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Neurology of endocrine disease

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Most neurological presentations, ranging from acute confusional states through to slowly progressive gait disturbance, have endocrine disease as a potential cause. These conditions include diabetes, hyper- and hypothyroidism, hyper- and hypoparathyroidism, acromegaly, adrenal insufficiency, glucocorticoid excess and diabetes insipidus. Patients with established endocrine disease also commonly present with a similarly wide range of neurological symptoms and signs. It is therefore vital to 'think endocrine' when assessing most patients with neurological symptoms, particularly because many of the underlying endocrine disorders are common, can be reliably diagnosed and may be treatable.

This awareness needs to be tempered with the appreciation that endocrine disease, particularly diabetes, is common in the general population. An adequate neurological history and examination remain vital. It is also important to be familiar with the spectrum of neurological complications associated with specific endocrine diseases, otherwise atypical features will not be noted, leading to misdiagnosis and inappropriate management. Standard neurological tests, such as computed tomography, magnetic resonance imaging, nerve conduction and electromyography (EMG) studies can be unhelpful or even misleading in the context of severe endocrine disturbance.

It is impossible in a short review to provide comprehensive coverage of all neurological presentations and complications of endocrine disease. This article therefore takes a practical approach to patients presenting with a range of neurological symptoms and signs, highlighting possible endocrine causes. (Readers are referred to the *Clin Med* CME sections on endocrinology[1] and diabetes.[2])

The cognitively impaired, confused or comatose patient

The features, diagnosis and management of patients with hypoglycaemic, diabetic ketoacidotic or non-ketotic hyperosmolar states will be familiar to all and will not be reviewed here. Rarely, hyperglycaemic states may result in status epilepticus, resistant to standard antiepileptic drugs but responsive to insulin without the need for chronic antiepileptic therapy. Coma is a rarer presentation of other endocrine conditions.

Both hyper- and hypothyroidism may lead to behavioural and cognitive changes, mimicking mania and depression, respectively. Severe hyperthyroidism may lead to reduced consciousness, usually in the context of a 'thyroid storm' following a precipitating event (such as infection or surgery). Monitoring and therapy in a high dependency environment are recommended as mortality from this condition is high. Profound hypothyroid states leading to 'myxoedema coma' may have similar precipitants, leading to a surprisingly acute combination of systemic disturbance (bradycardia, hypotension, hypothermia) and coma from hypoglycaemia, electrolyte disturbance and occasionally seizures.[3]

Patients with hyper- or hypoparathyroidism frequently present with acute confusional states and/or symptoms suggestive of depression or mania, usually related to disturbed calcium homeostasis. Hypocalcaemic states are additionally associated with a significantly raised incidence of seizures.[4] Rarely, adrenal hypofunction may be associated with significant hyponatraemia, leading to impaired consciousness.

Cognitive impairment associated with hypothyroidism was first noted over a century ago. Thyroid function tests continue to form an important part of the battery of cognitive screening tests in patients with suspected dementia. There may be a degree of specificity to

Key Points

- **Endocrine disorders are common and have a wide range of neurological presentations and potential complications**
- **Diabetes is a common cause of painful third and sixth nerve palsies, with good recovery over 3–6 months**
- **Diabetic lumbosacral radiculoplexus neuropathy (diabetic amyotrophy) presents with weight loss, lower back pain and asymmetric lower limb weakness**
- **Most patients with thyroid dysfunction will have neuromuscular symptoms**
- **Hypothyroid myopathy, in contrast to the proximal weakness of hyperthyroidism, is slow to respond to therapy**

KEY WORDS: diabetic complications, endocrine disease, neurological complications, neuromuscular complications, systemic disease

memory deficits, with verbal memory most significantly impaired and also responding to thyroid hormone replacement therapy.[5]

Hashimoto's encephalopathy

Hashimoto's encephalopathy is an extremely rare, poorly characterised, steroid-responsive encephalopathy associated with an elevated titre of thyroid autoantibodies. The clinical presentation is variable, with coma, seizures, neuropsychiatric changes and/or focal neurological deficits. The underlying pathogenesis is unclear, with an autoimmune vasculitis potentially responsible. The association with thyroid dysfunction is not established – patients frequently have normal thyroid function tests – and the condition does not respond to correction of thyroid hormone levels.[6]

The patient with visual or hearing disturbance

Cranial neuropathies

Diabetes is a common cause of cranial neuropathies, frequently presenting with a sixth nerve palsy in an elderly patient. Third nerve palsies can be more diagnostically challenging as ischaemic ocular motor cranial nerve palsies are usually painful, but the palsy is pupil sparing. The causative ischaemia predominantly involves the centre of the third nerve fascicle, whereas the pupillomotor fibres are distributed in the outer layers and relatively protected.[7] Nonetheless, neuroimaging to exclude a posterior communicating artery aneurysm is advisable. Recovery from a diabetic cranial neuropathy is usually complete over 3–6 months.

