Original articles

Management of the unexpected result: compensated hypothyroidism

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Summary

The combination of elevated serum thyrotropin and normal serum thyroxine is called compensated or subclinical hypothyroidism. This most commonly represents clinically silent autoimmune thyroiditis. Whether this condition warrants treatment or simply observation is still debated. The risk of developing overt hypothyroidism is high in females with elevated thyrotropin above 10 mU/l and/or positive thyroid microsomal antibodies. Males are also at high risk of progression towards overt hypothyroidism, regardless of antibody status or degree of thyrotropin elevation. We advise routine treatment of only those at high risk of developing overt hypothyroidism.

Keywords: hypothyroidism

The term compensated hypothyroidism (CH) is used to describe a specific combination of thyroid function tests, namely a raised serum thyrotropin (TSH) concentration (usually between 3.5 and 20 mU/l) in association with normal serum thyroxine (T₄). Some authorities include absence of symptoms in their definition of compensated hypothyroidism, hence the more commonly used synonym, subclinical hypothyroidism.

The recognised causes of CH are listed in box 1. In day-to-day practice this pattern of thyroid function tests is most frequently apparently idiopathic, having been unveiled during the search for disease in individuals with vague non-specific complaints such as tiredness and lethargy. Overt hypothyroidism may or may not have been a relevant differential diagnosis, but ticking the box for thyroid function tests on the laboratory request form is increasingly practised. Although overt hypothyroidism is not uncommon in the general population (prevalence in UK women 1.4% but < 0.1% in men), about eight cases of CH will be turned up for each case of overt hypothyroidism.¹ It is therefore clear that injudicious use of relatively cheap thyroid function tests may cause problems unless there is a clear idea beforehand about what to do with the result.

Management

It is easy to deal with patients with a raised serum TSH due to inadequate thyroxine replacement in previously diagnosed overt

hypothyroidism. Similarly, no one doubts the validity of thyroxine treatment in individuals with a raised serum TSH concentration on an inexorable course towards overt hypothyroidism, eg, beyond 2 years following surgery or radio-iodine treatment for hyperthyroidism.² Hypothyroidism and CH are well recognised in association with the use of certain drugs (box 2). In these cases, management should be individualised and of course the need to continue the offending treatment must be considered. Common sense suggests that, if there is any suggestion of symptoms or signs potentially attributable to hypothyroidism, the patient should be treated with thyroxine if the offending drug cannot be discontinued or the dose adjusted. After all, the condition is iatrogenic and represents deviation from normal physiology for that individual; TSH secretion is finely tuned with only a 10–20% fall in usual serum thyroxine levels triggering compensation. Occasionally, a raised TSH is seen in elderly individuals recovering from mild non-thyroidal illness, the clue being in the history. It is, however, less clear what to do in the case of apparently idiopathic CH.

Prevalence in iodine-replete elderly women

The term compensated hypothyroidism implies primary failure of the thyroid gland as the initiating pathophysiology. The hypothalamus

Causes of compensated hypothyroidism

- autoimmune thyroiditis
- inadequate thyroxine replacement
- surgery for thyrotoxicosis
- radio-iodine treatment for thyrotoxicosis
- drugs

Box 1

Medication that may cause hypothyroidism

- amiodarone
- iodine
- antithyroid drugs
- lithium
- cytokines

Box 2

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and pituitary gland supposedly compensate by increasing TSH secretion. Most authorities believe that the underlying pathology is indeed autoimmune thyroiditis (ie, either preclinical Hashimoto's disease or atrophic thyroiditis) with slow ongoing destruction of the gland. The evidence for the autoimmune hypothesis is mostly indirect and derived from numerous cross-sectional epidemiology studies from various parts of the world.¹⁻⁶ However, some good supportive evidence was produced with the identification of certain strong risk factors for progression to overt hypothyroidism in the 20 year follow-up of the Whickham survey.⁷ Overall, these studies support the hypothesis of an early immune attack on the thyroid, perhaps due to molecular mimicry involving gut bacterial antigens.⁸ There is an initial thyroid lymphocytic infiltrate which is then followed by the appearance of thyroid autoantibodies, raised TSH and finally overt hypothyroidism.⁹

Autopsy studies¹⁰ in iodine-sufficient areas of the world have shown that thyroid autoimmunity, as evidenced by a lymphocytic thyroid infiltrate, is so common in the general population (45% of Caucasian females and 20% of males > 20 years old) that it could be considered normal. The lymphoid infiltrate is already extensive in teenagers, the extent increasing very little beyond the 20s until about 70 years of age.¹⁰ Thyroid microsomal antibodies are directed against thyroid peroxidase (TPO-Ab), the enzyme responsible for iodination of tyrosine in the synthesis of thyroid hormone. This antibody is a very sensitive indicator of thyroid autoimmunity, being positive in at least 95% of cases of autoimmune hypothyroidism, thus making the measurement of thyroglobulin antibodies superfluous. In keeping with the autopsy studies (and the autoimmune hypothesis), the prevalence of TPO-Ab increases steadily with age (overall ~10% in women >18 years of age¹), being >30% in women over 70 years of age.¹¹

