PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

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ALPHONSUS N. ONYIRIUKA[1] & ANTHONY O. ATIMATI [2]

1. Endocrinology and Metabolism Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria.
2. Gastroenterology and Nutrition Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria.

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ALPHONSUS N. ONYIRIUKA[1] & ANTHONY O. ATIMATI [2]

3. Endocrinology and Metabolism Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria.
4. Gastroenterology and Nutrition Unit, Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria.

***Corresponding author**: alpndiony@yahoo.com
Submitted: March 2022; Accepted: May 2022

ABSTRACT:
In this report, we describe a rare case of a Nigerian male infant who presented with resistance to thyroid hormone associated with hyperthyroidism, cholestatic jaundice, a huge goitre and failure to thrive (weight faltering). He had delayed developmental motor milestones and at the age of 7 months, he has developed craniosynostosis. The hyperthyroidism persisted despite treatment with beta-blocker for tachycardia and antithyroid medications. The challenges encountered in the management of the patient are discussed.

Keywords: Resistance to thyroid hormone, Hyperthyroidism, Cholestatic jaundice, Craniosynostosis, Failure to thrive, Goitre, Weight faltering.

INTRODUCTION:

Resistance to thyroid hormone (RTH), also known as Refetoff syndrome [1], is a tissue-specific syndrome of decreased thyroid hormone responsiveness due to genetic defects in the thyroid hormone receptor [2]. Most cases are inherited as an autosomal dominant mutations in the thyroid hormone receptor beta gene (THRß) [2] but autosomal recessive inheritance occurs less commonly. About 15% of cases are sporadic [3]. The mutant receptor has a lower binding affinity for thyroid hormone, and as a consequence, thyroid-stimulating hormone (TSH) level remains unsuppressed despite elevated thyroid hormones [4]. The estimated incidence is one case per 40,000 to 50,000 live births [5,6], without gender predominance. Patients with RTH come to medical attention for a variety of reasons, particularly goitre which occurs in 75% of cases [7]. The clinical manifestation depends on the type of thyroid hormone receptor affected and the magnitude of the resistance. Symptoms often change with time and may improve spontaneously [2]. The characteristic biochemical profile is persistent hyperthyroxinaemia in a setting of non-suppressed thyroid-stimulating hormone (TSH)

level [3,4]. This pattern indicates defective feedback inhibition of the hypothalamic-pituitary-thyroid (HPT) axis and is presumably due to impaired pituitary responsiveness to thyroid hormone. Thyroid status varies among affected individuals, such that the patient may appear clinically euthyroid, hypothyroid or hyperthyroid [2]. There are no guidelines or expert consensus for the management of RTH [6].Therefore, approach to treatment must be individualized to the particular patient in question. Although cholestatic jaundice is more commonly associated with hypothyroidism, it has been reported in congenital hyperthyroidism [8,9]. Physiologically, the existence of a relationship between the thyroid gland and the liver is well established. In this context, thyroid hormones are important for normal hepatic function while glucuronidation and sulfation of thyroid hormones occur in the liver before excretion into the bile. The hepatic dysfunction is attributed to hypermetabolic state in thyrotoxicosis that increases hepatic oxygen consumption without increasing hepatic blood flow, accentuating the low oxygen tension in the centrilobular zones, resulting in dysfunction of the centrilobular hepatocytes [8]. Wafa et al [9] reported that the hepatic disorder rapidly improved after commencement of treatment for hyperthyroidism in their patients.

Failure to thrive (FTT), more appropriately called weight faltering, is characterized by sustained weight loss, failure to gain weight or persistent drop in weight from the child's normal growth percentile curve. In general, FTT results from three mechanisms, namely inadequate caloric intake, defective utilization of calories or increased metabolic demand. Hyperthyroidism is a typical example of FTT due to increased metabolic demand. Definition of failure to thrive (FTT) is controversial. Accepted definitions include weight-for-age less than fifth percentile on standardized growth charts, a decrease in weight percentile crossing two or more major percentile lines on the growth chart or less than the 80th percentile of median weight-for-height ratio [10]. It is important to identify and treat FTT because of its potential in causing developmental delay.

The purpose of this report is to increase the awareness of clinicians regarding a very rare form of thyroid disease in order to reduce the rate of misdiagnosis and consequently, inappropriate treatment.

