Three clinical problems*

Weird thyroid function tests, difficult gout, and dementia

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Speakers at the course were given vignettes describing one or more clinical scenarios on which to base their talks, selected because they represent common but challenging problems likely to be encountered by any physician practising in general internal medicine. Three of the subjects covered – weird thyroid function tests, difficult gout, and dementia – are presented here.

Weird thyroid function tests

A 74-year-old man admitted acutely with a diagnosis of congestive cardiac failure secondary to ischaemic heart disease complains of having 'no energy at all'. Thyroid function tests are performed: TSH 7 mU/l (reference range, 0.5–5), fT4 12 pmol/l (9–25). What should be done?

Thyroid function should not be tested routinely in the acute medical setting unless there is a specific clinical indication, eg atrial fibrillation. Of patients admitted on take, 15% will have isolated alteration of thyroid stimulating hormone (TSH), usually either mild suppression (0.1–0.5 mU/l) or modest elevation (5–20 mU/l), but 2-3% will have marked suppression (<0.1 mU/l) or elevation (>20 mU/l). These changes can occur as a response to non-thyroidal illness or medication (eg steroids or dopamine) and should not be presumed to imply significant thyroid pathology, although an eventual diagnosis of thyroid disease *is* more likely when TSH is either undetectably low or >20 mU/l. In virtually all cases the sensible clinician will do nothing when confronted with abnormal thyroid function tests in the acute setting other than arranging for repeat assay in two months, together with thyroid autoantibodies if the serum TSH is above the reference range.

If this man's results remained the same two months later, then mild thyroid failure would be diagnosed, defined as elevated serum TSH >5 mU/l with normal fT4 being most often caused by chronic autoimmune thyroiditis in iodine-replete communities. This condition affects 8% of women and 3% of men and is of doubtful clinical significance, but some of these patients will progress to overt hypothyroidism. The risk of progression can be stratified in relation to thyroid autoantibodies – if positive, then progression is much more likely, especially in men. An appropriate treatment strategy for mild thyroid failure is:

- fT4 normal and TSH >10 mU/l – treat
- TSH 5–10 mU/l and thyroid antibody positive – repeat annually and commence thyroxine once TSH >10 mU/l
- TSH 5–10 mU/l and antibody negative – check every 3–5 years.

A 38-year-old woman is admitted with pleuritic chest pain and dyspnoea. She is in atrial fibrillation with a heart rate of 120/min. The diagnosis of pulmonary embolism is confirmed by imaging and she is anticoagulated. Thyroid function tests are reported as: TSH 1 mU/l and, fT4 40 pmol/l. What should be done?

This woman has an elevated fT4 in the context of a normal TSH, which would be inappropriate if she had primary hyperthyroidism. The list of potential causes is:

- interfering antibodies to thyroid hormones
- intermittent thyroxine therapy or overdose
- resistance to thyroid hormone
- TSH-secreting pituitary tumour
- amiodarone
- acute psychiatric illness.

Interference in the assay of fT4 by antithyroid antibodies is very likely. This should be suspected particularly if fT3 and fT4 assays give significantly disparate results, and the presence of such antibodies is more common if there is evidence of thyroid autoimmunity. Once interference is confirmed, then thyroid function can be monitored by TSH levels alone: this woman did not have thyroid disease.

A 68-year-old woman with ischaemic heart disease is commenced on amiodarone for paroxysmal atrial fibrillation. A year later her thyroid function is: TSH 22 mU/l and fT4 10 pmol/l. What should be done?

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Amiodarone produces both hypo- and hyper-thyroidism. Its main effect is to inhibit the de-iodination of T4 and thereby reduce T3 production. Thyroid function and antithyroid antibodies should be checked before the start of treatment and every six months thereafter: patients who have antithyroid antibodies are at greater risk of developing significant thyroid disease and a low threshold of suspicion should be maintained for re-testing.

Amiodarone-induced hypothyroidism (as in this case) is primarily a biochemical diagnosis. It rarely produces symptoms. Ideally, amiodarone would be discontinued, but this is rarely achievable and in this patient thyroxine should be given with the aim of normalising TSH. If TSH is 5–20 mU/l and fT4 is normal, the presence of thyroid autoantibodies should prompt treatment: if negative for thyroid autoantibodies, watch and repeat the assay in six months.

