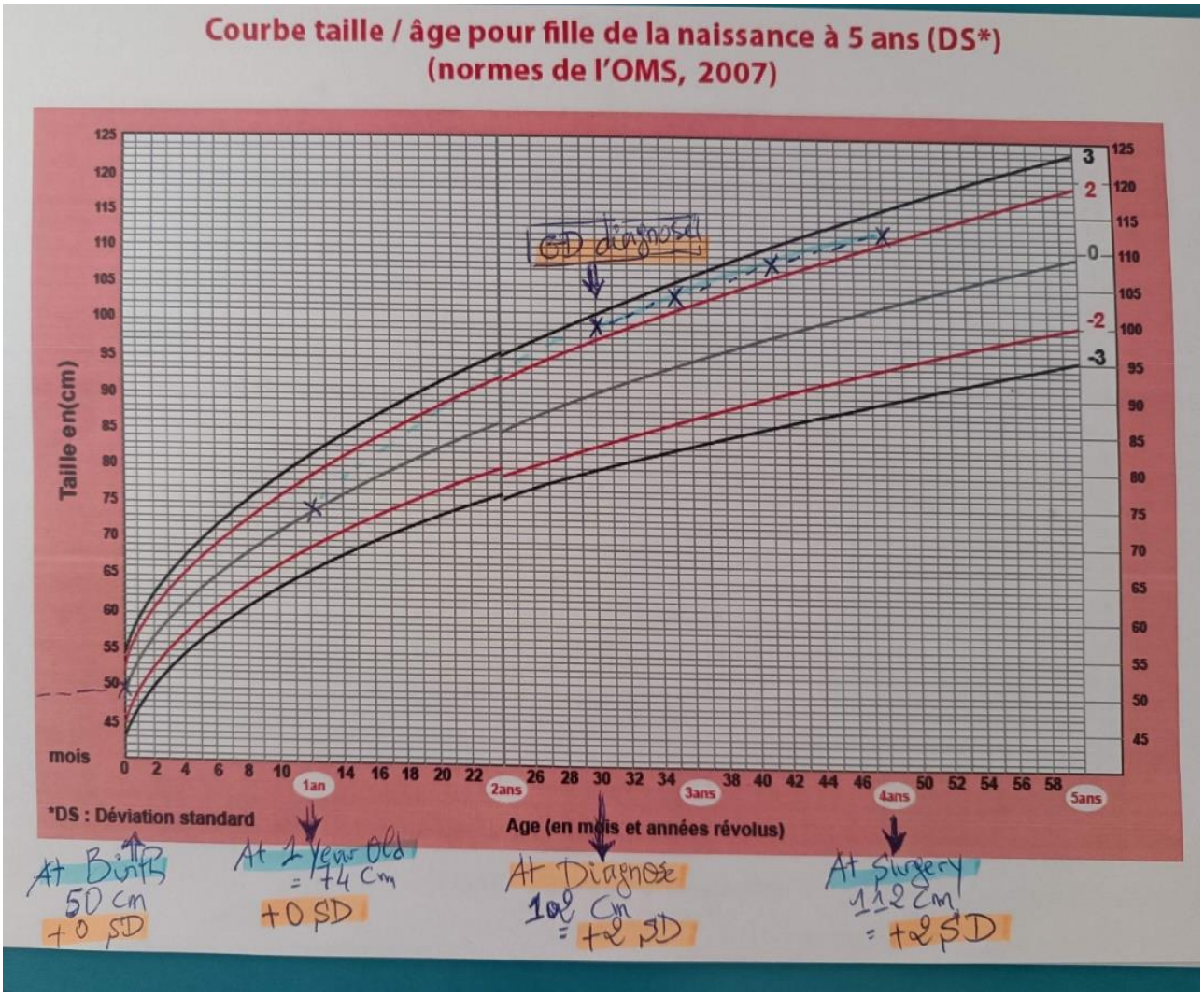

Figure 1: The growth curve of our patient showing an advancement of height at the moment of diagnose +2 SD, preceded by a normal height phase at birth and at one year old

