Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS)

Pieter A. van Doorn

Erasmus MC, Department of Neurology, Rotterdam, The Netherlands

Correspondence:
Pieter A. van Doorn, Erasmus MC, Department of Neurology’s-Gravendijkwal 230, 3015CE Rotterdam, The Netherlands.
p.a.vandoorn@erasmusmc.nl

Summary

Guillain-Barré syndrome (GBS) is an acute polyneuropathy with a variable degree of weakness that reaches its maximal severity within 4 weeks. The disease is mostly preceded by an infection and generally runs a monophasic course. Both intravenous immunoglobulin (IVIg) and plasma exchange (PE) are effective in GBS. Rather surprisingly, steroids alone are ineffective. Mainly for practical reasons, IVIg usually is the preferred treatment. GBS can be subdivided in the acute inflammatory demyelinating polyneuropathy (AIDP), the most frequent form in the western world; acute motor axonal neuropathy (AMAN), most frequent in Asia and Japan; and in Miller-Fisher syndrome (MFS). Additionally, overlap syndromes exist (GBS-MFS overlap). About 10% of GBS patients have a secondary deterioration within the first 8 weeks after start of IVIg. Such a treatment-related fluctuation (TRF) requires repeated IVIg treatment. About 5% of patients initially diagnosed with GBS turn out to have chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with acute onset (A-CIDP). It is yet unknown whether GBS patients who remain able to walk (‘mildly affected GBS patients’), or patients with MFS, also benefit from IVIg. Despite current treatment, GBS remains a severe disease, as about 25% of patients require artificial ventilation during a period of days to months, about 20% of patients are still unable to walk after 6 months and 3–10% of patients die. Additionally, many patients have pain, fatigue or other residual complaints that may persist for months or years. Pain can also be very confusing in making the diagnosis, especially when it precedes the onset of weakness. Advances in prognostic modelling resulted in the development of a simple prognostic scale that predicts the chance for artificial ventilation, already at admission; and in an outcome scale that can be used to determine the chance to be able to walk unaided after 1, 3 or 6 months. GBS patients with a poor prognosis potentially might benefit from a more intensified treatment. A larger increase in serum IgG levels after standard IVIg treatment (0.4 g/kg/day for 5 consecutive days) seems to be related with an improved outcome after GBS. This was one of the reasons to start the second course IVIg trial (SID-GBS trial) in GBS patients with a poor prognosis. This study is currently going on. The international GBS outcome study (IGOS) is a new worldwide prognostic study that aims to get further insight in the (immune)pathophysiology and outcome of GBS, both in children and adults. Hopefully these and other studies will further help to improve the understanding and especially the outcome in patients with GBS.
Almost a century ago, the French neurologists Guillain, Barré and Strohl described two soldiers who developed acute paralysis with areflexia that spontaneously recovered [1]. They reported the combination of increased protein concentration with a normal cell count in the CSF, or albuminocytological dissociation, which differentiated the condition from poliomyelitis. Despite the fact that Landry had already reported similar cases in 1859, the combination of these clinical and laboratory features became known as Guillain-Barré syndrome (GBS) [2]. GBS most frequently is a post-infectious disorder, mostly with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus or *M. pneumoniae* [3–6]. In typical cases, among the first symptoms are pain, numbness, paraesthesia, or weakness in the limbs. The main features of GBS however are rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory or cranial nerve-innervated muscles. By definition, maximal weakness is reached within 4 weeks, but most patients have reached their maximal weakness already within 2 weeks [7]. Patients then have a plateau phase of variable duration ranging from days to several weeks or months. This phase is followed by a recovery phase of variable duration (figure 1). Despite the positive effect of intravenous immunoglobulin (IVIg) or plasma exchange (PE), about 20% of the patients unable to walk unaided (‘severely affected patients’) remain unable to do so after half a year. Moreover, many patients remain otherwise disabled or severely fatigued. Even 3–6 years after onset, GBS had great impact on social life and the ability to perform activities [8,9]. It is clear that GBS often remains a severe disease for which better treatment is required, at least in a proportion of patients [10].

**Diagnosis of Guillain-Barré syndrome (GBS)** [7]

**Clinical features**
The diagnosis of GBS is often straightforward, especially when weakness is preceded with an infection within 1–3 weeks from onset (box 1). In some patients however, the diagnosis can be more difficult especially when pain is present already before the onset of weakness, or when weakness initially is only present in the legs [11]. Also in children, the presence of pain may initially suggest other disorders like discitis, which may seriously delay the diagnosis and may even be very troublesome because progressive respiratory weakness may be missed [12]. Therefore, several features especially should raise doubt about the diagnosis (box 2). Several disorders or conditions that may mimic GBS need to be excluded or made unlikely before the diagnosis of GBS can be made (box 3).

