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An Overview of Guillain-Barré Syndrome

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Abstract

Guillain-Barré Syndrome (GBS) is an acute, autoimmune polyradiculoneuropathy that carries great patient morbidity, and significant mortality, worldwide. The manifestations are highly heterogeneous at the clinical, electrophysiological and biochemical levels, which means that it is better to conceptualise GBS as a spectrum of disorders rather than a singular one. Despite the diverse range of presentations, the management of GBS is relatively stereotyped, albeit guided by the level of clinical severity. Treatment is largely restricted to general supportive measures, Intravenous Immunoglobulin (IVIG) and Plasma Exchange (PLEX), with no current role for oral or intravenous corticosteroids in clinical practice. Several validated prognostic-scoring systems, which can predict the probability of long-term residual disability, may assist in targeting intensive therapies to high-risk patient groups. The aim of this article is to provide a practical overview of GBS, with particular emphasis on the clinical presentation, investigation and management of this important spectrum of neurological conditions.

Keywords: Guillain-Barré syndrome, Acute inflammatory demyelinating polyneuropathy, Acute motor axonal neuropathy, Electrophysiology, Intravenous immunoglobulin, Plasma exchange.

Abbreviations: AIDP-Acute Inflammatory Demyelinating Polyradiculoneuropathy, a-CIDP-acute-onset Chronic Inflammatory Demyelinating Polyneuropathy, AMAN-Acute Motor Axonal Neuropathy, AMSAN-Acute Motor and Sensory Axonal Neuropathy, BP-Blood Pressure, CMAP-Compound Muscle Action Potential, CSF-Cerebrospinal Fluid, EGOS-Erasmus GBS Outcome Scale, FVC-Forced Vital Capacity, GBS-Guillain-Barré Syndrome, ICU-Intensive Care Unit, IGOS-International GBS Outcome Study, IVIG-Intravenous Immunoglobulin, PLEX-Plasma Exchange, RCTs-Randomised-Controlled Trials, TRF-Treatment-Related Fluctuation.

Introduction

Guillain-Barré Syndrome (GBS) is an acute, monophasic, autoimmune polyradiculoneuropathy, described just over a century ago, and remains an important cause of neuromuscular paralysis worldwide [1-4]. The clinical presentation of GBS is heterogeneous and can range from a mild self-limiting muscle weakness to a life-threatening quadriplegia with respiratory failure necessitating artificial ventilation. There is an increasing awareness of the diverse range of not only clinical, but also electrophysiological and autoantibody profiles that characterize GBS, suggesting that it is not a singular condition, but rather a spectrum of related disorders [5-7].

The aim of this article is to provide an overview, and an update, of GBS, with discussions pertaining to its epidemiology, aetiology, clinical presentation, investigation, diagnosis, management and prognosis of this acute neurological disorder.

Epidemiology

Most epidemiological studies on GBS have been undertaken in Europe and North America. The overall annual incidence of GBS is estimated to be 1-2/100,000 per year [2] though this figure rises with age above 50 years to up to 3.3/100 000 per year [2,4] and men are more frequently affected than women (3:2) across all ages [2]. Various epidemiological studies have also demonstrated a bimodal age distribution in incidence of GBS, although there is some disagreement between studies and the age categories in which these peak incidences, if they are identified, are variable [8-13].

GBS exists in both demyelinating (Acute Inflammatory Demyelinating Polyradiculoneuropathy [AIDP]) and axonal (Acute Motor Axonal Neuropathy [AMAN] and Acute Motor and Sensory Axonal Neuropathy [AMSAN]) forms [14-17]. The recent International GBS Outcome Study (IGOS) has shown that geographical location exerts a major influence in GBS clinical phenotype, disease severity and patient outcomes, but also electrophysiological subtype [15]. AIDP was the predominant subtype in all regions investigated (Europe/Americas: 55%, Asia: 45%, Bangladesh: 40%), whereas the axonal subtype was more frequent in Bangladesh (36%) than in Europe/Americas (6%) and other Asian countries (6%) [15]. In all regions assessed, patients with the axonal subtype showed a trend towards poorer recovery [15].

