On the diagnosis of subclinical hypothyroidism

Subclinical hypothyroidism is usually an asymptomatic condition, diagnosed when there are no specific symptoms or signs of thyroid dysfunction but the patient has an elevated serum thyroid stimulating hormone (TSH) in the face of normal circulating thyroid hormone levels. The diagnosis is therefore biochemical, based almost entirely on a raised TSH concentration. Furthermore, at TSH concentration of 10 mU/L or above, thyroid replacement may be considered.[1,2] The prevalence of this condition in different population studies varied from 1% to 17%, with the highest prevalence in the elderly.[1,3,4]

TSH in serum is measured by immunoassay technology which relies on an 'induced fit' between the antibody and the antigen. In this interaction, the antibody essentially recognises shape; that is, the antigen three-dimensional shapes plus the electron cloud at the site of binding. For this reason, immunoassay technology is inherently less robust than conventional routine biochemical tests and is more prone to produce analytically wrong results if endogenous interfering antibodies are present. Furthermore, this form of interference could occur despite the strictest laboratory control schemes because interference is unique to a particular sample.[5]

The prevalence of analytical interference leading to erroneous immunoassay results is in all probability 0.4%, and would indicate that in every 250 TSH measurements, one could be analytically wrong and clinically misleading.[5,6] However, this is purely an analytical and not a clinical error rate. In fact, to calculate the probability of a correct and diagnostically elevated TSH, the prevalence of subclinical hypothyroidism must be taken into account.[7] For the purpose of this note, the prevalence of subclinical hypothyroidism in both sexes and at all ages will be assumed to be 2%. To compute the probability of an accurately raised and truly diagnostic TSH result, the number of expected 'true cases of subclinical hypothyroidism' in say 1000 patients would be 20 (assuming no false-negatives for simplicity); this figure of 20 would then be divided by the sum of 'true cases plus false elevated TSH cases caused by analytical interference that is, 20 + 4 patients'. The above guesstimate would suggest that the probability of a raised TSH result being accurate, and therefore diagnostically correct, may be 83% (the range which encompasses extremes of quoted prevalence is 71.4–97.7%). So what is the potential impact of analytically inaccurate results on the diagnosis of subclinical hypothyroidism?

Interference from endogenous antibodies may be transient in many patients, caused by viral/bacterial infection, immunisation, blood transfusion, monoclonal therapy, or persistent and/or permanent caused by pets or autoimmune diseases.[5] In transient cases, interference is expected to normally decline as the levels of endogenous interfering immunoglobulin antibodies are reduced. However, because the half-life of immunoglobulins is 1 month, interference may still occur if repeat analysis (to confirm the first TSH result) is requested within weeks and if also elevated, it could lead to a wrong diagnosis. If the patient is subsequently treated and TSH levels showed a decline thereafter, it could be justifiably construed as a response to treatment which may continue for life. It is therefore not inconceivable that some patients may be receiving lifelong unnecessary treatment for a phantom disorder!

What could be done to improve the utility of TSH measurement and avoid the probability of incorrect diagnosis and potentially unnecessary lifelong treatment? Most importantly, the results of thyroid function tests must be interpreted in conjunction with the patient's clinical state. Many patients whose tests show thyroxine levels in the reference range and elevated TSH will have no clear symptoms of thyroid dysfunction. Where there are symptoms consistent with thyroid dysfunction, there is rarely any urgency to treat. It would be prudent to resist any temptation for a therapeutic trial of thyroxine until the trend in TSH is clearly established. Analyses of TSH should be repeated preferably three times at intervals of 3 months. Measurement of thyroid peroxidase by the laboratory may help identify those patients with underlying autoimmune aetiology.[1] It should also be remembered that the relatively rare Addison's disease can present with elevated TSH levels.[8] TSH concentrations may be also raised for several months during recovery from a severe non-thyroidal illness or viral thyroiditis.[1,2] When these conditions have been excluded, consideration should be given to asking the laboratory to investigate the possibility of interference as a cause of persistent and significant elevation in TSH measurement.[6,9,10]

Is it important to identify analytical interference in these patients? The answer is yes for three reasons; firstly interference could affect other unrelated tests performed by the same technology that is, immunoassay.[5,6] Such adverse and wider effects are random[10] and totally unpredictable.[11] Secondly, it may recur again at a later time for example, re-infection. Even mothers could pass her endogenous interfering immunoglobulin antibodies to her newborn and this could produce falsely elevated TSH in the neonatal hypothyroid screening programme.[12] Finally, such misdiagnosis may have financial implications (beneficial to some individuals) because patients on thyroid replacement (like diabetics) are entitled to receive all other prescribed NHS medications free of

charge. Because interference could be potentially a lifelong problem in some cases, it should be documented in patient's clinical notes and/or pathology computer records to help interpreting any future data produced by immunoassays.

In conclusion, the error rate and inaccuracy of TSH measurements essential in the diagnosis of subclinical hypothyroidism is not insignificant when both the disease prevalence and the error rate of analyses (both rise with age) are taken into account. Stricter protocol and repeat TSH analyses over 9 months may be justified or even necessary before initiation of treatment. This would be prudent because apart from the prompt need to treat children and pregnant women, the potential benefits and risks of therapy in adults have been debated for some two decades with a consensus still lacking.[4,13–14]

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