Research – Guillain Barre Syndrome

Brief	Research on Guillain Barre Syndrome & the different variants including Acute Motor Sensory Axonal Neuropathy (AMSAN) Detail on recovery including timeframes of each variant. For example, a diagnosis of what period of time would be reasonable to consider if the diagnosis is going to be or likely to be permanent. Stats on cases where permanency is established.
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The Research Team are unable to ensure that the information listed below provides an accurate & up-to-date snapshot of these matters.

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1 Contents

2 Summary

- Guillain–Barré syndrome has many variants and can be placed into subtypes using electrophysiological/nerve conduction studies. However, the literature investigating recovery and long term outcomes present results for the condition as a whole rather than within these classifications.
- The prognosis of GBS is generally considered favourable with most recovery occurring in the first 12 months.
- Patients have been shown to experience a range of long-term residual problems, including incomplete recovery of motor and sensory function, as well as fatigue, pain and psychological distress.
    - These poor outcomes have been shown to be present up to 10 years after the acute phase.
    - One literature review found that GBS cause's severe persistent disability in 14% of patients at 1 year.
    - Other studies have shown that improvements can occur 2-5 years after diagnosis, however, this does not mean they have completely recovered.

3 Overview

Guillain–Barré syndrome (GBS) is an inflammatory disease of the peripheral nervous system (PNS) and is the most common cause of acute flaccid paralysis, with an annual global incidence of approximately 1–2 per 100,000 person-years [1]. GBS occurs more frequently in males than in females and the incidence increases with age, although all age groups can be affected [1].

Patients with GBS typically present with weakness and sensory signs in the legs that progress to the arms and cranial muscles. Clinical presentation of the disease is heterogeneous and the diagnosis of GBS is based on the patient history and neurological, electrophysiological and cerebrospinal fluid (CSF) examinations.

In lower resource countries where Electrophysiological studies are not available, the Brighton Criteria is utilised to make a diagnosis. The table below is used to rank level of severity [2].

Brighton criteria for GBS

+, present; -, absent; +/−, present or absent; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; NCS, nerve conduction study

Diagnostic criteria	Level of diagnostic certainty			
	Level 1	Level 2	Level 3	Level 4
Absence of alternative diagnosis for weakness	+	+	+	+
Diminished or absent deep tendon reflex in weak limbs	+	+	+	+/–
Monophasic course and time between onset and nadir, 12 hours to 28 days	+	+	+	+/–
Bilateral and flaccid weakness of limbs	+	+	+	+/–
CSF cell count < 50 cells/microL	+	+	-	+/–
CSF protein concentration > normal value	+	+/–	-	+/–
NCS findings consistent with one of the subtypes of GBS	+	+/–	-	+/–

4 Variants and Subtypes

Clinical variants of GBS exist, with some patients having a distinct and persistent clinical variant of GBS that does not progress to the classic pattern of sensory loss and weakness [3]. These variants include [3]:

- Classic Sensorimotor GBS:
  - Rapidly progressive symmetrical weakness and sensory signs with absent or reduced tendon reflexes, usually reaching nadir within 2 weeks
  - 30-85% of cases
- Pure motor
  - Motor weakness without sensory signs
  - 5-70% of cases
- Paraparetic
  - Paresis restricted to the legs
  - 5-10%
- Pharyngeal–cervical– brachial
  - Bilateral facial weakness, paraesthesias and reduced reflexes
- Bilateral facial palsy with paraesthesias
  - Bilateral facial weakness, paraesthesias and reduced reflexes
  - <5%
- Pure Sensory

    - Acute or subacute sensory neuropathy without other deficits
    - <1%
- Miller Fisher syndrome
    - Ophthalmoplegia, ataxia and areflexia. Incomplete forms with isolated ataxia (acute ataxic neuropathy) or ophthalmoplegia (acute ophthalmoplegia) can occur. Overlaps with classical sensorimotor GBS in an estimated 15% of patients.
    - 5-25% of cases
    - Weakness limited to the cranial nerves (bilateral facial palsy with paraesthesias)
- Bickerstaff brainstem encephalitis
    - Ophthalmoplegia, ataxia, areflexia, pyramidal tract signs and impaired consciousness, often overlapping with sensorimotor GBS.
    - <5% of cases

In general, GBS variants are rarely 'pure' and often overlap in part with the classic syndrome or show features that are typical of other variant forms.

