**Universidad de Cantabria**
**Facultad de Medicina**
**Departamento de Medicina y Psiquiatría**
**Hospital Universitario Marqués de Valdecilla**
**Servicio de Neurología**
**Santander**

**Trabajo de Fin de Grado**

# *Forma axonal del síndrome de Guillain-Barré.*
# *Axonal form of Guillain-Barré síndrome*

**Alumna: María Castiñeiras Ortega**

**Directores**
**María José Sedano Tous (Médico Adjunto de Neurología y Profesora Colaborador Clínico, UC)**
**José Ángel Berciano Blanco (Profesor emérito, UC)**
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**Facultad de Medicina**

***Departamento de Medicina y Psiquiatría***

María José Sedano Tous y José Ángel Berciano Blanco certifican que el trabajo titulado "Forma axonal del síndrome de Guillain-Barré (Axonal form of Guillain-Barré syndrome)", que presenta María Castiñeiras Ortega como Trabajo de Fin de Grado, ha sido efectuado bajo nuestra dirección.

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## Contents

## Abbreviations

- AIDP: acute inflammatory demyelinating polyneuropathy
- AMAN: acute motor axonal neuropathy
- AMSAN: acute motor sensory axonal neuropathy
- ASAN: acute sensory ataxic neuropathy
- CI: confidence intervals
- GBS: Guillain-Barré syndrome
- ICU: intensive care unit
- MRC: Medical Research Council
- MSCT: one-time multislice-CT
- MRI: magnetic resonance imaging
- US: ultrasonography

## Abstract

Fifty-two patients with Guillain-Barré syndrome (GBS) were retrospectively selected from a defined area (Cantabria) in Nothern Spain, from January 2009 to December 2016. According to clinico-electrophysiological data these patients were categorized as follows: 35 acute inflammatory demyelinating polyneuropathy (AIDP), 15 acute motor or motor-sensory axonal neuropathy (AMAN/AMSAN), 1 acute sensory ataxic neuropathy (ASAN), and 1 Miller-Fisher syndrome. As a whole, the annual crude incidence of GBS over the 9-year period was 1.12 cases per 100,000 population, which was similar to a previous Cantabrian survey performed between 1975 and 1988. Conversely the percentage of axonal GBS, encompassing AMAN, AMSAN and ASAN, increased from 5.8% to 30.8%, which is in line with recent Italian studies. Certainly, better knowledge of axonal GBS nosology and the introduction of serial electrophysiological evaluation account for better recognition of axonal syndromes that were thought to be so prevalent only in East Asia. There were antecedents, and particularly diarrhoea, in the great majority of axonal GBS patients, 62% of them showing positive serology for antiganglioside antibodies. Clinical picture and outcome were similar to those reported in AIDP, the only departure features being lesser frequencies of cranial nerve involvement and dysautonomia.

**Key words:** AIDP; AMAN; AMSAN; ASAN; antiganglioside antibodies; axonal degeneration; epidemiology; Guillain-Barré syndrome; incidence.

## Resumen

Retrospectivamente, se seleccionaron 52 pacientes de síndrome de Guillain-Barré (SGB) estudiados en Cantabria desde enero de 2009 a diciembre de 2016. De acuerdo con los datos clínico-neurofisiológicos, los pacientes se subdividieron del siguiente modo: 35 AIDP, 15 AMAN/AMSAN, 1 ASAN, y 1 síndrome de Miller-Fisher. En conjunto, la incidencia cruda anual fue de 1.12 casos por 100.000 habitantes, que es similar a la reportada en un estudio epidemiológico previo realizado en Cantabria entre 1975 y 1988. Por el contrario, el porcentaje de SGB axonal, incluyendo AMAN, AMSAN y ASAN pasó del 5,8% al 30,8%, lo cual está en línea con recientes estudios realizados en Italia. Tal incremento porcentual, comparable al de ciertos países asiáticos, se relaciona con el mejor conocimiento de la nosología del SGB axonal y con la práctica de exploraciones neurofisiológicas consecutivas. Hubo antecedentes, sobre todo diarrea, en la gran mayoria de paciente con SGB axonal, el 62% de los cuales tenía una serología positiva para anticuerpos antigangliósido. El cuadro clínico y la evolución fueron comparables a los de los pacientes de AIDP, excepto por una menor frecuencia de paresia de nervios craneales y disautonomía.

**Palabras clave:** AIDP; AMAN; AMSAN; anticuerpo antigangliósido; ASAN; degeneración axonal; epidemiología; incidencia; síndrome de Guillain-Barré.