CASE PRESENTATION:

We report a case of a 26-day-old Nigerian boy, born to non-consanguineous parents who was referred from a private-health facility. He presented with jaundice, paleness of stools, passage of dark urine noticed on the second day of life. Poor weight gain was noticed at the age of 2 weeks despite adequate feeding on breast milk and infant formula. He also had fever at presentation. The blood group of both parents is O Rhesus positive. The paleness of stools was intermittent The patient did not respond to oral Ampicillin/Cloxacillin suspension administered

by mother at home, warranting presentation in a private hospital at the age of 17 days where he was admitted for 8 days before referral to our health facility. Mother was clinically euthyroid during pregnancy and had no exposure to iodine-containing products. There was no reported family history of thyroid-related illness or autoimmune conditions. He is a product of normal delivery at 37 weeks gestation and his birth weight was 2.0kg.

Examination revealed an ill-looking male neonate, weight was 1.6kg (<3rd percentile), icteric with a greenish hue, febrile (38.2^{o}C), oxygen saturation was 96% in room air and had hepatomegaly of 4cm. There was developmental delay but no café au lait spot. At the age of 11 months, the patient is unable to sit, even with support. Craniosynostosis was present at 7 months of age. There was no galactorrhoea. A complete blood count showed WBC 14,300/µL, Lymphocyte 37.5%, granulocyte 54.5%, monocyte 8.0%, haematocrit 26.5%, platelets 215,000/ µL. The serum electrolytes and urea were normal. Tests for HbSAg, Hepatitis C, VDRL, urine for reducing sugar were negative. Mother is HIV negative. Abdominal ultrasound scan report was suggestive of biliary sludge without signs of cirrhosis. The blood clotting profile was normal. Total protein 6.7g/dl (6.0 – 8.3), Albumin 3.8g/dl (3.3 – 5.2), globulin 2.9g/dl (2 – 3.9). Results of thyroid function tests and liver function test are summarized in Tables 1 and 2, respectively.

Table 1: Summary of results of thyroid function tests

Thyroid function tests	Results	Comments
T3 (Reference interval 0.58-1.59)	6ng/ml	High
T4 (Reference interval 4.87-7.20)	24µg/ml	High
TSH (Reference interval 0.35-3.94)	37.15U/ml	Very high
Six months later:		
T3 (Reference interval 4.4-7.3)	45.4pmol/L	Very high
T4 (Reference interval 7.2-16.4)	37.69pmol/L	High
TSH (Reference interval 0.70-5.80)	52.82miu/L	Very high

Table 2: Summary of results of liver function test

Liver function test	Results	Comments
ALP (Reference interval 40-150),	312 IU/L	High
AST (Reference interval 5 – 34),	260 IU/L	High
ALT (Reference interval 0 – 55),	224 IU/L	High
Total bilirubin	12mg/dl,	High
Conjugated bilirubin	8.4mg/dl,	High

