

# Two patients with atypical low triiodothyronine syndrome: primary deiodinase abnormalities?

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## Summary

Low triiodothyronine (T<sub>3</sub>) concentrations in the presence of normal thyroxine (T<sub>4</sub>) and TSH levels, referred to as the low T<sub>3</sub> syndrome (LT<sub>3</sub>S), are common. LT<sub>3</sub>S may be caused by starvation, various non-thyroidal illnesses (NTIs) and some medications. Reverse T<sub>3</sub> (rT<sub>3</sub>) concentrations are elevated in the more severely ill, and they characteristically fail to respond to exogenous levothyroxine (L-T<sub>4</sub>) therapy. The biochemical abnormalities have been explained on the basis of altered peripheral deiodinase activities. Herein, we report on two patients with hypothyroid symptoms who on testing were found to have LT<sub>3</sub>S. They were atypical clinically in not having LT<sub>3</sub>S due to any of the usual causes, had no increased rT<sub>3</sub> concentrations, and had a normal negative TSH feedback response to L-T<sub>4</sub>. One (patient 1) had previously been diagnosed with Hashimoto's autoimmune primary hypothyroidism and was on L-T<sub>4</sub> therapy. Both had T<sub>4</sub> concentrations in the reference range. TSH levels were elevated in patient 1 and in the reference range in patient 2. Starting or increasing L-T<sub>4</sub> doses resulted in no clinical improvement and no increase in T<sub>3</sub> levels in spite of a marked increase in T<sub>4</sub> levels. It is suggested that in the absence of the usual causes, lack of elevated rT<sub>3</sub> levels, response to treatment and intact negative TSH feedback these two patients differ from the usual secondary causes of decreases in deiodinase activity. It is speculated that they may represent primary alterations in deiodinase enzymes possibly due to genetic variations in the deiodinase-encoding genes.

## Learning points:

- LT<sub>3</sub>S is commonly found secondary to starvation, NTIs and use of some medications.
- Low T<sub>3</sub> levels are the result of alterations in the activity of deiodinase enzymes.
- LT<sub>3</sub>S without the usual causes may represent a primary disturbance in deiodinase activity.

## Background

In normal, euthyroid individuals, 20% of the circulating active thyroid hormone triiodothyronine (T<sub>3</sub>) comes directly from the thyroid gland and 80% is produced in non-thyroidal tissues by the activation of the inactive prohormone thyroxine (tetraiodothyronine, T<sub>4</sub>) (1) (2). Low T<sub>3</sub> concentrations are found during starvation and in various acute and chronic illnesses (3) (4) (5). This condition is variously referred to as the euthyroid sick syndrome (ESS), non-thyroidal illness (NTI) syndrome or the low T<sub>3</sub> syndrome (LT<sub>3</sub>S) (4) (5) (6). In critically ill

patients, T<sub>4</sub> concentrations may also be low, and the degree of disturbance in the circulating thyroid hormone concentrations is related to the severity of the NTI, with a decrease in the T<sub>3</sub> concentration only being more benign (5) (6). LT<sub>3</sub>S as found in ESS is caused by a decrease in enzymatic deiodination at the 5' position of the outer, phenol ring of the iodothyronines (2) (7). In more severe NTIs, there is a further reduction in T<sub>3</sub> concentrations due to increased deiodination at the 5 position of the inner, tyrosyl ring reducing it to the inactive diiodothyronine (T<sub>2</sub>) and producing inactive reverse T<sub>3</sub> (rT<sub>3</sub>) from T<sub>4</sub>, thereby yet

further reducing T<sub>3</sub> generation because of decreased substrate availability (2) (7) (8). Evidence of a disturbance in the thyroid-stimulating hormone (TSH) feedback loop has also been found (4) (5) (6) (8). LT<sub>3</sub>S is also found in response to some drugs, including propylthiouracil (PTU) (9), beta-blockers (10) and amiodarone (11) (12).

The enzymes responsible for these alterations are the deiodinases (D) D1, D2 and D3 (2) (7). D2 is an activating enzyme that converts T<sub>4</sub> to T<sub>3</sub> (and rT<sub>3</sub> to T<sub>2</sub>) and is found in the endothelial reticulum of skeletal muscle, CNS, pituitary, thyroid, heart muscle and brown adipose tissue. D3 is a deactivating enzyme that converts T<sub>4</sub> to rT<sub>3</sub> and T<sub>3</sub> to T<sub>2</sub> and is found in the CNS and other tissues. D1 has both activating and deactivating activities and is found in the plasma membranes of liver, kidney, thyroid and pituitary tissue. Together, these three enzymes play a vital role in the maintenance of tissue and circulating thyroid hormone levels (2) (7).

