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N Woodhouse and others | Euthyroid athyroxinemia

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Euthyroid athyroxinemia – a novel endocrine syndrome

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Summary

A 55-year-old female was referred with abnormal thyroid function tests (TFTs); the free thyroxine level (FT4) was undetectable <3.3 pmol/L (normal: 7.9–14.4), while her FT3, TSH and urinary iodine levels were normal. She was clinically euthyroid with a large soft lobulated goitre that had been present for more than thirty years. She received an injection of recombinant human TSH (rhTSH) following which there was a progressive rise of the FT3 and TSH levels to 23 pmol/L and >100 mIU/L respectively at 24 h, The FT4 however remained undetectable throughout. Being on thyroxine 100 µg/day for one month, her FT4 level increased to 15 pmol/L and TSH fell to 0.08 mIU/L. Four years earlier at another hospital, her FT4 level had been low (6.8 pmol/L) with a normal TSH and a raised Tc-99 uptake of 20% (normal<4%). We checked the TFTs and Tc-99 scans in 3 of her children; one was completely normal and 2 had euthyroid with soft lobulated goitres. Their Tc-99 scan uptakes were raised at 17% and 15%, with normal TFTs apart from a low FT4 7.2 pmol/L in the son with the largest thyroid nodule. This is a previously unreported form of dyshormonogenesis in which, with time, patients gradually lose their ability to synthesize thyroxine (T4) but not triiodothyroxine (T3).

Learning points:

- This is a previously unreported form of dyshormonogenetic goitre.
- This goitre progressively loses its ability to synthesize T4 but not T3.
- The inability to synthesize T4 was demonstrated by giving rhTSH.

Background

This is a report of a novel condition of a defect in T4 synthesis, which we were able to diagnose by giving a trial of rhTSH and monitoring FT4, FT3 and TSH levels.

Case presentation

A 55-year-old female was admitted for an elective laparoscopic cholecystectomy and was referred to the endocrine unit as she had a large soft goitre and abnormal thyroid function test (TFT). She was being dialysed three times per week after having undergone nephrectomy four years ago for polycystic kidney disease. She had three other surgeries in the past without any complications. She was clinically euthyroid and apparently had the goitre for more than 30 years.

Investigation

The patients presenting FT4 was <3.2 pmol/L with a normal FT3 (5.3 pmol/L) and TSH (2.2 mIU/L). Four years ago, when admitted for a nephrectomy, she was evaluated for this goitre and her TFT revealed a reduced but measurable FT4 of 6.8 pmol/L and a normal TSH. She had a patchy increased uptake on Tc-99 scan of 20% (normal range is 1–4%, which is determined from our population and is measured 20 min post Tc-99 injection

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during the scan). Her ultrasound thyroid showed that both lobes were enlarged with heterogeneous echotexture and increased vascularity (right lobe 43×44×61 mm, left lobe 31×40×75 mm and isthmus 20 mm in diameter). It also showed multiple nodules in both the thyroid lobes, largest in the right was 28 mm×23 mm, and the largest in the left measured 22×22 mm. To establish whether or not her thyroid was able to synthesize T4, she was given a single 0.9 mg injection of recombinant human thyroid stimulating hormone (rhTSH), with measurements of FT4, FT3 and TSH levels at 0, 30, 60, 90 min and 24 h (Table 1). There was a progressive increase in her FT3 to 23 pmol/L at 24 h, along with her TSH levels. However, the FT4 remained undetectable throughout. We gave her thyroxine 100 µg once a day for a month, which caused her FT4 to rise to 15 pmol/L with a suppression of TSH to 0.09 mIU/L, with no clinical signs or symptoms of hyperthyroidism. This suggested that there was no antibody interference with the FT4 assay. Her FT3 levels were not checked at this time. As her attendant son also had a large multinodular goitre and was euthyroid, we evaluated three of her eight children aged 24, 26 and 34 years respectively. Their TFTs, Tc-99 scans and ultrasound thyroid were performed. One was completely normal, and two had a multinodular goitre with high Tc-99 uptakes (17 and 10.7% respectively). However, the TFTs were normal, except for a reduced FT4 value of 7.2 pmol/L in the son with the largest thyroid nodule. Urine iodine levels were obtained for the patient and her son with the reduced FT4 value, which was 116 µg/L and 158 µg/L respectively (according to OMS 2004 normal: 100–199 µg/L).

Treatment

No active treatment was needed.

Outcome and follow-up

The patient is undergoing regular dialysis at another centre. We have been following up with her nephrologist who has done her TFT, and it remains unchanged over the past 18 months.

Table 1 Progressive rise in FT3 levels after injection of rhTSH at time 0, while the FT4 remains unrecordably low.

	0 min	30 min	60 min	90 min	120 min	24 h
FT4	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2
FT3	5.5	6	6.6	8	12	22
TSH	1.8	>35	>62	>79	>100	>100

FT3 and FT4 values in pmol/L and TSH in mIU/L.

Discussion

In the last 15 years, we have encountered two unrelated families with similar abnormal TFTs: undetectable FT4 and normal FT3 and TSH levels. They had refused investigation. Our third unrelated case consented to a trial of rhTSH, which confirmed the inability of the thyroid to synthesize T4. To be noted, her FT4 in 2013 was low, 6.8 pmol/L, and now has become undetectable. Her son too has a low FT4, 7.2 pmol/L. There was no history of consanguinity in the patient's parents. This is a unique form of dyshormonogenesis, which is not associated with the development of hypothyroidism. Iodine deficiency is unlikely in Omanis, as the majority of the population eat fish, and iodised salt was introduced in 1995. Deficiency was excluded by finding normal urinary iodine levels measured in the two patients. This type of defect, to the best of our knowledge, has not been previously described. Dyshormonogenetic goitres are genetically determined thyroid hyperplasia due to enzyme defects in thyroid hormone synthesis. Hypothyroidism is not a necessary feature of these defects (1). The various defects described are a defect in iodine transport (or trapping) because of a mutation in the Na/I symporter gene (2), iodine organification and coupling defects because of deficiency in the quantity or activity of thyroid peroxidase or in hydrogen peroxide generation (3), defects in thyroglobulin biosynthesis result from decreased production or the production of a truncated molecule (4) or a defect that has amino-acid substitutions within it (5), defects in iodotyrosine deiodinase that result from mutations in *DEHAL1* (iodotyrosine deiodinase 1 gene), so that the iodine contained in the iodotyrosine residues of thyroglobulin is not recycled (6). It is also associated with Pendred syndrome, which is characterized by both goitre and sensorineural deafness (not caused by hypothyroidism) (7). We were not able to find a defect similar to our patients on literature review. The patient and her family members will be monitored regularly with a thyroid ultrasound and thyroglobulin levels in the unlikely event, they develop differentiated thyroid cancer, which can occur occasionally (1, 8, 9).

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient.

Author contribution statement
Nicholas Woodhouse, Fatima Bahowairath and Omayma Elshafie were responsible for the diagnosis and management of the patient throughout and preparation of the manuscript.

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