The Whickham survey looked at a random population sample of some 2779 British individuals who were representative of the general population as regards age, sex and social class. These were studied at baseline¹ and again after 20 years of follow-up.⁷ Not only did the prevalence of thyroid antibodies increase with age, but so did the prevalence of raised TSH, which overall was 7.5% in women over 18 years of age and in 2.8% in men of the same age. This is paralleled by the age-specific incidence of overt hypothyroidism which rarely presents before the age of 45 and peaks around the age of 80 years.⁷ The positive relationship between the extent of TSH elevation in CH and the prevalence of TPO-Ab can be taken as further supportive evidence for the autoimmune hypothesis. Britain is relatively iodine-sufficient, but it is well recognised that iodine influences thyroid autoimmunity, iodination programmes being accompanied by an increased incidence of clinical thyroid autoimmune diseases.¹² This was recently illustrated in a Hungarian study of 80-year-olds¹³ and in a comparative study¹⁴ of 68-year-olds in Jutland, Denmark (low iodine intake: about 50 µg/day) and Iceland (high

iodine intake: about 300 µg/day), where the prevalence of a raised TSH above 5 mU/l was 3.4% in women in Denmark but 20.4% in Iceland. As expected, this was about four times the male frequency.

Progression to overt hypothyroidism

There are in fact only two reasons for wishing to detect apparently idiopathic CH. The first would be if symptoms or important signs were shown conclusively to be due to the condition. The other reason, however, would be if overt hypothyroidism were the inevitable outcome. Therefore we must ask how we can identify those at greatest risk of progression.

The very high prevalence and early appearance of thyroid lymphocytic infiltration contrasts with population prevalence of overt hypothyroidism. If the autoimmune hypothesis is true, this must mean that the progression of CH is extremely slow. Alternatively there is no connection between lymphocytic infiltration, CH and overt hypothyroidism. In the Whickham survey,⁷ only 33% of women with CH (negative antibodies initially) developed overt clinical or biochemical hypothyroidism over 20 years. The progression thus appears to be very slow indeed and it is likely that a number of individuals will succumb to unrelated illnesses before ever reaching the stage of overt hypothyroidism.

One group of investigators has even suggested that a subgroup with CH will not progress to overt hypothyroidism and that these can be identified by a normal 24-h ¹³¹I-uptake after either TSH or triiodothyronine (T3) pre-treatment.¹⁵ The hypothesis is that an isolated insult to the thyroid has reduced the synthetic capacity of the thyroid gland which, however, is able to maintain normal thyroid hormone output in the face of raised TSH (a new setpoint), the patient being "euthyroid with a reset thyrostat". It is of course possible that such a group exists, which then presumably does not have autoimmune hypothyroidism and is at insignificant risk of progression to overt disease. It is important to confirm CH with a second test at 3–6 months as mildly elevated TSH levels may return to normal and it is known that TPO-Ab disappear in about 10% of cases.⁷ The role of blocking TSH receptor antibodies in CH has not been studied, but these have been described in 10–20% of cases of autoimmune hypothyroidism.¹⁶

According to the Whickham survey,⁷ the risk of progression to overt hypothyroidism is about five times greater in men than in women and the risk is closely associated with the presence of TPO-Ab and TSH elevation, but not family history or (surprisingly) goitre. The risk of developing overt hypothyroidism increases significantly at levels as low as at 2 mU/l, the 20-year probability for antibody-negative women being 6% if initial TSH is 6 mU/l but rising to 19% if initial TSH is 12 mU/l. It is thought⁹ that 80–90% of women with TSH > 10 mU/l have positive thyroid antibodies and these, according to the Whickham study,

Groups at high risk of progression to overt hypothyroidism

- men
- women with positive TPO-Ab, TSH > 10 mU/l, or those previously treated for Graves' disease with surgery or radioiodine

Box 3

significantly influence the risk of progression to overt hypothyroidism. Thus, the odds ratio for a woman developing overt hypothyroidism was eight if she had either positive antibodies alone (95% confidence interval (CI) 5–15) or raised TSH above 6 mU/l alone (95% CI 3–20). That equates to about 2.1–2.6% annual risk, but the odds rise sharply to 38 (95% CI 22–65) for women with both positive antibodies and raised TSH (4.3% annual risk).

Benefits of thyroid hormone replacement

This is a difficult area if not only for the fact that some authors include absence of symptoms in their definition of CH. However, if we believe the autoimmune hypothesis, ie, that CH represents the earliest stages of thyroid failure, then we should expect to find mild symptoms or at least subtle signs of hypothyroidism if we look closely enough. Obtaining conclusive proof is, however, fraught with difficulties as many of the symptoms associated with hypothyroidism are vague and non-specific. At the outset, it is therefore important to realise that only very large studies are likely to have the power to demonstrate significant associations. Sadly the literature is full of small uncontrolled inconsistent groups which only serve to cloud the issue.

