The scope and impact of thyroid disease

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Aspects of the incidence and demographics of common thyroid disorders in the US (and elsewhere, to a lesser extent) are reviewed. The impact of healthcare reform and the efforts of managed care organizations to impose cost-effective management for the diagnosis and treatment of thyroid disorders are bringing unusual pressures to bear on both clinical laboratories and practicing endocrinologists. I discuss the potential dangers of utilization of suboptimally focused diagnostic approaches and of the inefficiencies in clinical management by primary-care providers, who often lack sufficient expertise, as opposed to endocrinologists. More than dollars are at stake, and the suboptimal management of common thyroid disorders presents several significant risks. Finally, I propose a general blueprint for the ongoing development of a structure for continuing quality improvement of the laboratory and clinical diagnosis, treatment, and long-term follow-up of patients with thyroid disease.

INDEXING TERMS: managed care • epidemiology

As an introduction to this working conference to develop standards of practice for the diagnosis and monitoring of thyroid disorders, I present an overview of aspects of the epidemiology of thyroid disease and of some problems of special impact. Given the extraordinary increasing economic pressures on clinical medicine, it seems appropriate to include in the latter category some comments on the impact of managed care. Managed care approaches emphasize use of primary-care providers as opposed to endocrinologists, and I suggest that, unchecked, this process will result in suboptimally focused diagnostic approaches and inefficiencies in clinical management, with both dollars and quality of care at stake.

DEMOGRAPHICS OF COMMON THYROID DISORDERS

To broadly generalize, the most common disorders of the thyroid that generate laboratory testing include hypothyroidism, hyperthyroidism, thyroid nodules, goiter, cancer, thyroiditis, and pituitary disease causing abnormal thyrotropin (TSH; thyroid-stimulating hormone) secretion1. There are, in addition, certain special situations in normal individuals without thyroid disease in which abnormalities in thyroid function may appear, such as in women in pregnancy and postpartum and in newborn children.

Some of the demographic factors influencing expression of thyroid disease include sex, age, iodine excess or deficiency, x-ray or radiation exposure, factitial disease, and family history. Autoimmune thyroid disorders such as Graves disease or Hashimoto disease are some five- to eightfold more common in women than men. Age is a factor, with Graves disease occurring more commonly in the third to fifth decades of life, whereas Hashimoto disease appears to have one peak presentation in young women as early as puberty and then a major peak in the fifth to eighth decades of life, presenting as hypothyroidism as the thyroid atrophies.

Iodine deficiency is no longer a problem in any portions of the US, but remains a tremendous problem elsewhere: Of the some 800 million people estimated worldwide, 190 million suffer from goiter and 3.2 million are actually cretinoid [1]. The adverse consequences of iodine deficiency are highly significant and include endemic goiter, abnormal thyroid function, frank hypothyroidism, decreased fertility, and increased perinatal and infant mortality rates.

In the US, iodine excess has replaced iodine deficiency as a potential health hazard [2]. In view of experimental data suggesting the iodine induction of autoimmune thyroid disease and thyroiditis, some speculate that the much higher prevalence of Hashimoto disease in the US in contrast to Europe may be related to differences in iodine intake. The mechanism may relate to the fact that highly iodinated thyroglobulin is more immunogenic. Iodine may also induce goiter in susceptible individuals, and will fuel new thyroid hormone synthesis in thyroid glands with underlying autonomous function such as those with hyperfunctioning ("hot") nodules, or in patients with Graves disease. Iodine excess may precipitate hypothyroidism in patients with Graves disease who are euthyroid after thyroidectomy or radioiodine therapy, as well as in euthyroid Hashimoto disease patients. The source of iodine excess in many patients

1 Nonstandard abbreviations: TSH, thyrotropin (thyroid-stimulating hormone); T₄, thyroxine; and T₃, triiodothyronine.
includes kelp tablets sold by organic health food shops; the many iodides or iodates used as preservatives in foodstuffs, water sources, red dyes, and vitamins; and organic contrast dyes used in radiologic procedures such as myelography, lymphangiography, computerized tomography, cholecystography, intravenous pyelography, and coronary angiography.

There are several examples of the impact of radiation exposure on the demographics of thyroid disease. For example, the vogue in the US of treating enlarged tonsils and adenoids with 400-1500 R of external radiation during the period 1940–1965 led to thousands of cases of thyroid neoplasia, both benign and malignant [3]. A more recent example is the nuclear power plant accident in Chernobyl, Belarus, in April 1986. The proportion of all patients in the Chernobyl region [4] with thyroid cancer averaged 0.5% during the decade of 1975 to 1985 before the accident, rose to 4.5% in the first 4 years after the accident, and by the fifth year (1991) had increased to an incredible 16.1%!