## Introduction

Guillain-Barré syndrome (GBS) is an acute-onset, immune-mediated disorder of the peripheral nervous system, which is currently divided into several subtypes based on electrodiagnostic, pathological and immunological criteria (Hughes and Cornblath, 2005; van Doorn et al., 2008; Yuki and Hartung, 2012; Kuwabara and Yuki, 2013; Wakerley et al., 2014). GBS includes at least three disease patterns: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal and motor-sensory axonal neuropathy (AMAN and AMSAN), and Fisher syndrome (Griffin et al., 1996). AIDP is pathologically characterized by demyelination and inflammatory infiltrates in spinal roots and nerves (Asbury et al., 1969; Honavar et al., 1991); in a variable proportion of cases, however, demyelination is accompanied or substituted by axonal degeneration (Albers et al., 1985; Feasby et al., 1986; Kanda et al., 1989; Triggs et al., 1992; Yokota et al., 1992). AMAN is a pure motor disorder frequently associated with serum antibodies against gangliosides, GM1, GM1b, GD1a or GalNAc-GD1a, and antecedent of *Campylobacter jejuni* enteritis (Hughes and Cornblath, 2005; van Doorn et al., 2008; Kuwabara and Yuki, 2013; Wakerley et al., 2014). Autopsy studies in AMAN have revealed axonal degeneration of motor fibers without demyelination, indicative that there may be an immune response directed primarily against the motor axolemma; it is now established that carbohydrate mimicry of the bacterial lipo-oligosaccharide by human gangliosides is an important cause of AMAN (Kuwabara and Yuki, 2013).

In a clinical set, distinction between axonal and demyelinating GBS relies on electrophysiological investigation, though detection of specific electrophysiological patterns, either axonal or demyelinating, may require serial nerve conduction studies (Hadden et al., 1998; Kokubun et al., 2014). GBS pathology characteristically exhibits both topographic variability from proximal to distal nerve trunks, and temporal variability given that lesions evolve over the clinical course (Asbury et al., 1969; Honavar et al., 1991; Berciano et al., 2017). Another additional difficulty in the interpretation of nerve pathology is that distal lesions may just be a mere bystander effect of more proximal and distinct changes, namely, neuropathological investigations of GBS are limited by the fact that it is a kind of “snap-shot” in a highly dynamic process (Rauschka et al., 2003). Therefore, to establish electrophysiological-pathological correlations in GBS may be challenging. Furthermore, detailed clinico-pathological studies in GBS examining from spinal roots to distal nerve trunks are scanty (Berciano et al., 2017).

Imaging techniques, including magnetic resonance imaging (MRI), one-time multi-slice-CT (MSCT) and ultrasonography (US), have proved to be useful for detecting the topography of muscle denervation, and for determining the distribution of nerve trunk pathological changes in peripheral neuropathies (Byun et al., 1998; Zuccoli et al., 2011; Zaidman et al., 2013; Berciano and Gallardo, 2015; Gallardo et al., 2015, 2015a).

The GBS crude average annual incidence rate in our Community (Cantabria, Spain) was 0.95 cases per 100,000 population (95% CI: 0.72-1.17) (Sedano et al., 1994). In our series just 4 out of 69 (5.8%) patients were diagnosed as having axonal GBS. In Europe and North America, GBS is usually caused by AIDP, whereas in East Asia a considerable

number of GBS patients have AMAN or AMSAN (McKhann et al., 1993; Griffin et al., 1995, 1996; Ho et al., 1995; Kuwabara and Yuki, 2013) (figure 1). It is worth noting that European prevalences underestimate the prevalence of AMAN (Kuwabara, 2010), as demonstrated in a recent Italian study using serial electrophysiological evaluation, which allowed the authors to detect reversible conduction failure, characteristically associated with AMAN, in 38% of their GBS patients (Uncini et al., 2010). Looking at figure 1, the only Spanish epidemiological datum on axonal GBS, 6%, is derived from the prevalence survey conducted in Cantabria between 1977 and 1988 (Sedano et al., 1994)

The objective of this paper is to re-assess the epidemiology of GBS in Cantabria, and particularly of the axonal subtypes over the period 2009-2016. We will compare the results with those of our previous survey.