**Cerebrospinal fluid (CSF) examination**
CSF examination is especially helpful to rule out other causes of weakness, for example Lyme disease or HIV-related radiculitis, both associated with increased number of mononuclear cells. If there is an increased cerebrospinal fluid total protein (without cellular reaction), this may help making the diagnosis, especially when there are some none-typical features. It is important to realise however that about 50% of GBS patients still have a normal CSF protein in the first week after onset of weakness, and that the absence of an increased CSF protein does not rule out the diagnosis.

**EMG examination**
EMG is especially helpful when it shows signs of a polyneuropathy in clinically not yet involved areas, for example when it...
shows signs of a polyneuropathy in the arms in patients with weakness only in the legs. It also enables to differentiate GBS in AMAN (axonal features) and AIDP (demyelinating features) [13].

**Anti-ganglioside antibodies**

Anti-ganglioside antibodies, as monomer or as complexes, can be found in a proportion of GBS patients, however especially in patients with AMAN (especially IgG anti-GM1 antibodies), and in patients with MFS (anti-GQ1b antibodies) that cross-react with *Campylobacter* [4,10,14–20]. Especially the presence of anti-GQ1b antibodies can be helpful in making the diagnosis in patients with MFS (table I). The results of these anti-ganglioside antibody essays however may last several days or weeks making these tests not always very suitable for use in clinical practise.

A recent paper based on yet published and well-discussed data proposed new criteria for GBS and Miller-Fisher syndrome. These criteria are mainly suggested to be helpful in immunization safety or epidemiological studies [21]. Three levels of diagnostic certainty about the diagnosis of GBS are categorized based on the presence of absence of clinical, EMG and CSF studies (table II). Whether these Brighton criteria also work in clinical practise now needs further evaluation. It is assumed that rare variants of GBS consisting about 1% of the total population are not captured within these criteria.

To further move on with the criteria for GBS, it especially would be helpful to have access to new carefully prospectively gathered data on a large group of well-described and followed GBS patients. This preferentially includes both mildly and severely affected GBS patients, both children and adults, and patients with AMAN (especially IgG anti-GM1 antibodies), and in patients with MFS (anti-GQ1b antibodies) that cross-react with *Campylobacter*. Especially the presence of anti-GQ1b antibodies can be helpful in making the diagnosis in patients with MFS. The results of these anti-ganglioside antibody essays however may last several days or weeks making these tests not always very suitable for use in clinical practise.

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from various regions around the globe (so to include reasonable large numbers of both AIDP and AMAN cases). These new data potentially give relevant information, also on less frequently encountered clinical subgroups, including on patients who do not fulfill all standard diagnostic criteria usually required to be randomized in controlled trials, e.g. on patients with a progressive phase of 4–6 weeks, having (near) normal reflexes, or on those having over 50 CSF WBC/ul or on patients having only weakness of their legs. This would help to have better insight in the complete spectrum of GBS.

**Table I**

Spectrum of Guillain-Barré syndrome (GBS) and serum anti-ganglioside antibodies

<table>
<thead>
<tr>
<th>GBS subgroup</th>
<th>Antibodies</th>
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<tbody>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy (AIDP)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)</td>
<td>GM1, GM1b, GD1a, GalNac–GD1a</td>
</tr>
<tr>
<td>Miller-Fisher syndrome/GBS overlap syndrome</td>
<td>GQ1b, GD3, GT1a</td>
</tr>
</tbody>
</table>

**Table II**

Criteria for Guillain-Barré syndrome (GBS) for vaccinations or epidemiological research [21]

<table>
<thead>
<tr>
<th>Items that are fulfilled/requested</th>
<th>Levels of diagnostic certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1. Bilateral and flaccid weakness of the limbs</td>
<td>+</td>
</tr>
<tr>
<td>2. Decreased or absent tendon reflexes in weak limbs</td>
<td>+</td>
</tr>
<tr>
<td>3. Monophasic illness pattern</td>
<td>+</td>
</tr>
<tr>
<td>4. Onset to nadir of weakness: 12 h - 28 days + subsequent plateau</td>
<td>+</td>
</tr>
<tr>
<td>5. Cytoalbuminologic dissociation # (i.e elevation CSF protein level and CSF white cells &lt; 50 x 10^6/L)</td>
<td>+</td>
</tr>
<tr>
<td>6. Electrophysiological (EMG) findings consistent with GBS</td>
<td>+</td>
</tr>
<tr>
<td>7. Absence of identified alternative diagnosis for weakness</td>
<td>+</td>
</tr>
</tbody>
</table>

Levels of diagnostic certainty range from 1 (most likely) to 3 (least likely).

