Upsala J Med Sci 95: 197–211, 1990

Medical Needs in the Evaluation of Thyroid Dysfunction

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ABSTRACT

The clinical examination has low sensitivity and specificity for the diagnosis of thyroid dysfunction. There is still, however, no consensus as regards the cost-effectiveness of biochemical screening for thyroid dysfunction; of possible target groups women post partum might be of particular interest. Current methodological developments center around thyrotropin (TSH), free thyroxine (T4), anti-thyroperoxidase antibodies and indicators of thyroid hormone action, and topics of main concern are the precision at low TSH concentration, the calibration of free T4 assays, and the precision of those assays of free T4 which claim higher accuracy compared with "one-step" methods. Thyroid function indices in non-thyroidal illness continue to confuse assayists. The clinical spectrum of conditions which lead to low serum TSH concentration is insufficiently explored.

NEED FOR LABORATORY INVESTIGATIONS IN THE DIAGNOSIS OF THYROID DISORDERS

Thyroid disorders are common, and laboratory testing for the diagnosis and follow-up of thyroid disease has a central role among hormone assays in the clinical laboratory. In this overview I intend to delineate the medical needs as well as current methodological trends and analytical needs. The presentation is restricted to thyroid follicular-cell dysfunction, thus does not include neoplasia of follicle cells or other cells normally located within the thyroid gland.

Two recent studies from Göteborg corroborate findings made by other investigators as regards the difficulties in the clinical diagnosis. In a study of consecutive patients with atrial

fibrillation during one year Fagerberg et al. (7) showed that up to one-fourth of patients finally classified as euthyroid had signs and/or symptoms considered as characteristic for hyperthyroidism. In a population study (5) Edén et al found approximately equal prevalence of signs and symptoms considered to be characteristic for hypothyroidism in 79-year-old subjects, when women with serum thyrotropin (TSH) concentration >10 mU/L were compared with women with TSH concentration <10 mU/L and with men. In a study in the US of 982 consecutive primary care (healthmaintenance organization) patients with suggestive symptoms of hypothyroidism, 1.7%, only, had clearly elevated TSH concentration (≥9 mU/L, 26).

There are only few prospective clinical studies comparing the diagnostic efficiency of clinical examination (plus history) and of biochemical evaluation of thyroid dysfunction. In a recent study of 2000 consecutive patients visiting a primary care center in Mölnlycke, a predominantly rural community outside Göteborg, 35 patients were suspected to have thyroid dysfunction at examination. None had supportive biochemical evidence. Of patients later found to have biochemical abnormality 19 were finally considered to require treatment for thyroid dysfunction (16 hypothyroid and 3 hyperthyroid cases, 6). Thus, the clinical examination has unacceptably low sensitivity and specificity as a diagnostic precedure for thyroid dysfunction.

SCREENING FOR THYROID DISEASE

There is no general agreement whether screening of adults for thyroid dysfunction would be a cost-effective procedure. The benefits would be not only the detection of asymptomatic individuals with thyroid disease with or without thyroid dysfunction, possibly also with other endocrine disorder(s) including gastric mucosal dysfunction, but also the detection of relatives with thyroid disease.

Biochemical screening for hyperthyroidism is generally considered not to be indicated. However, all patients with heart dysfunction such as atrial fibrillation should be evaluated for hyperthyroidism. There is also the possibility that long-term hyperthyroidism induces alterations of the energy metabolism;

showed in a retrospective study of patients successfully treated for hyperthyroidism in Göteborg there is an increased risk for the development of overweight (Nyström et al, unpublished). One may well ask, therefore, if one should not look for, and treat, hyperthyroidism more actively than is done today.

Arguments in favour of screening for primary hypothyroidism are (a) that it is common among women; (b) that the clinical diagnosis is difficult; (c) that even today some patients die from myxedema; (d) that hypothyroidism develops insidiously and may cause loss of life quality and working capacity for many years; (e) that early detection reduces society's costs for medical care including diagnostic evaluations, for sick leave and for health insurance; and (f) that the treatment is simple, effective and cheap; however, long-standing hypothyroidism may resolve first after 1/2-1 year and treatment may also be fatal if not performed carefully.