## Patients and Methods

Our study was performed in the Autonomous Community of Cantabria located in the Northern Spain with an extension of 5,321 $km^2$. All the patients included were diagnosed of GBS in the University Hospital "Marques de Valdecilla", which is the reference center for neurological pathology. The period of the study was from January 2009 to December 2016. In this time the population increased from 576,418 to 581,769 with a proportion of 51% women and 49% men that had been stable.

During the 8-year period of study, 52 patients were diagnosed of GBS, of whom 35 were classified as AIDP, 15 as AMAN or AMSAN, 1 as acute sensory ataxic neuropathy (ASAN), and 1 as Miller-Fisher syndrome.

Clinical data recorded during the acute phase of the illness included prodromal antecedents occurring four weeks before GBS onset, and presence and quality of pain at any disease stage. Weakness was assessed attending to the following movements: neck flexion, shoulder abduction, elbow flexion, wrist extension, intrinsic hand movement, hip flexion, knee extension and ankle dorsiflexion, and classified using the Medical Research Council (MRC) score ranging from 0 to 5 (table 1). Sensory deficits, cranial nerves involvement and the alteration in tendon reflexes were systematically screened. We also have recorded the presence and type of autonomic dysfunction, respiratory insufficiency, need for mechanical ventilation, and entrance into the Intensive Care Unit (ICU). Finally we assessed the ability to walk attending to the GBS disability scale (table 2).

Other clinical records included the following items: i/ cerebrospinal fluid examination; ii/ results of the electrophysiological studies; iii/ treatment received; and iv/ potential presence of serum antigangliosides antibodies. Outcome (prognosis) was assessed with serial examination at 6, 12 and 24 months according to the GBS disability score (table 2).

## Results

### *Epidemiological features*

In the current 8-year period of the study, 16 out 52 (30.8%) patients were diagnosed of axonal GBS, including here AMAN/AMSAN, and the single case of ASAN. There were 12 (75%) men and 4 (25%) women, ages ranging between 18 and 74 years. For all GBS subtypes, the crude annual incidence of GBS was 1.12 cases per 100,000 population (95% CI: 0.83-1.46), that for axonal GBS being 0.34 (95% CI: 0.19-0.55) (Kurtzke, 1984).

Focusing on axonal GBS, 15 (93%) patients had preceding events less than four weeks before onset: 12 diarrhoea, one respiratory infection, one fever of unknown origin, and one surgical procedure.

### *Clinical features*

Clinical features are summarized in table 3. All patients reach the peak of the deficit within 4 weeks: 4 in less than one week, 7 in the first one, 4 in the second, and 1 in the fourth week. At onset, 6 patients (37.5%) presented pain mainly in lower limbs. Limb weakness was observed in almost all patients: 12 of them showed upper- and lower-limb wekness, selective lower-limb weakness occurred in two patients (Berciano et al., 2016), whereas selective upper-limb weakess was noted in one case; the only ASAN patient exhibited no muscle weaknees. Universal areflexia was observed in 9 (56.25%), hypereflexia was observed in 2 (12.5%) patients, the remaining 5 (31.25%) showing normoreflexia. Five patients presented also sensitive deficit in form of paresthesia or hypoesthesia. The involvement of cranial nerves occurred only in two patients, one of them presenting paresis of the VIIth, IXth, Xth, XIth and XIIth, and remaining one sensitive involvement of the Vth and IXth. Three patients exhibited variable dysautonomia: 1 of them only cardiovascular (hypertension and tachycardia), 1 bilateral mydriasis, hypotension and constipation, and the remaining 1 diaphoresis.

Three patients required mechanic ventilation obliging them to be admitted in UCI. Another one required admission in UCI because of dysphagia.

Cerebrospinal fluid was examined in 14 patients and in 64% of them showing typical albumino-cytological dissociation. Antigangliosides antibodies were found in 10 cases (62%); 6 patients had only anti-GM1, two patients anti-GM1 and anti-GD1A, 1 anti-GM1 and anti-GD1B, and another 1 only GD1A.

All but one of the patients received intravenous inmunoglobulins (standard dose, 0.4g/kg/day over 5 days consecutive). Five were also treated with corticosteroids (pulses of methylprednisolone, 500 mg or 1 gr, over three days). Furthermore, in two cases plasmapheresis was administered (five and six sessions).

Sequential electrophysiological studies were performed, usually two tests in the first month after onset. Nine patients are classified as AMAN (one of them with the particularity of selective upper limb weakness), 6 as AMSAN, and 1 as ASAN with an axonal pattern consisting of selective absence or attenuation of sensory nerve action

potentials. In 9 (56%) patients electromyography showed denervation potentials in the acute phase of the disease.