Level 1: is the highest level (diagnosis of GBS is most likely). All items positive.

Level 2: items 1–4 positive; # 5 (CSF) positive, or when CSF is not collected/available: 6 (EMG) and 7 (absence of identified alternative diagnosis for weakness) positive.

Level 3: items 1–4 and 7 positive.

The beneficial effect of immunotherapy

It has been shown that plasma exchange (PE) is beneficial when applied within the first 4 weeks from onset, but the largest effect was seen when started early (within the first 2 weeks) [24–28]. The usual regimen is a five times PE during 2 weeks, with a total exchange of about five plasma volumes. A French PE trial showed that two PE sessions is more effective than no PE in patients being mildly affected form GBS [29]. The first RCT on the use of IVIg (0.4 g IVIg/kg bodyweight/day for five consecutive days) was published in 1992, demonstrating that IVIg is as effective as PE [30]. After these results were published, IVIg has replaced PE as the preferred treatment in many centres, mainly because of its greater convenience and availability [23]. The Cochrane review on the use of IVIg in GBS...
Consider specific treatment with IVIg or PE:

- **Fluctuations during course of disease or continued slow progression?**
  - Consider acute onset CIDP (A-CIDP) and treat accordingly.

**Rehabilitation and fatigue:**
- start physiotherapy early during course of disease;
- start rehabilitation as soon as improvement starts;

**Criteria for PE eligibility ( Including IVIg and PE):**
- respiratory failure requiring mechanical ventilation
- severe autonomic dysfunction
- Insufficient swallowing with high chance for pulmonary infection
- Severe autonomic dysfunction
- Use prognostic model to determine change for artificial ventilation [23].

**Box 4 (Continued)**

- consider a physical training program for severe fatigue;
- consider to contact patient organization for additional information and help.

showed that there was no difference between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability [31]. The combination of PE followed by IVIg was not significantly better than PE or IVIg alone [26]. It appeared that oral steroids (or intravenous methylprednisolone 500 mg/day for five consecutive days) alone are not beneficial in GBS [32]. The combination of IVIg and intravenous methylprednisolone was not more effective than IVIg alone, but there might be some additional short-term effects of this combined treatment when a correction was made for known prognostic factors [33]. The overall conclusion is that according to moderate quality evidence, corticosteroids given alone do not significantly hasten recovery from GBS or affect the long-term outcome. According to low quality evidence, oral corticosteroids may even delay recovery [34]. In a pilot-study, we studied the additional effect of a 6-week treatment of mycophenolate in GBS, which did not show a positive effect [35]. There definitely is an effect of immunotherapy on the course of GBS, but new studies improving also the final outcome of GBS remain urgently needed [27]. An ongoing RCT (SID-GBS) studies the effect of a second course of IVIg given shortly after the first IVIg course only in GBS patients with a poor prognosis. This study is currently running in The Netherlands. An international observational study on the effect of a second-dose IVIg in GBS patients with a poor prognosis (I-SID-GBS) has just started. This study is linked to the International GBS Outcome Study (IGOS), a study performed by the Inflammatory Neuropathy Consortium (INC).

**When should treatment be started?**

The North-American PE trial showed an effect of PE when applied within the first 4 weeks after onset/weakness. Most effect however was observed when PE was started within the first 2 weeks form onset. After the publication of this trial, most RCT’s have enrolled patients being within the time window of 2 weeks from onset of weakness and unable to walk without assistance [27].

**Should mildly affected patients be treated?**

Mildly affected is arbitrarily often defined as being able to walk, with or without assistance. A retrospective study demonstrated that these patients frequently have residual disabilities. The RCT’s evaluating the effect of IVIg did not study the effect in...
mildly affected patients. One large French trial studied the effect of PE also in patients who could walk with or without aid, but not run. Onset of motor recovery was faster in patients who received two PE sessions compared to no PE [29]. Based on this study there seems to be an indication also to treat mildly affected GBS patients with PE, but one must keep in mind that yet no randomized placebo controlled studies have evaluated the effect of PE or IVIg in these mildly affected GBS patients [10,27].

