ejpmr, 2017,4(7), 172-176

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Report

ISSN 2394-3211

EJPMR

ALTERNATE DAY PREDNISOLONE IS SAFE AND EFFECTIVE IN RELIEVING THE THYROTOXIC SYMPTOMS OF A CHILD WITH RESISTANCE TO THYROID HORMONE

Abdulmoein E. AL-Agha*[1], Ihab Abdulhameed[1] and Abdelhadi M. Habeb[2]

[1]*Pediatric Endocrine Unit, King Abdulaziz University Hospital, Jeddah, KSA.
[2]Pediatric Department, Prince Mohammed Bin-Abdulaziz Hospital, NGHA, Madinah, KSA.

***Corresponding Author: Abdulmoein E. AL-Agha**

Pediatric Endocrine Unit, King Abdulaziz University Hospital, Jeddah, KSA.

Article Received on 06/05/2017 **Article Revised on 27/05/2017** **Article Accepted on 17/06/2017**

ABSTRACT

Background: Resistance to thyroid hormone (RTH) due to *THRβ* gene mutations is characterized by high fT4 and fT3 with unsuppressed TSH. The management of symptomatic children with this condition is a challenge. Glucocorticoids can suppress TSH secretion; however their use in RTH has not been explored. **Aim**: to report the clinical and hormonal response to alternate day prednisolone in RTH child with thyrotoxic symptoms. **Methods**: The child had regular clinical and biochemical assessment. Direct sequencing of the *THRβ* gene was conducted in the family. **Results:** The boy presented at 19 months with tachycardia, sweating, hyperactivity and delayed cognitive function. He had raised fT4, fT3 and TSH with normal MRI pituitary. Sequencing of the *THRβ* gene identified heterozygous mutation (A317T) in the child and his father. Propranolol was ineffective and carbimazole raised the TSH without clinical improvement. Alternate day prednisolone + atenolol relieved the symptoms and maintained TSH in the lower limit of normal. During the 29 months treatment the child maintained normal growth without steroids side effects. **Conclusions:** Our experience indicates that, alternate day prednisolone is safe and effective in relieving the thyrotoxic symptoms of RTH. This regimen would be an option for some children with RTH.

KEYWORDS: Thyroid hormone resistance, Corticosteroids, TR beta receptor, children Established facts:

- The management of resistance to thyroid hormone (RTH) is a challenge and different agents have been used to suppress the TSH with variable success
- Steroids can suppress TSH but their use in RTH has not been explored

INTRODUCTION

Resistance to thyroid hormone (RTH) is a rare condition of reduced tissue responsiveness to thyroid hormone (TH) action. The biochemical hallmark of RTH includes high free T4 (fT4) and T3 (fT3) with unsuppressed thyroid stimulating hormone (TSH). Affected patients can have different clinical picture ranging from hypo, hyper or euthyroid status. Common reported features include tachycardia, goiter, growth delay, attention deficit, hyperactivity, recurrent ear infection and failure to thrive.[1-4]

The majority of RTH cases are caused by heterozygous mutations in the TH receptor beta (*THRβ*) gene with no identifiable genetic defect in 10-15% of cases (1). The mutant *TRβ* gene results in RTH either by reducing the receptor affinity to fT3[4] or impairing its interaction with cofactors mediating the TH action.[5] In few families severe RTH form due to homozygous *THRβ* gene mutations has been reported[6] and recently patients with *THRα* gene mutations have been described.[7,8]

Most patients with heterozygous RTH compensate for their receptor defect by secreting more TH and remain asymptomatic.[2-4] Those with only hypothyroid symptoms would benefit from thyroxine replacement and most hyperthyroid symptoms can be controlled by β-blockers alone.[9] However, in severe cases anti-thyroid medications[10] and agents that can reduce the TSH secretion (e.g. bromocriptine, somatostatin) or block the TH action such as triiodothyroacetic acid (TRIAC) have been used with variable success.[11-16] Glucocorticoids (GCs) are effective in reducing TSH secretion[17]; however their use in RTH has not been previously explored, possibly due to their side effects. We report our 18 months experience of using alternate day prednisolone combined with atenalol in a child with genetically proven heterozygous RTH and thyrotoxic symptoms.