***Outcome***

Three patients died during the follow-up period. One patient died in the fourth month of evolution due to respiratory insufficiency, the remaining two dying beyond the first year due to pneumonia and sepsis of urinary origin, respectively. So death within the first year occurred in 1 (6.25%) patient.

The other patients were evaluated at 6, 12 and 24 months after onset. As a whole, all of them improved their disability, even three achieved complete recovery. According to the GBS disability score we have separated the patients into four groups: normal (grade 0), mild (grades 1 and 2), moderate (grade 3) and severe (grades 4 and 5). Arbitrarily we consider grades 0-2 as "good outcome", and grades 3-5 as "poor outcome". The results are shown in figure 2. In the first year we completed the follow-up in 13 patients: nine with good outcome and four with poor outcome. In the second year the follow-up we were able to assess 11 patients: nine of them were asymptomatic or with mild disability, one moderate, and only one with severe disability.

Apart from the GBS scale that focuses solely on the disability of lower limbs, we would like to emphasize that five patients had problems carrying out precision manual tasks.

## Discussion

In the 8-year period of the current study, 52 GBS Cantabrian patients were identified who fulfilled the current diagnostic criteria of the disease (Hughes and Cornblath, 2005; van Doorn et al., 2008; Kuwabara and Yuki, 2013; Wakerley et al., 2014). The distribution of these patients was as follows: 35 were classified as AIDP, 15 as AMAN/AMSAN, one as ASAN, and the remaining one as Miller-Fisher syndrome. Taking together AMAN/AMSAN and ASAN subtypes, 16 cases are categorized as axonal GBS.

The crude annual incidence for the total series was 1.12 cases per 100,000 inhabitants, whereas that of axonal forms was 0.34 per 100,000. In a previous Cantabrian GBS survey, performed from 1978 to 1988, with 69 patients identified, the annual incidence ratio was established in 0.95 cases per 100,000 population (95% CI: 0.72-1.17) (Sedano et al., 1994); so, no variations occurred in relation to the crude incidence. Conversely, in that survey just 4 (5.8%) cases were diagnosed as axonal GBS, a percentange much lower than that, 30.8%, reported here. We interpret that the difference is accounted for by better knowledge of axonal forms of the syndrome (Feasby et al., 1986), which were increasingly recognized with the description of AMAN/AMSAN (McKhann et al., 1991, 1993; Griffin et al., 1995, 1996; Ho et al., 1996).

Figure 1 illustrates the frequencies of axonal GBS (usually AMAN) around the world, which is the predominant GBS subtype in Asiatic countries; note that in China up to 78% of GBS patients are classified within the AMAN subtype of GBS (Kuwabara and Yuki, 2013). In European countries the frequencies are extremely variable (see figure 1) ranging between 6% in Spain (although without referring to it, this datum was taken from the paper by Sedano et al., 1994) and 17% in Italy. Italian studies deserve separate comments.

Sekiguchi et al. (2012) compared electrophysiological data of Japanese and Italian patients with GBS. 20 (23%) of the 103 Japanese and 9 (17%) of 53 Italian patients had the AMAN pattern (see figure 1), which suggests little difference in prevalence between these two countries. In any case, the prevalence of AIDP was higher in Italy than in Japan (58% vs 37%).

Uncini et al. (2010) applied two current electrodiagnostic sets for AIDP and axonal GBS in 55 patients who had at least two serial recordings in three motor and sensory nerves. At first test, the electrodiagnosis was almost identical with both criteria: 65-67% of patients were classiable as AIDP, 18% as axonal GBS, and 14-16% were equivocal. At follow-up, 24% changed classification: AIDP decreased to 58%, axonal GBS increased to 38%, and equivocal patients decreased to 4%. This paper suggests that axonal GBS is presumably underestimated in Europe, more appropriate diagnostic criteria for the disorder being necessary (Kuwabara, 2010). Certainly, our findings give support to this notion, so around one third of European GBS patients are probably due to primary axonal pathology.

Infection by *Campylobacter jejuni* causing diarrhoea is the most frequent antecedent in patients with AMAN (Kuwabara and Yuki, 2013). In our series, 15 (93.3%) patients showed positive antecedents, in 12 of them consisting of diarrhoea.

