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Clinical Algorithm

Suspected thyrotoxicosis

A S M KHIR

A useful approach when dealing with a patient with suspected thyrotoxicosis is to ask the two questions, "Is the patient thyrotoxic?" and, "What is the underlying condition?" The answers can, in most cases, be easily found by clinical examination and a few simple investigations. The algorithm illustrates the steps towards establishing a functional and aetiological diagnosis and gives brief notes on the appropriate treatment of the underlying disorder.

Presentation

The clinical manifestations of excess circulating thyroid hormones are abundant. The box shows the main clinical features of thyrotoxicosis. It is common for dysfunction of one or two systems—for example, the cardiovascular or the neuropsychiatric—to dominate the presentation, but careful interview and examination will show most of the elements of the syndrome.

Unusual modes of presentation deserve special mention. This is especially likely in the elderly, in whom cardiovascular features predominate over the aforementioned classic symptoms and signs or, indeed, may occur alone. Hyperthyroidism should be suspected in elderly patients with refractory cardiac failure, especially if atrial fibrillation and a high cardiac output state are present. Also suggestive is failure of cardiac glycosides in usual dosage to control rapid heart rate. Older patients may also present with a retarded rather than the usual hyperactive physical and mental state; this is called apathetic thyrotoxicosis. Diagnosis may be less obvious if myopathy is the dominant presenting feature mimicking neuromuscular disease (such as carcinomatous myopathy) or if diarrhoea and weight loss seem to point to a gastrointestinal malignancy.

Main clinical features of thyrotoxicosis

SYMPTOMS

nervousness—irritability, emotional lability—
increased sweating,
intolerance of heat, palpitations,
undue fatigability ± muscular weakness,
weight loss usually with increased appetite,
dyspnoea or exertion ± ankle swelling,
eye complaints—prominence, "grittiness" (Graves)—
diarrhoea, thirst, menstrual irregularities,
dermatological—hair loss, pruritus

SIGNS

tachycardia, hyperkinesia, goitre ± bruit,
warm moist skin, tremor
eye signs—lid retraction, lid lag, and signs of
Graves' ophthalmopathy—
atrial fibrillation, myopathy,
signs of heart failure (high output)

Occasionally a patient with hyperthyroidism may present with thirst, polyuria, weight loss, and glycosuria; diabetes mellitus and thyroid overactivity may, however, coexist.

Although thyrotoxicosis can be readily confirmed by carrying out biochemical tests as outlined below, differential diagnosis may pose problems in the following clinical circumstances:

(1) Euthyroid goitre or ophthalmic Graves' disease, especially if associated with other causes for weight loss or tachycardia.

(2) Anxiety neurosis. The difficulty here may be compounded as this is often seen in young women who may be taking the combined oestrogen and progestogen contraceptive pill, which can affect the results of certain in vitro thyroid function tests.

(3) Occult neoplasm or infections such as tuberculosis.

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Suspected thyrotoxicosis 1

Suspected thyrotoxicosis 2**COMMON CAUSES**
(>95% of cases)

Diffuse toxic goitre (Graves' disease)
—may be associated with incidental non-functional nodules
Toxic nodular (solitary) goitre
—"toxic adenoma"
Toxic multinodular goitre

RARER CAUSES

Subacute (de Quervain's) thyroiditis
Silent thyroiditis
Thyrotoxicosis factitia/medicamentosa
Struma ovarii
Iodine induced (Jod-Basedow's) thyrotoxicosis
Choriocarcinoma, embryonal tumour of testis, molar pregnancy
TSH dependent hyperthyroidism ($\pm$ pituitary tumour)
Functioning thyroid carcinoma

(4) Chronic pulmonary disease, especially if the patient is taking bronchodilator drugs.

Even if thyrotoxicosis is clinically obvious it is advisable to carry out confirmatory thyroid function tests.

