The Association for Clinical Biochemistry & Laboratory Medicine

Model Answer: Clinical Biochemistry Case 2 – Abnormal thyroid function tests

Patient: 77 y/o male GP patient

Results (July 2021):

- FT4 = 8.24 pmol/L (7.5 – 21.1 pmol/L)
- TSH = 30.42 mIU/L (0.34 – 5.6 mIU/L)

Question 1 – What are the possible causes for this pattern of results?

Non-physiological pattern of TSH: Increased TSH with FT4 within the reference range.

Causes:

- Poor compliance with thyroxine in patients with primary hypothyroidism
- Subclinical hypothyroidism
- Malabsorption of thyroxine
- Drugs
- Assay interference
- Recovery phase of non-thyroidal illness
- TSH resistance

There are multiple drugs which can affect a number of different parts of the TSH/thyroid hormone pathway. In general, TSH is less affected by medication than the thyroid hormones (FT4/FT3), so if this pattern of results were due to a drug effect it is more likely to be related to a medication that is inhibiting the action/efficacy of FT4. There are two main mechanisms of action by which drugs may cause these results.

1. Drugs that cause impaired absorption of thyroxine – patients are advised to take their thyroxine at least four hours apart from these medications:
    a. Cholestyramine
    b. Ferrous sulphate
    c. Calcium carbonate
    d. Proton Pump Inhibitor

2. Drugs that inhibit T4 to T3 conversion:
    a. Amiodarone
    b. Glucocorticoids
    c. Beta blockers

Question 2 – List three possible causes of assay interference in FT4/TSH asays.

- Variant thyroid hormone binding proteins with altered affinity for FT3 eg. albumin in familial dysalbuminaemic hyperthyroxinaemia (FDH)
- Human anti-animal antibodies
- Heterophilic antibodies (or rheumatoid factor)
- Biotin interference in patients on high dose biotin treatment (eg. biotinidase deficiency)
- Macro-TSH
- High concentrations of heparin – causes displacement of free hormones from binding proteins

Question 3 – What steps could you take to investigate the possibility of assay interference?

1. Measurement of the analytes by another method – in order to be effective this requires a method which uses different antibodies (different epitope and different source) and ideally a different assay methodology, eg. one step vs two step, to that in use in the base laboratory.
2. Measurement of TSH at dilution to establish linearity of results – if either TSH or the assay reagents are weakly bound by interfering antibodies, this interaction may be disrupted by dilution and a non-linear dilution series will result. This method must not be used for investigation of potential interference in free hormone measurements.
3. Measurement of TSH pre- and post-addition of PEG or protein G/A – addition of these to samples will macro-TSH or high antibody concentrations will cause precipitation of antibodies from solution.
4. Referral of the sample to a specialist laboratory eg. Addenbrookes 'Funny Thyroid' service – measurement of total T3 and T3, measurement on multiple immunoassay platforms, equilibrium dialysis, and genetics for binding protein variants.

Patient history: Hypothyroid patient on 150 ug/day thyroxine

Previous results (April 2021)

- FT4 = 19.9 pmol/L
- TSH = 0.29 mIU/L

Repeat sample (August 2021)

- TSH = 2.76 mIU/L

Question 4 – Taking into account the information above, what is the most likely cause of the abnormal pattern of TFT results on July's sample? Please explain your answer.

The most likely cause is poor compliance with thyroxine replacement.

The feature which is most suggestive of this as a cause is the variation in TSH results over a relatively short period of time (4 months). This level of variation from suppression to significantly increased

values is non-physiological and is commonly seen in patients with unstable thyroxine replacement, either due to optimisation of therapy in patients starting thyroxine replacement or poor compliance with medication in those who have been on replacement for some time.

Non-thyroidal illness can give variable patterns of thyroid results (often described as 'sick euythroid') and therefore this is a possibility, however the classic pattern is of reduced FT4 with TSH within the reference range. The set of results above are not the typical for this. Discussion with the GP would help rule this out as a possibility.

In the case of subclinical hypothyroidism we would expect to see stable (above the reference range) or increasing levels of TSH with the level of FT4 remaining constant or falling within the reference range.

Abnormalities in thyroid function associated with drug therapy, malabsorption, assay interference or TSH resistance would also be expected to give predictable and stable patterns of results. As long as there has been no change in drug therapy between the three sets of results then the above are unlikely causes in this patient.