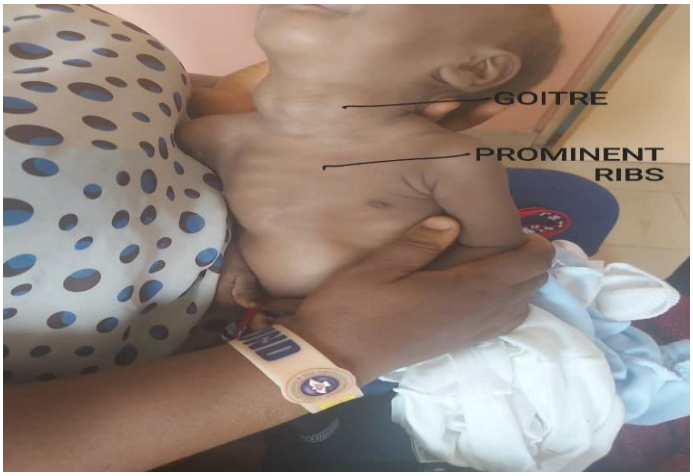

Figure 1 shows goitre and wasting in our patient

He was admitted and transfused with packed cells, commenced on antibiotics and vitamins A,D,E,K and was discharged home after 7 days. He is being followed up in the clinic. The liver function test and clotting profile were repeated 6 weeks later and found to be within normal range. On the 39th day of life, he presented with respiratory distress, stridor and a huge goitre. Jaundice was clearing, stools were pigmented, and urine was no longer dark in colour. He had tachycardia but there was no exophthalmos. A scan of the anterior neck showed enlargement of both lobes of the thyroid gland and the isthmus with no focal thyroid parenchymal mass or cyst. Maternal TSH receptor stimulating antibody was negative. An echocardiography showed a patent foramen ovale which was not structurally or hemodynamically significant. Treatment given consisted of blood transfusion, oxygen by nasal prongs (SPO_2 of 84-90%), gavage feeding, carbimazole, propranolol and antibiotics. He was discharged after 4weeks on admission. A repeat thyroid function test at the age of 6 months still showed elevated TSH, T4 and T3. We considered resistance to thyroid hormone because of the presence of elevated thyroid hormones with unsuppressed thyroid-stimulating hormone. In follow-up appointment the patient was noticed to have developed craniosynostosis by the age of 7 months.

DISCUSSION:

RTH is a very rare condition which is often misdiagnosed and mistreated [11]. The combination of persistently elevated serum levels of thyroid hormones with elevated thyroid-stimulating hormone (TSH) occurs uncommonly. In this clinical setting, once laboratory errors are excluded, the differential diagnoses should be between TSH-secreting

pituitary adenoma and resistance to thyroid hormone [2, 12]. We excluded laboratory error by performing the test in three different laboratories (using alternate assay platform) and by performing serial dilutions to confirm linearity. The results from all three laboratories revealed elevated thyroid hormones with markedly elevated TSH levels. Among patients presenting with hyperthyroidism, pituitary adenoma accounts for less than 1% of cases [13] and represents 0.5-3% of all pituitary adenomas [13,14] The explanation for its rarity is that thyrotropic cells comprise less than 5% of all pituitary cells [15].The reported prevalence is one in a million [6]. Yang et al [16] in China reported that age of onset of symptoms was 6.8-17.0 years with female to male ratio of 2:1. In contrast, the index patient presented at the age of 26 days. These epidemiological characteristics make TSH-secreting pituitary adenoma unlikely in our patient. The diagnosis of hyperthyroidism in the index patient was clearly established from the thyroid function test results. The absence of thyroid antibodies and the persistence hyperthyroidism beyond 4 months of age negates the diagnosis of neonatal Graves' disease. In literature, the key physical features in our patient (cholestatic jaundice, goitre and failure to thrive in early infancy) have been reported in hyperthyroidism [17,18]. According to Refetoff and Dumitrescu [5] the finding of elevated serum thyroid hormone levels associated with non-suppressed TSH usually leads to the diagnosis, as is the case in the index patient. Although gene sequencing is the gold standard for diagnosing RTH, this genetic testing service is not available in our country's health institutions.

Some of the clinical features present in our patient are worthy of note. The clinical features in RTH are goitre, tachycardia, hyperactivity, developmental delay and learning disability [3]. Our patient had goitre and in literature, this is found in 75% of cases [13]. The presence of delay in developmental motor milestones in our patient further points to the adverse effect of hyperthyroidism on the neurodevelopment of the infant. In the present patient, this is indicated by his inability to sit, even with support at the age of 11 months. The presence of tachycardia and failure to thrive suggests that the peripheral tissues were responding to thyroid hormone, at least partially. Despite the markedly elevated thyroid hormone levels in the index case, eye signs of thyrotoxicosis were absent. Absence of typical signs of hyperthyroidism is a recognized feature of RTH [12]. Jaundice in patients with hyperthyroidism has been attributed to various factors such as the relative changes in hepatic blood flow associated with hyperthyroidism itself, treatment with antithyroid drugs and conditions associated with autoimmune thyroid disease [19]. However, in the index case, there was no history of prior treatment with antithyroid drugs or conditions associated with autoimmune thyroid disease. Therefore, we postulate that it is due to the haemodynamic changes in blood flow in the centrilobular zone of the liver in

relation to hypermetabolism associated with hyperthyroidism. This is supported by the clearance of the jaundice with antithyroid drug therapy which decreased the metabolic demand on the liver. Antithyroid medication is aimed at bringing TSH level to near normal while following growth, bone maturation and cognitive development. Another reason for antithyroid medication in our patient is the presence of craniosynostosis, suggesting advanced bone maturation [20]. In two separate studies, skeletal survey at the age of 4.5 months [21] and at the age 5 months [22] confirmed advanced bone maturation. Affectation of the heart (tachycardia) and the bone (advanced bone maturation) in the index patient is not surprising because the heart and the bone express predominantly thyroid receptor alpha gene, thereby allowing high endogenous thyroid hormone levels to produce hyperthyroid effect on them [7,23]. Our propositus also had stridor and marked respiratory distress, suggestive of upper-airway obstruction due to the goitre. Similar presence of stridor in patients with goitre has been reported by Chester et al [21]. It is expected that reduction in serum TSH level will decrease the size of the goitre.

