CASE REPORT

Familial dysalbuminaemic hyperthyroxinaemia, a thyroid trap

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Paediatricians are frequently asked to see children who cause concern because of their slow growth or development. In this situation, despite the absence of any specific abnormal signs, thyroid function tests are commonly requested. They are nearly always normal.

We describe three patients, where abnormal results led to erroneous treatment for thyrotoxicosis. These patients had a diagnosis of familial dysalbuminaemic hyperthyroxinaemia (FDH), an interesting condition with euthyroid hyperthyroxinaemia where the patient is clinically euthyroid but has raised laboratory value of free thyroxine.[1] Euthyroid hyperthyroxinaemia encompasses a broad range of conditions that can easily be misinterpreted as hyperthyroidism.[2]

CASE 1

A 7 year old girl referred to the hospital, was seen by general practitioner because of poor and abnormal thyroid function test results performed in primary care: total thyroxine 248 nmol/l (normal 80–150 nmol/l), free thyroxine 38 pmol/l (normal 10–25 pmol/l), and TSH 0.94 mU/l (normal 0.4–4 mU/l) (Bayer competitive assay for total and free thyroxine) (table 1).

Her pulse rate was 106 per minute but she had no other clinical features of thyrotoxicosis. Treatment was commenced with carbimazole (30 mg) after discussion with the paediatric endocrinologist.

Eighteen months later, while on treatment, the thyroid function tests remained abnormal (total thyroxine 105 nmol/l, free thyroxine 28.6 pmol/l, TSH 31.1 mU/l). This prompted the paediatrician to start block and replace therapy with additional thyroxine.

Two years from diagnosis, despite euthyroid clinical status and normal growth, biochemical control was still not achieved. The total and free thyroxine were still raised. The local adult endocrinologist was asked to review her. He investigated her further (table 2) and was able to discontinue her antithyroid treatment without ill effects.

CASE 2

A 2 year old boy was investigated by his local hospital for failure to thrive. The thyroid function test results were abnormal (free thyroxine was 43.9 pmol/l and TSH was 4 mU/l (table 1). His resting pulse was recorded at 120 per minute.

Treatment was commenced with carbimazole. After six months the family moved and his care was transferred to our hospital.

On assessment in the clinic the parents reported no improvement since initiating treatment and he appeared clinically euthyroid. Following further endocrine investigations (table 2) including repeat thyroid function tests, carbimazole was discontinued.

CASE 3

A 34 year old male presented to his general practitioner with complaints of tremors, palpitations, and tiredness; he was known to suffer from chronic bipolar disorder. The general practitioner noticed tachycardia, but there was no goitre. However, the thyroid function tests were abnormal (thyroxine 196 nmol/l, free thyroxine 44.5 pmol/l, and TSH 1.27 mU/l). With a diagnosis of thyrotoxicosis, carbimazole was commenced.

After six months of treatment total T_4 was 148 nmol/l and TSH had increased to 12.88 mU/l. Hence he was commenced on block and replace therapy with 25 μg thyroxine.

There was no improvement in his biochemistry despite treatment for 15 months. He was referred to an endocrinologist who discontinued his treatment and investigated him further (table 2)

Table 1 Initial investigations and treatment

	Age (y)	TSH (mU/l) (N = 0.4–4)	Total T_4 (nmol/l) (N = 80–150)	Free T_4 (pmol/l) (N = 10–25)	Free T_4 on treatment	Duration of treatment
Case 1	8	2.5	248	31.5	62.4	2 y
Case 2	7	4.0	238	43.9	40.4	6 mth
Case 3	33	1.27	196	44.4	40.8	1 y 3 mth

N, normal; T_4, thyroxine; TSH, thyroid stimulating hormone.

Table 2 Further investigations

	Free T_4 (pmol/l) Equilibrium dialysis	TBG	Alpha subunit TSH	Antibodies T_4/T_3	FDH screen
Case 1	23.4 (normal)		Normal	Negative	Positive
Case 2	19.6	Normal		Negative	Positive
Case 3	18.6			Negative	Positive

TBG, thyroid binding globulin; T_4, thyroxine; T_3, triiodothyronine; TSH, thyroid stimulating hormone; FDH, familial dysalbuminaemic hyperthyroxinaemia.

