Guillain-Barré syndrome

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Key points

Guillain-Barré syndrome should be suspected in all patients with unexplained motor weakness or a sensory deficit affecting the limbs.

Mortality is 10%, usually as a result of complications.

Do not rely solely on pulse oximetry when assessing deteriorating respiratory function – desaturation is often a late consequence of neuromuscular respiratory disease.

Intravenous immunoglobulin therapy and plasma exchange are two recognised disease-modifying treatments. No significant difference in efficacy has been demonstrated.

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Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy which typically occurs as an autoimmune response following a gastrointestinal or respiratory infection. Potentially, it is a severely debilitating disorder affecting 1–3 per 100,000 of the population per annum in the Western world. Of sufferers, 10% will die from associated complications and a further 10% will suffer from long-term neurological sequelae and physical dependence.

Although Guillain, Barré and Strohl first described a disease affecting French soldiers (motor weakness, areflexia and CSF abnormalities) in 1916, descriptions of the disorder date back to 1859 when Landry described an 'ascending paralysis'. Despite the syndrome being well recognised and potentially fatal, initial presentation is still regularly misdiagnosed as hysteria. Even in those patients accurately diagnosed with the syndrome, ignorance and inadequate monitoring may lead to the subtle signs of decompensation being missed. The treatment options of GBS have been a source of research and debate over the last decade. We summarise the key points in the diagnosis and treatment of GBS in this article.

Causes

GBS affects individuals of all ages, although there is a bimodal tendency towards young adults and the elderly. There is a slight male preponderance. The disease affects children less severely. The majority of cases of GBS occur within a month of either a respiratory or gastrointestinal infection. Although the commonest pathogen is *Campylobacter jejuni*, many other organisms such as Epstein Barr virus, *Mycoplasma pneumoniae* and cytomegalovirus may be implicated.

C. jejuni tends to be associated with axonal degeneration in addition to the usual primary demyelination of peripheral nerves and spinal nerve roots found in GBS and may cause a more severe debilitating form of the disease. GBS is also recognised as a complication of HIV infection and there have been reports of associations with vaccines, surgery, epidural anaesthesia, bone marrow and organ transplantation, SLE, lymphoma, sarcoidosis, penicillin and anti-motility drugs. Pregnancy and the oral contraceptive pill are thought to confer some degree of protection against the disease.

Presentation

Several distinct clinical pictures of GBS have been described. These include:

1. Acute inflammatory demyelinating polyradiculopathy (AIDP).

2. Acute motor axonal neuropathy (AMAN).

3. Acute motor sensory axonal neuropathy (AMSAN).

4. Miller Fisher syndrome, *i.e.* ataxia, areflexia and ophthalmoplegia which may be accompanied by limb weakness, ptosis and facial and bulbar palsy.

The signs and symptoms of GBS are variable. The classical picture is that of an ascending limb weakness with areflexia, although a purely sensory variant has been well documented.

Features of GBS include:

1. Progressive motor weakness, usually ascending from the legs (proximal more than distal).

2. Areflexia.

3. Facial palsy and bulbar weakness.

4. Ophthalmoplegia.

Table 1 Investigations in Guillain-Barré syndrome (GBS)

Routine blood tests including:	
Full blood count	
Urea and electrolytes	SIADH may occur in association with GBS (syndrome of inappropriate ADH secretion is the presence of hypotonic hyponatraemia in the presence of inappropriately high urine osmolality and absence of volume depletion, oedema or other causes of hyponatraemia). Treatment of SIADH includes fluid restriction
Liver and renal function tests	Liver and renal function may be impaired in patients with GBS
Clotting screen	Abnormal clotting must be excluded if plasmapheresis is to be considered as a therapy
Calcium	Hypocalcaemia may be exacerbated by plasmapheresis therapy
Antibody tests and blood cultures	Serum should be analysed for the presence of antiganglioside antibody. (GM1 is a minor ganglioside found in human peripheral nerves and anti-GM1 antibodies are often found in patients with GBS. GM1 antibodies are associated with a poorer prognosis and GQ1 antibody is associated with Miller Fisher variant. Anti-GM1b antibody responds better with immunoglobulin therapy.) Antibodies to *Campylobacter jejuni*, cytomegalovirus, Epstein Barr virus, herpes simplex virus, *Mycoplasma pneumoniae* and human immunodeficiency virus should also be analysed
Inflammatory markers	CRP and plasma viscosity elevation may indicate underlying sepsis
Stool cultures	Stool cultures should be examined for evidence of *Campylobacter jejuni* infection
Electrocardiogram	The ECG should be examined for evidence of pending autonomic dysfunction. Changes seen in GBS include ST segment depression, T-wave inversion and a prolonged QT interval. Arrhythmias may develop
Head CT scan	To exclude raised intracranial pressure or other causes of focal neurological signs prior to lumbar puncture
Lumbar puncture and CSF analysis	Typical findings in GBS are increased protein and < 10 mononuclear cells mm^{-2}. Protein concentrations may, however, be normal in the first week of symptoms, but concentrations will rise on subsequent LPs GBS associated with HIV infection leads to pleocytosis (elevated CSF leukocytes)
Electrophysiological studies	Electrophysiological studies aid the diagnosis of GBS and help to differentiate it in the ambulant patient from other neuropathies such as critical care polyneuropathy. Each subtype of GBS shows has a different feature on electrophysiological studies. Typical features may take a few weeks to become evident. Early findings include absence of the H reflex, abnormal upper extremity sensory nerve action potential, and abnormal f waves. Specific patterns such as low compound muscle action potential (CMAP) amplitude are associated with a poorer prognosis
Gadolinium-enhanced MRI of the spinal cord	MRI scans may show spinal nerve root enhancement with gadolinium in inflammatory conditions, and selective anterior root enhancement seems specific for GBS