The failure to thrive (FTT) observed in our patient suggests, at least, partial response to thyroid hormones at the tissue level. The same is true of the tachycardia present in our patient. Chester et al [21] reported FTT in their patient at the age of 2 months. In principle, management of FTT involves identifying the underlying aetiology and addressing the caloric deficit. We identified the cause (hyperthyroidism) of FTT in our patient and commenced antithyroid medication to reduce the hypermetabolic state of the patient. To address the caloric deficit, effort was made to increase caloric density of the patient's feeds. The volume of feeds could not be increased significantly because of the limited gastric capacity of the patient. The resultant effect of this management approach was a modest increase in weight from 1.6kg at presentation to 4.4kg at the age 6 months. His weight at the last clinic visit 3 months ago was 5.9kg, representing a total increase of approximately 73.0%.

We encountered some challenges in the management of this patient. First, there is currently no available therapy to fully correct the thyroid hormone beta gene defect. Therefore, management of RTH is tailored to the specific symptoms of thyroid hormone excess or inadequacy encountered in the affected individual patient. In literature, it is stated that patients who present with symptoms of hyperthyroidism should be treated symptomatically with beta-blockers or antianxiety medication, depending on the dominant symptom [24]. Our patient has tachycardia, we therefore placed him on a beta-blocker to prevent heart failure. A challenging decision for us was whether to use antithyroid medication, knowing they can result in hepatic complications, particularly as our patient had cholestatic jaundice. The estimated incidence of

antithyroid-drug-associated hepatotoxicosis is 0.1-0.2% and higher doses of antithyroid medication is a risk factor for hepatic injury [25]. In general, treatment with antithyroid medication is not supported. The young age (11 months) of our patient precluded the use of ablation radiotherapy. Expertise for thyroidectomy in that age is not readily available in the area where we practice. Referral to outside health facility with the requisite human and material resources is out of the question because of financial constraint in the index family. Currently, 3,5,3-triiodothyroacetate (TRIAC), a physiological metabolite of T3, is the most promising drug for reducing thyroid hormone and TSH levels [11,26] but it is not readily available. Reduction in TSH level has the potential to reduce the size of the goitre. Our ultimate plan for the patient is total thyroidectomy because of symptomatic goitre (indicated by stridor) and advanced bone maturation (indicated by craniosynostosis with its implication for brain growth). The resultant hypothyroidism will be managed with supraphysiological doses of Levo-thyroxine. To avoid iatrogenic thyrotoxicosis, regular assessment of TSH and indices of peripheral thyroid hormone action are required. Financial constraint as well as non-availability of the required expertise are hampering this proposed approach of treatment. It has been documented that the goitre tends to re-occur after thyroidectomy [27]. Another management challenge was lack of access to genetic testing services for confirmation of diagnosis and determination of type of mutation in the index patient. We could not perform thyrotropin-releasing hormone (TRH) stimulation test to assess the response of TSH which would have enabled us to further exclude TSH-secreting pituitary adenoma, a condition in which there is no TSH response. We could not perform pituitary imaging with magnetic resonance imaging (MRI). Inadequate laboratory facility in area where we practice hindered performance of some investigations. Additionally, financial constraint prevented sending the relevant sample abroad. Despite this shortcoming, we strongly believe this is a case resistance to thyroid hormone based on the typical biochemical profile, absence of typical features of hyperthyroidism and presence of goitre in our patient. Goitre is present in 75% of cases of RTH [13]. Additionally, the age of the patient at manifestation of the disease negates TSH-secreting pituitary adenoma. In summary, available literature indicates that treatment of RTH remains challenging and individualized treatment is advocated, according to the patient's clinical manifestations.

CONCLUSION:

Although RTH is a rare clinical condition, it should be considered in the differential diagnoses of any patient presenting with goitre, elevation in thyroid hormones and non-suppressed serum TSH level in order to avoid misdiagnosis and unnecessary treatment. In addition, it is suggested that the presence of

FTT and craniosynostosis in early infancy should direct the clinician to perform thyroid function test to exclude hyperthyroidism.

Conflict of interest: We have no conflict of interest

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