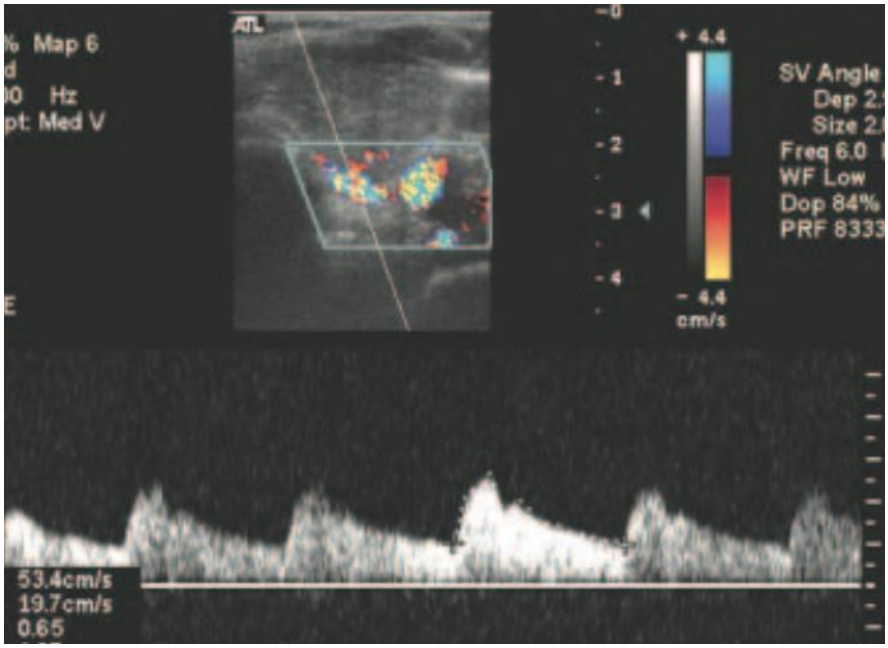

Figure 2: Pulsed Doppler thyroid ultrasound in our patient showing high systolic velocities with diffuse vascular resistance throughout the thyroid body>

DISCUSSION

Although GD may affect anyone at any age, but it's more common among women especially between 30-60 years old. The risk of GD is 3 % in women and 0,5 % in men and the annual incidence of GD is 16 cases /100.000 women and 3 cases /100.000 men [12]. An American study have shown a peak age-specific incidence in patients between 20-39 years of age [13]. Regarding pediatric population, in a national population-based study of thyrotoxicosis from the United Kingdom and Ireland, the annual incidence was 0.9 per 100,000 children <15 years of age, with Graves' disease accounting for 96 % of cases [8]. In Denmark the incidence was of 0.79 per 100,000 in children <15 years of age in the time period of 1980°, with a doubling to 1.58 per 100,000 in the years between 1998 to 2012 [14]. It is in fact an organ-specific autoimmune disorder associated with the presence of circulating TSH-R antibodies, resulting from the breakdown of immune tolerance against thyroid antigens. The genetic predisposition accounts for about 79 % of the risk for GD, while environmental factors for about 21 % [15]. The Graves' disease when occurs in children can seriously impact the quality of life; in a study, Graves' patients reported a lower total QoL score compared with the healthy cohort (p = .003) [16]. we wonder about the particularities of the diagnosis of GD in children, and what are the existing therapeutic modalities? as well as the prognosis and success rates in this population?

How to diagnose GD in children?

In children with suspected hyperthyroidism, serum FT4, FT3 and TSH should be measured. As long as GD is the most frequent etiology of hyperthyroidism in childhood, anti-TSH receptor and anti-thyroperoxidase antibodies should be measured [2]. One of the particularities not to be omitted is the rate of free T3; that is a highly sensitive marker of overt hyperthyroidism than FT4 in children [2]. But if the clinical picture is suggestive of GD while thyroid antibodies are absent, they should be repeated a few weeks later. If there are still no signs of thyroid autoimmunity, thyroid ultrasonography, scintigraphy – preferably with Tc-99m-pertechnetate – and additional laboratory investigations can be considered [2]. Furthermore, thyroid ultrasonography with Doppler blood flow assessment is preferred over scintigraphy with the aim of avoiding radiation exposure [17].

Long term Antithyroid drug in pediatrics Graves' disease

The preferential ATD for GD in children is the thioamide carbimazole (CBZ) or its active metabolite methimazole [17]. The use of thionamides is beneficial through its immunomodulatory properties [22]. However, PTU is contraindicated given its high liver toxicity. the doses and method of titration following the 2022 ETA guidelines are given as follow; The initial antithyroid drug dose is between 0.15 and 0.5 mg/kg of MMI, or between 0.25 and 0.75 mg/kg of CBZ daily. While for dose titration (DT) : with a DT approach, a starting dose of 0.15–0.3 mg/kg MMI or 0.25–0.5 mg/kg CBZ will normalize thyroid hormone concentrations in most patients within the first 4–6 weeks. The dose is then reduced by 25–50% according to prevailing thyroid function tests. Then for larger doses of ATD up to 0.5 mg/kg MMI or 0.75 mg/kg CBZ can be administered in more severe cases [17]. For the therapeutic method to choose, the current concept admits the fact of no significative difference between the dose titration DT and block-replace BR [4].