Graves' disease

The ophthalmopathy associated with Graves' disease is unlikely to be mistaken for a straightforward cranial nerve palsy. Symptoms and signs are subacute with vertical gaze palsies (the inferior rectus muscle is most commonly affected) and with inflammatory and possible myopathic changes. Rarely, the ophthalmopathy can be so severe as to cause compressive neuropathies at the orbital apex (potentially involving the second, third, fourth, sixth and first division of the fifth cranial nerves). Urgent decompressive surgery is warranted to preserve vision.

Other presentations

Ocular manifestations of endocrine disease include a reversible ptosis in 60% of patients with hypothyroidism, thought to be related to alterations in sympathetic tone.[8] Other cranial nerve palsies are rare, with the exception of sensorineural hearing loss, common in hypothyroidism and sometimes with associated tinnitus. This responds to thyroxine supplementation. Papilloedema is rarely observed in the context of endocrine disease but has been reported in hypocalcaemic states, often without measurable changes in cerebrospinal fluid pressure.[9]

Neuromuscular presentations of endocrine disease

Neuromuscular symptoms and signs are extremely common in patients with endocrine disease. The distal sensory neuropathy seen in diabetes is familiar, but other endocrine disease may also be responsible. One prospective study of patients with thyroid dysfunction found neuromuscular symptoms in 79% and 67% of hypothyroid and hyperthyroid patients, respectively.[10]

The clinical assessment of a weak patient must include details of the tempo (onset and evolution) and pattern (facial, limb, proximal, distal, fatiguable) of weakness, providing important diagnostic information. In addition, associated sensory symptoms or signs should be detailed. Sphincter disturbance should be looked for but would be unlikely to result from endocrine dysfunction.

The patient with weakness

Thyrotoxic periodic paralysis

A rare but important cause of acute weakness is thyrotoxic periodic paralysis (TPP). This syndrome typically presents in male, oriental Asian patients aged 20–40 years. Patients experience recurrent attacks of proximal muscle weakness of variable severity. Bulbar and respiratory muscles are usually not affected, sensation and sphincter function are intact, and tendon reflexes usually depressed. Episodes are of variable duration (minutes to days) and are provoked by heavy carbohydrate intake or rest after exercise. Serum potassium levels are frequently low, but not invariably. Thyroid function tests are often only mildly abnormal. Treatment involves supportive therapy of the acute episode, with control of thyroid function curing TPP.

TPP is distinct from the familial (hyperkalaemic or hypokalaemic) periodic paralyses, rare but relatively straightforward autosomal dominant channelopathies. Mutations in voltage-gated calcium, potassium or sodium channels lead to abnormalities of muscle depolarisation and consequent weakness.[11] An important recent study suggests that TPP is also a genetically mediated channelopathy, resulting from mutations in a previously unidentified potassium channel (Kir2.6). The promoter region for this protein contains thyroid response elements, providing a mechanism for the association with thyrotoxicosis.[12]

Subacute weakness

Causes of subacute weakness (evolving over weeks) include diabetic lumbosacral radiculoplexus neuropathy (previously termed diabetic amyotrophy), most commonly found in male patients with type 2 diabetes. They present with significant weight loss (sometimes 10–20 kg), severe lower back pain, with lower limb weakness evolving over days to weeks. Weakness is usually proximal and unilateral but frequently becomes bilateral and may spread to distal musculature. Nerve conduction and EMG studies are diagnostically helpful. Overall prognosis is reasonable, with significant functional recovery, but taking many months.[13]

Chronic weakness

Chronic weakness evolving over months is commonly the result of endocrine myopathies. Patients will typically manifest with proximal limb weakness, myalgia, pain and/or spasms, in the context of preserved reflexes and sensation. Creatine kinase levels are either normal or only modestly elevated (up to 1,500 U/l) and do not correlate with the severity of weakness. Although both hyper- and hypothyroid patients may present with proximal weakness, the evolution of weakness is faster in hyperthyroidism and resolves completely with treatment. In contrast, weakness in hypothyroidism is more long lasting and resistant to therapy.[10] Most patients have systemic features of hypothyroidism (bradycardia, constipation, cold intolerance), but many of these symptoms are relatively non-specific and/or may be missed.

Other causes of weakness

In contrast to hypoadrenal states, in which myopathic symptoms are rare, primary or secondary Cushing syndromes commonly present with significant proximal weakness. EMG studies demonstrate myopathic findings, and muscle biopsies show selective type IIb fibre atrophy as these are least able to tolerate disturbed glycolytic metabolism.[14,15] Hyperparathyroidism commonly manifests with myopathic weakness and may have associated muscle atrophy. It is also important to remember that several neurological diseases co-segregate with endocrine disease, particularly autoimmune hyperthyroidism. Myasthenia gravis is found in only about 1% of patients with hyperthyroidism and will complicate assessment and therapy, particularly as many patients develop a component of proximal weakness secondary to steroid therapy.