CASE REPORT

A 4 –year- old boy presented with tachycardia, excessive sweating, hyperactivity and disturbed sleep for nearly 6 months. Apart from few upper respiratory infections his systemic review was unremarkable. He was born at term following uneventful pregnancy with a birth weight of 2.9 kg and had no neonatal problems. He was the first child to Saudi parents who subsequently had 2 healthy children. There was no family history of thyroid disease; however an extended family pedigree (fig 1) revealed that his paternal uncle underwent thyroidectomy at the age of 14 yrs and has been on thyroxine replacement since then.

On examination his weight was 10.6 kg and height was 82 cm (both between 25^{th}-50^{th} percentile on the Saudi growth chart). He was hyperactive and his resting pulse rate was120/min. There was no goiter, thyroid bruit, exophthalmos, or clinical features of hypothyroidism. Developmental assessment at 19 months revealed age appropriate gross motor function for age with normal vision and hearing; but his fine motor and social skills were at 12- month old level. Initial TSH was 34.90 IU/L (NR 0.35-5.5), fT4 52.1pmol/l (NR=10.4 - 22.7) and fT3 25.09 pmol/L (NR = 3.5 - 7.14). His thyroid peroxidase and thyroglobulin antibodies were negative. The bone age was compatible with chronological age and MRI brain scan showed normal looking pituitary gland. Biochemical assessment of the family revealed high fT4 and unsuppressed TSH in his asymptomatic father in keeping with autosomal dominant RTH. Other family members, including the paternal uncle who had thyroidectomy, had normal thyroid function.

He was started on propranolol, which reduced his tachycardia to 105/min within 3 weeks. During the following four months his heart rate ranged between 105-110/min without significant improvement of other symptoms. At 25 months old the family reported more hyperactivity and disrupted sleep. A clinical review revealed tremor and poor weight gain. His sleeping pulse was 105/min with similar thyroid function results (fig 1). He had no exophthalmos and thyroid gland was normal for age on ultrasound scan. At that point carbimazole was introduced at 0.5 mg/kg/day and propranolol was changed to atenolol. During the following 6 months there was no significant improvement of clinical symptoms or language/cognitive function despite increasing the dose to1mg/kg/day. In addition mild goiter was noticed, TSH rose to 64 IU/L and fT4 and fT3 remained high on serial thyroid function tests (fig 1) Following a discussion with the family carbimazole was stopped, child continued on atenolol, and a trial of alternate day prednisolone 2mg/kg alternate was started at 34 months old. Four weeks later the TSH level returned to normal and TH were reduced but remained above the normal range (fig 1). His resting heart rate reduced to 94/min and his behavior improved. At 38 months old (4 months after prednisolone) his sleep pattern, attention span and hyperactivity improved to allow for toilet training, Throughout the following 14 months his symptoms continued to improve gradually with average resting heart rate of 92/min. He maintained normal linear growth (figure 3) with no apparent CS side effects. Developmental assessment at 52 months old (18 months after alternate prednisolone) revealed appropriate language and cognitive functions for age.

Genetic testing

After obtaining formal consent DNA was extracted from peripheral blood of family members using the standard methods. Direct sequencing of the *THRβ* gene was conducted at the Institute of Metabolic Science, Cambridge, UK. A known disease-causing heterozygous mutation (A317T) was detected in the child and his father confirming the diagnosis of RTH. This mutation is located in CG dinucleotide hot spot and resulted from a base pair substitution of an adenine for a threonine. Other family members, including the paternal uncle, were homozygous for the wild type A317T.

