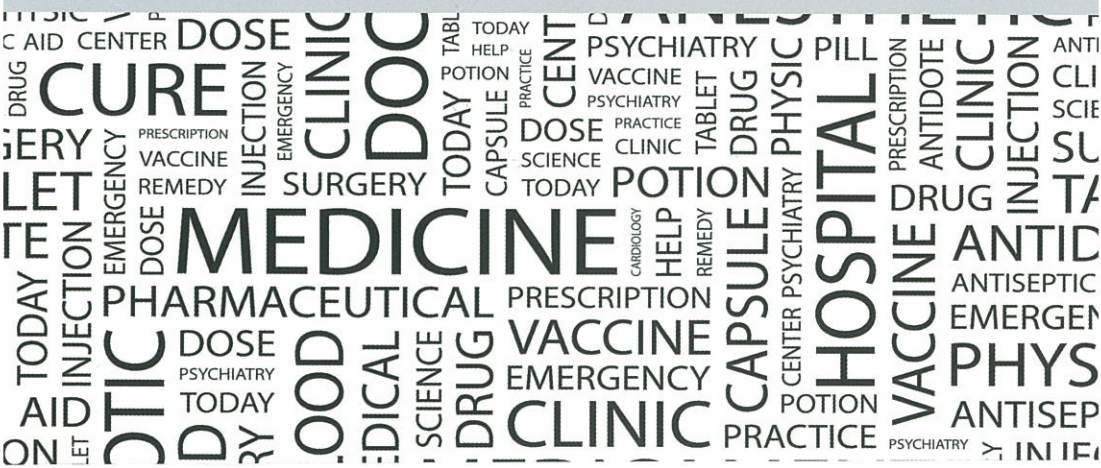
GBS Support Group

Guidelines for Medical Professionals



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Guidelines for health professionals

Guillain-Barré Syndrome

by Richard AC Hughes, Professor of Neurology

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Introduction

Guillain-Barré syndrome (GBS) is the commonest cause of acute neuromuscular paralysis in the United Kingdom (UK), with an annual incidence of between 1 and 2 per 100,000. Even with modern treatment, 8% of patients die — of respiratory failure, cardiac arrhythmias and pulmonary embolism — and a further 10% are still severely disabled one year later. The underlying pathology is usually multifocal inflammation and demyelination throughout the peripheral nervous system, with secondary axonal degeneration in the most severely affected[1]. Between 5-10% of cases are due to acute motor and sensory, or pure motor, axonal neuropathy[2].

Aetiology

Two-thirds of cases of GBS are preceded by an infection, including one-quarter caused by Campylobacter jejuni, which can be cultured in the stool for up to six weeks after diarrhoea has stopped. About 10% are caused by cytomegalovirus and a small percentage by Epstein-Barr virus or Mycoplasma pneumoniae, which can be identified by the presence of 1gM antibodies to these organisms in the blood. The nature of the preceding infection has not been consistently shown to affect the response to treatment, although evidence of Campylobacter infection, or even just a preceding history of diarrhoea, is an adverse prognostic factor[3].

Despite the generally accepted hypothesis that the pathogenesis is autoimmune, the target antigen has not been identified and no disease-specific autoantibodies have been identified. Antibodies to ganglioside GM1, especially of the IgG class, are present in the serum of 25% of patients, especially in those who develop severe axonal degeneration, but they are not sufficiently specific or sensitive to be useful as a diagnostic test[4].

Diagnosis

Clinical

The diagnosis should be established urgently so that treatment can be started as soon as possible. The possibility of GBS should be entertained in any patient with acute neuromuscular paralysis developing rapidly over one to several days. It presents with weakness of at least two limbs — commonly all four — which may be distal, proximal or both. There are usually sensory symptoms, but not necessarily marked deficit, and the tendon reflexes are diminished or usually absent. Preserved or brisk reflexes and extensor plantar responses suggest another diagnosis, although in the first few hours the reflexes may be preserved — which presents diagnostic difficulty to the general practitioner.