DIAGNOSIS OF THYROID DISEASE

This Symposium will be presenting and recommending guidelines for the laboratory diagnosis of thyroid disease, but primarily only in regard to those tests on blood. These will include assays for the quantity of the thyroid hormones (both total and free), thyroxine (T4) and triiodothyronine (T3), TSH, and thyroglobulin. The principal utility of thyroglobulin measurement is as a tumor marker for differentiated thyroid cancer in patients who are essentially athyreotic after having been operated on and ablated with radioiodine. The assays to be discussed later in the Symposium include those still done by RIA and the newer immunochromiluminescent or immunoradiometric assays, which have largely replaced the former. The utility of assays of various methodologies for the antibodies in autoimmune thyroid disease against the thyroglobulin molecule and against the thyroid microsomes or thyroid peroxidase will be perhaps more controversial.

Patients with unexplained high or low concentrations of T4 or T3 may have abnormal hormone binding—excessive or deficient, respectively—and often may be categorized as “euthyroid hyper- or hypothyroxinemia” with the abnormal hormone binding being the result of either genetic alterations in binding proteins, drugs, or illness. Some of these patients may fall under the rubric of the “sick euthyroid syndrome” [5, 6]. Specific RIAs for the binding proteins, thyroxine-binding globulin or thyroxine-binding prealbumin (transthyretin), are rarely needed. Some insight into binding aberrations may be inferred from the resin T3 uptake, but this test may soon be a thing of the past as it provides little useful information on thyroid function otherwise.

Stimulation tests with thyrotropin-releasing hormone (thyroliberin; protirelin) are also rarely performed these days—primarily because of the advent of the highly sensitive third-generation TSH assays that can routinely distinguish between thyrotoxicosis and euthyroidism. Thyroliberin tests may still be of use in problem diagnostic cases with normal T4 and T3 but immeasurable TSH, and in suspected pituitary disease. Performance of the provocative test with exogenous T3 (T3 suppression test) to assess a possibly abnormal thyroid–pituitary axis in Graves disease should no longer be necessary.

Other useful diagnostic tests for thyroid disease that are outside the purview of this Symposium include ultrasound examinations for anatomic abnormalities, radionuclide uptake and scan studies, and fine-needle aspiration cytology.

Data on the frequency of occurrence of Graves disease are varied and probably incomplete [7]. In Great Britain, the frequency has been cited as 25–30 per 10 000 women or as much as 2% of the population, with an incidence of 3 cases per 1000 per year. Figures from the Mayo Clinic in the US suggest an incidence of 3 per 10 000 per year. In population surveys in Great Britain, 3.3 new cases of hypothyroidism were identified per 1000 people, and ~14–19 cases of previously diagnosed hypothyroidism per 1000. Because hypothyroidism increases in frequency with age, the prevalence rates will vary with the age of the population sampled; i.e., the highest rates can be found in geriatric units. Reported prevalence rates will also depend on which tests were used for screening (T4 or TSH), and have ranged from 2% to 15% of elderly populations. Apparent hypothyroidism is particularly common in elderly hospitalized patients, but this frequency may be confounded by transient effects of illness on thyroid-function studies, i.e., the euthyroid sick syndrome.

Perhaps 90% or more of cases of hypothyroidism are due to Hashimoto disease, data on the prevalence of which will also vary with the detection test used. When pathological criteria are used, such as the presence of lymphocytic infiltration at autopsy, the prevalence is as high as 22% of women and 6% of men for a criterion of 10 lymphocytic foci/cm² but drops to 4.5% of women and 1.1% of men when a more strict criterion of 40 foci/cm² is used [8]. A diagnosis of autoimmune lymphocytic thyroiditis can be inferred from positive serologic tests for autoantibodies, but confounding variations in reported antibody titers in the same or similar patients can result from technical differences in assays, differing definitions of significant titers, differences in the populations screened, and the fact that histologic evidence of Hashimoto disease can be present in the absence of seropositivity. In the Whickham survey in Great Britain [9], 3% of the population (5% of the women; 1% of the men) had both positive antibodies and a high TSH, confirming the diagnosis of Hashimoto disease with hypothyroidism; indeed, 60% of individuals with a TSH >6 IU/L and 80% of those with a TSH >10 had positive antibodies.

THYROID DISEASE FROM THE ASPECT OF MANAGED CARE

 Pitfalls in disease management. In addition to our usual concerns about quality, the economic pressures of modern times now call for cost-effective diagnosis and management of thyroid disease. Several pitfalls inherent in the management of patients with thyroid disorders provide the potential for misuse of healthcare resources and unnecessary cost burdens. Most of these potential pitfalls relate to patient management by healthcare providers who are less skilled than endocrinologists: e.g., inappropriate selection of diagnostic tests and procedures; mistaken interpretation of test results (e.g., nonthyroidal illness in sick patients); too frequent monitoring of tests, leading to unnecessary expen-
ditures of dollars; too infrequent monitoring of tests, leading to adverse outcomes; and, in the case of T4 medications, unawareness of altered dose requirements for T4 in pregnancy, old age, and various diseases, as well as unawareness of the many drug interactions with T4.