Summary and key points

- FDH patients may be mistakenly thought to be thyrotoxic and hence subjected to treatment, which is often unnecessary.
- To avoid this trap: on finding a patient with high free thyroxine, resist the temptation to treat unless the clinical and biochemical picture is consistent. We would recommend measurement of basal TSH using a highly sensitive assay, which will be normal if the patient has FDH; this confirms that the patient is in the euthyroid state and prevents unnecessary treatment.
- Clinicians should be aware of the conditions causing euthyroid hyperthyroxinaemia.
- When FDH has been diagnosed, screening of the patient's immediate family should be carried out, to avoid fruitless diagnostic studies and unnecessary treatment.

FURTHER INVESTIGATIONS

Because of diagnostic uncertainty the patients' serum was further assessed by thyroid two step assay (equilibrium dialysis). This was normal in all the patients. In this method free thyroxine is first separated from binding proteins and then assayed independently, thus excluding protein interference.[3]

Tests for thyroid antibodies were negative in all cases.

FDH screen, a protein electrophoresis[4] looking for abnormal albumin, was positive in all cases.

All patients received treatment for a duration of 6 months to 2 years, fortunately without any ill effects. The patients remained well off treatment. Careful follow up confirmed normal growth of the two children.

DISCUSSION

Normally 99.9% of thyroxine transported in blood is in the bound form. Seventy five per cent is bound to thyroid binding globulin (high affinity binding); the remainder is bound to pre-albumin (10–15%) and albumin (10–15%) (low affinity binding).[1 3] In FDH, however, up to 30% of thyroxine is bound to abnormal albumin while the unbound free concentration remains normal.[1 3 5 6]

Due to the development of single step techniques (analogue free thyroxine assays), measurement of free thyroxine is easy and is widely used as the first line test of thyroid function. Thyroid assay by analogue free thyroxine is based on the assumption that only 10% of the thyroxine in plasma is albumin bound.[5] In FDH, the analogue employed in ''analogue free thyroxine assays'' shows high affinity for the mutant albumin; spuriously high free thyroxine levels are therefore produced by this method, whereas free thyroxine is normal in the patients. This binding protein interference is excluded in equilibrium dialysis, a two step method, in which free hormone is extracted from serum first and then analysed independently.[7]

In 1979 Henneman and Lee first described FDH, an autosomal dominant condition characterised by strikingly increased total thyroxine and free thyroxine, and normal TSH; patients are clinically euthyroid.[8 9]

In FDH, binding to albumin is 30% (normally 10%). Hence albumin becomes the main binding protein, especially as it is available in a large quantity compared to TBG, but binding of thyroxine to triiodothyronine is normal.[1 3 6 10 11] In 1994, Peterson *et al* showed that the increased binding is due to substitution of arginine to histidine at position 218 on the albumin protein.[12]

The incidence of FDH is not known, mainly due to the fact that the condition is diagnosed by chance when thyroid function tests are ordered.[1] Patients who are anxious when examined in the clinic may show signs such as tachycardia and sweating. The physician can misinterpret these signs as features of thyrotoxicosis, especially since he may have been primed by knowledge of the abnormal thyroid blood results.[1]

Clinicians should be aware of the technical limitations of conventional one step thyroid assays and should be suspicious of diagnosing hyperthyroidism when there are no eye signs or goitre, and most importantly when the TSH concentration is in the normal range.[1] Whenever a result for free thyroxine concentration seems inappropriate to the patient's clinical state, the clinician should question the ''clinical chemistry'' results, particularly the analogue free thyroxine assays. Euthyroid hyperthyroxinaemia (high total and free thyroxine with a normal TSH) should be suspected in these situations to prevent inappropriate therapy.[1 3 9]

The conditions which can cause this are:

- Increased thyroid binding globulin
- Familial dysalbuminaemic hyperthyroxinaemia
- Thyroid antibodies
- Resistance to thyroid hormones: central and peripheral
- Drugs: amiodarone prevents peripheral conversion of thyroxine to triiodothyronine
- Acute psychiatric illness.

We end this paper with classical a quote from undergraduate teaching: ''Treat the patient, not the laboratory report''.

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