The neurological features should allow distinction from brainstem infarction or encephalitis, spinal cord disease including poliomyelitis, cauda equina lesions, neuromuscular conduction block, as in botulism, and muscle disease. Electrolyte disturbances, especially hypokalaemia, should always be considered. Alternative causes of neuropathy, such as alcohol, drugs, organophosphate or heavy metal poisoning, Lyme disease and diphtheria are usually evident from the history. Since acute neuropathy can be a presenting feature of other diseases, particularly vasculitis, systemic lupus erythematosus and porphyria, it is usually necessary to test the blood for antinuclear factor and the urine for porphyrins[5].

Nerve conduction

Detailed tests usually reveal conduction block in motor nerves at multiple sites from the onset of weakness. However, as sites of conduction block may not be easily accessible in routine studies, normal or only mildly abnormal results do not rule out the diagnosis during the first week. At later times, marked slowing of nerve conduction and diminution of both evoked muscle and sensory nerve action potentials are nearly always detected.

Cerebrospinal fluid

The characteristic abnormality is an increased protein concentration with a normal or only slightly raised white cell count. However, during the first week of the disease (which is when most patients have a lumbar puncture) the cerebrospinal fluid is often normal. A markedly raised white cell count raises the possibility of HIV infection, poliomyelitis or Lyme disease[2].

General management

Respiratory

In any patient with rapidly progressive neuromuscular paralysis, the possibility of respiratory failure should be considered and respiratory function monitored by repeated measurements of forced vital capacity. Arterial blood gases will only show oxygen desaturation when a hypoxic respiratory arrest is imminent. If a vital capacity monitor is not available on the ward the patient cannot be managed safely and should be transferred to a better-equipped unit. Peak expiratory flow is not an adequate substitute since it is the amount of air breathed, not the speed of air flow that is important. Patients with a rapidly falling vital capacity or one below 20 mL/kg (about 1.5 L in an adult) must be moved to an intensive care unit. The decision to institute ventilatory support will depend on a global assessment of the patient's condition including the presence of bulbar palsy, breathlessness on slight exertion, or fatigue. Intubation should be oral rather than nasal because of the risk of sinusitis from prolonged nasal intubation. If the patient requires intubation or tracheostomy, depolarising agents such as suxamethonium must be avoided because they can open potassium channels and induce dangerous hyperkalaemia, especially in denervated muscles. Tracheostomy should be performed as soon as it becomes clear that ventilatory support is going to last more than a few days because it is much more comfortable than oral intubation. A percutaneous bougie leaves a more acceptable scar than a surgical tracheostomy. Avoidance of atelectasis and chest infections in ventilated patients can be achieved by intermittent maximal lung expansion, bronchial suction and physiotherapy[6].

Cardiovascular

Autonomic instability causes fluctuating pulse and blood pressure and extreme sensitivity to

the hypotensive effects of sedative and analgesic drugs. There is also an increased incidence of cardiac arrhythmia, especially bradycardia induced by vagal stimulation, which can occur even before ventilation is required. All patients who are bedbound or have bulbar palsy should be attached to a continuous electrocardiograph (ECG) monitor and nursed where they can be resuscitated if necessary. This monitoring may need to begin from the time of admission, so that investigations come to the patient and not vice versa, and continue after discharge from the intensive care unit until the tracheostomy tube has been removed[6].

The risk of development of deep-vein thrombosis should be reduced by giving prophylaxis (such as heparin 5,000 units subcutaneously twice daily) for as long as patients are bedbound.

General measures

The intensive care of patients with GBS is complicated and can be very prolonged. The outcome may be better if patients are transferred to regional neurological intensive care units with more experience of the condition. Careful positioning, intermittent splinting of wrists, fingers and ankles and passive full-range joint movements can prevent contractures. Intensive care needs to encompass hydration and nutrition (in severe cases often best achieved with a percutaneous endoscopic gastrostomy), artificial tears for corneal exposure, prevention of pressure sores, bladder catheterisation, laxatives and analgesia. Repeated reassurance is more beneficial than sedation.