The less-skilled healthcare provider is more likely to be unaware of appropriate guidelines for testing, which tests to order, which are the most highly qualified laboratories to perform the tests, and the fine points of test result interpretation in regard to not overlooking marginal or "subclinical" disease. Resulting errors can lead to a greater frequency of office or clinic visits, and repeat or unnecessary testing, all at greater cost and leading to waste of healthcare resources.

Risks of mismanagement of hypothyroidism. Most hypothyroid patients can be readily managed with adjustments of their T4 replacement therapy based on periodic measurements of TSH [10]. Monitoring these patients too infrequently, or by the wrong tests, or misinterpreting results and using incorrect dosages of T4 are not unusual practices by unwitting primary-care providers or nonendocrine specialists.

The risks of such mismanagement include inadequate control of the hypothyroidism with either over- or underdosage and may result in infertility, miscarriage, fetal abnormalities, postpartum depression, and in the most severe case myxedema coma. Overdosage with T4 replacement therapy may increase risk of bone mineral loss, osteoporosis, and fracture, as well as increasing cardiac work with resulting rapid heart rates, arrhythmias, and cardiac enlargement [11].

Risks of mismanagement of hyperthyroidism. Hyperthyroidism may be treated with antithyroid drugs, surgical thyroidectomy, or radioiodine ablation. Unskilled management of antithyroid drug therapy can lead to problems with either under- or overdosage, including reactions such as agranulocytosis and resulting life-threatening infections. With inappropriate referral for, or performance of, thyroidectomy, the surgical complications can include hoarseness, vocal cord paralysis, and hypoparathyroidism requiring calcium and vitamin D therapy for life. Without expert management, Graves disease patients may be at greater risk for worsening ophthalmopathy, cardiac arrhythmias, congestive heart failure, osteoporosis, fractures, and even death.

Endocrine specialist or primary-care physician? Various insurance sources have claimed that specialists have a higher cost profile than primary-care providers, particularly because of a greater propensity to order expensive tests. Such statistics overlook the fact that specialists treat cases of more complexity and higher acuity, which demand greater degrees of evaluation and management. The results of the recent Diabetes Mellitus Control and Complications Trials, which provided intensive management by specialists, clearly demonstrated the actual and potential cost savings [12]. With the billions of dollars spent on care of hospitalized diabetics with nephropathy, retinopathy, infections, or ketoacidosis [13], this study points the way to major savings with close control of the disease, control that requires expert management by specialists. Indeed, in one U.S. Health-care study, only 3% of the HMO members had diabetes but these accounted for use of 15% of the acute bed days and made up 9% of all admissions. In the U.S. Healthcare HMO gatekeeper system, 20% of the diabetic patients never saw a physician, 40% did not have a semiannual hemoglobin A1c determination, and 50% were never checked for renal disease. In contrast, diabetics seen by an endocrinologist have 73% fewer hospitalizations, 78% shorter hospital stays, and an average savings of $193 per patient per month [14]. Another recent study demonstrated a differential reduction in hospital length of stay for diabetics from 8.2 ± 6.2 days to 3.6 ± 1.7 days between a no-consultation and an endocrine-consultation management approach, respectively [15].

For the delivery of high-quality, cost-effective care, it is imperative that the specialist have a significant role in any system of reformed healthcare delivery in the future. The endocrine or thyroid specialist will be able to reduce nonindicated, costly, and invasive procedures and develop outcomes analyses to assess efficacy. The specialist is the physician best trained to keep costs down because of his or her greater awareness of issues, data-driven use of tests, most appropriate use of therapies, and avoidance of adverse outcomes.

Future practices of cost-effective diagnosis and management of thyroid disease will perform need to incorporate guidelines for diagnosis and guidelines for treatment, and must permit the specialist time to educate primary-care providers about the subtleties of subclinical disease, premalignant disease, and conditions that entail referral to an endocrinologist. The healthcare industry must also remember that the endocrinologist, as a specialist in internal medicine, is fully qualified to be a primary-care provider, and reimbursement policies that preclude primary care by endocrinologists are counterproductive to saving costs.

These comments were designed to provide an overview of thyroid disease as a background for discussions on development of guidelines for choices of laboratory tests for diagnosis and monitoring of patients with thyroid disease. Such discussions cannot occur in a vacuum, however, and given the forces of managed healthcare that are influencing disease management, clinicians and laboratory directors alike must maintain vigilance and awareness of the potential for inappropriate use of resources under managed care and the consequences on both cost and quality of healthcare.

References


