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Guillain-Barré syndrome

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Guillain-Barré syndrome (GBS), with an annual incidence of 1–2 per 100,000, is the most common cause of neuromuscular paralysis in the western world. Even with modern intensive care and intravenous (iv) immunoglobulin (Ig) treatment there remains an associated mortality rate between 3.5% and 12% in the acute phase[1] and residual disability rate of 20% or more. Many other patients are left with long-term fatigue.

History and examination findings

GBS can be difficult to diagnose early as it can present with vague symptoms of weakness, neck or back pain and paraesthesia. It can also be difficult in atypical cases, with unusual distribution of weakness, for example presenting in the upper limbs or focusing on respiratory muscles with relative preservation of limb strength. An initial discharge from casualty is not uncommon, but patients with suspected GBS should be admitted and carefully observed in case paralysis and/or life-threatening bulbar dysfunction evolve rapidly.

There is little diagnostic doubt once it evolves into the classical picture of symmetrical quadriplegia, possibly also with respiratory muscle, facial and bulbar weakness. Weakness can appear 'pyramidal' in distribution, with hip and knee flexor weakness without other features of 'upper motor neurone' pathology. Total areflexia may evolve over a few days from initial hyporeflexia. By definition, the evolution of progression of weakness of two or more limbs from normality to nadir should be less than four weeks[2] and usually two weeks or less. A small minority have subacute symptom progression over 4–8 eight weeks, but any longer would suggest an alternative diagnosis. Very occasional patients appear to have a relapsing variant of GBS. Sensory symptoms and signs are usually mild. Other variants include the Miller-Fisher syndrome (MFS), originally described as ataxia, ophthalmoplegia and areflexia, but also including patients with more widespread cranial nerve involvement. MFS features can overlap with GBS.

GBS does not usually cause visual failure, hearing loss or early sphincter involvement. There should not be fever due to GBS nor a sharp sensory level.

Approximately two-thirds of patients report antecedent infection (eg diarrhoea, classically due to *Campylobacter jejuni*[3] or upper respiratory tract infection) in the previous six weeks. Anecdotal reports have reported GBS after vaccination, but only the USA 1976 swine flu vaccination programme has been causally linked to GBS.[4]

Aetiology

GBS is believed to be due to an autoimmune attack on peripheral nerves, occurring in previously healthy patients without evidence of other autoimmune diseases. Some of the antecedent infections most commonly associated with GBS (eg C. *jejuni*) are known to share structural similarities with components of peripheral nerves. Post-mortem studies and nerve biopsies show antibody and complement deposition, T cell and macrophage infiltration of nerves. Multiple immunological derangements have been described in the acute phase of GBS, the most robust of which are antibodies directed against individual or combinations of gangliosides.

Differential diagnosis (Table 1)

The differential diagnosis is relatively wide early in the syndrome, the initial focus being on locating the pathology in the nerve roots and peripheral nerves rather than elsewhere in the nervous system. When a diagnosis of a neuropathy has been made, the differential diagnosis includes:

- infection (lyme, diphtheria)
- inflammatory (neurosarcoid)
- paraneoplastic
- malignant (due to infiltration of nerve roots)
- vasculitic
- metabolic (beri-beri due to vitamin B1 deficiency)
- postinfectious/autoimmune in origin (GBS).

Confirmatory tests

GBS is a clinical diagnosis arrived at following exclusion of other mimics and with supportive tests.[5]

Neurophysiology is helpful – initial abnormalities are found in 85% of cases – but may be subtle (eg prolonged 'f' wave latencies, dispersed motor potentials and prolonged distal motor latencies).[6] Neurophysiology helps to subclassify

Table 1. Differential diagnosis of anatomical site of cause of progressive paralysis, with underling possible aetiologies.

Brainstem lesion	Stroke Encephalitis
Spinal cord	Polio virus Japanese encephalitis Enterovirus 71 West Nile virus Inflammatory, infectious, compressive cord or cauda equina lesions
Neuromuscular junction	Myasthenia gravis Botulism
Muscle	Metabolic Low K/PO4 Inflammatory Infectious

Key Points

- Guillain-Barré syndrome (GBS) is a clinical diagnosis, with progressive weakness and areflexia evolving over less than four weeks
- Antiganglioside antibodies are present in 25% of patients with typical acute demyelinating GBS; in Miller-Fisher syndrome 95% of patients possess antibodies against GQ1b ganglioside
- More than 10 white cells in cerebrospinal fluid should raise concern of alternative diagnoses including HIV
- Emergency management must include vital capacity and cardiac monitoring, together with early intubation for patients with declining respiratory and bulbar function
- Standard treatment is intravenous immunoglobulin 0.4 g/kg/day for five days in non-ambulant patients

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disease as predominantly demyelinating or axonal. Axonal variants are relatively rare in the UK, whereas they dominate in China after seasonal outbreaks of C. *jejuni*.[7]

A *lumbar puncture* should be done before treatment. A cerebrospinal fluid (CSF) white cell count of over 10/μl raises the possibility of leptomeningeal malignancy, HIV or an alternative infectious diagnosis (eg Lyme disease or poliomyelitis), but in clinical trials CSF cell counts up to 50/μl are permitted. IvIg can very occasionally cause an aseptic meningitis. Typically, the CSF protein is raised after the first week, often to more than 1 g/l.