Electrophysiological/nerve conduction studies provide evidence of PNS dysfunction and can distinguish between the subtypes of GBS, however, these tests are not required to make a clinical diagnosis of GBS and should not delay treatment [3, 4]. Subtypes include:

- **Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)**
    - Characterized by progressive areflexic (muscles don't respond to stimuli) weakness and mild sensory changes. Sensory symptoms often precede motor weakness. AIDP is the most common form of GBS in North America and Europe
- **Acute motor axonal neuropathy (AMAN)**
    - Key clinical features of pure motor weakness, areflexia, absence of sensory symptoms, and lack of neurophysiologic evidence of demyelination.
- **Acute motor sensory axonal neuropathy (AMSAN) [5]**
    - Characterised by acute onset of distal weakness, loss of deep tendon reflexes and sensory symptoms
    - Electrophysiological studies show mildly reduced nerve conduction velocities combined with a marked reduction of muscle action and sensory nerve action potentials.

5 Clinical Course

Disease progression can be rapid, and most patients with GBS reach their maximum disability within 2 weeks. About 20% of patients with GBS develop respiratory failure and require mechanical ventilation. Cardiac arrhythmias and blood pressure instability can occur owing to involvement of the autonomic nervous system [6]. This involvement of the

autonomic nervous system contributes to mortality, which is estimated at 3–10% for patients with GBS even with the best medical care available [6, 7].

After the initial progressive phase, patients with GBS reach a plateau phase that can last from days to weeks or months, after which they start to recover, and 60–80% of patients with GBS are able to walk independently 6 months after disease onset, with or without treatment [8, 9]. GBS is a monophasic illness (a disorder that causes only one episode of inflammation in the central nervous system), although some patients can deteriorate after first stabilizing or improving on therapy — a phenomenon that is referred to as a treatment-related fluctuation (TRF). Relapses of GBS can occur in 2–5% of patients [8, 10, 11]. Willison, Jacobs [6] have developed a figure (below) which describes the clinical course of the disease.