GBS is an immune-mediated disorder preceded by respiratory infection or gastroenteritis (classically by *Campylobacter Jejuni*), within 4 weeks of onset of muscle weakness, in nearly two-thirds of adult patients [18]. The occurrence of such prodromal illnesses may also explain seasonal fluctuations in the incidence of GBS cases, though this has only been reported in certain geographical regions [19]. In more extreme case scenarios, GBS has been demonstrated to closely track infectious outbreaks spatially and temporally. This has been seen in outbreaks of *C. Jejuni* infection in North America [20] and also more recently highlighted by the dramatic rise in incidence of GBS

cases in Brazil and Colombia in 2015-2016 following the *Zika* virus outbreak [21,22]. Thus, the epidemiology of GBS is dynamic and at least partly sculpted by the incidence and distribution of certain antecedent -infective illnesses.

Aetiology

Many microbial causes have been implicated in antecedent infection preceding GBS. These include *Influenza A* virus, *Cytomegalo*virus, *Epstein-Barr* virus, *Mycoplasma Pneumoniae*, *Hepatitis E* and more recently *Zika* virus [18,22]. However, the commonest antecedent infective cause is *C. Jejuni*, which has been linked to the axonal variant of GBS [23]. Precisely why less than 0.1% of patients with *C. Jejuni* enteritis develop GBS within the following 2 months is not entirely clear [24]. This may be due to a combination of host genetic susceptibility factors and infection with subtype-specific strains of this bacterium, which can be highly variable [25]. Similar principles may be relevant with other microbes.

An important mechanism underlying the aetio-pathogenesis of GBS is believed to be molecular mimicry, whereby antibodies generated by the host, against target microbial antigens, cross-react with neural epitopes. In the case of GBS following *C. Jejuni* infection, antibodies cross-react with certain ganglioside antigens clustered on axonal membranes, such as GD1a or GM1, resulting in the AMAN GBS variant [23,25]. Anti-ganglioside antibody generation also occurs in association with complement activation, which further drives peripheral nerve degeneration. Indeed, blocking complement can be neuro-protective in mouse models of GBS [26].

Clinical Presentation

In classic cases, GBS presents as an acute, ascending, symmetrical, flaccid muscle paralysis, which can progress over the course of days to several weeks, to quadriplegia with or without cranial nerve involvement. Involvement of diaphragmatic and intercostal muscles may lead to respiratory failure requiring intensive care support and invasive mechanical ventilation, in up to 20-30% of hospitalized patients, which is usually associated with a poor outcome and significant mortality [27-31].

GBS is a monophasic illness, which reaches nadir within 4 weeks in the majority of patients, but typically within 2 weeks [32]. If there is clinical progression beyond 4 weeks, then this should suggest an alternative diagnosis, (although 3% can progress to week 6) [32]. **Table 1** lists the differential diagnoses of GBS.

• Spinal cord injury (disc prolapse, epidural abscess/haematoma, anterior cord infarction).
• Transverse myelitis (infective/inflammatory).
• Anterior horn cell destruction (infective [Polio, West Nile, enterovirus 71, HIV]).
• Other acute peripheral neuropathy (infective, toxic [TTX, lead, arsenic], metabolic [Porphyria]).
• Neuromuscular junction disorders (myasthenia gravis, botulism).
• Others: Myositis, genetic (e.g. hypo or hyperkalaemic periodic paralysis), functional.

Table 1: Differential diagnoses of GBS.

Despite usually being recognized as a disease restricted to lower motor neurons, with hypo- or areflexia, approximately 10% of patients have normal or brisk deep tendon reflexes, suggesting that concomitant upper motor neuron involvement occurs in some cases [33].

Aside from weakness, patients can develop autonomic dysfunction such as arrhythmias (which in some cases necessitate pacemakers), blood pressure lability, hyperhydrosis or ileus [34]. Pain, particularly

severe back pain, is also a commonly associated clinical feature [35], and in cases of bilateral flaccid lower limb weakness, may complicate the differential as this could also suggest the possibility of cauda equina syndrome or acute cord pathology - the more prominent and persistent bladder and/or bowel disturbance with saddle paraesthesia or sensory level, and confirmation with an urgent MRI spine, will help distinguish these differential diagnoses.

The diagnosis of GBS can be made using the Brighton criteria. This takes into consideration the level of diagnostic certainty (graded from 1 to 4) for each category of clinical examination findings (bilateral flaccid muscle weakness, hypo- or areflexia, monophasic disease course from onset time to nadir), ancillary investigations (CSF cell count <50/µl, raised CSF protein, supportive nerve conduction study findings) and absence of an alternative explanation for muscle weakness. Importantly, this has been validated in several studies [32,36-38].