An 83-year-old man with a past history of multinodular goitre begins treatment with amiodarone for recurrent ventricular tachycardia. Six months later he presents with weight loss of 5 kg and dysphagia. His thyroid function tests reveal TSH <0.01 mU/l, fT4 40 pmol/l and fT3 6 pmol/l (3–7 pmol/l). What should be done?

Amiodarone-induced hyperthyroidism is less common than hypothyroidism (2% *vs* 13%) and bears little relation to the dose of drug or duration of treatment. The long half-life of amiodarone means that the condition can occur months after discontinuation of the drug, emphasising the need for continued monitoring of patients for up to 12 months after drug withdrawal. Presentation is not straightforward and should be considered in cases of new or recurrent atrial arrhythmias, heart failure and weight loss. Thyroid function tests in this case show that TSH is undetectable with high fT4. The level of fT3 should be high in thyrotoxicosis induced by amiodarone but can be within the reference range (as in this case). Low/normal levels of fT3 are to be expected in patients receiving long-term treatment with amiodarone.

Amiodarone-induced hyperthyroidism is divided into two groups:

- *Type I* – Previous thyroid abnormality, increased hormone synthesis, normal/elevated ^{131}I uptake.
- *Type II* – Previously normal thyroid, increased hormone release, low/absent ^{131}I uptake.

If possible, amiodarone should be stopped. Type I rarely responds: high-dose carbimazole and potassium perchlorate (blocks iodide uptake) are usually needed, sometimes progressing to thyroidectomy/radioiodine. Withdrawal alone may be adequate in Type II, but steroids can be a useful adjunct. Clinically, the distinction between the two types is often blurred, with carbimazole and prednisolone often instituted as a therapeutic trial. The situation is more difficult if amiodarone cannot be stopped: amiodarone-induced thyrotoxicosis is often refractory to standard treatments.

Difficult gout

A 55-year-old man with moderate chronic renal impairment (cause unknown, creatinine 177 µmol/l) has been troubled with gout for many years. He has a history of peptic ulceration associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) and does not like colchicine because of diarrhoea and vomiting 'after only a few tablets' on a previous occasion. He cannot take allopurinol because it caused an extensive skin rash. How should acute gout be managed and attacks be prevented?

Gout results from the formation of urate crystals where conditions of solute excess combine with favourable local conditions – temperature, pressure, nucleating and growth promoting factors, and the absence of tissue inhibitory factors. Crystals are deposited and may then shed into the joint space to trigger inflammatory attacks.

Primary urate gout occurs in 1% of men aged 30–50 years, the usual reason being a constitutional reduction in renal excretion of urate. Risk factors include obesity, high intake of beer, meat and seafood, hypertension and a positive family history. The syndrome typically presents with acute attacks of joint pain of very rapid onset (6–18 h), usually affecting the feet, most typically the first metatarsophalangeal joint. Untreated, the condition may slowly progress over several decades to chronic tophaceous gout with a wider distribution (feet/hands/knees/elbows), significant joint damage and chronic symptoms, plus continued acute episodes.

Secondary gout, as is likely in this case, occurs in older patients, with an equal distribution both in terms of sex and involvement of the hands and feet. Tophi may be as much of a problem as acute attacks, and the pathology often evolves faster than in chronic, primary gout, with a more atypical distribution (eg there may be involvement of the axial skeleton). Osteoarthritis is an additional risk factor. Causes include:

- chronic renal impairment
- chronic diuretic use (>2 years)
- calcineurin inhibitor use (ciclosporin and tacrolimus).

Particular problems with secondary gout are limited uricosuric options (because of an increased risk of renal urate deposition and worsening of chronic renal impairment), increased likelihood of toxicity with NSAIDs or colchicine, greater allopurinol sensitivity, and frequent interactions with pre-existing medication (eg myelosuppression with allopurinol and azathioprine, gastrointestinal bleeding with allopurinol/NSAIDs and warfarin).

So, how should this patient be treated? First, is the diagnosis gout? Always re-consider in 'the difficult case': gout can be mimicked by other crystals (eg 'pseudogout' – calcium pyrophosphate crystals, calcific periarthritis – apatite, oxalate crystals) and palindromic rheumatism, to name a few, and take care to exclude co-existent sepsis if the clinical context makes this possible. If the diagnosis is 'difficult gout', then treatment requires rapid relief of acute episodes and management of the chronic metabolic derangement, remembering that this is one of the few curable arthropathies.