The 5'-deiodinase activity of D1 is inhibited by fasting, PTU and amiodarone (3) (9) (11) (12). Melmed *et al.* (11) have shown that the decreased generation of T<sub>3</sub> caused by chronic amiodarone administration in euthyroid patients causes a compensatory increase in TSH and T<sub>4</sub> concentrations. It is accompanied by a more modest increase in rT<sub>3</sub> concentrations, which is partially explainable by the mass action effect of the marked increase in TSH-stimulated T<sub>4</sub> secretion by the thyroid gland, but in addition represents some increase in D1 activity through its increased half-life caused by the increased secretion of T<sub>3</sub> by the intact thyroid gland in response to the increased TSH concentration (2) (7).

Treatment of LT<sub>3</sub>S secondary to NTIs with levothyroxine (L-T<sub>4</sub>) has generally been found to be unsuccessful (4) (5) (6).

Herein, we report on two patients with clinical evidence of hypothyroidism and LT<sub>3</sub>S without any of the usual causes.

## Case presentations

### Case 1

A 63-year-old man, diagnosed at the age of 31 years with primary hypothyroidism due to Hashimoto's autoimmune thyroiditis when he received the first of two mitral valve replacements, was referred for continued severe cold intolerance, low physical energy and marked mental lethargy in spite of free T<sub>4</sub> concentrations being near the upper limit of the reference range on L-T<sub>4</sub> replacement. His weight was 98 kg. There was no goitre. He was on warfarin and on candesartan, verapamil,

furosemide and digoxin therapy for hypertension and congestive heart failure and on allopurinol therapy for gout. There was no history of herpes or any other chronic viral infection.

### Case 2

A 60-year-old woman was referred for the evaluation of fatigue, cold intolerance, muscle cramps, depression and obesity of long duration. Her weight was 99 kg. There was no goitre. She was on candesartan and nifedipine therapy for hypertension. There was no history of herpes or any other chronic viral infection.

## Investigation

### Case 1

Thyroid tests revealed elevated thyroid peroxidase antibody (TPOA) levels, free T<sub>4</sub> levels near the upper limit of the reference range, markedly elevated TSH levels and low free T<sub>3</sub> levels. The T<sub>4</sub>:T<sub>3</sub> ratio was high, rT<sub>3</sub> concentrations were in the normal reference range, and the T<sub>4</sub>:rT<sub>3</sub> ratio was more than double mid-normal. Plasma iodine concentration was within the reference range (Table 1).

### Case 2

Thyroid tests revealed normal TPOA levels and TSH and T<sub>4</sub> levels within their reference ranges, but low T<sub>3</sub> concentrations and an elevated T<sub>4</sub>:T<sub>3</sub> ratio (Table 1).

Thyroid hormone measurements were carried out by LifeLabs Laboratory Services, 3680 Gilmore Way, Burnaby, BC, V5G 4V8, Canada, using a competitive immunoassay with direct chemiluminescent technology for TSH, T<sub>4</sub> and T<sub>3</sub> and electrochemiluminescent immunoassay for TPOA. The rT<sub>3</sub> concentration was measured by Associated Regional and University Pathologist (ARUP), Inc., 500 Chipeta Way, Salt Lake City, UT, 84108, USA, using a competitive RIA. Plasma iodine measurement was carried out by the London Laboratory Services Group, PO Box 5010, London, ON, N6A 5W9, Canada, using high-resolution inductively coupled plasma mass spectroscopy.