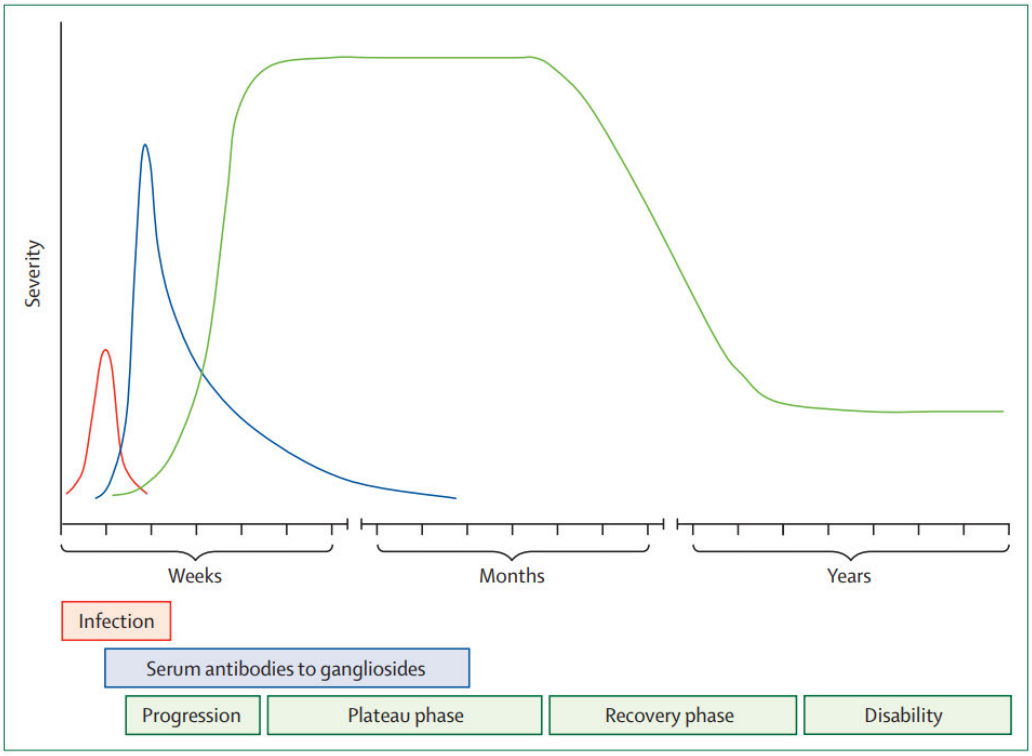

Figure 1: **Guillain-Barré syndrome time course**

6 Prognosis

The **prognosis of GBS is generally considered favourable**. Despite the demonstrated efficacy of plasma exchange (PE) and intravenous immunoglobulins (IVIg), GBS however

remains a disabling disease in a significant proportion of patients, and these treatments have not improved mortality which ranges between 3-7% depending on the country [6, 7].

The clinical course and long term outcome of the disease is highly variable and early recognition of patients with poor outcome is needed to personalise and improve treatment. **Prognostic models do not exist** (for variants or subtypes), however, development of these could help to identify patients who need additional treatment and monitoring.

Patient characteristics consistently related to poor prognostic outcome in GBS are [6, 12]:

- High age (aged 40 years and over)
- Preceding diarrhoea (or C jejuni infection in the past 4 weeks)
- Greater disability/weaker muscles at admission
- Short interval between symptom onset and admission
- Mechanical ventilation
- Absent/ low amplitude compound muscle action potentials

The modified Erasmus GBS outcome score (mEGOS), which is based on these clinical characteristics, can be used 2 weeks after admission to predict the ability of the patient to walk at 6 months [13]. The mEGOS requires the Medical Research Council (MRC) Scale for Muscle Strength score instead of disability and can predict outcome as soon as 1 week after admission, when therapeutic interventions are probably even more effective [3, 6]. The risk of respiratory failure is associated with rate of disease progression, severity of limb weakness, peroneal nerve conduction block, and low vital capacity. This risk can be predicted for individual patients using Erasmus GBS Respiratory Insufficiency Score (EGRIS); based on the severity of weakness (expressed as MRC sum score); onset of weakness; and facial palsy, bulbar weakness, or both [14]. These models have not been validated for use in children and patients with axonal forms of GBS.

7 Long Term Outcomes

The long-term follow-up system of patients with GBS is not well established worldwide [15]. Many follow up studies only review patients 12 months after the acute state. Nonetheless, long-term function has been shown to be compromised in a significant proportion of subjects. Clinical improvement is usually most extensive in the first year after disease onset and can continue for >5 years [3, 15, 16].

Patients with GBS have been shown to experience a range of long-term residual problems, including incomplete recovery of motor and sensory function, as well as fatigue, pain and psychological distress [16-18].

A high quality literature review by Rajabally and Uncini [12] was conducted to determine outcomes and predictors in adequately treated (with PE and IVIg), adult-onset GBS. The table below shows the results from this review. Key findings include that GBS cause's severe

persistent disability in 14% of patients at 1 year and loss of full strength, persistent pain and need for professional change occurs in about 40% of patients.

Table 1 Summary of preselected outcomes evaluated from data of prospective analyses of adequately treated Guillain–Barré syndrome (GBS) patients with plasma exchange (PE) or intravenous immunoglobulins (IVIg) and pooled results

