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CORE TRAINING FOR DOCTORS

Acute peripheral weakness and suspected Guillain–Barré syndrome

Guillain–Barré syndrome is the commonest cause of acute flaccid paralysis and an important neurological emergency (Yuki and Hartung, 2012). The majority of patients with Guillain–Barré syndrome describe antecedent infectious symptoms and occurrence is therefore often seasonal in the UK and more frequently encountered in winter months (Webb et al, 2014).

Typically patients with classical Guillain–Barré syndrome present with ascending limb weakness, which is often accompanied or preceded by distal paraesthesias. In 90% of patients deep tendon reflexes become diminished or lost during disease course, but in 10% they may remain present or even appear exaggerated (Yuki et al, 2012). A significant proportion of patients also develop bulbar weakness, respiratory depression and dysautonomia, which may require admission to the intensive care unit and ventilator support. Overall outcome is good, especially when diagnosed early, which allows prompt administration of immunotherapy. The differential diagnosis for Guillain–Barré syndrome remains broad (Wakerley and Yuki, 2015), but can be significantly narrowed based on history and recognition of core clinical features.

The Guillain–Barré syndrome spectrum

Guillain–Barré syndrome is the umbrella term used to describe a spectrum of related autoimmune neuropathies, which include classical Guillain–Barré syndrome and Miller Fisher syndrome. Classical Guillain–Barré syndrome is characterized by tetraparesis and often associated with multiple cranial neuropathies, whereas Miller Fisher syndrome is characterized by external ophthalmoplegia and cerebellar-like ataxia in the absence of limb weakness.

There are a number of Guillain–Barré syndrome and Miller Fisher syndrome subtypes, which together form a continuum of discrete and overlapping syndromes (Wakerley et al, 2014). For example, 5% of patients with Miller Fisher syndrome will develop limb weakness during their disease course, indicating overlap with Guillain–Barré syndrome. Patients with the pharyngeal-cervical-brachial subtype of Guillain–Barré syndrome typically develop bulbar symptoms associated with upper limb weakness and relative sparing of the lower limbs (Wakerley and Yuki, 2014).

Pathology

Guillain–Barré syndrome is a post-infectious neuropathy (Wakerley and Yuki, 2013). Two thirds of patients report recent infectious symptoms before development of neurological symptoms, but in many cases infection may be subclinical. Typically infections are gastrointestinal or respiratory. *Campylobacter jejuni*-associated gastroenteritis is the commonest cause and identified in up to a third of cases. Other micro-organisms commonly associated with Guillain–Barré syndrome include cytomegalovirus, Epstein–Barr virus and *Mycoplasma pneumoniae*.

Neurophysiological studies indicate that there are two distinct patterns of abnormality associated with Guillain–Barré syndrome: demyelinating-type neuropathy and axonal-type neuropathy (Yuki and Hartung, 2012). Demyelinating-type neuropathy is more common in Europe and North America, whereas axonal-type neuropathy is more common in Asia.

The exact pathogenesis of Guillain–Barré syndrome remains unknown, but mistaken identity (molecular mimicry) between antigens on the surface of microbial agents and components of peripheral

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nerves, known as gangliosides, may induce anti-ganglioside antibodies and lead to axonal-type Guillain–Barré syndrome (Yuki and Hartung, 2012). Patients with axonal-type neuropathy often display antibodies against gangliosides such as GM1a and GD1a, whereas recognized antibodies have not been isolated from patients with demyelinating-type disease.

Clinical features

In the majority of cases Guillain–Barré syndrome can be diagnosed on the basis of history and examination alone (Wakerley and Yuki, 2015). Recognition of certain core clinical features (*Table 1*) aids early diagnosis and treatment and avoids unnecessary investigations.

History

When assessing patients with limb weakness the history should provide clues as to the rate of disease progression and possible precipitants (*Table 2*). Typically, neurological symptoms in Guillain–Barré syndrome develop between 3 days and 6 weeks after antecedent infectious symptoms. Infection can be subclinical and therefore family members should also be questioned. Other medical conditions (e.g. HIV, lupus erythematosus, non-Hodgkin lymphoma), recent surgery and immunosuppressive drugs (e.g. anti-tumour necrosis factor alpha therapy) are associated with an increased risk of infection and may trigger Guillain–Barré syndrome (Wakerley and Yuki, 2013). In the majority of cases patients complain of distal paraesthesias (numbness, tingling and pain) before or during the onset of weakness. Back pain, probably the result of inflamed spinal nerve roots, is often reported by patients with classical Guillain–Barré syndrome. Some patient may present with double vision or bulbar symptoms indicating cranial neuropathy. Symptoms suggestive of dysautonomia are rare at presentation, but some patients may complain of reduced sweating and heat intolerance or urinary hesitancy.