Two placebo-controlled reports have used symptom scores in an attempt to clarify matters and are often cited as evidence for a benefit associated with thyroid hormone replacement in CH. Cooper and colleagues¹⁷ studied 32 individuals in a one-year double-blind randomised placebo-controlled trial. The dose of thyroxine was adjusted to keep TSH $\leq$ 3.5 mU/l in the thyroxine group. Symptoms were assessed using a questionnaire on which the symptom score was not statistically different in the two groups at the outset. At the end of the study, total symptom score was not compared again, but rather the change in symptom score, with the authors reporting no change in the placebo group but slight improvement in the thyroxine group. This difference was reported as significant by the authors ($p < 0.05$). Several markers of end-organ thyroid hormone action were also studied. In short, no differences were found and no correlation with improvement in symptoms was observed. There are several weaknesses in this study. The study was small and not pre-powered and a minority of invitations to participate were taken up. Almost all the subjects had previously been hyperthyroid due to Graves' disease, a population characterised by high prevalence of post-treatment

dissatisfaction, in particular regarding weight gain, irrespective of post-treatment thyroid status.¹⁸ We have already suggested above that this subgroup of CH should be treated regardless of symptoms, as the risk of progression to overt hypothyroidism is very high.

The other placebo-controlled study by Nyström and colleagues¹⁹ employed a double-blind 2×6 month cross-over design. Although the numbers were again small, the subjects were randomly selected from a population study on the basis of thyroid biochemistry only. Twenty out of 22 individuals took up the invitation to participate and all received the same daily dose of thyroxine (150 μ g). Using an arbitrary definition of improvement in three psychometric tests, the authors identified four responders who all correctly identified the treatment period and reported a feeling of improvement whereas only six of 13 non-responders correctly identified the treatment period and five reported a feeling of improvement. Overall, symptoms scores improved significantly during active treatment ($p < 0.01$). No relationship was observed between any biochemical parameters and improvement as defined above and no pre-treatment parameters could be used to identify 'responders'. Unfortunately, we do not know if any of the individuals in the study were rendered subclinically hyperthyroid (suppressed TSH but normal T₄), as it is well-known that patients 'feel better' when taking a dose of T₄ in excess of that required to normalise serum TSH.²⁰

While a number of studies support the above notion that CH may be associated with impaired cognitive function or even depression,^{21–22} these are small, uncontrolled, observational or unblinded, and further studies are clearly needed before a firm conclusion can be reached. The same applies to the myriad of studies on potential markers of peripheral thyroid hormone action. Although it is not surprising that CH has been shown to be associated with mild abnormalities in, for example, skeletal muscle lactate and pyruvate production²³ or systolic time intervals,²⁴ not only the association but also improvement with treatment is controversial and therefore it remains difficult to recommend treatment of patients on the basis of such observations alone.

Classic teaching states that overt hypothyroidism is associated with high total and LDL cholesterol, low HDL cholesterol and high prevalence of ischaemic heart disease. A meta-analysis on the effect of thyroid replacement on lipids in subclinical and overt hypothyroidism was recently published.²⁵ The authors reviewed 148 studies published between 1976 and 1996. The conclusion was that normalisation of TSH (and not suppression) in CH resulted in a reduction of total cholesterol by 0.4 mmol/l (95% CI 0.2–0.6 mmol/l). The effect on HDL cholesterol was inconsistent. While the effect on total cholesterol was independent of the initial cholesterol level (a mild abnormality as expected in the first place), the effect in overt hypothyroidism was not only slightly greater, but dependent on the

initial cholesterol level. Thus, if initial cholesterol was < 8 mmol/l, the reduction with thyroxine replacement was 1.2 mmol/l (95% CI 0.9–1.5 mmol/l), but with initial cholesterol above 8 mmol/l the reduction achieved was 3.4 mmol/l (95% CI 3.0–3.7 mmol/l). The cholesterol reduction achieved in CH is minimal in the era of HMG-CoA reductase inhibitors (statins) and, in the absence of evidence and associated fall in cardiovascular morbidity or mortality, is not an argument for thyroid hormone replacement.

Exercise clinical judgement and do no harm

In summary, the evidence for benefit of thyroid hormone treatment in CH is far from conclusive and we are unable to detect beforehand

those few¹⁹ that potentially might benefit. Also, suppressed TSH is common in individuals treated with thyroxine,²⁶ and subclinical hyperthyroidism is not without morbidity.²⁷ Instituting thyroxine treatment in CH will thus not simplify follow-up. As the progression to overt hypothyroidism is very slow, we believe that only those at high risk of progression ($\geq 5\%$ annually) to overt hypothyroidism should be routinely treated. These are females with mildly elevated TSH and positive TPO-Ab, females with TSH > 10 mU/l (80–90% are antibody positive), and males with elevated TSH regardless of antibody status. In other cases clinical judgement should prevail but follow-up every 2–5 years, at which both TSH and TPO-Ab should be measured, is probably adequate.

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