Study	Design	Outcome 1 (ability to walk with aid at 4 weeks)	Outcome 2 (ability to walk unaided at 4 weeks)	Outcome 3 (need for ventilatory support at 4 weeks)	Outcome 4 (ability to walk unaided at 6 months)	Outcome 5 (relapse at 1 year)	Outcome 6 (recovery of full motor strength at 1 year)	Outcome 7 (ability to walk unaided at 1 year or later)	Outcome 8 (persistence of severe motor sequelae at 1 year or later)	Outcome 9 (need to change employment due to GBS)	Outcome10 (death within 1 year of diagnosis)
Greenwood *et al*, 1984[11]	Therapeutic (PE), controlled	NA	NA	2/14	NA	1/14	4/14	NA	1/14	NA	2/14
Osterman *et al*, 1984[12]	Therapeutic (PE), controlled	12/18	7/18	4/18	NA	1/18	16/18	NA	1/18	NA	1/18
The GBS Study Group, 1985[14]	Therapeutic (PE), controlled	NA	NA	26/122	100/122	2/122	NA	NA	22/122	NA	3/122
French Cooperative Group, 1987[15]	Therapeutic (PE), controlled	13/109	15/109	12/109	NA	6/109	70/109	NA	11/109	NA	7/109
Färkkilä *et al*, 1987[17]	Therapeutic (PE), controlled	NA	NA	NA	NA	NA	12/13	NA	0/13	NA	2/13
Van der Meché Schmitz, 1992[18]	Therapeutic (PE vs IVIg), controlled	NA	NA	NA	NA	NA	NA	NA	NA	NA	3/150
French Cooperative Group, 1997[19]	Therapeutic (PE), controlled and 'dose-ranging'	6/45‡	13/45‡	0/45**	NA	14/361¶	210/361¶	NA	41/361¶	NA	14/361¶
PE/Sandoglobulin Trial, 1997[20]	Therapeutic PE versus IVIg versus PE+IVIg	NA	NA	NA	NA	NA	NA	NA	57/365* †	NA	19/379
van Koningsveld *et al*, 2004[21]	Therapeutic IVIg+PE versus IVIg+ placebo	NA	NA	NA	NA	NA	NA	184/225§	41/225††	NA	10/225§
Bernsen *et al*, 2002[24]	Therapeutic (PE vs IVIg), controlled	NA	NA	NA	NA	NA	NA	108/122	14/122	31/82	NA
Total		31/172 (18%)	35/172 (20.3%)	44/308 (14.3%)	100/122 (82%)	24/624 (3.8%)	312/515 (60.6%)	292/347 (84.1%)	188/1349 (13.9%)	31/82 (37.8%)	61/1391 (4.4%)

The values in bold correspond to the percentages for each outcome.
*Excluding missing data in each treated group.
†Considering 48-week instead of 52-week follow-up data.
‡Only data for these outcomes were available for patients in the 'mild' group (obtained from the Cochrane review).
§Including both treated groups which were equivalent and averaging.
¶Including all patients in the effectively treated groups (ie, 46 in the two PE in the group for mild disease; the 155 treated by four PE in the moderate disease group; all 161 treated patients by four or six PE in the severe disease group).
**Included mild group.
††Only including those unable to walk independently at 1 year.
NA, not applicable.

The first long-term study of residual health status was published in 1997 analysing a cohort of 123 GBS patients followed up 3-6 years after their illness [19]. The authors found residual altered psychosocial function in all GBS patient groups whether or not they had persistent residual symptoms. However, the 'physical sickness impact profile' score correlated with the GBS functional score [19].

The same group later showed long-term reduction in health-related quality of life despite good physical recovery [20]. They also studied the effects on private life of GBS patients 3-6 years after the illness, with 31% showing moderate to serious physical residual symptoms after a functional assessment [21]. Also, and importantly, employment change was needed

in 38% of cases and leisure activities had altered in 52% after the illness. However, over 20% of patients still noticed improvement 2.5-6.5 years after onset [21].

Long term outcomes in patients requiring mechanical ventilation has shown that 21% do not regain independent ambulation [22]. This group has the highest mortality rate – which is 20%.

A 3 year follow up study to investigate the outcomes of 82 patients found that [23]:

- Poor functional outcome was found in 39% of patients at year 1 and 30% at year 3.
- Paresthesias/dysesthesias were detected in 60% of patients after 1 year and 43% after 3 years.
- Musculoskeletal pain was present in 40% of patients at year 1 and 33% at year 3.
- Significant fatigue after 1 year was found in 21% of subjects and after 3 years in 7%.

The longest study to date (up to 10 years) included a small sample of 29 patients. Results showed that at 10 years, the facial paralysis found in 5 participants at 2 years was still present, 11 participants (38%) experienced paresthesia, 6 (21%) had limitations in their arms, and 15 (52%) had limitations in walking [16].

8 References

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