**Should patients with Miller-Fisher syndrome (MFS) be treated?**

No RCT’s have been performed on the effect of PE or IVIg in patients with MFS. Observational studies suggested that the final outcome in patients with MFS generally is good [36]. From a large Japanese uncontrolled observational study, it was found that IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia, but the times of disappearances of these symptoms were similar among the IVIg, PE and no-treatment group. It was concluded that IVIg and PE seem not to have influenced MFS patients’ outcome, presumably because of good natural recovery [37–39].

**What to do if a patient continues to deteriorate after treatment?**

A proportion of GBS patients continue to deteriorate after PE or a standard course of IVIg. In these cases, it is unknown what would be the best option: wait and see, or to start additional treatment. The reason why some patients continue to deteriorate and may be paralytic for months is not known. These patients might have a severe or prolonged immune attack causing severe axonal degeneration. Treatment might act insufficiently in these individuals. It is presently not known how to treat patients who continue to deteriorate. Do these patients need PE after they have been treated with IVIg? This has not been investigated, but it has been shown that the combination of PE followed with IVIg is not superior compared to PE or IVIg alone [26]. A small open study suggested that a repeated course of IVIg may be effective in severe unresponsive GBS patients [40]. Additionally it has been shown that a larger increase in serum IgG levels, 2 weeks after starting a first IVIg course, was associated with a better outcome [41]. The international trial studying the effect of a second IVIg dose in patients with a poor prognosis (I-SID-GBS), based upon the modified Erasmus Guillain-Barré Outcome score (mEGOS), is currently running [42].

**What to do if a patient deteriorates after initial improvement?**

About 5 to 10% of GBS patients deteriorate after initial improvement or stabilization following IVIg treatment, a condition named “treatment-related clinical fluctuation” [43,44].

**Figure 2**

Guillain-Barré syndrome (GBS), treatment-related fluctuations (GBS-TRF) and acute onset CIDP (A-CIDP)

Although no RCT has evaluated the effect of a repeated IVIg dosage in this condition, it is common practise to give a second IVIg course (2 g/kg in 2–5 days), since these patients are likely to improve after re-initiating this treatment [27]. It is considered that these patients may have a prolonged immune-response that causes ongoing nerve damage needing treatment for a longer period of time. Some of these GBS patients may even have several episodes of deterioration. This often raises the question whether these patients may have chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) (figure 2) [45].

**How many deteriorations would alter the diagnosis from GBS to A-CIDP?**

This is an important question, but the answer is not fully known yet. We have evaluated our series of patients and concluded that the diagnosis of A-CIDP should be suspected when patients initially diagnosed with GBS, do have three or more of these deteriorations or when they have a subsequent deterioration after 9 weeks from onset of GBS [45] (box 5). It is important to look for these secondary deteriorations because GBS patients may improve after a new course of IVIg and some of these patients turn out to have a variant of CIDP with acute onset (A-CIDP) needing chronic maintenance treatment [45].

**Importance of pain in the acute and chronic phase of GBS**

Pain is a common and severe symptom in patients with GBS. Recognition of pain is important, especially in patients unable to communicate due to intubation. Pain as a presenting symptom of GBS, before the onset of weakness, may be misleading in making the diagnosis of GBS. Pain has been described in up to 89% of patients with GBS. Recognition of the presence and type
RCT however still needs to be done. Although the effect of the functional outcome, and quality of life were also improved. A reported fatigue scores decreased significantly. Physical fitness, were neurologically rather well recovered from GBS, and self-training program we used was well tolerated in patients who CIDP patients [49]. The rather intensive, three times weekly fatigued but neurologically well-recovered GBS and four stable training however was likely to be effective in 16 severely most disabling symptoms [48]. A 12-week bicycle exercise percent of patients reported fatigue as being among their three severe fatigue was even present in 60–80% of patients. Eighty of pain is important because specific treatments can be offered [11,46].

**Autonomic failure**

Autonomic dysfunction, like labile blood pressure, tachycardia or heart rate disturbances, often occurs in GBS patients. Recognition of autonomic dysfunction is important, because it may be an important cause of death in GBS. Three to 10% of patients die, presumable partly due to (sudden) autonomic failure. It is yet not well possible to predict which patients will develop serious autonomic failure and therefore need continue monitoring [47]. From observational studies, it seems that patients not only die while being admitted on an ICU due to serious autonomic failure or pulmonary problems, but also the first period after discharge from an ICU can be a high-risk period especially when a patient has a tracheostoma and stasis of sputum.