## Treatment

### Case 1

Increasing L-T<sub>4</sub> dose to 100 µg had no effect on the symptoms in spite of T<sub>4</sub> concentrations rising to supra-physiological levels, TSH concentrations falling to half

**Table 1** Clinical features and thyroid hormone levels in the two patients with atypical low T<sub>3</sub> syndrome.

Patient, age, gender and treatment	TSH (mU/l)	T <sub>4</sub> (pmol/l)	T <sub>3</sub> (pmol/l)	T <sub>4</sub> /T <sub>3</sub> (Ratio)	rT <sub>3</sub> (nmol/l)	T <sub>4</sub> /rT <sub>3</sub> (Ratio)
1. 63 years, male and TTPH on 75 µg L-T <sub>4</sub>	<b>38.8</b>	19.2	<b>3.0</b>	<b>6.4</b>		
Repeat on 75 µg L-T <sub>4</sub>	<b>36.5</b>	17.5	<b>3.1</b>	<b>5.6</b>	0.19	<b>92.1</b>
On 100 µg L-T <sub>4</sub>	<b>20.6</b>	<b>23.6</b>	<b>3.4</b>	<b>6.9</b>		
Repeat on 100 µg L-T <sub>4</sub>	<b>14.7</b>	<b>22.5</b>	<b>3.1</b>	<b>7.3</b>	0.23	<b>97.8</b>
2. 60 years, female and before treatment	1.50	19.8	<b>3.4</b>	<b>5.8</b>	–	–
On 150 µg L-T <sub>4</sub>	< <b>0.06</b>	<b>21.6</b>	<b>3.3</b>	<b>6.5</b>	0.54	40.0
<b>Analytical units</b>						
Normal reference range	0.38–5.5	10.5–20	3.5–6.5		0.14–0.54	
Mid-normal values	1.5	15.3	5.0	3.1	0.34	45

TTPH, thyroxine-treated primary hypothyroidism. Analyte levels are given in bold if outside the reference range. Patient 1: plasma iodine: 0.29 (n: 0.24–0.63 µmol/l).

their previous levels, a minimal to no increase in T<sub>3</sub> concentrations, and a further rise in the T<sub>4</sub>:T<sub>3</sub> ratio. The rT<sub>3</sub> concentration rose minimally and continued to fall within the reference range, and the T<sub>4</sub>:rT<sub>3</sub> ratio remained more than double normal (Table 1). Because of the patient's heart failure, it was thought inadvisable to further increase the dose of L-T<sub>4</sub>.

## Case 2

Treatment with 150 µg L-T<sub>4</sub> had no clinical effect, increased T<sub>4</sub> concentrations and T<sub>4</sub>:T<sub>3</sub> ratio, and suppressed TSH concentrations, but had no effect on T<sub>3</sub> concentrations. The rT<sub>3</sub> concentration remained within the reference range, and the T<sub>4</sub>:rT<sub>3</sub> ratio was near the mid-normal level (Table 1).

## Discussion

Herein, we report on two patients with atypical LT<sub>3</sub>S in that they reported none of the usual causes such as NTIs, including chronic viral infections, starvation and mediations known to cause impaired T<sub>3</sub> generation or its increased destruction. Their rT<sub>3</sub> concentrations were not elevated, as is the case in more severe NTIs or if on amiodarone therapy (2) (7) (8) (11) (12). In both patients, the negative TSH feedback mechanism was intact in that their TSH levels fell in response to increasing doses of L-T<sub>4</sub>, albeit that in patient 1 the levels remained markedly elevated. Both presented with clinical symptoms of hypothyroidism, but neither responded clinically to elevating the T<sub>4</sub> concentrations to supra-physiological levels, and nor was there a consistent increase in T<sub>3</sub> concentrations.

The findings in patient 1 are reminiscent of those found in euthyroid patients on amiodarone therapy as reported by Melmed *et al.* (11) and Rosene *et al.* (12), except that TSH levels remained markedly elevated even at supra-physiological concentrations of T<sub>4</sub> and that the T<sub>4</sub>:rT<sub>3</sub> ratio was elevated (Table 1). It is consistent with an absent response of the thyroid gland to elevated TSH levels because of the patient's primary hypothyroidism. In fact, he might not have come to attention if he had not also had primary hypothyroidism in that the elevated TSH levels would presumably have resulted in increased secretion of thyroid hormones and suppression of TSH secretion. Inhibition of the deiodinases due to elevated serum iodine levels was ruled out (Table 1). The findings are most consistent with a marked decrease in D1 activity including normal rT<sub>3</sub> concentrations, which might be considered inappropriately low given the elevated T<sub>4</sub> concentrations, resulting in a high T<sub>4</sub>:rT<sub>3</sub> ratio (Table 1).