Table 1. Clinical features

Antecedent infectious symptoms
Presence of distal paraesthesias at or before onset of weakness
Symmetrical pattern of weakness in all four limbs and/or weakness of cranial nerve-innervated muscles or respiratory depression
Diminished or absent deep tendon reflexes (90% of cases)
Monophasic disease course with interval between onset and nadir of weakness of 12 hours to 28 days, followed by clinical plateau

Examination

Patients with Guillain–Barré syndrome typically develop flaccid tetraparesis, i.e. weakness in all four limbs in the absence of deep tendon reflexes. In many cases proximal leg weakness and disturbance of gait are the chief presenting complaint. In 10% of cases, however, deep tendon reflexes may appear normal or exaggerated during the disease course (Yuki et al, 2012). Weakness, whether involving the cranial nerves or limbs, is typically symmetrical. Cerebellar-like ataxia in association with external ophthalmoplegia indicates Miller Fisher syndrome. Internal ophthalmoplegia (absent pupillary responses) may also be apparent.

Sensory examination is often abnormal distally. The presence of a well-defined sensory level is more suggestive of spinal pathology than Guillain–Barré syndrome. Some patients develop cranial neuropathy and therefore bulbar function should be assessed regularly. Respiratory depression occurs in 25% of patients with Guillain–Barré syndrome and may indicate the need for ventilator support (van den Berg et al, 2014). Around 20% of patients with Guillain–Barré syndrome develop dysautonomia, which may manifest as blood pressure lability or in some cases cardiac arrhythmias.

Progression and prognosis

Disease course in Guillain–Barré syndrome is monophasic with progression of neurological weakness over 12 hours to 4 weeks before clinical plateau. Alternate diagnoses should therefore be made in patients with no progression (e.g. stroke), frequent fluctuations (e.g. myasthenia gravis), or progression over 4 weeks (e.g. chronic inflammatory demyelinating polyneuropathy).

Guillain–Barré syndrome is a neurological emergency as up to 5% of patients die and a significant proportion are left with permanent disability (Yuki and Hartung, 2012). Mortality is often related to complications associated with prolonged hospital admission (e.g. venous thromboembolism) or mechanical ventilation (e.g. chest infection), or as a result of dysautonomia (e.g. cardiac arrhythmias). Factors predictive of poor prognosis include advanced age, rapid onset of weakness before presentation, severe weakness on admission, preceding diarrhoeal illness and the need for mechanical ventilation (Rajabally and Uncini, 2012). Prognostication in Guillain–Barré syndrome is difficult and is highly variable. At the nadir, two thirds of patients are unable to walk independently and a fifth of severely affected patients are unable to walk at 6 months (Hughes et al, 2007).

Investigations

Although Guillain–Barré syndrome can be diagnosed clinically, where there is uncertainty, specific investigations are useful in the acute setting to exclude important differential diagnoses (Wakerley and Yuki, 2015). Neuroimaging with magnetic resonance imaging is primarily used to exclude ischaemic, inflammatory or structural lesions in the brain and spinal cord, but may reveal enhancement of spinal nerve roots and cauda equina in Guillain–Barré syndrome.

Unless contraindicated CSF analysis should be carried out in all patients with suspected Guillain–Barré syndrome and may help to exclude other conditions. In Guillain–Barré syndrome typically CSF demonstrates albuminocytological dissociation (raised protein level with few inflam-

Table 2. Important questions to ask

Recent travel? (e.g. regions where poliomyelitis is endemic)
Antecedent infectious symptoms? (e.g. upper respiratory tract or gastroenteritis)
Insect or animal bites? (e.g. tick bite causing Lyme disease)
Exposure to toxins? (e.g. organophosphates, lead)
Drugs or contaminated food? (e.g. botulism)
Systemic symptoms? (e.g. fever or rash suggestive of vasculitis)
Trauma? (e.g. cervical cord injury)
Family history? (e.g. familial hypokalaemic periodic paralysis)
Psychiatric history? (e.g. functional illness)

matory cells). However, half of patients with Guillain–Barré syndrome have normal CSF in the first week and therefore it should not be relied upon. Significant CSF pleocytosis (> 50 white blood cells per μl) is suggestive of infection, lymphoma or occasionally HIV. In such cases, CSF flow cytometry and cytology as well as HIV testing are indicated. In general CSF examination should not be done out of hours unless meningitis or encephalitis is suspected.

Similarly neurophysiological assessment if abnormal supports diagnosis but is often non-diagnostic in early disease and should not be relied upon or delay treatment. Repeated assessment is more useful and increases diagnostic yield (Uncini et al, 2010).

Anti-ganglioside antibodies support diagnosis when present, but it may take several weeks to get the results. While the majority of patients with Miller Fisher syndrome display anti-GQ1b antibodies, only patients with axonal-type Guillain–Barré syndrome display anti-ganglioside antibodies (Yuki and Hartung, 2012).

Respiratory insufficiency is common in patients with Guillain–Barré syndrome and therefore forced vital capacity should be monitored in all patients. This can be done twice daily initially, although more frequent recordings are indicated if the patient is deteriorating. Monitoring should be done in the same position (e.g. sitting on edge of bed or supine) each time. Facial weakness can result in poor technique and this can be reduced by using a face mask. A review from intensive care physicians should be considered if the forced vital capacity is <1.0–1.5 litres or if the trend of forced vital capacity is worsening.