**The presence and treatment of severe fatigue after Guillain-Barré syndrome (GBS)**

Fatigue after GBS is an important problem. It was found that severe fatigue was even present in 60–80% of patients. Eighty percent of patients reported fatigue as being among their three most disabling symptoms [48]. A 12-week bicycle exercise training however was likely to be effective in 16 severely fatigued but neurologically well-recovered GBS and four stable CIDP patients [49]. The rather intensive, three times weekly training program we used was well tolerated in patients who were neurologically rather well recovered from GBS, and self-reported fatigue scores decreased significantly. Physical fitness, functional outcome, and quality of life were also improved. A RCT however still needs to be done. Although the effect of the physical training program cannot fully be explained yet, it seems to help, possible also by ensuring and changing lifestyle.

**Prognosis of Guillain-Barré syndrome (GBS)**

Several studies have been published on the prognosis in GBS. Some of these found a relationship between electromyographic (EMG) features and an increased chance to need artificial ventilation or to have a poorer outcome. One large study showed that demyelinating features when assessing the peripheral nerve was related with a high chance needing artificial ventilation [50]. We recently constructed and validated a prognostic model, Erasmus GBS Respiratory Insufficiency Scale (EGRIS) that can be used already at the day of admission to determine the change for artificial ventilation [23]. Days between onset of weakness and admission, Medical Research Council sum score, and presence of facial and/or bulbar weakness were the main predictors of mechanical ventilation. This simple model only requiring clinical features potentially can be of great help to make decisions where to admit patients: at a general neurology ward or at the intensive care unit. Regarding the prognosis of outcome after one to 6 months from onset, age is generally considered to be a poor prognostic factor. Another prognostic model (Erasmus GBS Outcome Scale) has been constructed and validated to determine outcome after 6 months [51]. A modification of this model (mEGOS) showed that it is already possible to determine outcome 1 week after hospital admission. When using three simple clinical factors: high age, preceding diarrhea, and low Medical Research Council sum score both at hospital admission and at 1 week were independently associated with being unable to walk at 4 weeks, 3 months, and 6 months (all \( P < 0.05 \)). This model offers the possibility to select patients with a poor prognosis already within the first week after admission. This is important, not only for counseling, but also when considering more intensified treatment for GBS already early in the course of disease. In this early phase of disease, it is more likely that intensified treatment is still effective because irreversible nerve damage has not yet been occurred. We now use this mEGOS to select patients to study the effect of a second-dose immunoglobulin (SID-GBS trial). Prognosis of GBS is an important issue because treatment really needs to be improved. In light of this, it is of extreme importance that the Inflammatory Neuropathy Consortium (INC) has recently started a large international collaborative study. This International GBS outcome study (IGOS) is conducted by a worldwide consortium of neurologists, it investigates outcome especially in relation to clinical, immunological, microbiological, and genetic factors.

**Future directions**

New treatment options in GBS are absolutely necessary because the prognosis in a large group of GBS patients is
still far from good. One option in the acute phase could be a second IVIg treatment in patients with a poor prognosis. The SID-GBS RCT is going on in The Netherlands, and the international second-dose IVIg study (I-SID-GBS) has been started. Recent experiments indicate that agents that interfere with complement activation are potentially attractive candidates to be tested in a very early phase of GBS [52]. Since it is now possible to predict outcome in individual patients more accurately, new drugs like eculizumab or other regimens could be tested especially in a restricted GBS population with a poor prognosis. Focus also on the pathophysiological effect of treatment, such as studying the mechanism of action of IVIg, potentially could also lead to more personalized treatment once it is shown that some patients require other IVIg dosages or treatment regimens. Treatment trials, especially in rare diseases, usually require a long period of time to include sufficient patients. A new trial design in a selected population (like is being done in the SID-GBS RCT) uses covariate adjustment which reduces the sample size required to reach sufficient power [53]. Using the most appropriate outcome measurements to evaluate the effect of treatment is essential. This is currently under investigation in the Peripheral Neuropathy Outcome Study (Perinoms) [54]. New trials investigating less aggressive treatments are also indicated in mildly affected patients, and possibly also in patients with MFS. More attention should be paid to pain, autonomic dysfunction, and severe fatigue, all yet often under-recognized conditions. The Inflammatory Neuropathy Consortium (INC) is an excellent platform to conduct these studies.

Disclosure of interest: the author initiated the ongoing randomized controlled second-dose IVIg trial in GBS patients with a poor prognosis (SID-GBS), sponsored by Sanquin; and the international second-dose IVIg prospective follow-up study in GBS (I-SID-GBS) sponsored by Talecris.

References

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