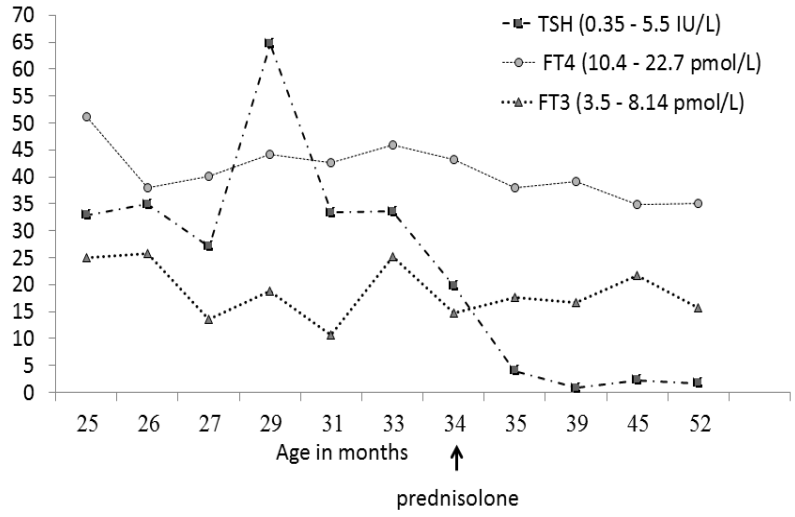

Figure 1: serial thyroid function tests of the affected boy since starting treatment. The small arrow indicates the age at starting the alternate day prednisolone.

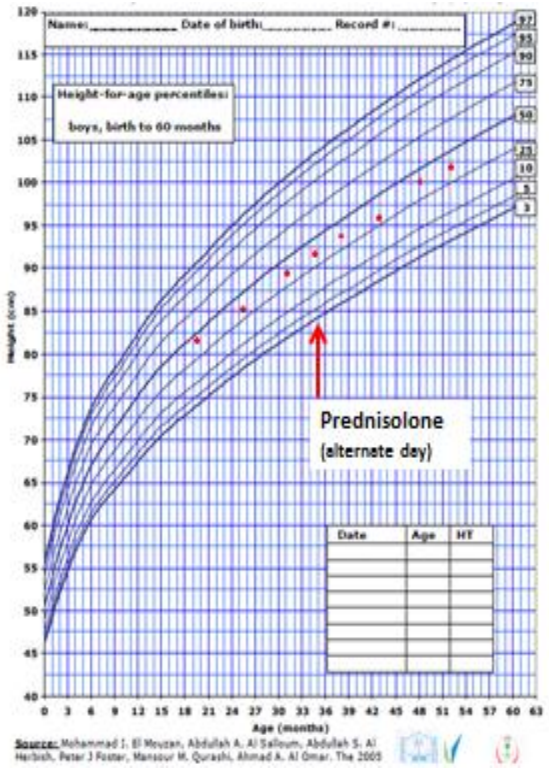

Figure 2: height growth chart of the child since presentation

DISCUSSION

To the best of our knowledge this the first report of using CSs in the management of patients with RTH. In our patient alternate day prednisolone and atenolol relieved the thyrotoxic symptoms, improved the cognitive function and maintained TSH level in the lower limit of normal. During the 18 months period the child had normal growth velocity without GC side effects

In RTH a mixed picture of TH excess and deficiency can coexist in the same patient, possibly due to variable tissue resistance to TH action.[2-3] Our patient presented with thyrotoxic symptoms and had mild developmental delay which is usually a sign of thyroid depletion. Although he appeared to have RTH with mixed picture, in young children some thyrotoxic symptoms such as attention deficit, hyperactivity and disrupted sleep can have negative impact on cognitive function. The fact that his language and fine motor functions improved with treatment indicate that the developmental delay was due to poor concentration and disrupted sleep rather than TH depletion. The initial TSH level in our patient was higher than usually reported in RTH patients.[1-4] This could reflect a severe pituitary resistance to TH feedback suppression. Interestingly the father has been asymptomatic despite having the mutation and the biochemical features of RTH. This variation in phenotype between patients with the same *THRβ* mutation was reported in RTH[3,4] and could be related to non-genetic factors. It is also possible that the father was symptomatic during childhood but his condition improved due to decreased sensitivity of peripheral tissues to elevated thyroid hormone over time.