Patient 2 had previously not been diagnosed with hypothyroidism and had a negative TPOA concentration. Unlike in patient 1, the rT<sub>3</sub> concentration at the upper limit of the reference range was appropriate for the elevated concentration of its substrate T<sub>4</sub>, as indicated by the mid-normal T<sub>4</sub>:rT<sub>3</sub> ratio (Table 1). It is evidence that the activity of D1 at the 5 position of the inner ring was not impaired. As the enzymatic activities of D1 at the 5 and 5' positions have been shown to proceed in an equimolar fashion (2), it makes decreased D1 activity an unlikely cause of the low circulating T<sub>3</sub> levels, suggesting impaired D2 activity as a more likely alternative. She also differed from patient 1 in not having an elevated TSH concentration, albeit that the 1.5 concentration was higher than expected for a T<sub>4</sub> concentration at the upper limit of the reference range (Table 1). It has long been known that TSH secretion is controlled by a negative

feedback mechanism responsive to circulating T<sub>4</sub> concentrations (1). It is the concentration of T<sub>3</sub> at the nuclear T<sub>3</sub> receptors of the thyrotrophs produced by the resident D1 and D2 enzymes as well as the T<sub>3</sub> from the circulation that ultimately controls TSH secretion (2). Christoffolete *et al.* (13) have demonstrated a unique behaviour of D2 in thyrotrophs in being able to overcome ubiquitination, thereby sustaining net increased T<sub>3</sub> production at increasing T<sub>4</sub> concentrations. One might speculate that in patient 2 the postulated decreased D2 activity might be sufficiently ameliorated by its atypical expression in the thyrotrophs to result in no or only minimally elevated TSH levels. An additional possible mechanism may be that reduced T<sub>3</sub> levels in the hypothalamus caused by decreased D2 activity in the third ventricle tanocytes have reset the TSH response of the thyrotrophs (14). The lack of a markedly elevated TSH concentration in patient 2 may be akin to what has been observed in patients on amiodarone therapy in whom after an initial elevation in TSH concentrations in response to impaired deiodinase activity (11) (12), there is a gradual return to normal or nearly normal levels.

The theoretically possible alternative cause for the low circulating T<sub>3</sub> levels of a deficiency in T<sub>3</sub> production by the thyroid gland is not applicable in patient 1 who had Hashimoto's primary hypothyroidism, while in patient 2 the 32% observed reduction from mid-normal levels exceeds the 20% of the total T<sub>3</sub> contributed by the thyroid (1) (2), and nor would it explain the lack of an increase in T<sub>3</sub> concentrations as the T<sub>4</sub> concentration rose in response to increasing the dose of L-T<sub>4</sub>. Furthermore, no such case has been reported. It was not ruled out in either patient that further increases in their T<sub>4</sub> concentrations by increased doses of L-T<sub>4</sub> might have resulted in an increase in T<sub>3</sub> concentrations.

The fact that both patients responded with a decrease in TSH concentrations in response to an increase in circulating T<sub>4</sub> concentrations indicated an intact negative TSH feedback axis, supporting evidence for the lack of NTIs as a potential cause for the abnormalities found (4) (6) (8). This, together with the lack of clinical evidence that their LT<sub>3</sub>S was secondary to fasting, NTIs or drugs, suggests that the alterations in circulating thyroid hormone levels were not secondary, but might represent primary abnormalities in deiodinase activity. In support of this speculation, Peeters *et al.* (15) have demonstrated polymorphism of deiodinases associated with circulating iodothyronine concentrations and their ratios, while Panicker *et al.* (16) using a similar approach of nucleotide measurement of genes involved in thyroid hormone

metabolism found that 26% of patients with primary hypothyroidism on replacement therapy had polymorphism in the *DIO2* gene resulting in a decreased T<sub>4</sub>:T<sub>3</sub> ratio and clinical manifestations. Considering this frequency in genetic polymorphism, it is not unexpected that patients might be encountered with primary D2 and D1 enzyme abnormalities causing LT<sub>3</sub>S.

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#### Declaration of interest

The author declares 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 consent was obtained from both patients to publish the case report.

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#### Author contribution statement

The author was the only contributor. The author is a consultant endocrinologist and was and continues to be the physician responsible for the endocrine care of both patients. Both were referred by the family physician.

