

NHS Lanarkshire Clinical Biochemistry

Central Hypothyroidism Primary Care Guideline

Adults with low free T4 and normal TSH levels

The finding of a free T4 (fT4) concentration below the reference range, together with a TSH in the reference range, is a common occurrence. It may be due to a number of causes, including non-thyroidal illness, and various medications, but may also reflect underlying pituitary TSH deficiency “central hypothyroidism” (CH), with or without dysfunction of other pituitary hormones. It is not always obvious when to pursue investigation for CH and pituitary dysfunction.

In 2018, the European Thyroid Association (ETA) produced a guideline with 34 recommendations (1).

In 2019, NHSL Biochemistry undertook a follow-up audit of 160 relevant cases identified in October 2018 (2). In this audit, in 95% of cases the initial result was not clearly related to patient outcome, but 9 cases were identified where treatment was changed, including three cases of pituitary macroadenoma, where the patient benefited from targeted treatment.

This short guideline is based on these two papers, and the clinical experience of the authors.

FURTHER REPEAT TEST RECOMMENDED (3-6 months)

- Concurrent interfering drug (see appendix) or significant non-thyroidal illness
- Patient with mild symptoms and free T4 between 9.0 and 10.9 pmol/L

FURTHER INVESTIGATION RECOMMENDED in these circumstances:-

- Moderate symptoms of hypothyroidism, including menstrual disturbance in a premenopausal woman, visual field defect, **AND** fT4 < 9.0 pmol/L, normal TSH (note that concurrent cortisol deficiency may cause weight loss rather than gain)
- Concurrent interfering drug, or significant non-thyroidal illness, and **REPEAT fT4** < 7.5 pmol/L or fT4 more than 1.5 pmol/L lower than first specimen
- Mild symptoms, no interfering drugs or concurrent illness, and **REPEAT fT4** < 9.0 pmol/L with normal TSH

FURTHER INVESTIGATION DETAILS

- FSH is a good way to exclude panhypopituitarism in a post-menopausal woman
- Prolactin in men and women
- 09.00h cortisol, if no exogenous steroids are being taken
- Thyroid peroxidase antibody if TSH is high normal or there is a personal or family history of auto-immune disease

ENDOCRINE REFERRAL

- History of radiotherapy to brain
- Clinical concern with persisting low fT4, regardless of results of further investigations
- FSH < 20 U/L in a post-menopausal woman
- Prolactin > 1000 mU/L (excluding drug causes) in any gender

TREATMENT

- Discussion with an endocrinologist should take place before considering thyroxine treatment. It is especially important to exclude cortisol deficiency before treatment.

REFERENCES

- 1) 2018 ETA Guidelines on the Diagnosis and management of central hypothyroidism DOI: 10.1159/000491388
- 2) NHSL Clinical Biochemistry Audit of adult subjects with low free T4 and normal TSH levels, November 2019

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Central Hypothyroidism Guideline Appendix –

Drug influence on thyroid testing.

Ian Gunn 04/03/20

ANALYTICAL INTERFERENCE IN FREE T4 (FT4) ASSAY

The effect of analytical interference is important because an artefactually low FT4 means that the patient is actually euthyroid. The NHS Lanarkshire uses Roche methodology. This particular company's assays for thyroid tests are known to be strongly affected by the patient taking biotin, especially in high doses. The Roche Free T4 III method sheet (07976836 190, October 2019) states that in vitro tests were performed on 16 commonly used pharmaceuticals, and that no interference with the assay was found. However the pharmaceuticals which were tested are not stated. Information on how specific tests affect specific manufacturers' assays is not often readily available. For example, I published a short report in 1995 about how apopropazone specifically interfered with FT4 analysis in the Ciba Corning analyser we used at the time. The initial finding was serendipitous, the journal impact factor was 1.87, and the finding never reached any relevant review paper.

In summary, it is not always obvious when a medication might be causing analytical interference.

CLINICAL SIGNIFICANCE OF DRUG INDUCED ALTERED THYROID TESTS

There are many ways in which drugs can alter free T4 levels (see below). In many cases it is not clear whether there is genuine secondary hypothyroidism in which the patient might benefit from thyroxine therapy. The 2018 European Thyroid Association Guideline on the Diagnosis and Management of central hypothyroidism (CH) (Eur Thyroid J DOI: 10.1159/000491388) identifies only 2 drugs (rexinoids and mitotane) which cause clinical CH. The paper states - "Several other drugs (e.g. gluco-corticoids, anti-epileptics, somatostatin) have transient or controversial TSH-suppressive effects". Their table 3 lists, in addition, dopamine, cocaine, anti-psychotics and metformin as causing biochemical features that could lead to an erroneous diagnosis of CH.

In summary, the clinical importance of drug-induced biochemical CH lacks good evidence.

MECHANISMS/EXAMPLES OF DRUG INDUCED ALTERATIONS IN THYROID FUNCTION TESTS

The following list is from Surks MI, Sievert R. Drugs and thyroid function; NEJM 1995; 333: 1698-94

Decrease TSH secretion, e.g Dopamine, Glucocorticoids, Octreotide

Decreased thyroid hormone secretion e.g. Lithium, Iodide, Amiodarone, Aminoglutethimide

Increased thyroid hormone secretion e.g. Iodide, Amiodarone

*Increase serum TBG concentration e.g. Estrogens, Tamoxifen, Heroin, Methadone, Mitotane

*Decrease serum TBG concentration e.g. Androgens, Anabolic steroids, glucocorticoids

Displacement from protein-binding sites e.g. Furosemide, Fenclofenac, Mefenamic acid, Salicylates

Increased hepatic metabolism e.g. Phenobarbital, Rifampin, Phenytoin, Carbamazepine

Decreased T4 5-deiodinase activity e.g. Propylthiouracil, Amiodarone, Beta- agonists, Cytokines

*Alterations in TBG may have assay specific effects, for example the Roche assay has a lower free T4 reference range for pregnant women