Arguments against screening for primary hypothyroidism are (a) that it does require resources; (b) that benefits or efficiency are not well characterized; (c) that the methodology is not settled (screening as well as follow-up tests); (d) that decision limits for serum hormone concentrations (e g of TSH) for treatment are poorly defined; (e) that it requires insight not only by laboratorians byt also by physicians; (f) risks of maltreatment if analytical artefacts are not well understood by the screening laboratory.

The following groups of individuals might be considered for screening: (a) middle-aged women; (b) elderly women and men; (c) women 2 and 6 months post partum; and for case-finding: (a) patients with certain disorders such as pustulosis palmoplantaris, dermatitis herpetiformis, diabetes mellitus (type 1), multiglandular autoimmune endocrine disease (autoimmune gastritis, Addison's disease etc); and (b) patients before, during and after certain drug treatment such as amiodarone, cytokines and lithium. Smoking was recently identified as a risk factor for hypothyroidism in a 12-year study of women (Nyström et al, unpublished).

Postpartum thyroiditis may deserve particular attention. Even if most cases resolve spontaneously there seems to be a high risk of recurrence, also for the development of permanent thyroid

dysfunction (10). Furthermore, this might be the most rewarding group for the study of possible familial occurrence of thyroid dysfunction, as the patients are fairly young and relatives in different generations may be more easily found than when older individuals are screened.

DIAGNOSTIC GOALS FOR THE BIOCHEMICAL THYROID EVALUATION

The biochemical thyroid evaluation should include search for evidence for thyroid dysfunction (in terms of abnormal hormone concentrations) or disease (as witnessed by antithyroperoxidase antibodies or anti-TSH receptor antibodies). If hormone-concentration changes are found this might be a result of

- thyroid disease;
- pituitary or hypothalamic disease;
- carrier protein abnormality;
- functional adaptation [e.g. receptor abnormality (thyroid hormone resistance), adaptation to present nonthyroidal illness (low TSH and low T3 concentrations) or to past nonthyroidal illness (high TSH concentration)];
- acute psychiatric disorder;
- drug effect.

MULTIPLICITY OF FACTORS AFFECTING RESULTS FROM THYROID HORMONE DETERMINATIONS IN NON-THYROIDAL ILLNESS

Non-thyroidal illness (NTI) has been, and still is, a source of confusion in the interpretation of results from thyroid function tests. Summarized below are in vivo factors which may affect the results from thyroid-hormone measurements in patients with NTI:

- hypothalamic-pituitary adaptation to NTI (decreased activity in the acute phase, increased activity in the recovery phase);
- altered hormone metabolism;
- altered cellular uptake;
- altered properties of hormone-binding proteins,
- drugs affecting central regulatory functions (dopamine, corticosteroids), protein binding (salicylates, anticon-

vulsants, furosemide?, iodinated drugs eg amiodarone, fenclofenac) and/or hormone metabolism (nonselective beta-adrenergic blockers, iodinated drugs).

Not only may the extent of pertubation vary between individuals but it may also vary during the course of the disease (8). There may also be factors which affect the in vitro assays; in fact, a series of publications in the early and middle '80s show not only wide discrepanicies in the values for free thyroid hormone concentrations between different methods (see below) but also poor agreement between cullular uptake of hormone and free-hormone estimates by methods considered to be reference methods for free hormone determination. Of considerable interest is the recent report on upgrading of some tissue receptors for 3,5,3'-triiodothyronine (T3,34) further indicating that, in this situation, analysis of serum does not adequately reflect the metabolic effects by thyroid hormones. Thus, the thyrometabolic status in NTI patients cannot easily be defined.