5. Sensory symptoms.

6. Severe pain, often affecting the girdle area.

7. Weakness of the respiratory musculature leading to respiratory failure.

8. Autonomic dysfunction causing under or over activity of both the sympathetic and parasympathetic systems leading to arrhythmias, wide fluctuations in blood pressure and pulse, urinary retention, ileus and excessive sweating.

Pathological changes in patients with GBS tend to affect the nodes of Ranvier and include Wallerian degeneration, peri-axonal macrophages and minimal lymphocytic response.

Investigations and diagnosis

GBS should be suspected in all patients with unexplained motor weakness or a sensory deficit affecting the limbs. The typical examination findings are those of a progressive muscle weakness and areflexia. Following a full history and examination, patients should be admitted for observation and further investigations.

Patients should be monitored for potentially fatal arrhythmias on a cardiac monitor. Signs of respiratory muscle weakness should be sought by at least three times daily measurements of vital capacity. Measurement of vital capacity may be difficult in those patients with bulbar weakness due to difficulty in forming an adequate seal around the mouthpiece.

Further investigations are described in detail in Table 1.

Treatment

Treatment of GBS involves both supportive therapy such as ventilatory support and physiotherapy, and treatments aimed to reduce neural inflammation and expedite recovery such as immunoglobulin administration and plasmapheresis.

Supportive therapy

GBS tends to run a long progressive course followed by a slow gradual period of recovery. Patients are often debilitated and hospitalised for many months. Supportive therapy should take the form of a multidisciplinary approach involving medical and nursing staff, physiotherapists and occupational therapists. Because of the incidence of depression associated with GBS, psychiatric support and counselling services may be required for both patients and their families.

Physiotherapy and occupational therapy

Of patients suffering from GBS, 10% will not be able to walk unaided one year into their illness. They will require long-term intensive work with the physiotherapy and occupational therapy teams to improve their disability and ensure appropriate supportive aides are provided. Patients requiring ventilatory support need regular physiotherapy input to minimise secretion retention and the development of nosocomial respiratory infections. Limb weakness may lead to peripheral nerve palsies and contractures if not closely monitored and appropriately treated.

Counselling

There is a support group available to patients and their relatives. They may be contacted via the internet on:

<http://www.gbs.org.uk/>

Nutrition

Nutritional support and dietetic input should be available, particularly for patients unable to swallow due to bulbar involvement and those requiring intubation and ventilation.

Analgesia

Pain control in GBS can be difficult and involvement of both the acute and chronic pain teams should be considered. In addition to the pain caused by immobility in areas such as the sacrum and spine, patients with GBS suffer from neuropathic pain often within the proximal muscles. Patients may well require opioids to alleviate their pain, although the sedative effects of opioid therapy should be minimised in order to encourage weaning from respiratory support. Carbamazepine has been shown to be effective and other drugs used for neuropathic pain can be considered.

Thrombo-embolic prophylaxis

Non-ambulant patients with GBS are at risk of thrombo-embolic disease. Prophylaxis with low molecular weight heparin and gradient compression stockings should be routine in patients with no clotting abnormalities.

Respiratory support

Approximately 25% of patients with GBS will require ventilatory support. Several factors contribute to the development of respiratory failure in GBS. These include: (i) facial, bulbar and laryngeal weakness; (ii) inability to clear secretions; (iii) respiratory muscle and diaphragmatic weakness; (iv) secondary pulmonary infections; and (v) increased upper airways resistance due to upper airways collapse with bulbar and orofacial weakness.

Patients often develop nocturnal decompensation in the supine position leading to undesirable semi-elective out-of-hours intubation with its associated risks. There has been some work identifying those patients with GBS at particular risk of respiratory decompensation. It is essential to monitor, closely and regularly, the vital capacity in all patients with GBS to detect impending respiratory failure. Pulse oximetry should also be used as an additional aid to detect deterioration of respiratory function. However, it is important not to rely solely on pulse oximetry as desaturation due to hypoxaemia is often a late consequence of neuromuscular respiratory disease. Serial post-intubation pulmonary function tests may also help predict ventilatory needs and aid the decision to proceed to tracheostomy. Clinical clues that the patient is likely to require intubation and ventilation include bulbar involvement, bilateral facial weakness, dysautonomia and rapid disease progression. It is important to be aware that patients with autonomic dysfunction may develop cardiovascular instability following tracheal suction.