Thyroid function tests

The diagnosis of thyrotoxicosis is best established by showing high circulating concentrations of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). In centres where assays of free thyroxine and triiodothyronine are available raised thyroid hormone concentrations will confirm the diagnosis of thyrotoxicosis biochemically. On the other hand, serum total thyroxine and triiodothyronine measurements are certainly widely available and are adequate for confirming thyrotoxicosis unless factors are present that alter the binding capacity of thyroxine binding globulin. Thyroxine binding globulin concentration may be increased by drugs such as oestrogen or by pregnancy or be congenitally high (or low). They may be decreased by drugs such as androgens and corticosteroids or by diseases such as severe hepatic insufficiency, the nephrotic syndrome, malnutrition, or severe stress. The binding capacity of thyroxine binding globulin may also be reduced by drugs that compete for binding—for example, salicylate, sulphonylureas, phenytoin. An increase in thyroxine binding globulin can therefore lead to a falsely raised serum total thyroxine concentration (total triiodothyronine result less affected) in a euthyroid person, whereas reduced thyroxine binding globulin capacity may lead to the finding of normal thyroxine concentration in a thyrotoxic patient. This problem can be resolved by measuring free thyroxine and free triiodothyronine concentrations directly, but in centres where assays of free hormone concentrations are not available an indirect assessment of free thyroxine concentration is usually made. This is done by measuring the unoccupied thyroxine binding sites on thyroxine binding globulin by the triiodothyronine resin uptake test and deriving an index of free thyroxine concentration—for example, free thyroxine index or effective thyroxine ratio. In recent years direct assays of thyroxine binding globulin concentration have become available. Alteration in thyroxine binding globulin concentrations can be documented directly and total thyroxine to thyroxine binding globulin ratio be used as an indication of free thyroxine concentration.

In most patients with thyrotoxicosis both thyroxine and triiodothyronine are raised. So called "triiodothyronine toxicosis" deserves special mention. In this syndrome the triiodothyronine concentration is excessive without thyroxine being raised. This should be considered in clinically thyrotoxic patients with a normal serum thyroxine concentration. It can be associated with any cause of thyrotoxicosis but is more likely to be associated with toxic nodular goitre. The algorithm shows other circumstances in which the two thyroid hormones are discrepant. As these are rare they do not warrant further mention.

Tests of thyroidal uptake of radioactive iodine with or without triiodothyronine suppression are rarely necessary in confirming thyrotoxicosis. Triiodothyronine suppression tests may in fact be risky in elderly patients with heart disease, but thyroidal radioactive iodine uptake tests may be useful in borderline cases or in diagnosing conditions causing thyrotoxicosis with low thyroid uptake—for example, subacute or "silent" thyroiditis, struma ovarii, or thyrotoxicosis factitia.

Measurement of basal serum thyroid stimulating hormone concentration is not a useful test in diagnosing thyrotoxicosis. Thyroid stimulating hormone is undetectable in thyrotoxic patients (and also in some normal people owing to insensitivity of the assay). A high concentration of thyroid stimulating hormone in a hyperthyroid patient indicates pituitary thyroid stimulating hormone dependent hyperthyroidism, which is a rare disorder, but routine measurement of thyroid stimulating hormone concentration in every thyrotoxic patient cannot be justified. A thyrotrophin releasing hormone stimulation test is unnecessary in straightforward cases of thyrotoxicosis but is useful in borderline or doubtful cases. It is certainly an excellent test to exclude thyrotoxi-

cosis if a normal rise in thyroid stimulating hormone concentration is shown. One difficulty with the thyrotrophin releasing hormone stimulation test is that the thyroid stimulating hormone response can be attenuated in cases of autonomous thyroid nodule without excessive production of thyroid hormones, in patients with ophthalmic Graves' disease, and in some patients with Graves' disease who are in clinical remission. A flat thyrotrophin releasing hormone stimulation test result can also be caused by non-thyroid conditions—for example, treatment with corticosteroid or dopaminergic drugs or endogenous depression.

A new immunoradiometric assay (IRMA) for thyroid stimulating hormone is now becoming available, which is highly sensitive and able to detect concentrations as low as 0.05 mU/l. It can discriminate between basal concentrations in euthyroid and hyperthyroid patients and may obviate the need for thyrotrophin releasing hormone stimulation tests.