Pain is a common problem, arising from immobility, inflamed nerves and denervated muscles. Adequate analgesia is often difficult to achieve. Careful, frequent repositioning, supportive mattress design, and good nursing are most important. Standard analgesics may not be sufficient and opiate analgesics may be necessary, although these can cause hypotension and aggravate constipation. Carbamazepine can sometimes be helpful for painful paraesthesiae but may exacerbate hyponatraemia, which can occur in GBS as a consequence of inappropriate antidiuretic hormone (ADH) secretion. Amitriptyline can also help in the management of pain, but aggravates constipation. A visit from a patient who has lived through the experience can be helpful and can be arranged through the Guillain-Barré Syndrome Support Group.

Immunotherapy

In large randomised controlled trials, plasma exchange has been shown to hasten recovery in both mildly and severely affected patients[7,8,9]. Various regimens have been used but the most common involves five plasma exchanges, each of one plasma volume, conducted on alternate days. Treatment is more effective if started during the first week after onset of the neuropathy than later[10].

However, intravenous immunoglobulin is now preferred to plasma exchange and two large randomised controlled trials have shown that it is equally effective in patients who are so severely affected that they require aid to walk[11,12]. The cost of the two treatments is approximately the same but intravenous normal immunoglobulin probably has fewer adverse effects and is certainly more convenient to use and more widely available. The standard regimen is 0.4 g/kg daily for five consecutive days. Intravenous immunoglobulin should be avoided in patients with renal failure, which it can worsen — possibly because of haemoconcentration. As anaphylaxis is a rare complication each infusion should be started very slowly, the patient should be monitored carefully and resuscitation equipment with intramuscular adrenaline should be immediately available. About 10% of patients relapse

within two to ten weeks of treatment with either plasma exchange or intravenous immunoglobulin; these patients are usually treated again with the same treatment as was used previously. Further relapses or gradual progression suggest that the patient is developing subacute or chronic inflammatory demyelinating polyradiculoneuropathy, for which repeated treatment or corticosteroids may be necessary.

Randomised controlled trials in GBS have shown no benefit from corticosteroids and their use should be discouraged[13]. The only alternative immunosuppressive regimen to have been tested in a sufficiently large trial is plasma exchange immediately followed by intravenous immunoglobulin, which was found no more effective than either alone[12].

Rehabilitation and prognosis

Older age, a history of preceding diarrhoea, and severe arm as well as leg weakness all predict a slower recovery with an increased probability of not being able to walk unaided a year later. It is helpful in dealing with the convalescent phase to warn patients at an early stage that, while improvement is almost universal and many people recover completely, some are left with persistent symptoms. Persistent disability is not necessarily directly due to the physical deficit and a better outcome may be achieved by a multidisciplinary, holistic approach to behavioural attitudes, coincidental medical disorders, anxiety, depression and social problems[14]. There is no good evidence that current vaccines cause GBS or trigger a relapse but information is limited[15]. General practitioners need to reinforce the advice that major improvement is likely and complete recovery possible to reduce the risk of prolonged illness behaviour. At the same time, the support needed by the 10% with severe persistent disability must be recognised and provided. The Guillain-Barré Syndrome Support Group offers a helpful support service and has produced a short awareness presentation for health professionals.

Conclusions

- Guillain-Barré syndrome should be considered in all cases of acute neuromuscular paralysis.
- The diagnosis should be established urgently so that treatment can be started quickly.
- Monitoring should include vital capacity measurement and continuous electrocardiograph recording.
- Low-dose subcutaneous heparin should be given to bedbound patients.
- Intravenous immunoglobulin is the preferred treatment for patients who are affected severely enough to require aid to walk.

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Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a chronic demyelinating neuropathy which is regarded by some as a rare variant of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), but others view it as a separate entity because it has different clinical features from 'standard' CIDP and responds differently to treatment.

