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Endocrinology Quiz – Case 7

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A 51-year-old lady was referred to the outpatient endocrine clinic by her general practitioner because of raised TSH of 52.9 mU/L (0.35–5.50 mU/L) while on levothyroxine (LT-4) 75 mg/day. She was diagnosed with hypothyroidism due to Hashimoto's thyroiditis 10 years previously. She had a goitre with compression symptoms (mild dysphagia and hoarseness of voice). She was known with depression and took amitriptyline 20 mg nocturnal. She did not report any cardiovascular history, diabetes or recent change of medications. She was a smoker, unemployed and had no allergies. Her sister also had a history of thyroid disease.

On assessment, she reported feeling tired and low mood. She was concerned about recent change in her voice and mild increase in the size of the goitre. She asked for surgical removal of the goitre. On examination she had nodular goitre firm in consistency but she did not have palpable cervical lymph nodes. Management plan included repeat thyroid function tests (TFTs), absorption screen (which included tissue transglutaminase [tTG] IGA antibodies to check for coeliac, serum folate, serum vitamin B_{12} and vitamin D levels), thyroid ultrasound scan (US), and referral to the surgeons for consideration of thyroidectomy. Results revealed raised TSH 50 mU/L (0.35–5.50 mU/L), FT4 4.0 pmoL/L (10.0–20.0 pmoL/L), serum folate 3.60 ug/L (>4.0 ug/L) and anti-tTG IGA antibodies 0.2 IU/mL (0.0–7.0 IU/mL). Thyroid US findings included a markedly enlarged heterogeneously hypoechoic thyroid gland without a discrete nodule, and a small cervical lymph node which appeared benign. Because of the size, firm consistency of the goitre with and the suspicion of lymphoma, core biopsies and fine needle aspiration were examined and confirmed the benign nature of the goitre. Computed tomography (CT) imaging of the neck and thorax was also requested. The appearances were of bulky nodular thyroid with a relatively minor tracheal narrowing and displacement to the right (fig. 1). Meanwhile, the levothyroxine dose was increased. Patient was reminded of the instructions to take levothyroxine tablets first thing in the morning an hour before food, drink and other tablets. Vitamin B_{12} and folate were replaced and the patient was referred to gastroenterology for assessment of possible malabsorption problems.

Few months later, the patient was reviewed in clinic. Repeat routine bloods showed TFTs similar to previous levels with higher levels of serum vitamin B_{12} and serum folate. Non-concordance with LT-4 was explored. Patient denied non adherence but agreed to carry on a test to check whether she absorbed LT-4. The patient was fasted from midnight and admitted to the Medical Investigations Unit (MIU) the next morning. She was given 1,000 mg levothyroxine whole tablets under observation; she remained under observation for an hour and bloods were collected for TFTs at baseline before LT-4 loading, 120 and 240 minutes after LT-4 loading. Results revealed improvement in FT4 levels with a peak of 19.5 pmoL/L (10.0–20.0 pmoL/L) at 120 minutes (fig. 2).

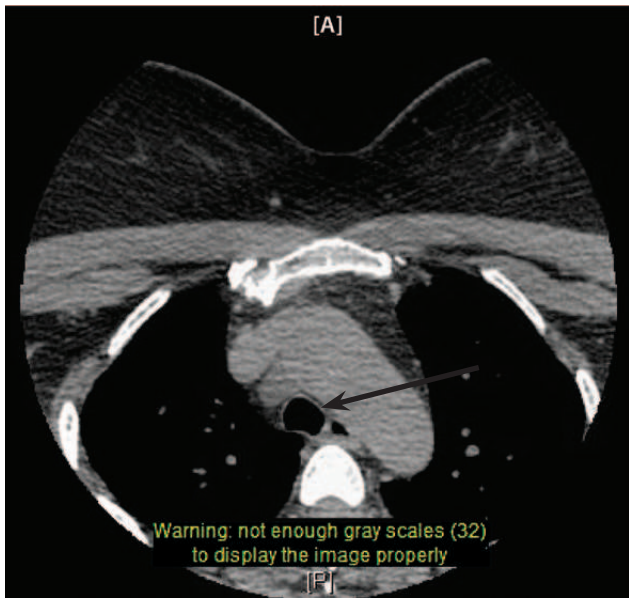

Figure 1. Non contrast computed tomography (CT) neck and thorax showing slight compression of the left lateral aspect of the trachea with marginal displacement to the right. The transverse diameter of the trachea is 11 mm with a measurement of 15 mm at the level of the lower pole of the left thyroid lobe and a similar diameter below the vocal cords in the upper portion of the thyroid.

Comment

Poor adherence with medications is a problem in many chronic conditions and can be difficult to demonstrate or confirm, if it is denied by the patient. For patients who remain hypothyroid despite what would appear an appropriate amount of L-T4, the exclusion of interfering drugs and possible pathological causes need to be considered.