The patient with sensory disturbance

Diabetic distal polyneuropathy

The most common diabetic neuropathy is symmetric distal polyneuropathy (often with autonomic neuropathy). It preferentially affects small (pain and temperature) fibres in, as the name suggests, a symmetrical distal ('glove and stocking') distribution. Absent ankle reflexes are near universal, with knee and upper limb areflexia in 65% and 25% of cases, respectively. This is a length-dependent process, so upper limb sensory loss should be matched by lower limb sensory impairment to around mid-thigh. Weakness is usually less prominent and confined to the feet. Similarly, the diabetic autonomic neuropathy is usually clinically mild (Table 1).

More rarely, at diagnosis or during periods of poor glycaemic control, patients may experience a period of acutely painful distal neuropathy. The hyperglycaemic neuropathy normally resolves with improved glucose control.

Other neuropathic variants

Other variants include an 'insulin neuritis', with a painful sensory neuropathy developing on the context of tightly controlled glucose levels. A 'diabetic neuropathic cachexia' may

Table 1. Peripheral nervous system complications of diabetes.

Type	Comments
Polyneuropathies	• Distal sensory polyneuropathy with small fibre involvement (pain and temperature) most common
	• Acutely painful distal neuropathies during poor glucose control
Mononeuropathies	• Cranial neuropathies, especially 6th and 3rd third nerves
	• Entrapment neuropathies (median, ulnar nerves) more common
Radiculopathies	• Lumbosacral radiculoplexus neuropathy (diabetic amyotrophy) with back pain, weight loss and asymmetric proximal lower limb weakness at onset
Autonomic neuropathy	• Rarely symptomatic outside the context of marked peripheral neuropathy
	• May present with cardiovascular (postural hypotension), gastrointestinal (gastroparesis), or sphincter disturbance (urinary or erectile dysfunction)

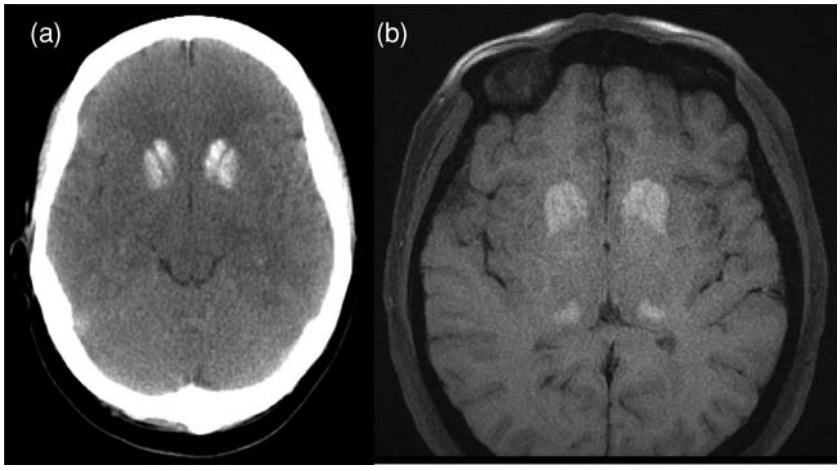

Fig 1. Imaging abnormalities in hypoparathyroidism. Computed tomography (CT) and magnetic resonance imaging (MRI) appearances in a patient presenting with headaches, visual disturbance and hypocalcaemia secondary to hypoparathyroidism: (a) non-contrast CT; (b) T1 weighted MRI, showing extensive calcification of the basal ganglia.

develop in patients with unstable type 1 diabetes. Prominent weight loss is associated with a severe distal sensory neuropathy. This resolves slowly as weight recovers.

Both sensory and entrapment neuropathies are common for other endocrine conditions. In one survey, a sensorimotor axonal neuropathy or carpal tunnel syndrome was found in 42% and 29% of hypothyroid patients, respectively. In contrast, hyperthyroidism was associated with a neuropathy in 19% of patients, but there were no cases of carpal tunnel.[10]

The patient with a movement disorder

The low amplitude, high frequency (enhanced physiological) tremor of hyperthyroidism is familiar. Other movement disorders are uncommon, although choreas secondary to hyperglycaemic, hypoglycaemic and hyperthyroid states have all been reported, typically resolving with treatment of the endocrine disorder. Parkinsonian signs (particularly bradykinetic states and/or rest tremor) have been reported in the context of hypoparathyroidism.[16] The direct or indirect relationship to deranged calcium metabolism is not clear, particularly as hypoparathyroidism (and pseudohypoparathyroidism) may present with basal ganglia calcification (Fig 1).[17]

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