CURRENT TRENDS IN THE EVALUATION OF THYROID DYSFUNCTION BY LABORATORY METHODS

First-line tests and follow-up tests

There is no consensus as regards the optimal thyroid evaluation in clinical practice. Clinical laboratories in general, as opposed to specialized endocrine units, need simple procedures which can cover all common situations whereas the smaller unit may choose an approach suitable for any single patient according to demands from a small number of physicians with special interests. For reasons detailed below it is desirable to use a combination of two tests for the initial evaluation, viz. TSH by a high-detectability assay and free thyroxine (free T4). Depending on the results then obtained the clinical chemist may choose either to proceed with further within-laboratory assessment or just to leave the results for the physician's judgement. Outlier values, such as cases with normal TSH concentration but high free T4 concentration, and cases with markedly high TSH but normal free T4 concentration, should first be analyzed with respect to possible interferents (see below). The overall

procedure may be summarized as follows, and details are commented upon below.

Patients without previous thyroid disease

* Initial assays of serum TSH and free T4. Within-laboratory assessment of outliers.
* Follow-up when TSH concentration is 6-20 mU/L: determine antithyroperoxidase antibodies to establish autoimmune etiology.
* Follow-up for suspected hyperthyroidism: if the free T4 concentration is markedly elevated and that of TSH is low: determine the etiology; if not, determine T3 (free T3):
  - if the T3 (free T3) concentration is markedly high, determine the etiology.
  - if the T3 (free T3) concentration is above the population median but not markedly high: perform a TRH (thyroliberin) stimulation test. If abnormal, determine the etiology.

Follow-up of treatment for hyperthyroidism

* TSH and free T4.

Follow-up of thyroxine treatment

* No assays in clinically "stable" cases (traditional opinion) or TSH determination to optimise dosage (controversial at present).
* If evidence for toxicity, determine T3 (concentration above 3.0 nmol/L indicates autonomous function if TBG concentration is normal).
* If evidence for noncompliance, determine TSH.

Determining the etiology of hyperthyroidism by laboratory procedures:

* Autoimmune etiology (Graves' disease and "Hashitoxicosis"): determine antibodies against thyroperoxidase and antibodies against the TSH receptor.
* Destruction-type thyroiditis such as subacute and silent thyroiditis, part of the post-partum thyroiditis cases: determine the thyroidal radioiodine uptake.

* Multinodular goiter, autonomous adenoma: perform thyroid scintigraphy.
* Secondary to pituitary tumor or to selective pituitary hormone resistance to thyroid hormones (rare): TSH (non-suppressed!), TRH stimulation test, glycopeptide-hormone alpha subunit.

Reference intervals and decision limits

Reference intervals for thyroid hormone concentrations may vary with age (changes seem to be minor, though), sex, type of drug therapy etc. For instance, whereas the upper reference interval for total T3 has been found to be 2.9 nmol/L for women 26-72 years, as defined from a population study (unpublished), 2.9 nmol/L for 79-year-old women and 2.8 nmol/L for 79-year-old men (5) the upper limit for a mixed population of atrial fibrillation patients was 2.5 nmol/L (7). A diagnostic algorithm, therefore, must take these differences into account, and adequate decision limits must be defined. Such limits may be used either to indicate further within-laboratory testing or to establish the diagnosis.

The TRH (thyroliberin) stimulatin test: is it useful?

The TRH stimulation test was proposed to be obsolete after the introduction of "sensitive" TSH assays. However, patients with undetectable TSH by current assays may have well detectable values after TRH, a finding which is evidence against clinically important hyperthyroidism. Current decision limits for TSH rise (0.50-4.0) mU/L) probably are too high (7).

TSH assays with high detectability

These assays, often referred to as "sensitive" TSH assays, by definition have low detection limits and are little affected by serum matrix. The definition of "sensitivity" is by no means unambiguous, however (12, 19, 27, 29); also, it should be noted that the term sensitivity in this context is at variance with IFCC recommendations. A study group of The American Thyroid Association (30) recommends 0.10 mU/L as decision limit for hyperthyroidism. However, most current assays have poor precision in this low range.