Acute attacks

Joint aspiration with intra-articular steroid injection is rarely used by non-rheumatologists but is the most effective means of treatment for acute attacks involving a large joint. It provides very fast relief through rapid reduction in intra-articular pressure and produces no systemic side-effects. Aspirated samples allow diagnostic confirmation and the exclusion of infection. Steroids *should* be injected at the same time as aspiration: if there is a concern regarding infection, antibiotics can be commenced after microbiological confirmation (within 48 h of the procedure) and intra-articular steroid may actually reduce some of the damage wrought by sepsis.

Steroids can be used as systemic therapy, but relatively high doses are required, eg prednisolone 40–50 mg once daily for one week, rapidly reducing over a subsequent week, or depot methylprednisolone 80–120 mg IM once.

This patient has suffered adverse effects with colchicine in the past, but it may be that this was at the dosage suggested by the *British National Formulary* (1 mg stat with 0.5 mg thereafter every 2–3 h until symptoms abate or side-effects become intolerable; the old adage that you 'run before you walk'). A starting dose of 0.5 mg twice daily provides symptom control in most cases without significant co-morbidity. A *short* course of an NSAID (with additional gastric protection) can be considered if the need to control symptoms outweighs the risk of deterioration in renal function.

Do not forget that local application of ice will help while systemic treatments have their effect, and also that if patients are taking allopurinol when an acute attack develops, this should be continued at the same dosage while acute treatments are given.

Long-term treatment

The principles of long-term treatment are to educate the patient, address modifiable risk factors, institute life-long hypouricaemic medication and control symptoms. Risk-factor modification may include the following:

- Reduce weight and blood pressure. If antihypertensives are needed, amlodipine is hypouricaemic and losartan uricosuric.
- Reduce beer consumption (rich in guanosine) – wine is a better alternative.
- Stop diuretics if possible – if not, try changing to bumetanide which is less hyperuricaemic.
- Reduce the dose of calcineurin inhibitors or change to other immunosuppressives, eg sirolimus, mycophenolate mofetil.

Life-long hypouricaemic treatment is clearly required in a case such as that described. In patients with renal impairment (or the elderly, or those taking diuretics), allopurinol should be started at a low dose of 100 mg once daily and titrated up cautiously. Low-dose colchicine or NSAIDs can be used to cover the commencement of allopurinol, but it is probably easier to start at a low dose and gradually increase. 'Cure' can be achieved when the serum uric acid level is maintained at *less than* 250–350 μmol/l. The allopurinol hypersensitivity reaction (severe skin rash) in this patient is a contraindication to further treatment, but desensitisation can be effective in 50% of cases. Oxipurinol (the active metabolite of allopurinol) can be used, but there is 50% cross-reactivity. Tisopurine (100–400 mg daily) is an alternative, but requires special ordering on a named-patient basis. Other agents are still in the developmental stage.

Renal impairment is a contraindication to most uricosuric agents (eg probenecid, sulphinpyrazone), but benzbromarone (50-200 mg once daily) is safe in mild-to-moderate chronic renal impairment, although it is only available on a named-patient basis. Therapies for the future include exogenous uricase, an enzyme which metabolises uric acid that is absent in humans. A recombinant form – Rasburicase – is licensed for use in tumour lysis syndrome but requires further development before being suitable for widespread application.

The treatment of difficult gout can be summarised as follows:

- Diagnose correctly.
- Address modifiable risk factors.
- Aspirate if possible.
- Use low drug doses in at-risk patients.
- Lower the serum uric acid level sufficiently.

Dementia: will treatment help?

A 72-year-old man is referred by his general practitioner because his memory is gradually failing. Over the last 12 months he has become increasingly forgetful and on one occasion appeared to have 'got lost', with difficulty finding his way back from the local shops. He has no significant past medical history, is on no regular medications and physical examination is unremarkable. What is the underlying pathology? What investigations are appropriate and how should he be managed?

Dementia is defined as 'a syndrome consisting of progressive impairment in two or more areas of cognition sufficient to interfere with work, social function, or relationships'. Worldwide, 15–30 million people are affected, with Alzheimer's disease responsible for 75% of cases. Other common causes are frontotemporal dementia, cortical Lewy body disease and cerebrovascular disease. The clinical features of each condition depend on their distinctive pathologies.