Clinical indications for intubation and ventilation include: (i) vital capacity < 20 ml kg^{-1}; (ii) maximal inspiratory pressure (MIP) < 30 cmH$_2$O; (iii) maximal expiratory pressure (MEP) < 40 cmH$_2$O; and (iv) decrease of $> 30\%$ in vital capacity, MEP or MIP.

Non-invasive ventilation is generally not useful in GBS as it does not solve the problem of inability to eliminate secretions due to muscular weakness. Patients with respiratory decompensation due to bulbar weakness also suffer from upper airways collapse, subsequently leading to a problematic increase in airways resistance.

Specific therapies

Intravenous immunoglobulins and plasma exchange

The two currently recognised disease-modifying modalities are intravenous immunoglobulin therapy and plasma exchange.

There have been several studies over the last decade examining the difference in efficacy between immunoglobulin therapy and plasmapheresis and no significant difference has been demonstrated. They are approximately equal in cost. However, immunoglobulin therapy has the advantage of easier administration and fewer side-effects, particularly in the elderly, and is generally the initial treatment of choice. Immunoglobulin therapy or plasmapheresis should be commenced when the patient becomes non-ambulatory or develops respiratory decompensation.

The recommended dose of intravenous immunoglobulin therapy is 0.4 mg kg^{-1} daily for 5–6 days. Therapy should be commenced within 2 weeks of the onset of symptoms. Contra-indications to treatment include IgA deficiency (increased incidence of anaphylaxis) and previous anaphylaxis to immunoglobulin therapy. IgA levels must be checked in all patients prior to administration of immunoglobulin. Extreme caution must be taken in patients with renal impairment as renal function may deteriorate further with immunoglobulin therapy. Severe congestive cardiac failure is also a relative contra-indication.

Immunoglobulin therapy is relatively easy to administer and is therefore suitable for use in smaller centres, reducing the need for inter-hospital transfers. Side-effects (< 5% of patients) tend to be mild and include nausea, fever, headache, transient rise in liver enzymes, encephalopathy, meningism and malaise. More serious side-effects include skin reactions (*e.g.* erythroderma), hypercoagulability, deterioration in renal function due to renal tubular necrosis and anaphylaxis.

Plasmapheresis was the first disease-modifying therapy to be used in GBS. It has been shown in several studies to reduce duration of ventilator dependence and hospital stay and leads to earlier mobilisation if commenced within 2 weeks of the onset of illness. However, it is associated with more significant side-effects and contra-indications compared with immunoglobulin therapy. Administration is limited to specialist centres. Typically, up to 5 exchanges are performed substituting 250 ml kg^{-1} of plasma with 4.5% human albumin solution.

Contra-indications to plasmapheresis include haemodynamic instability, uncontrolled sepsis and severe haemostatic problems. Side-effects include hypotension, hypocalcaemia, coagulation abnormalities and septicaemia.

Corticosteroids

It is generally now accepted that corticosteroids should not be used as a therapy in GBS. Studies to date have shown no advantage with, or instead of, immunoglobulin administration or plasmapheresis. However, there is an on-going study examining the efficacy of corticosteroid therapy in addition to immunoglobulin administration.

CSF filtration

There have been a few case reports describing an improvement in symptoms associated with CSF filtration after plasmapheresis and immunoglobulin therapy has been unsuccessful. However, like plasmapheresis, the logistics of this therapy are difficult and it is unlikely to replace intravenous immunoglobulin as a treatment of choice.

Outcome of Guillain-Barré disease

Mortality is approximately 10%; patients usually die from complications such as cardiac arrest secondary to autonomic dysfunction, respiratory infections, sepsis, pulmonary embolism, ARDS and respiratory failure. A further 10% of those affected will be unable to walk unaided at one year, although weakness may continue to improve for at least two years. An adverse outcome is associated with: (i) *Campylobacter* spp. infection; (ii) old age; (iii) need for ventilatory support; (iv) anti-GM1 antibody; (v) neurone specific enolase and S-100 proteins in the CSF; (vi) absent or reduced compound muscle action potential (CMAP); and (vii) inexcitable nerves and upper limb paralysis.

Recurrence of acute symptoms in GBS occurs in 2–5% of cases. It should be considered especially in patients with a previous episode of GBS who are not making an expected improvement when on the critical care unit for another disorder. Patients with GBS are often cared for within the critical care unit for prolonged time periods and medical staff may be lead into a false sense of security in deeming their conditions to be 'stable' – thus failing to identify the potential subtle signs of decompensation or complicating factors. Therefore, all patients should be regularly reassessed to ensure maximal recovery.

Suggested reading

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Hughes RAC, Raphael J-C, Swan AV, van Doorn PA. *Intravenous immunoglobulin for Guillain-Barré syndrome.* [Cochrane Review on CD-Rom]. Oxford, England : Cochrane Library, Update Software; 2000; issue 2

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See multiple choice questions 32–35.