MMN consists of a slowly progressive or stepwise lower motor neuron syndrome causing weakness which is often asymmetric and can predominantly affect distal or upper limb muscles. A characteristic finding is the presence of differential weakness in muscles innervated by the same nerve, suggesting a patchy pathological process rather than complete damage to that individual nerve. There should be no (or minimal) sensory symptoms. There must be no upper motor neuron signs, tendon reflexes are decreased or absent, and there are no abnormalities in cranial nerve distribution (other than tongue involvement in occasional reports). This mixture of clinical features means that MMN mimics a subtype of motor neuron disease in which only lower (and not upper) motor neurons are affected.

There is no specific diagnostic test for MMN but its hallmark is the neurophysiological finding of 'conduction block' (a drop in motor amplitude of at least 30%-50% between two points along a nerve in a site not prone to compression). No additional tests are necessary in a patient with an appropriate clinical scenario who meets neurophysiological criteria. There is debate over whether the criteria for neurophysiological diagnosis are too stringent, as it can be difficult to detect conduction block and since this is the defining feature of the disease there is concern that some patients may miss out on benefiting from treatment (Slee et al., 2007). Blood tests may show IgM anti-GM1 ganglioside antibodies in about 50% of cases but these are not specific for MMN. Lumbar puncture tests are usually normal, unlike in CIDP where the protein is often raised. Magnetic Resonance Imaging (MRI) scans of the brachial plexus may show increased signal intensity, hypertrophy or enhancement.

A nerve biopsy does not need to be performed to diagnose MMN but can be useful to exclude alternative diagnoses (eg vasculitic neuropathy)

There have been very few randomised controlled trials of treatment in MMN, but a review of those that are published (van Schaik et al, 2005) showed that 78% of 34 patients responded to intravenous immunoglobulin (IVIg) with improved strength and a non significant trend to reduce disability. IVIg is thus recommended by the Department of Health for treating MMN and is the treatment of first choice. Typical doses are 1g/kg every 2-4 weeks or 2g/Kg every 4-8 weeks, tailored to individual needs. A small number of patients go into spontaneous remission whilst the majority can go into remission with repeated IVIg courses (Leger et al., 2008). During prolonged treatment the effectiveness of IVIg may be reduced, perhaps because of axonal degeneration. Attempts to add in other immunosuppressive agents (eg mycophenolate mofetil, cyclophosphamide, rituximab), to reduce IVIg requirements, have not met with significant success.

If IVIg does not work initially, is contraindicated or ceases to be effective for MMN it becomes more difficult to treat MMN with any firm evidence base. Patients with MMN differ from patients with CIDP in their response to treatment as there have been reports that MMN can be

made worse by steroids and plasma exchange, unlike in CIDP. There is only scanty evidence for the use of other immunosuppressive agents eg azathioprine, ciclosporin, cyclophosphamide, ?-interferon and rituximab (Umapathi et al, 2005; EFNS taskforce, 2006).

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Management of paraproteinaemic demyelinating neuropathies

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Summary

Paraprotein-associated neuropathies have heterogeneous clinical, neurophysiological, neuropathological and haematological features.

1. Patients with paraproteinaemic demyelinating neuropathy (PDN) should be investigated for a malignant plasma cell dyscrasia.

2. The paraprotein is more likely to be causing the neuropathy if the paraprotein is immunoglobulin (Ig)M, antibodies are present in serum or on biopsy, or the clinical phenotype is chronic distal sensory neuropathy with demyelinating neurophysiology.

3. Patients with IgM PDN usually have a distinct syndrome of predominantly distal sensory impairment, with prolonged distal motor latencies, and often anti-myelin associated glycoprotein antibodies.

4. IgM PDN sometimes responds to immune therapies. Their potential benefit should be balanced against their possible side-effects and the usually slow disease progression.

5. IgG and IgA PDN may be indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy, clinically, electrophysiologically, and in response to treatment.

6. For POEMS syndrome, local irradiation or resection of an isolated plasmacytoma, or melphalan with or without corticosteroids, should be considered, with haemato-oncology advice.

Introduction

This is a summary of guidelines prepared by a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society and published in 2006 (1). This summary is a practical guide aimed at non-specialist doctors, nurses and other health professionals, covering the diagnosis, investigation and treatment of patients with both a demyelinating neuropathy and a paraprotein.