Aetiological diagnosis

As the algorithm shows, biochemical investigations of function are coupled with clinical and laboratory tests to determine the cause of thyrotoxicosis. It is rarely necessary to resort to many tests to diagnose the three common causes of hyperthyroidism—namely, Graves' disease, toxic adenoma, and toxic multinodular goitre.

Clinical assessment of goitre may be supplemented by isotopic thyroid scanning, which may: confirm diffuse active goitre of Graves' disease, and may incidentally show the presence of "cold" nodules in which case toxic multinodular goitre may be wrongly clinically diagnosed; confirm clinical diagnosis of solitary toxic adenoma or multiple "hot" nodules; or show the presence of multiple nodules in a gland in which only a single nodule is palpable.

The diagnosis of Graves' disease is further strengthened by a positive family history of thyroid disorders or other related autoimmune diseases, as well as the presence of exophthalmos and, less commonly, pretibial myxoedema. It is worth checking antithyroid antibodies; 80% of patients with Graves' disease have positive antimicrosomal antibodies and 30% antithyroglobulin antibodies. The measurement of thyroid stimulating immunoglobulins is not widely available and is not at present of practical diagnostic importance.

The classic picture of de Quervain's thyroiditis is not difficult to diagnose but, as the algorithm shows, there may be some cases where the aetiology is not so clear. In these patients thyroid scanning, thyroidal radioactive iodine uptake testing, thyroid stimulating hormone with or without thyrotrophin releasing hormone stimulation testing, and skull x ray examination will need to be done to diagnose the rarer causes of thyrotoxicosis. An important group are those with reduced thyroidal uptake of radioactive iodine. Silent thyroiditis (commoner in USA) causes transient thyrotoxicosis, and correct diagnosis will prevent unnecessary ablative treatment. Struma ovarii can be diagnosed by scanning the pelvis. Thyrotoxicosis factitia must be suspected in those, such as paramedical staff, with access to thyroid hormone tablets.

Hyperthyroidism caused by raised chorionic gonadotrophins is uncommon. Molar pregnancy should, however, be considered in young women with thyrotoxicosis and amenorrhoea, and if the diagnosis is established the uterus must be evacuated.

Thyroid stimulating hormone dependent hyperthyroidism is also very rare. The patient may have other features of a pituitary tumour and may be acromegalic. Some cases are non-tumorous and may be caused by microadenoma or selective pituitary resistance to thyroxine. These cases need further investigation (such as measurement of α subunits, thyrotrophin releasing hormone stimulation tests, neuroradiology), but detailed consideration of such rare conditions is outside the scope of this article.

Treatment

The choice lies between medical treatment, surgery, and ablative treatment with iodine-131.

MEDICAL TREATMENT

This can be with β adrenoceptor blocking drugs and antithyroid drugs such as carbimazole, methimazole, propylthiouracil. It would be appropriate in Graves' disease, in which remission occurs in about half the cases, but it is not recommended in toxic adenoma, in which thyrotoxicosis invariably recurs once the treatment has been stopped.

The use of β blockers is mainly for symptomatic relief. An advantage of this treatment is that it does not interfere with thyroid function tests. It is useful in those conditions in which thyrotoxicosis is transient—for example, silent thyroiditis, for which antithyroid drugs and ablative treatment would be inappropriate. Drugs like propranolol are used as adjuncts to antithyroid drugs or iodine-131 treatment. Its use as sole preparation in patients undergoing thyroid surgery is not widely accepted and may be risky outside centres where this is done routinely and the necessary precautions are taken.

Antithyroid drugs are given for 12-18 months. This form of treatment may be preferred in children and young adults, especially if the goitre is not large and the disease is not severe. Relapse occurs in over 50% of cases after a full course. Patients should be told this and be informed of possible adverse effects. In the event of relapse further courses of antithyroid drugs, surgery, or treatment with iodine-131 may be chosen, though ablative treatments are prefer-

able in recurrent cases. As adverse effects tend to occur within the first two months of treatment indefinite use of antithyroid drugs is sometimes justified in older patients.