Other subtypes of GBS are recognised [5,7], which include:
Classical Miller-Fisher syndrome (MFS) (10%): Triad of ophthalmoplegia, areflexia and ataxia associated with anti-GQ1b antibodies in 80-90% of cases [39].
Paraparetic GBS (7%): flaccid weakness of both lower limbs with relative sparing of other muscle groups.
Pharyngeal-cervical-brachial subtype (5%): weakness of bulbar, neck and upper limb muscles, and is associated with anti-GT1a antibodies. This clinical syndrome may be misdiagnosed as myasthenia gravis or botulism [7,40].
Bifacial weakness with paraesthesia (3%): the sensory disturbances (e.g. tingling) typically affect the distal extremities.
Bickerstaff brainstem encephalitis (2%): MFS phenotype but with associated encephalopathy and disrupted consciousness due to involvement of the ascending reticular activating system [41,42].

Investigations

Although largely a clinical diagnosis, several ancillary investigations can be helpful when confronted with a case of suspected GBS. Neurophysiology facilitates a confident diagnosis, but also allows differentiation of the axonal (AMAN and AMSAN) from demyelinating (AIDP) subtypes [14], which can assist in predicting short and long-term prognoses [43-45].

The neurophysiological features of demyelinating variants include abnormal F waves (which along with loss of the H reflex is amongst the earliest of features within 1 week of muscle weakness), slowing of motor conduction velocities, prolongation of distal motor latencies and temporal dispersion [46]. Sparing of the sural Sensory Nerve Action Potential (SNAP) is particularly characteristic of GBS. A significant reduction in the distal Compound Muscle Action Potential (CMAP) amplitude (<80% of the lower limit of normal), alongside the absence of demyelinating features, suggests axonal GBS [14,47]. Electrophysiological abnormalities are evident in over 85% of patients at least 2 weeks after the start of muscle weakness [48] and thus may be normal early during its natural history. Thus, the diagnosis in the acute setting is largely clinical.

Analysis of Cerebrospinal Fluid (CSF) is helpful and classically reveals a raised protein with normal cell count (albuminocytological dissociation), the sensitivity of which is dependent on timing of lumbar puncture (raised CSF protein is seen in 49% at day 1 and 88% after 2 weeks of weakness) [32]. CSF white cell counts greater than 50 cells/µl would suggest an alternative diagnosis [32] such as infective, inflammatory or neoplastic infiltration of the brain, cord and/or meninges.

Spinal MRI imaging is useful in excluding alternative differential diagnoses that sometimes mimic classic GBS such as acute spinal disc prolapse, epidural abscess/hematoma, cord infarction or transverse

myelitis [7]. Nerve root enhancement on gadolinium contrast MRIs can positively support a diagnosis of GBS, and may provide useful information in electrophysiologically equivocal cases [49].The diagnostic utility of testing serum for anti-ganglioside antibodies can be of assistance such as for anti-GQ1b antibodies in MFS [50], anti-GD1a and anti-GM1 for AMAN [51,52] and anti-GT1a for the PCB variant of GBS [53]. However, the absence of anti-ganglioside antibodies does not exclude the diagnosis for each GBS subtype.

Management

Due to the heterogeneity of the disease, management is tailored to individual patients and should be based on their pattern and severity of clinical presentation. Various parameters must be closely monitored to identify those individuals who are at risk of deterioration and require urgent supportive care. Respiratory function should be observed and must include frequent checks of the patient's Forced Vital Capacity (FVC). As a generic rule, FVC values less than 20ml/kg require escalation of care to the Intensive Care Unit (ICU) for close monitoring and possibly endotracheal intubation – if the FVC is less than 15ml/kg, then this would require more serious consideration for prompt intubation and mechanical ventilation [54]. Clinical models have been generated, which allow for the prediction of risk of respiratory insufficiency and subsequent requirement for mechanical ventilation within 1 week of symptom onset [55]. Of note, pulse oximetry and arterial blood gas measurements are inadequate for early detection of respiratory failure and they should not be solely relied upon [56].

Haemodynamic monitoring of Blood Pressure (BP) and heart rate/rhythm is imperative owing to risk of BP lability and cardiac autonomic disturbances, which in severe cases, can lead to atrioventricular block or asystole necessitating pacemaker insertion [57,58].