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[1] This text was written by Dr Robert Hadden and approved by the Medical Advisory Board of the Guillain-Barré Syndrome Support Group of the UK in 2008. It is a summary of an original article by a Task Force appointed jointly by the European Federation of Neurological Societies and Peripheral Nerve Society (1). The full text of the original article is available free at **http://pns.ucsd.edu**. The membership of the Task Force included RDM Hadden, E Nobile-Orazio, C Sommer, A Hahn, I Illa, E Morra, J Pollard, RAC Hughes (Chair), P Bouche, D Cornblath, E Evers, CL Koski, JM Léger, P Van den Bergh, P van Doorn, IN van Schaik.

Both paraproteins and neuropathies are common, and when they occur together there is often uncertainty as to whether the neuropathy is caused by the paraprotein and how they should be treated. Generally these are chronic conditions managed as an outpatient.

The neuropathies associated with paraproteins are heterogeneous and there is no agreed diagnostic classification.

Many patients with paraproteinaemic demyelinating neuropathy (PDN) have a neuropathy that is indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and there is no consensus as to whether these should be considered the same or different diseases. We have chosen to concentrate in this guideline on demyelinating neuropathies.

Possibly the most useful way to classify PDN is by the immunoglobulin type. As distinct from IgG and IgA PDN, IgM PDN tends to have a typical clinical phenotype, pathogenic antibodies, a causal relationship between paraprotein and neuropathy, and different evidence about treatment. Nevertheless, there is significant overlap.

A. Investigation and classification of the paraprotein

A paraprotein indicates an underlying disease of plasma cells in bone marrow, which may be malignant or a monoclonal gammopathy of uncertain significance (MGUS) (2). Serum immunofixation electrophoresis is a more sensitive technique than standard serum protein electrophoresis and is recommended in all acquired demyelinating neuropathies.

If a paraprotein is detected, investigations should be considered to assess the cause and effects (general medical and haematological) of the paraprotein, perhaps including serum cryoglobulins and radiographic x-ray skeletal survey. Referral to a haematologist is usually recommended to consider bone marrow examination, etc. The full guideline (1) gives definitions of when a paraprotein may be considered to be a MGUS and prognostic features to assess the risk of malignant transformation.

B. Typical syndromes of paraproteinaemic demyelinating neuropathy

The most common types of PDN are those with demyelinating neuropathy and MGUS, with no symptoms other than the neuropathy. The neuropathy is defined as demyelinating if it satisfies electrophysiological criteria for CIDP (3).

1. IgM PDN

Most patients with IgM PDN have the "distal acquired demyelinating symmetrical" (DADS) clinical phenotype of predominantly distal, chronic (duration over 6 months), slowly progressive, symmetric, predominantly sensory impairment, with ataxia and relatively mild or no weakness, and often tremor. On nerve conduction studies, most patients have disproportionately prolonged distal motor latencies, more severe sensory than motor involvement, and no conduction block. Almost 50% of patients with IgM PDN have high titres of antibodies to myelin-associated glycoprotein (MAG), and this is the best defined syndrome of PDN (4). Some patients with IgM PDN have IgM antibodies against various gangliosides, which increase the probability of a pathogenetic link between the paraprotein and the neuropathy.

2. IgG or IgA PDN

Patients with IgG or IgA PDN usually have both proximal and distal weakness, with motor and sensory impairment, and are indistinguishable clinically and electrophysiologically from typical CIDP. In patients with IgG or IgA paraprotein, antibody testing is not helpful.

C. Other neuropathy syndromes associated with a paraprotein

POEMS

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal band and Skin changes) syndrome usually has an underlying osteosclerotic myeloma, with IgA or IgG lambda paraprotein, or sometimes Castleman's disease. POEMS neuropathy has similar clinical features to CIDP. Many patients are initially thought to have CIDP or ordinary PDN, until POEMS is suggested by the presence of systemic features such as sclerotic bone lesions, hepatosplenomegaly, lymphadenopathy, endocrinopathy, papilloedema, skin changes (hypertrichosis, hyperpigmentation, diffuse skin thickening, finger clubbing, dermal haemangiomas, white nail beds) and oedema (5). There is no specific diagnostic test for POEMS.