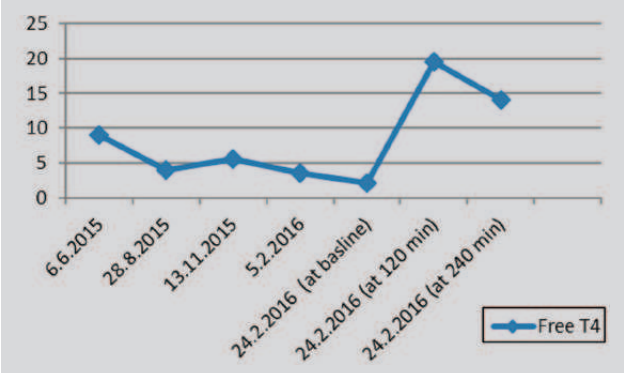

Figure 2. Free T4 results before and after supervised administration of L-T4 1 mg whole tablets.

A literature review of levothyroxine pharmacokinetics summarized its absorption, bioavailability and elimination. Levothyroxine is mainly absorbed in the small intestine, more specifically through the duodenum, jejunum and ileum. The time to maximum serum concentration (T_{max}) occurs at approximately 2 hours in euthyroid volunteers while it is delayed to approximately 3 hours in hypothyroid patients. The daily turnover (elimination) rate for T4 is approximately 10% while it is approximately 50–70% for T3, with a slightly faster turnover rate in normal volunteers compared with patients with primary hypothyroidism. This equates to a half-life for T4 of 7.5 days in hypothyroid patients and 6.2 days in euthyroid individuals, while the T3 half-life is approximately 1.4 and 1.0 days for hypothyroid and euthyroid volunteers, respectively.

The oral absorption of levothyroxine can be impaired by various substances, such as food, soy bean, papaya and grapefruit. Coffee can also reduce the absorption of certain levothyroxine formulations. Proton-pump inhibitors lansoprazole and omeprazole (famotidine and esomeprazole had no such effect), aluminium hydroxide, dietary fibre, calcium carbonate, calcium citrate, calcium acetate, ferrous sulphate, cholestyramine, orlistat and cimetidine can impair LT-4 absorption. Oral estrogens interfere with LT-4 given their first pass metabolism, increase thyroid binding globulin (TBG) and lower FT4 and hence may increase LT-4 requirements; this is not an issue with transdermal estrogen preparations which may be preferred when menopausal hormone therapy needs to be used concurrently with LT-4. Similarly, conventional antiepileptics (such as phenytoin and carbamazepine) medications can induce a hypothyroid state (reduced FT4, increased TSH) and this is thought to relate to hepatic CYP450 enzyme induction with resultant accelerated thyroid hormone metabolism, albeit a more central mechanism has also been proposed; this interaction does not seem to occur with newer antiepileptics.

A combination of a T4 absorption test, aiming to determine adequate absorption, followed by weekly L-T4 bolus (supervised) administration, has previously identified adherence issues in 75% of cases. Other studies used a variable bolus dose between 1 mg and 2 mg, but in other studies they used a weight-related dose in each case.

In one of the previous studies into levothyroxine loading test, the study cohort was split into two centres. In one centre, patients were given LT-4 as whole tablets and in the other patients were given crushed LT-4 tablets. They reported that patients with severe hypothyroidism (TSH >150 mU/L) had the lowest actual rise in fT4 at 120 min. Possible reason is the impaired absorption in severe hypothyroidism, presumably due to oedema of the small bowel mucosa. Crushing of L-T4 tablets has been shown to cause no reduction in the drug availability and in some cases it may actually enhance absorption. Six patients failed to improve with the weekly L-T4 administration from the group in which patients were given their tablets whole. Nevertheless, the authors raised the possibility that some of these patients may not have swallowed the tablets and that the poor adherence may have continued to be an issue. They did not specifically ask about grapefruit juice or ingestion of soy protein supplements both of which have been shown to affect absorption. The authors recommend that the measurement of serum fT4 concentration 120 min after the ingestion of a weight related dose of crushed L-T4 can be used to show maximal T4 absorption; weekly administration of the same dose of L-T4 and measurement of serum fT4 and TSH concentration thereafter should be used to demonstrate non-adherence with treatment.

After poor adherence is identified, different strategies can be adopted to improve treatment outcomes. A closer understanding of the patients' perspectives of their illness, lifestyle and health beliefs, rather than the perceptions and expectations of health care professionals may link to favorable outcome. Similarly, the improvement of the doctor-patient relationship is expected to improve patients' adherence with treatment. Various interventions have been developed (such as The AIDES method for improving medication adherence) with little evidence on their efficacy but combined cognitive, behavioural and affective interventions are perhaps more effective than isolated interventions. Indeed, whatever intervention is followed it should be tailored to the individual patient's conceptual and practical needs and in selected cases psychology input may be warranted.

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