These assays were recommended as single first-line test for the evaluation of thyroid dysfunction by several groups. However, immunometric assays may give falsely high values because of cross-linking anti-immunoglobulin antibodies ("heterophilic" antibodies, 21, 33). Such interferents may also cause falsely low values depending on the specificity of the antisera used. Other problems with immunometric assays are the high-dose hook effects. We have encountered one immunometric assay where falsely low values were a result of interference between the SST gel and the bridge used for linking the antibody complex to the solid phase.

Thus, there is a place for TSH determination by classical radioimmunoassay for the evaluation of high values from immunometric assays when there is a suspicion of interferents. Also, the laboratory must establish routines for the further assessment of low values (<0.20 mU/L) as hyperthyroidism may be responsible only for a minor fraction of the low values found in unselected clinical populations as discussed below.

Subclinical hyperthyroidism - a misnomer?

There is no unambiguous definition of "subclinical" hyperthyroidism (9). Undoubtedly there does exist a group of patients, for instance those with multinodular goiter, who tent to develop overt hyperthyroidism over the years. As a group they tend to have lower TSH concentration than normals (2). The problem is that a low TSH concentration often has been taken as the criterion for a state of hyperthyroidism which at present lacks clinical signs and symptoms but will ultimately cause overt hyperthyroidism. First during recent years has it been studied whether this would hold for unselected clinical populations, thus not hte selected population of patients visiting thyroid units.

It was repeatedly shown for hospitalized and very sick patients that TSH might be undetectable in serum, and this has been attributed to NTI and/or to drugs such as corticosteroids and dopamine (28). However, in the Mölnlycke study of primary-care patients, most of whom had minor medical ailments, 68 patients (out of 2000) had TSH <0.20 mU/L; ten, only, had thyroid disease (three were hyperthyroid) (6). In a recent study of 85-year-olds in Göteborg hyperthyroidism was again an infrequent cause of low TSH values (31). The Mölnlycke study disclosed one case of

abnormality of thyroxine-binding globulin with low binder capacity in relation to the concentration by immunoassay. The patient had repeatedly undetectable TSH, before as well as after TRH, as long as she received nonsteroidal antiinflammatory drugs including acetylsalicylic acid. The causes for the majority of low values, however, can only be speculated upon, possibilities being the acute phase of non-thyroidal illness, other thyroidal stimulators than TSH (cf the lower TSH concentration in smokers, 4) and commonly used drugs not indentified so far. Serum free or total T3 concentration might be useful as discriminator between hyperthyroidism and other causes.

Thus, with presently generally available assays hyperthyroidism seems to be an uncommon cause of low TSH values in unselected patient populations, and this finding in an individual with thyroid-hormone concentrations within reference intervals cannot without further qualification be ascribed to "subclinical" hyperthyroidism.

Free thyroxine (free T4)

Clinical chemists face an embarras de richesse as regards methods for the determination of free T4, such as

- calculated from total T4, thyroxine-binding globulin and transthyretin (prealbumin);
- equilibrium dialysis;
- ultrafiltration;
- "free-thyroxine index" from T4 and T3 (or T4) uptake;
- "one-step" procedures e g ligand-analogue procedures;
- "two-step" procedures (immunoextraction and back titration);
- encapsulated antibody - microsphere systems;
- column adsorption method;
- labeled-antibody method.

The subject was recently reviewed by Liewendahl (13) and has been the subject of several recent papers in **Clinical Chemistry** (e g the April 1990 issue). It may suffice here to state that, above all, there is an urgent requirement for a consensus as regards reference method to yield calibrators for other methods. Another major problem concerns the precision; only one-step

methods today seem to be able to satisfy the analytical goals stated by the Fraser group (3). These methods suffer, however, from inaccuracy with samples containing abnormal plasma protein binders such as anti-iodothyronine antibodies and thyroxine-binding albumin, furthermore some of them vary with the albumin concentration of the sample as well as the ratio of nonesterified fatty acids vs. albumin (the in vivo heparin effect, 15). Most other methods may also suffer from interference by the last-mentioned factor, possibly also uncharacterized displacing agents in NTI patients, and the direction of the change varies between methods. For this reason, and for reasons given below, we have regarded the results from free T4 measurements mainly as guidelines to other assays which to a lesser extent suffer from the same interferences (17).