CANOMAD

The syndrome of Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Monoclonal gammopathy, cold Agglutinins and Disialoganglioside (IgM anti-GD1b/GQ1b) antibodies (CANOMAD) is a rare neuropathy similar to chronic (Miller-)Fisher syndrome, with mixed demyelinating and axonal electrophysiology (6).

Other

Axonal neuropathy is often present in patients with MGUS, but the pathogenesis and causal relationship vary.

AL-amyloidosis should be suspected in the presence of prominent neuropathic pain or dysautonomia, and may be demonstrated by abdominal fat aspirate or biopsy of nerve, rectum, bone marrow or kidney. .

In patients with lytic multiple myeloma (usually associated with IgA or IgG paraprotein) neuropathy may be caused by heterogeneous mechanisms, including amyloidosis, metabolic and toxic insults, and cord or root compression due to vertebral collapse from lytic lesions.

Subacute weakness similar to Guillain-Barré syndrome may be caused by extensive infiltration of nerves or roots by lymphoma or leukaemia.

D. Is the paraprotein causing the neuropathy?

A causal relationship is more likely with an IgM paraprotein (compared with IgG or IgA), especially if there are anti-MAG antibodies or nerve biopsy shows widely-spaced myelin on electron microscopy. IgG or IgA PDN may merely be CIDP with a co-incidental paraprotein.

E. Cerebrospinal fluid and nerve biopsy

The CSF protein is elevated in most patients with PDN. CSF examination is most likely to be helpful in suspected malignant lymphoproliferative infiltration, or in patients without definite demyelinating electrophysiology where a raised CSF protein would help to suggest that the neuropathy is immune-mediated.

The presence of widely spaced myelin on electron microscopy of nerve biopsy is highly sensitive and specific for anti-MAG neuropathy. Nerve biopsy is most likely to be helpful in cases of suspected amyloidosis, vasculitis (e.g. due to cryoglobulinaemia), or malignant lymphoproliferative infiltration of nerves.

F. Treatment of paraproteinaemic demyelinating neuropathies

Monitoring of haematological disease.
In MGUS there is a 1% annual risk of malignant transformation, so paraprotein and immunoglobulin concentrations should be monitored at least annually.

IgM PDN
There is so far inadequate reliable evidence to recommend any particular immunotherapy (7;8). Most of the trials have been small and uncontrolled, often with contradictory results.
Plasma exchange and intravenous immunoglobulin (IVIg) may give short term benefit. The usage of IVIg is now subject to a demand management programme in the UK (www.ivig.nhs.uk). Chlorambucil and cyclophosphamide have often given benefit, usually in combination with corticosteroids. Interferon-alpha has given inconsistent results. There are recent anecdotal reports on the efficacy of fludarabine, cladribine, and high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation.

Rituximab, a humanised monoclonal antibody against B-lymphocytes, has recently shown benefit in several open pilot trials but results of randomised controlled trials are not yet available. It appears to have a better ratio of benefit to adverse effects than other treatments. Benefit may last several years from a single course of rituximab, which may then be repeated.

In conclusion, patients without significant disability may be offered symptomatic treatment for tremor (e.g. propranolol) and paraesthesiae (e.g. tricyclic or gabapentin), with reassurance that symptoms are unlikely to worsen significantly for several years. In patients with significant or rapidly worsening disability, rituximab may be considered as initial treatment.

IgG and IgA PDN
In patients with a CIDP-like neuropathy, the detection of IgG or IgA MGUS does not justify a different treatment approach from CIDP without a paraprotein (9).

POEMS
There are no controlled trials on the treatment of neuropathy in POEMS. Patients should be managed in consultation with a haemato-oncologist. Patients with a solitary plasmacytoma may benefit from local radiation or surgical excision. Melphalan (with or without corticosteroids) should be considered for patients with multiple or no detectable bone lesions. Autologous peripheral blood stem cell transplantation induced neurological improvement or stabilization in 14 of 16 patients but has significant morbidity.

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