It is now established that AMAN/AMSAN are disorders frequently associated with serum antibodies against gangliosides, GM1, GM1b, GD1a or GalNac-GD1a (Hughes and Cornblath, 2005; Kuwabara and Yuki, 2013; Wakerley et al., 2014). In our series 10 (62%) patients had positive antiganglioside serology. Antibodies that bind to GM1 or GD1a gangliosides at the nodes of Ranvier activate complement and disrupt sodium-channel clusters and axo-glial junctions, which leads to nerve conduction failure and muscle weakness (Kuwabara and Yuki, 2013). Intriguingly this conduction failure may be reversible, a fact that explains unexpected and rapid recovery in an axonal pathology, classically associated with denervation leading to residual paralysis.

Leaving the ASAN patient aside, the clinical picture in our axonal GBS patients were entirely comparable to that reported in the previous Cantabrian survey (Sedano et al., 1994). Given the low number of patients and the rarity of axonal GBS in that series, we did no carry out stastistical analyis. Suffice it to say that, as characteristic of AMAN, the frequencies of cranial nerve involvement (2 patients) and dysautonomia (3 patients) were relatively low in comparison with those observed in AIDP (Hiraga et al., 2005; Kuwabara and Yuki, 2013).

As in our previous epidemiological survey (Sedano et al., 1994), outcome was assessed by means of serial clinical examination performed between 6 and 24 months after symptom onset (see figure 2). Patients were graded using a functional scale 0 to 5 (see table 1), good outcoming being grades 0-2 and poor outcoming the remainder. At 12 and 24 months just 2 (15.4%) and 1 (9%) of the corresponding evaluated patients showed poor outcome. These data are comparable to those reported in GBS (Rajabally and Uncini, 2012), and indicate that functional prognosis in axonal GBS does not differ from that in AIDP (Kuwabara et al., 1998; Hiraga et al., 2005). As suggested in AMAN original descriptions (McKhann et al, 1991, 1993), it has been demonstrated that the disorder may result from either simple axonal degeneration or transient conduction block in the distal or proximal nerve segments (Hiraga et al., 2005), this notion explaining that prognosis in the disorder is not necessarily poor as might have been expected in any proximo-distal axonal degeneration.

In this series, 1 (6.2%) patient died within the first year after symptom onset, a percentage almost identical to that of observed (6.7%) in our previous epidemiological survey (Sedano et al., 1994). Death within the first year is one out of the 10 preselected outcomes evaluated from data of prospective analyses of adequately treated GBS patients with plasma exchange or intravenous immunoglobulins (for review, see Rajabally and Uncini, 2012). Total deaths occurred in 81/1,391 (4.4%) patients, a percentage fitting in well with those observed in our studies.

In conclusion, this 8-year observational study in Cantabrian GBS patients indicates that the crude annual incidence is comparable to a previous epidemiological survey performed between 1975 and 1988, though the frequency of axonal GBS has drastically increased from 5.8% to 30.8%, which in line with other recent European epidemiological studies.

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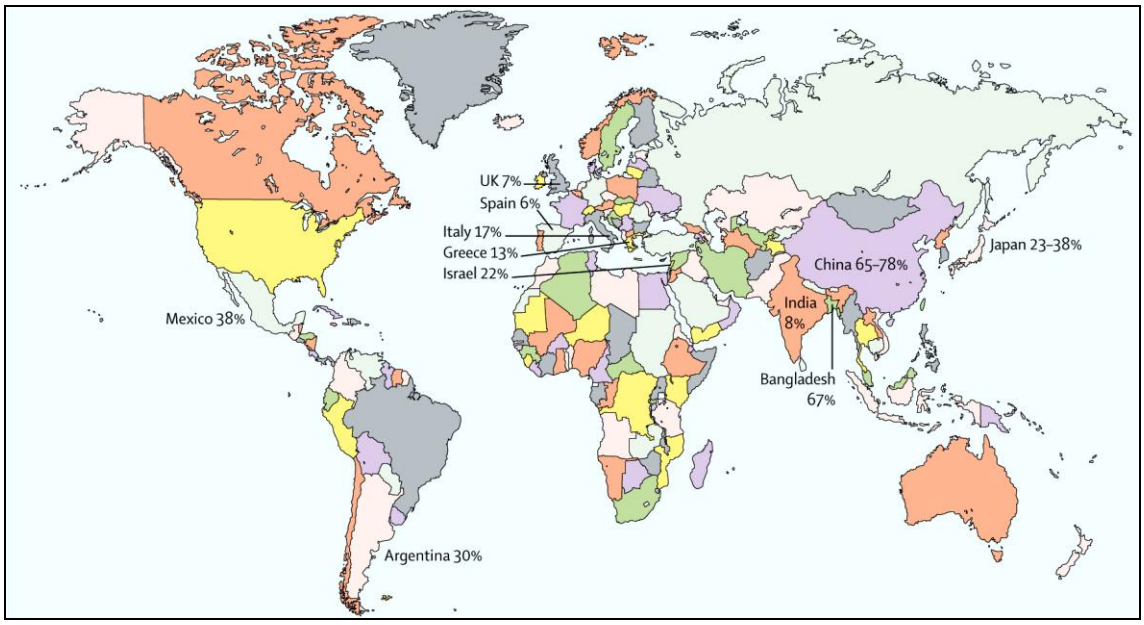


