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Case Report

Resistance to thyroid hormone in a child with thyroid agenesis: A case report with review of the literature

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ABSTRACT

Introduction: The coexistence of thyroid dysgenesis and resistance to thyroid hormone (RTH) is a very rare occurrence. The current study aims to report a unique case of thyroid agenesis with RTH in a pediatric patient.
Case report: A 5-year-old male patient presented with poor feeding, excessive somnolence, and a noticeable umbilical hernia since the age of 2 months. He was initially diagnosed as a case of congenital hypothyroidism, and since then, he had been placed on thyroid replacement therapy. No further investigations were conducted until the age of 5 years. Recent laboratory findings revealed an elevated TSH level (42.41 μIU/mL). X-ray examination showed delayed bone age (30 months). Ultrasound (US) examination demonstrated the complete absence of thyroid lobes, isthmus, and ectopic thyroid tissue, but small 2.7 x 2.5-mm non-echoic, cystic, and hypo-vascular nodules were seen in the bed of the right thyroid lobe. The patient was kept on thyroid replacement therapy (levothyroxine) and under close follow-up. On follow-up, the patient's thyroid function status revealed resistance to exogenous thyroid hormone.
Discussion: Thyroid agenesis is the complete absence of the thyroid gland. Meanwhile, RTH is a hereditary disease characterized by decreased sensitivity of body tissues to thyroid hormone. Most cases of RTH are due to mutations in the gene encoding for THRβ. However, recently RTH due to THRα mutations has also been reported. The presentations of RTH cases in general and with thyroid dysgenesis are quite heterogenous.
Conclusion: Although the combination is exceedingly rare, thyroid agenesis can coexist with RTH.

1. Introduction

Congenital hypothyroidism (CH) is a condition that results from inadequate thyroid hormone production from birth. It has a worldwide incidence of 1:3000 to 1:4000 [1]. The condition can be categorized in terms of etiology as thyroid agenesis (22–42%), ectopy (35–42%), or gland in situ abnormalities (24–36%) [2]. Thyroid hormone therapy must be given to hypothyroid infants, as in symptomatic CH cases, with the aim of attaining a euthyroid state as quickly as possible [3]. Resistance to thyroid hormone (RTH) is an uncommon hereditary disease characterized by decreased sensitivity of body tissues to thyroid hormone, which is mostly due to mutations in the thyroid hormone receptor beta (THRβ) gene [4]. The first ever case of RTH was described by Refetoff and associates in 1967 [5]. Throughout the literature, there have been a few documented cases of RTH that have coexisted with thyroid dysgenesis [6]. However, there have only been two reported cases of thyroid agenesis and RTH so far [7,8].

The aim of this study is to report a very rare case of RTH with thyroid agenesis in a child. In the writing of this report, the SCARE 2020 guidelines were considered [9].

2. Case presentation

Patient information: A 5-year-old male presented with poor feeding, hypersomnolence, and a noticeable umbilical hernia since the age of 2 months. He was born by normal vaginal delivery and did not require admission to the neonatal care unit. The symptoms were noted 2 months after birth, and the baby was initially diagnosed as a case of

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congenital hypothyroidism. Since then, he had been placed on thyroid replacement therapy (levothyroxine, 25 μg). However, no further investigations were conducted until the time of his presentation to our clinic at the age of 5 years. He had no history of previous surgery, and his family history was unremarkable.

Clinical findings: The findings were insignificant, with a heart rate of 92 bpm, a respiratory rate of 28 cpm, an oral temperature of 36.8 °C, a body weight of 17.8 kg (25th percentile), and a height of 105 cm (25th percentile).

Diagnostic approach: Thyroid function tests at the age of 6 months showed a TSH level of >60 μIU/mL (normal range: 0.6–7.3 μIU/mL), T4 of 130.8 nmol/L (normal range: 92.6–202 nmol/L), and T3 of 3.32 nmol/L (normal range: 1.61–3.76 nmol/L). At the age of 2.5 years, the patient was referred to an otorhinolaryngologist for evaluation, and he found mild nasal allergy, a normal postnasal space, a slightly hypertrophied pharynx, and a lack of nasal cartilages. The physician had also misdiagnosed the presence of ectopic thyroid tissue. Recent laboratory findings at the age of 5 revealed a TSH level of 42.41 μIU/mL (normal range: 0.7–6.6 μIU/mL), T4 of 112.5 nmol/L (normal range: 82.4–173.8 nmol/L), T3 of 2.78 nmol/L (normal range: 1.61–4.13 nmol/L), FT4 of 15.11 pmol/L (normal range: 10.3–23.17 pmol/L), FT3 of 5.01 pmol/L (normal range: 4.19–7.6 pmol/L), and mild anemia (hemoglobin 10.8 gm/dL). The level of insulin-like growth factor-1 (64.48 ng/mL) and other laboratory findings were normal for his age. Normal developmental milestones were observed based on growth charts for his age, but his radiologic bone age was delayed (30 months) (Fig. 1). A neck ultrasound (US) was performed and revealed the complete absence of thyroid lobes, isthmus, and ectopic thyroid tissue, but small 2.7 x 2.5-mm non-echoic, cystic, and hypo-vascular nodules were seen in the bed of the right thyroid lobe.

Therapeutic intervention: Thyroid replacement therapy (levothyroxine) was continued for the patient in high dose under close follow-up.

Follow-up and outcome: On follow-up, the patient's thyroid function status revealed resistance to thyroid hormone replacement.