Evaluation of new methods e.g. for the determination of free T4, may reguire the access to large numbers of well characterized patients in order to reveal unexpected interferences (16). As general guideline for the laboratory adopting a new free T4 assay, choose a procedure based on well recognized analytical principles and use reagents of a composition which is disclosed to the customer (to enable understanding possible analytical artefacts); if a one-step procedure is used, establish routines to detect analytical interferences (may also be necessary for total-hormone assays!); if a two-step procedure is used, take the most precise one if the calibration is acceptable.

Anti-thyroperoxidase antibodies

These antibodies were previously referred to as "cytoplasmic" antibodies or "antimicrosomal" antibodies (14). They may be used clinically as indicators of autoimmune thyroid disease, and the diagnostic sensitivity for chronic thyroiditis (Hashimoto) may approach 100% with ligand assays (1, 18), cases of atrophic thyroiditis as well as elderly thyroid patients possibly having a lower prevalence of elevated concentrations. They may be used to assess the significance of moderately elevated TSH concentration, and to indicate risk for thyroid dysfunction with certain drugs (see above), possibly also risk for postpartum thyroiditis. Their concentration may decrease during therapy with L-thyroxine (23). Classical methods involve hemagglutination in

serial dilutions but these methods will undoubtedly be replaced by ligand assays (1, 18, 25), an area of current methodological interest.

Anti-TSH-receptor antibodies

Determination of antibodies against the thyroidal cell receptor for TSH is useful for the examination of pregnant women with suspected Graves' disease and in the evaluation of neonatal hyperthyroidism (20). Follow-up of thyrostatic treatment is of little interest in the Nordic countries as non-pharmacological treatment of hyperthyroidism is preferred, such as that using radioiodine or surgery. We have encountered single diagnostically unclear cases with alternating hyper- and hypothyroidism who were found to have markedly elevated values, and this determination may therefore find a wider application than is common today.

Indicators of thyroid hormone action

The possibility that the circulating concentrations of thyroid hormones might not adequately mirror thyrometabolic status, for instance in cases with altered receptor activity, has stimulated interest in peripheral indicators of thyroidal activity. Currently used indicators are sex-hormone binding globulin, ferritin and osteocalcin, but they are all nonspecific and may have low sensitivity for altered thyroid homeostasis. Determination of aminoterminal procollagen-III peptide (22, 24) or carboxyterminal procollagen-I peptide may be advantageous inter alia because these compounds are not derived from the liver (of value in the assessment of the need for L-thyroxine therapy). Of current interest is the possibility that L-thyroxine substitution treatment may induce increased turnover in bone tissue with increased risk for osteopenia during longterm treatment; possibly, determinations of "intact" parathyroid hormone may be helpful to assess this risk when larger patient groups are evaluated.

FURTHER NEEDS

There is a requirement for better assessment of the thyrometabolic status in cases of selective secondary hypothyroidism, in

some cases of thyroid hormone resistance (particularly the cases which inappropriately received thyroid-destructive therapy), and for thyroxine substitution programs (for the evaluation of cases found by biochemical screening). The determination of basal metabolic rate with improved methods may find a place, possibly also a more systematic use of clinical scores of signs and symptoms as well as of mental and physical capacity (11, 22).

CONCLUSIONS

A priority list of analytical needs in this area of laboratory medicine, in my opinion, would include TSH assays with a high precision at concentrations 0.10 mU/L and lower; consensus as regards reference methods for free T4 determination for calibration purposes; free T4 assays with total CV's not exceeding 5%; and improved methods for the determination of anti-thyroperoxidase antibodies.

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