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#### References

- 1 Schimmel M & Utiger RD 1977 Thyroidal and peripheral production of thyroid hormones. Review of recent findings and their clinical implications. *Annals of Internal Medicine* **87** 760–768. (doi:10.7326/0003-4819-87-6-760)
- 2 Bianco AC & Kim BW 2006 Deiodinases: implications of the local control of thyroid hormone action. *Journal of Clinical Investigation* **116** 2571–2579. (doi:10.1172/JCI29812)
- 3 Vagenakis AG, Portnoy GI, O'Brian JT, Rudolph M, Arky RA, Ingbar SH & Braverman LE 1977 Effect of starvation on the production and metabolism of thyroxine and triiodothyronine in euthyroid obese patients. *Journal of Clinical Endocrinology and Metabolism* **45** 1305–1309. (doi:10.1210/jcem-45-6-1305)
- 4 Wartofsky L & Burman KD 1982 Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". *Endocrine Reviews* **3** 164–217. (doi:10.1210/edrv-3-2-164)



- 5 Adler SM & Wartofsky L 2007 The nonthyroidal illness syndrome. *Endocrinology and Metabolism Clinics of North America* **36** 657–672. (doi:10.1016/j.ecl.2007.04.007)
- 6 Chopra IJ 1997 Euthyroid sick syndrome: is it a misnomer? *Journal of Clinical Endocrinology and Metabolism* **82** 329–334. (doi:10.1210/jcem.82.2.3745)
- 7 Maia AL, Kim BW, Huang SA, Harney JW & Larsen PR 2005 Type 2 iodothyronine deiodinase is the major source of plasma T<sub>3</sub> in euthyroid humans. *Journal of Clinical Investigation* **115** 2524–2533. (doi:10.1172/JCI25083)
- 8 Peeters RP, Debaveye Y, Fliers E & Visser TJ 2006 Changes within the thyroid axis during critical illness. *Critical Care Clinics* **22** 41–55. (doi:10.1016/j.ccc.2005.08.006)
- 9 Saberi M, Sterling FH & Utiger RD 1975 Reduction in extrathyroidal triiodothyronine production by propylthiouracil in man. *Journal of Clinical Investigation* **55** 218–223. (doi:10.1172/JCI107924)
- 10 Tevaarwerk GJM & Boyd D 1979 Propranolol in thyrotoxicosis. II. Serum thyroid hormone concentrations during subtotal thyroidectomy. *Canadian Journal of Surgery* **22** 264–266.
- 11 Melmed S, Nademanee K, Reed AW, Hendrickson JA, Singh BN & Hershman JM 1981 Hyperthyroxinemia with bradycardia and normal thyrotropin secretion after chronic amiodarone administration. *Journal of Clinical Endocrinology and Metabolism* **53** 997–1001. (doi:10.1210/jcem-53-5-997)
- 12 Rosene ML, Wittmann G, Arrojo e Drigo R, Singru PS, Lechan RM & Bianco A 2010 Inhibitors of the type 2 iodothyronine deiodinase underlies the elevated plasma TSH associated with amiodarone treatment. *Endocrinology* **151** 5961–5970. (doi:10.1210/en.2010-0553)
- 13 Christoffolete MA, Ribeiro R, Singru PS, Fekete C, da Silva WS, Gordon DF, Huang SA, Crescenzi A, Harney JW, Ridgway EC *et al* 2006 Atypical expression of type 2 iodothyronine deiodinase in thyrotrophs explains the thyroxine-mediated pituitary thyrotropin feedback mechanism. *Endocrinology* **147** 1735–1743. (doi:10.1210/en.2005-1300)
- 14 Costa-e-Souza RH & Hollenberg AN 2012 Minireview: the neural regulation of the hypothalamic–pituitary thyroid axis. *Endocrinology* **153** 4128–4135. (doi:10.1210/en.2012-1467)
- 15 Peeters RP, van Toor H, Klootwijk W, de Rijke YB, Kuiper GG, Uiterlinden AG & Visser TJ 2003 Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. *Journal of Clinical Endocrinology and Metabolism* **88** 2880–2888. (doi:10.1210/jc.2002-021592)
- 16 Panicker V, Cluett C, Shields B, Murray A, Parnell KS, Perry JRB, Weedon M, Singleton A, Hernandez D, Evans J *et al* 2008 A common variation in deiodinase 1 gene DIO1 is associated with the relative levels of free thyroxine and triiodothyronine. *Journal of Clinical Endocrinology and Metabolism* **93** 3075–3081. (doi:10.1210/jc.2008-0397)

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