Routine blood tests should include creatine kinase, biochemistry and Ig levels. These are done to exclude other causes of weakness and to reduce the risks of ivIg. In renal failure ivIg is relatively contraindicated and it is more likely to cause anaphylaxis in patients with IgA deficiency.

Antiganglioside antibodies are usually tested in GBS but their absence does not exclude the diagnosis. Increasing evidence suggests that they are pathogenic.[8] Gangliosides are widespread in the nervous system as they help maintain cell membrane structure:

- 25% of patients with the acute inflammatory demyelinating (AIDP) GBS variant possess antiganglioside (usually GM1) antibodies
- 95% of patients with Miller-Fisher syndrome possess anti-GQ1b antibodies
- 50% of patients with axonal variants (acute motor axonal neuropathy) possess anti-GM1 antibodies.

Life-saving measures (Table 2)

Cardiac arrhythmias and declining respiratory function can be life-threatening. A cardiac monitor and regular vital capacity (VC) measurements are essential, at least until the patient is mobile. The frequency of VC monitoring (eg hourly to qds) should be tailored according to the clinical state. Peak expiratory flow rates are no substitute. Intensive care should be alerted early if there is any clear bulbar involvement, and elective intubation instituted as VC approaches 15 ml/kg.[9] Declining oxygen saturations and changes in arterial blood gas values may mean that respiratory arrest is imminent. Prevention of deep vein thrombosis is paramount with thromboembolic disease stockings and subcutaneous heparin.

Table 2. Suggested emergency/acute medical unit management steps.

- Vital capacity hourly
- CXR
- Oxygen saturations/ABG as baseline
- Cardiac monitoring
- Swallow assessment
- TED stockings
- Bloods to include CK, ESR, biochemistry, Ig

ABG = arterial blood gas; CK = creatine kinase; CXR = chest X-ray; ESR = erythrocyte sedimentation rate; Ig = immunoglobulin; TED = thromboembolic deterrant.

Treatment

Randomised controlled trials show that the recovery of non-ambulant patients treated within two weeks of symptom onset is hastened by 0.4 g/kg/day ivIg for five days or 4–6 plasma exchanges.[10,11] Plasma exchange can help ambulant patients and those with symptoms of up to 30 days. By extrapolation, a similar benefit might be inferred from ivIg, but trials have not been conducted in these patient groups.

Treatment should be started as soon as possible, but there is no evidence that starting it 12 hours earlier (eg overnight) makes any difference. First-line treatment is now usually ivIg because of its ease of administration. Some patients respond initially to ivIg but the effect wears off within six weeks. Anecdotal evidence supports the use of further ivIg in these 'treatment-related fluctuations' (reviewed in Ref 12). For those patients not responding to treatment there is no evidence that giving a second course of ivIg is of any benefit. This is now being tested in a trial (personal communication; Inflammatory Neuropathy Consortium).

There is no evidence that steroids help, although they do not hinder so should be given if needed for other reasons,[13] or that giving plasma exchange followed by ivIg is better than plasma exchange alone.

Rehabilitation

Adequate pain relief and a multidisciplinary approach to rehabilitation are essential, as is patient education during the slow but steady recovery, with improvements to be expected for up to two years. The GBS Support Group has a useful website (www.gbs.org.uk) and support phone line. The US equivalent is the GBS Foundation International (www.gbs-cidp.org).

News

GBS is receiving more media coverage due to anxiety about whether the current swine flu outbreak will lead to more cases. All cases of GBS either in isolation, or linked to swine flu or the swine flu vaccine should be notified to the British Neurological Surveillance Unit. Recent analysis of historical data suggests, at least for seasonal influenza, that the virus itself is far more likely than its vaccine to lead to GBS.[14] Individuals are advised to talk to their general practitioner and neurologist or consult the advice pages of the GBS Support Group for general advice about vaccine use after GBS.

The future

Much remains to be done to reduce the burden of disability after GBS. Early determination of potential non- or poor responders to current treatment might alter their management. Recent work suggests that patients exhibit varying pharmacokinetics of ivIg metabolism and thus might require different or repeated doses of ivIg.[15] Better understanding of the pathogenesis and target antigen for the immune response in the usual AIDP GBS variant will be critical. The treatment of a monophasic autoimmune disease such as GBS is hampered by the limited ability to switch off a process already well underway before signs develop.

Biological treatments currently under investigation include monoclonal antibodies directed against components of the complement pathway; these prevent antiganglioside antibody-induced neuropathy in murine models.[16] Trials of novel treatments are likely to be hindered to some degree by the need to add them to ivIg as the current gold standard, and paradoxically by the now swift treatment of patients in district general hospitals where it will be more difficult to recruit an occasional patient to a treatment trial in GBS compared with the days of the large ivIg and plasma exchange trials.

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