Alzheimer's disease first affects the hippocampal region, causing initial problems with explicit memory impairment, eg 'I forgot where I put my keys two minutes ago'. As the disease spreads anteriorly within the cerebral hemispheres, language impairment, visuospatial symptoms, behavioural and then psychiatric problems arise; the symptoms track the underlying disease process into the frontal lobes.

In *frontotemporal dementia* (previously known as Pick disease) there is atrophy of the frontal and/or anterior temporal lobes. With pure frontal lobe involvement personality and social behaviour are affected, whereas a progressive aphasia reflects temporal lobe atrophy.

Lewy body disease produces a different symptom complex resulting from the distribution of pathology in the cortical and subcortical structures/substantia nigra. The clinical diagnosis is based on the finding of progressive memory impairment together with Parkinsonian motor features, visual hallucinations (often very vivid), fluctuating cognition and neuroleptic sensitivity.

Cerebrovascular dementia is suggested by stepwise progression in the patient with vascular disease, which may be very obviously manifest as repeated strokes.

A thorough history and physical examination are the essential first steps in the diagnosis of dementia. The 30-point Mini-Mental State Examination (MMSE) is insensitive but a good screening measure for the general take or clinic, not least because of its widespread use. A score of 24 out of 30 is the lower limit of normal: patients with early dementia can score above this, requiring formal neuropsychiatric testing to identify subtle pathology. This has led to the concept of 'mild cognitive impairment' as a transitional state between normal and demented, patients within this category having a 10–15% risk for developing dementia each year.

Investigation

Standard investigations aim to identify and exclude treatable conditions that might cause dementia or, more likely, exacerbate the condition. A suitable approach would involve:

- full blood count and erythrocyte sedimentation rate (or CRP)
- serum electrolytes, calcium, renal and liver function
- serum iron, vitamin B12 and folate
- thyroid function tests
- syphilis serology
- chest radiograph
- head CT scan.

Treatment

Once a diagnosis of dementia has been made, communication with the patient and carers is crucial: there is a need for all involved to understand the progressive nature of the condition and the practical problems that may arise, eg legal and financial issues. Recording the patient's wishes regarding terminal care is appropriate at an early stage.

Medication may help with symptom control, even if there is no effect on underlying disease progression. Acetylcholinesterase inhibitors (Table 1) are the first line of treatment in mild-to-moderate Alzheimer's disease and can be helpful in other neurodegenerative diseases, possibly through increasing attention and thereby reducing agitation and improving behaviour. Side-effects are minimised by commencing the drug at the lowest dose and titrating upwards. Trials in Alzheimer's disease demonstrate improvement in cognition, but unfortunately most studies have only lasted for six months and hence the optimum length of treatment is unclear, although patients may continue to derive benefit for up to 2–3 years. It is reasonable practice to try one drug for 3–6 months, switching to another if there is no appreciable benefit after this period. NICE guidance suggests that acetylcholinesterase inhibitors should be stopped if the MMSE score falls below 12 points.

Table 1. Medication to improve cognition in Alzheimer's disease.

Medication	Class	Dosage
Donepezil	Acetylcholinesterase inhibitor	5–10 mg daily
Rivastigmine	Acetylcholinesterase inhibitor	1.5–6.0 mg twice daily
Galantamine	Acetylcholinesterase inhibitor	4–12 mg twice daily
Memantine	NMDA receptor antagonist	5 mg once daily to 10 mg twice daily

NMDA = *N*-methyl-D-aspartate.

Memantine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist (Table 1), is another agent that modifies the symptoms of dementia, but probably not the disease process. It is licensed in the UK and Europe for moderate-to-severe Alzheimer's. There is some evidence that statins and high-dose vitamin E supplements have some benefit in Alzheimer's disease, but more data are required.

Behavioural and psychiatric disturbance may also need treatment. Non-pharmacological management is very important, but medication may be required. Atypical antipsychotic medications are most useful and have the lowest incidence of side-effects, eg risperidone 0.5 mg once daily, quetiapine 25 mg once daily and olanzapine 2.5 mg once daily (initial doses). Antidepressants can also be of benefit in selected cases.