SURGERY

This may be preferable in those patients with Graves' disease who have large goitres or in patients who have relapsed after previous antithyroid drug treatment. Surgery is the treatment of choice in young patients with toxic nodular goitre. Surgical treatment should be chosen in patients with evidence of compression of neighbouring structures by their goitre. Adequate preparation before surgery with antithyroid drugs, iodine, or β blockers must be ensured.

RADIOACTIVE IODINE (IODINE-131) TREATMENT

This is chosen in the older patients with Graves' or toxic nodular goitre, especially if thyrotoxicosis has recurred after surgical or medical treatment. Owing to a theoretical risk of genetic damage, its use in women is usually limited to those beyond childbearing age (certainly in the UK). In toxic nodular goitre large doses are necessary, but the usual complication of this treatment, hypothyroidism, is less likely in this group.

From the PHLS

Virus meningitis and encephalitis 1978-82

The commoner viral infections of the nervous system encountered in Britain, with the exception of herpes simplex encephalitis, tend to be benign, but they may cause substantial morbidity. During

TABLE I—Virus meningitis 1978-82: annual reports to Communicable Disease Surveillance Centre

	1978	1979	1980	1981	1982	Total
Adenovirus	46	32	52	35	39	204
Coxsackie A	25	56	30	33	71	215
Coxsackie B	136	69	74	171	51	501
Echovirus	680	308	778	386	298	2450
Herpes simplex	103	98	107	109	95	512
Varicella zoster	43	25	39	30	32	169
Influenza A	13	8	15	6	8	50
Influenza B	1	23	—	3	30	57
Measles	44	32	46	30	23	175
Mumps	479	260	182	240	108	1269
Mycoplasma pneumoniae	31	39	18	20	26	134
Other viruses	65	79	71	54	51	320
Total	1666	1029	1412	1117	832	6056

TABLE II—Age of patients reported: 1978-82

Age	<1 month	1-11 months	1-4 years	5-9 years	10-14 years	15-44 years	45-64 years	≥65 years	Not stated	Total
Adenovirus	1	36	61	39	19	37	1	1	9	204
Coxsackie A	4	13	18	48	21	96	4	1	10	215
Coxsackie B	35	70	81	72	32	171	14	2	24	501
Echovirus	60	208	203	444	399	978	32	6	120	2450
Herpes simplex	12	22	45	40	29	170	124	48	22	512
Varicella zoster	—	2	6	21	9	69	18	41	3	169
Influenza A	—	—	7	11	8	17	1	3	3	50
Influenza B	—	—	1	8	16	22	4	3	3	57
Measles	—	3	37	46	30	52	4	1	2	175
Mumps	—	20	348	506	86	242	18	5	44	1269
Mycoplasma pneumoniae	—	—	17	18	24	56	7	10	2	134
Other viruses	5	80	73	43	23	61	14	7	14	320
Total	117	454	897	1296	696	1971	241	128	256	6056

the five years 1978-82 laboratories reported 6056 cases of virus associated meningitis and encephalitis. Many patients with meningitis are probably not investigated virologically, and of those who are, not all would have been proved to have evidence of viral infection. Moreover, laboratory evidence of viral infection does not necessarily imply a causal association, and certainly in many of the 6056 cases reported no such association was present. Nevertheless, some trends are apparent from the data available.

The echoviruses, Coxsackie viruses, and mumps virus are most likely to be causally associated with virus meningitis or encephalitis. Of the 6056 cases reported, 2450 (40.5%) were associated with the echoviruses, 1269 (21.0%) with mumps, 501 (8.3%) with Coxsackie B, and 215 (3.6%) with Coxsackie A (table I). The relative proportions that each of these virus groups contributes vary each year—the echoviruses usually tend to be most important, and were especially so in 1978 and 1980: in 1980 they accounted for more than half the cases (55.1%). The most commonly reported echovirus in 1978 was type 11 and in 1980 type 30. Mumps virus accounted for a high proportion (28.8%) in 1978 and