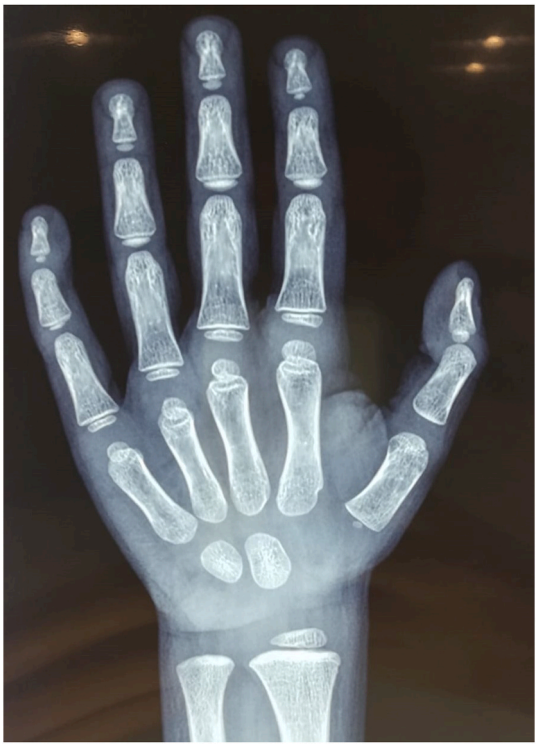

Fig. 1. Bone age estimated to be 30 months; ossification centers of capitate, hamate and distal radial epiphysis have developed. Ossification centers of all metacarpals and phalanges have developed (except the first proximal phalanx).

3. Discussion

CH is a very common endocrine condition that used historically to be one of the leading causes of mental retardation before the introduction of neonatal screening. Thyroid dysgenesis accounts for the majority of CH cases (80–85%) [10]. The condition was initially regarded as a sporadic disease, but some familial cases have since been identified [11]. Some studies have highlighted the involvement in thyroid gland development of multiple genes (TSHR, PAX8, HHEX, FOXE1, and TITF1), which if mutated, can lead to thyroid gland abnormalities [12]. Meanwhile, RTH, as an autosomal dominant or recessive genetic condition, manifests with impaired sensitivity to thyroid hormone. Human cells have two types of thyroid hormone receptors: THRβ and THRα. Most cases of RTH are due to mutations in the gene encoding for THRβ. However, recently RTH due to THRα mutations has also been reported [4]. Thyroid dysgenesis has been reported with RTH only 6 times in the literature, of which 4 of them were due to ectopic thyroid tissue [6,12–14] and the other two cases were due to thyroid agenesis [7,8].

Grasberger and colleagues reported the first case of thyroid gland ectopy in the sublingual area with RTH due to THRβ mutation [13]. Guo et al. reported a similar case, but no mutation in the THRβ and THRα genes was discovered in their case. In 2018, Scavone et al. described the first case of thyroid agenesis with RTH caused by THRβ mutation [7]. Soon after, in 2021, a second case of thyroid agenesis and RTH was reported by Salas-Lucia and associates [8]. Our patient is the third case of its kind; however, this study lacked the result of genetic testing to determine the causative mutation.

Generally, a higher female predominance has been observed in cases with thyroid dysgenesis [11]. On the other hand, equal occurrences of RTH have been reported between the sexes [15]. Meanwhile, five out of the six reported cases of RTH with thyroid dysgenesis were female [6,7,12–14]. The current case was a male. RTH symptoms vary greatly from one patient to another, ranging from asymptomatic to hypothyroidism or hyperthyroidism [6]. Additionally, in the same patient, one tissue might show signs of thyrotoxicosis, while another might show hypothyroidism [1]. When the patient is symptomatic, goiter, delayed bone age, sinus tachycardia, learning disabilities, short stature, hyperactivity, hearing difficulty, sleep disturbance and fatigue are amongst the most frequent presentations of RTH [4,7]. The case reported by Scavone et al. showed symptoms of hypothyroidism during infancy, but lacked symptoms of hypothyroidism, and had normal growth and a normal developmental milestone at the age of 6 [7]. The patient in this study presented with poor feeding, hypersomnolence, a noticeable umbilical hernia since infancy, and a delayed bone age at the age of 5.

In CH cases, thyroid US can easily detect the absence of a thyroid gland [7]. The diagnosis of RTH when it coexists with other thyroid conditions is very challenging, as in the case of thyroid dysgenesis [14]. In cases of RTH with thyroid dysgenesis, TSH is generally elevated since birth due to decreased or absent thyroid hormone production, and they are usually associated with upper limit of normal or elevated FT3 and FT4 levels [16]. The current patient had a hard-to-control elevated TSH level with normal levels of T3, T4, FT3, and FT4. The gold standard to confirm the diagnosis of RTH is genetic testing for mutations in the THRβ and THRα genes [17].

If patients with RTH are euthyroid, they will not require additional therapy since the increased production of thyroid hormone in these cases will compensate for the resistance. However, thyroid hormone, thyroid hormone analogues, and β-adrenergic blockers can be used to treat cases of hypothyroidism [4,17]. The optimum thyroid hormone dose to be given to these cases and the TSH level to be reached are very difficult to be determined, as cases like these are exceptional [14]. As the patient in this study lacked thyroid tissue, thyroid replacement was necessary.

In conclusion, although the combination is exceedingly rare, thyroid

agenesis can coexist with RTH. Hence, it is crucial to consider such a diagnosis in infants with CH that is hard to control in order to prevent future adverse effects on their growth and development.

Consent

Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

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Author contribution

Abdulwahid M. Salh: major contribution of the idea, final approval of the manuscript. Karzan M. Hasan: physician managing the case, final approval of the manuscript. Fahmi H. Kakamad: Writing the manuscript, literature review, final approval of the manuscript. Rawa M. Ali, Berwn A. Abdulla, Soran H. Tahir, Bilal A. Mohammed, Shaho F.Ahmed: literature review, final approval of the manuscript.

Guarantor

Fahmi Hussein Kakamad.

Declaration of competing interest

None to be declared.

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