**Figure 1.** Frequencies of AMAN in populations of patients with GBS. The frequencies are based on electrodiagnostic criteria, but include electrophysiologically unclassified patients and, therefore, the actual frequencies might be underestimated (from Kuwabara and Yuki, 2013).

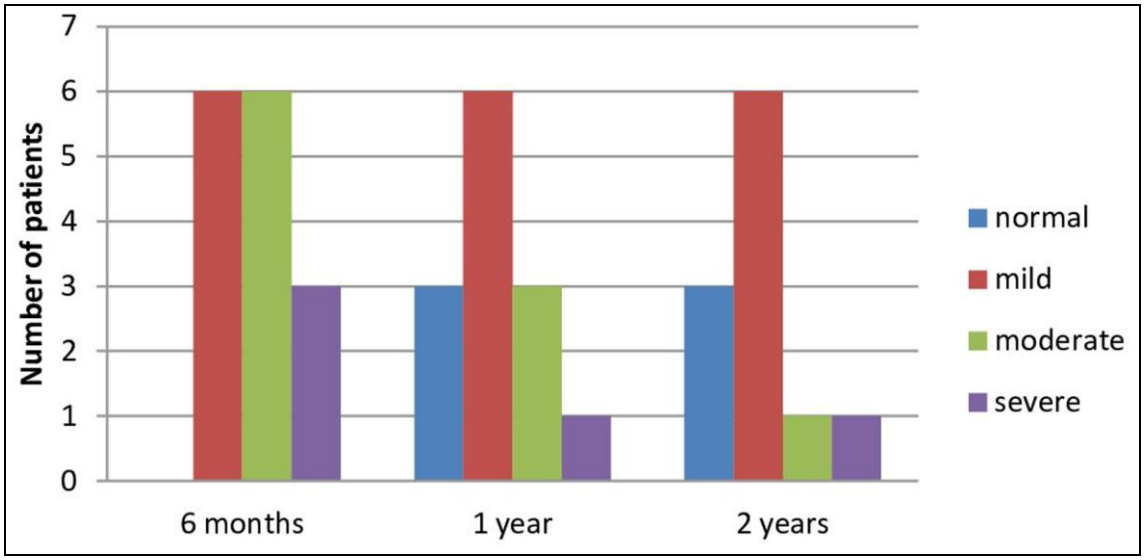


**Figure 2.** Functional grades of the patients at 6, 12 and 24 months after onset of symptoms.

**Table 1. MRC sum score**

| |
|---|
| 0 No visible contraction |
| 1 Visible contraction without movement of the limb |
| 2 Active movement of the limb, but not against the gravity |
| 3 Active movement against the gravity over the full range |
| 4 Active movement against gravity and resistance |
| 5 Normal strength |

**Table 2. GBS disability score. Adapted from Hughes et al (1978)**

| |
|---|
| 0 healthy |
| 1 Minor symptoms and capable of running |
| 2 Able to walk 10 metres or more without assistance but unable to run |
| 3 Able to walk 10 metres across an open space with help |
| 4 Bedridden or chairbound |
| 5 Requiring assisted ventilation for at least part of the day |
| 6 Dead |

**Table 3. Clinical features at the time of maximum deficit**

| Clinical features | Number of patients (%) |
|---|---|
| Motor weakness | 15 (94) |
| Upper and lower limbs | 12 (80) |
| Lower limbs only | 2 (13) |
| Upper limbs only | 1 (7) |
| Generalized areflexia | 9 (56) |
| Sensory loss | 5 (31) |
| Cranial nerve disturbances | 2 (12) |
| Dysautonomia | 3 (19) |
| Respiratory insufficiency | 3 (19) |
| Albumino-cytological dis. | 9/14 (56) |
| Antiganglioside antibodies | 10 (62) |

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