Dysautonomia may occur and therefore patients with labile pulse or blood pressure recordings need cardiac monitoring and sometimes admission to the intensive care unit. Hyponatraemia is relatively common and patients should have their renal function tested every few days.

Stool testing for *C. jejuni* and viral serology are sometimes helpful if the diagnosis remains unclear, but are not always indicated.

Important differential diagnoses

Other causes of acute flaccid paralysis (*Table 3*) should also be considered in patients with suspected Guillain–Barré syndrome and in many cases can be excluded based on history and examination (Wakerley and Yuki, 2015). Acute spinal cord injury (e.g. anterior spinal artery ischaemia) may cause flaccid paralysis, which typically does not progress. In elderly patients always ask about the history of falls as this may cause acute cervical cord compression. Carcinomatous or lymphomatous meningitis may mimic Guillain–Barré syndrome, but can usually be excluded following CSF analysis.

Other rapidly progressive neuropathies (e.g. critical illness neuropathy) should be considered in the appropriate clinical setting and initially may be difficult to distinguish from Guillain–Barré syndrome. Myasthenia gravis may mimic Guillain–Barré syndrome or Miller Fisher syndrome, but weakness is often fluctuant and sensory disturbance is absent. Acute myositis and hyokalaemic periodic paralysis may also cause tetraparesis and can be diagnosed in the presence of an elevated serum creatinine kinase level or hypokalaemia respectively. Although a diagnosis of exclusion, functional illness should also be considered in some patients, especially if the neurological examination is inconsistent.

Treatment

Unlike many autoimmune conditions there is no role for steroids in Guillain–Barré syndrome. Instead patients benefit from either intravenous immunoglobulin or plasma exchange (van den Berg et al, 2014). Therapy is usually reserved for those patients who are rapidly deteriorating, cannot walk, or have bulbar symptoms or respiratory depression.

For practical reasons intravenous immunoglobulin (0.4 g/kg/day for 5 days) is the initial treatment of choice and is available in most hospitals. Out of hours, the priority is assessing and managing respiratory failure and other complications of Guillain–Barré syndrome. Intravenous immunoglobulin should be commenced when practicably possible. Repeat dosing of intravenous immunoglobulin can be given at 2–3-week intervals but it remains unclear whether this is of benefit.

Other important areas of management include venous thromboembolism prophy-

Table 3. Common differential diagnosis

Viruses targeting anterior horn cells or motor neurons (e.g. poliomyelitis syndrome caused by West Nile virus, Japanese encephalitis, herpes simplex virus)
Transverse myelitis (e.g. *Mycoplasma pneumoniae*)
Spinal cord injury (e.g. acute spinal stenosis, anterior spinal artery occlusion)
Acute peripheral neuropathies (e.g. herpes simplex virus, Lyme disease, porphyria, thallium poisoning)
Neuromuscular junction disorders (e.g. myasthenia gravis, botulism)
Neuromuscular weakness related to critical illness (e.g. critical illness neuropathy and myopathy)
Muscle disorders (e.g. acute myositis, periodic paralysis)
Functional

TOP TIPS

- In the majority of cases, Guillain–Barré syndrome and Miller Fisher syndrome can be diagnosed based on history and examination alone.
- Very few conditions other than Guillain–Barré syndrome cause acute onset flaccid tetraparesis and facial palsy.
- Lumbar puncture for CSF analysis is important, but rarely needed out of hours.
- Patients with Guillain–Barré syndrome are at high risk of developing pressure ulcers.
- Forced vital capacity measurement and cardiac monitoring are mandatory.
- Always check serum immunoglobulin levels before administering intravenous immunoglobulin as patients with immunoglobulin-A deficiency are at risk of developing hypersensitivity and anaphylactic reactions.

laxis, pressure area monitoring, pain control (e.g. gabapentin), psychological support, and physiotherapy and occupational therapy input (Hughes et al, 2005). BJHM

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KEY POINTS

- Guillain–Barré syndrome is a post-infectious neuropathy and antecedent infectious symptoms can be identified in the majority of cases.
- Diagnosis of Guillain–Barré syndrome is aided by recognition of core clinical feature, which include presence of antecedent infectious symptoms, distal paraesthesias, symmetric cranial nerve or limb weakness, and areflexia.
- Deep tendon reflexes are preserved or exaggerated in up to 10% of patients with Guillain–Barré syndrome.
- CSF albuminocytological dissociation and abnormal neurophysiological assessment support diagnosis, but should not be relied upon, especially in early disease.
- Axonal-type Guillain–Barré syndrome is associated with anti-ganglioside antibodies.
- Early administration of intravenous immunoglobulin or use of plasma exchange improves outcome in Guillain–Barré syndrome and avoids need for ventilator support.