The management of symptomatic RTH patients is a challenge as currently there is no therapy to correct the mutant *THRβ* gene neither a consensus on the treatment. Our objective was to relieve the child symptoms rather than normalizing TH or TSH levels. As the child's symptoms were not controlled by β-blocker alone; our preferred option was to block the TH action using TRIAC. This TH analogue has higher affinity to THβ receptors than TH and has been shown to be effective in some children with RTH.[11,12] However TRIAC is currently not available in KSA. The recent positive experience with methimazol in RTH child with similar symptoms[10] prompted us to try this agent in our patient. The use of anti-thyroid agents in RTH has been associated with a rise in TSH secretion, increasing the goiter size and the risk of pituitary adenoma[10, 11, 15]; however our patient has no thyroid swelling and will be monitored for the possibilities of thyroid hyperplasia and pituitary adenoma. Before carbimazole was started we switched propranolol by atenolol, which does not inhibit the conversion of T4 to T3, to minimize the risk of depriving the TH resistant cells of TH which is desirable in RTH. Despite reaching a higher carbimazole dose than recently used by Tsai et al[10], there was no improvement in the clinical picture apart from reducing the tachycardia, which is more likely due to atenolol. We initially raised the possibility of none compliance because It is often a challenge to give medications to a hyperactive 3 year old child several times a day. However the rise in TSH level, the reduction of TH levels and the development of goiter indicates that the child was receiving enough carbimazole. Another

strategy to control the thyrotoxic symptoms in RTH is to decrease the TH levels by reducing TSH secretion using dopaminergic drugs and somatostatin analogs; but they have low success rate in maintaining TSH suppression[13,14] and given the age of our patient we were reluctant to use them as they may suppress growth hormone secretion.

CSs are effective in reducing TSH levels in both hypothyroid patients and normal subjects[17] more likely through reducing TRH secretion.[18,19] However they were not used in RTH patients, possibly due to their side effects. After a discussion with the family it was agreed to try them. This decision was based on: 1- failure of available agents to control the symptoms 2- GCs have been widely used in children and the patient will be under regular monitoring of growth and other side effects. Our impression was that the CS treatment will be for a limited period of time. This is based on the fact that his father is currently asymptomatic and an age-related improvement in thyrotoxic symptoms has been reported in RTH[20], Both dexamethasone and prednisolone have been shown to suppress TSH[21] but the dose and regimen needed for RTH patients are unknown. We chose 2mg/kg/alternate day prednisolone because this regimen is generally associated with less GCs side effects[22] and has been reported to have lower adverse effects on growth in children with post renal transplant.[23] In addition, the alternate day administration would ensure better compliance with treatment. On this regimen a marked drop in the high TSH was noticed after 4 weeks and the level remained in the lower limit of normal throughout the18 treatment period. As expected there was a reduction in the fT4 and fT3 levels following TSH suppression; however their values were comparable to those observed during carbimazole therapy. The hormonal changes were associated with improvement in the thyrotoxic symptoms which subsequently disappeared.

In conclusion, our experience indicates that in RTH children with thyrotoxic symptoms alternate day prednisolone for 18 months is safe and effective in relieving the thyrotoxic symptoms and maintains the TSH in lower limit of normal. We suggest that this regimen would be an option for some RTH children with thyrotoxic symptoms. A large study including an assessment of markers of TH action over a longer period would provide more insight into the role of CSs in the management of RTH.

ACKNOWLEDGEMENT

The authors would like to thank Dr Carla Moran and Prof. Krishna Chatterjee, Cambridge, UK for conducting the genetic testing.

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