In children, GD treatment often lasts longer than in adults. Otherwise, there is no consensus on the duration of treatment with ATD in children GD, but it is recommended to continue the treatment as long as possible, and each time it is well tolerated until euthyroidism is achieved [17]. In a 20 years single-center experience, with a number of 195 patients, the cumulative remission rates were 3.3%, 19.6%, 34.1%, 43.5%, and 50.6% within 1, 3, 5, 7, and 10 years of starting ATD, respectively [18]. In this same trial FT4 level at diagnosis (P = 0.001) was the main predicting factor for remission [HR, 0.717 (95% CI, 0.591 – 0.870), P = 0.001] [18]. In general, the remission rates for GD in children and adolescents are variable with a tendency to be less than in adults, oscillating between 21-49% [19, 20]. The remission rate tends to rise each time the duration of treatment is longer, reaching up to 50% in many studies of more than 10 years [20]. However, it does not appear to increase beyond that, and some research indicates that these rates plateau [21]. In large-scale literature reviews, Jelmer M van Lieshout and al. (Of 1890 articles, 29 articles consisting of 24 patient cohorts were included with a total of 3057 patients), had demonstrated through a meta-analysis that the overall remission rate in methimazole-treated pediatric GD is only about 28.8% [23]. The same author concluded that in a pooled remission rates based on treatment duration were 23.7, 31.0, 43.7, and 75% respectively after 1.5–2.5 years, 2.5–5 years, 5–6 years (two studies), and 9 years (single study) treatment duration [23]. As for the side effects of ATD, the majority of effects occur in the first 3 months, with a higher rate observed in younger children [25] on the one hand, and on the other hand the side effects follow a dose-dependent mode [26]. the side effects observed in our patient probably had both mechanisms combined; the doses were high and the age of our patient was very low.

The Definitive treatment in pediatric GD, An endless debate

Indications for definitive treatment are based on several parameters that must be carefully considered, and of which we can cite; serious or persistent side effects of ATD, poor compliance or obstructive symptoms from a large goiter [24]. For the 2022 ETA guidelines, children aged under the age of 5 years must not undergo a radioiodine therapy [17]. This was the reason why we did not choose radioiodine in the case of our patient. Otherwise for patients in whom radioiodine is considered, new guidelines advise aiming for thyroid ablation in order to avoid the risk of recurrence and malignant transformation of persistent, viable but radiation-damaged cells [17]. In a trial which evaluate RAI in children and adolescents, the average dose delivered was about 340,4 MBq (247,9-555), euthyroidism was achieved in all cases, of which 7 patients achieved euthyroidism and 8 fell into hypothyroidism [27]. Total thyroidectomy, as was chosen for the patient in question, is by the way the preferred definitive treatment option for GD younger than 10 years, for whom with a relative contraindication for RAI treatment and for those with a large or nodular goiter. The concern with thyroid surgery in children is mainly postoperative complications, which constitute a great cause of worry for the parents; In a large review, including 22 mainly retrospective cohort studies, evaluating short- and long-term morbidities in 1,424 children and adolescents: The frequency of transient hypocalcemia was 22.2% (269/1,210) (a range of 5.0–50.0%), however, the frequency of permanent hypocalcemia was 2.5% (36/1,424) (a range of 0–20.0%). Transient and permanent recurrent laryngeal nerve injury were reported less frequently, with frequencies between 0–20.0 and 0–7.1%, respectively [28].

CONCLUSION

The aim for GD management is to achieve a favorable long-term and permanent outcome, thus a both secretory and immunological remission, and the preservation of functional thyroid tissue, while avoiding iatrogenic as much as possible. Recent progress is mainly focused on targeted therapies as a route of immunomodulation [29]. Latest thing to bear in mind is that, as clinicians, our main mission is to improve the quality of life of our patients as best we can.

Abbreviations:

ATD: antithyroid drug
BR: block-replace
CBZ : carbimazole
DT : dose titration
GD : Graves' disease
MMI: methimazole
RAI: radioiodine therapy
WBC: white blood counting

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