Deep vein thrombosis prophylaxis with low molecular weight heparin should be considered in patients if there are no contraindications, pain should be treated with analgesics and bladder and/or bowel dysfunction should be managed appropriately. Physiotherapy input to facilitate mobilization, and to prevent muscle deconditioning, alongside psychosocial support to help manage any concomitant symptoms of depression or anxiety are also both crucial aspects of supportive care [59].

The cornerstone of therapy for GBS is Intravenous Immunoglobulin (IVIG) or Plasma Exchange (PLEX) and their equivalent short and long-term benefits against morbidity have been demonstrated in multiple Randomised-Controlled Trials (RCTs) [60-63]. Oral corticosteroids or intravenous methylprednisolone are not effective in hastening recovery or impacting long-term outcome in GBS [64].

IVIG or PLEX should be commenced in patients with GBS who are unable to walk 10m unaided (GBS disability scale score ≥ 3) at the earliest opportunity following symptom onset [60]. IVIG hastens recovery from GBS as much as PLEX if given within 2 weeks of symptom onset and RCTs have shown that IVIG is more likely to be completed than PLEX, probably due to greater patient convenience (rates of adverse events are equivalent overall in both groups) [62].

IVIG is administered as a total dose of 2g/kg divided over 2 or 5 days, though it remains unclear which duration, if any, is superior. Approximately 10% of patients may clinically deteriorate following a period of stabilization after their first treatment course of IVIG or PLEX, a phenomenon referred to as Treatment-Related Fluctuation (TRF) [65]. Although, common practice involves commencing a second course of the same treatment in such patient groups, the evidence for this is sparse at the present time. Patients who continue to relapse after 8 weeks of symptom onset should have their diagnosis revised to acute-onset Chronic Inflammatory Demyelinating Polyneuropathy (a-CIDP), which has long-term therapeutic

implications as these patients may require further courses of IVIG and/or initiation of corticosteroids [66].

PLEX is beneficial if given within 4 weeks of symptom onset, but the effect sizes are greater if given earlier, especially within 2 weeks [60-63]. It is typically administered in 5 sessions over 2 weeks, with an exchange of 2-3L of plasma per session, depending on body weight. The combination of PLEX followed by IVIG is not superior to either treatment given alone [60-63]. The role of IVIG or PLEX in mildly affected patients who remain ambulatory is unclear and the evidence remains limited. As a pragmatic approach, and according to expert opinion [67], treatment with IVIG/PLEX should be considered if such patients also have significant autonomic dysfunction, bulbar or facial weakness [67]. Similarly, in patients with MFS, IVIG/PLEX should be given if there is additional limb weakness during its course (MFS-GBS overlap), facial, bulbar or respiratory weakness; otherwise in uncomplicated cases, supportive treatment alone is often sufficient [67].

Prognosis

Despite the aforementioned treatments, GBS has an overall estimated mortality of 3-12% and up to one-fifth of survivors cannot walk unaided after 6 months [68,69]. Various prognostic models, such as the Erasmus GBS Outcome Scale (EGOS) and the modified EGOS, have been generated and validated. These have shown that certain clinical parameters, namely greater age (which is associated with greater disability) [36,70], preceding diarrheal illness and a higher level of disability within 1-2 weeks into the clinical course, are collaboratively associated with a lower probability of independent ambulation at up to 6 months [71,72]. Thus, these models can be used to predict which patients are more likely to suffer from long-term residual disability, enabling more intensive therapies, and future planning of supportive treatments, to be targeted to such high-risk groups. However, it is important to note that residual disability is not restricted to muscle weakness, but also encompasses fatigue, pain and psychological morbidity, which can all impact on activities of daily living, occupation and social functioning, and are not incorporated in these models.

Conclusions

GBS remains a significant worldwide cause of rapidly progressive muscular paralysis. Although it is predominantly a clinical diagnosis, neurophysiology, CSF analysis and neuroimaging are all helpful in excluding potential mimics (and corroborating the diagnosis), which may otherwise lead to diagnostic conundrums and therapeutic dilemmas. The majority of studies that have assessed the role of therapies in GBS, namely IVIG and PLEX, have been undertaken in North America and Europe, which have a higher proportion of demyelinating GBS variants. The impact of these therapies specifically in axonal GBS, which is more prevalent in certain Asian countries, is less clear but nonetheless routinely recommended in clinical practice. Better disease-modifying therapies are still required in GBS as a significant fraction of patients suffer residual long-term neurological disability.

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