Chapter

Neuromuscular Effects and Rehabilitation in Guillain-Barré Syndrome Associated with Zika Virus Infection

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Abstract

The 2015–2017 Zika Virus outbreak caused a high increase in patients with Guillain-Barré syndrome (GBS), a post infectious autoimmune disease of the peripheral nerves. The severity of GBS can range from mild impairment with fast recovery to complete paralysis including severe respiratory or autonomic failure. Recovery may take months and even years and may be incomplete despite disease modifying treatment with IVIG or plasma exchange. Therefore, optimal supportive care and effective rehabilitation remain crucial. Multidisciplinary rehabilitation is recommended but may be challenging in the acute phase because of limited patient participation due to profound muscle weakness and severe pain. Inactive denervated muscles will inevitably undergo rapid degeneration resulting in wasting, weakness, and contractures as major long-term complications in severely affected patients. In this chapter, the current evidence of rehabilitation on the short- and long-term motor function in GBS is reviewed, including newly obtained experiences with neuromuscular electrical stimulation (NMES). Rehabilitation remains an area lacking well designed and controlled clinical studies and thus a clear lack of evidence-based guidelines.

Keywords: Guillain Barré syndrome, prognosis, chronic disability, rehabilitation, exercise, neuromuscular electrical stimulation

1. Introduction

Guillain Barré Syndrome (GBS) is an acute inflammatory disease affecting peripheral nerves and nerve roots [1, 2]. Most commonly, GBS is preceded by an infection a few weeks prior to neuropathic symptoms [3]. Thus, incidence of GBS can increase during outbreaks of infectious diseases. This was most recently observed during the 2015 to 2017 Zika Virus epidemic in the French Polynesia and Latin America with a highly increased incidence of GBS in several countries [4–9]. GBS typically presents with muscle weakness and sensory symptoms combined with loss of tendon reflexes. Symptoms initially present in the lower extremities progressing to the upper extremities and the respiratory and cranial muscles [10]. The progressive phase usually last for days to weeks with most patients reaching nadir within four weeks of symptom debut followed by a plateau phase and a slow

recovery. Beside the typical presentation of sensory and motor neuropathy, patients may have clinical variants like the triad of ophthalmoplegia, ataxia and areflexia known as the Miller Fischer Syndrome, pure motor, paraparetic or pharyngea-cervical-brachial variant [11], and in association with Zika Virus infection a case of GBS with ocular flutter, ataxia, tetraparesis and areflexia has been reported [12]. Furthermore, neuropathy can be classified as demyelinating or axonal according to the electrophysiological examination [13].

The prognosis of GBS is very heterogeneous. Some patients are mildly affected with a fast recovery and no disabilities irrespective of receiving any treatment. Between 20 and 30% of patients develop complete paralysis, severe respiratory or autonomic failure and receive treatment in the intensive care unit (ICU) for months [14]. In a group of prolonged mechanically ventilated patients, 31% were able to walk after one year and 58% after maximum time of follow up [15]. The sudden increase of patients with Zika Virus-related GBS was a challenge for health care systems in low income countries such as Brazil with limited resources for diagnostics, treatment, ICU capacity as well as rehabilitation facilities [1, 2]. Despite the lack of evidence, multidisciplinary supportive care and rehabilitation are important in GBS. In the acute phase, consensus- based recommendations include (1) monitoring of respiratory and autonomic function in a setting with available artificial ventilation and neuro-intensive care, (2) prophylactic antithrombotic treatment for deep vein thrombosis, (3) pain management, (4) management of nutrition as well as bladder and bowel dysfunction and (5) physiotherapy to prevent muscle shortening and joint contractures [16]. All of these interventions should be followed by a rehabilitation and exercise program to regain physical abilities as fast as possible. Recovery can take months and even years and end up with significant chronic disabilities despite immunomodulatory treatment. As shown in the largest prospective cohort of patients with GBS studied to date, a large proportion of patients had long-term motor dysfunction with 17% of patients from Europe and America were unable to walk unaided after 12 months [17], emphasizing the importance of identifying more effective neuromuscular rehabilitation. Motor dysfunctions such as weakness, wasting and contractures are major long-term complications in severely affected patients. In this review, we present an overview of existing evidence of treatment to prevent muscle weakness and disabilities after GBS with special emphasis on the effect of neuromuscular rehabilitation in the acute and chronic phases of the disease.

2. Treatment and rehabilitation in GBS

Pharmacological treatment. In several large randomized controlled clinical trials, treatment with plasma exchange (PE) or intravenous immunoglobulin (IVIG) initiated in the acute phase of GBS have proven effective. Compared to placebo, treatment with PE or IVIG result in reduced need for respiratory support and an increased chance to regain mobility and muscle strength after 1 month and 12 months [18, 19]. Despite immunomodulatory treatment, a group of patients with GBS still have a very poor prognosis. In a combined cohort study of 526 patients and a cross sectional study including 63 ventilated patients [15], 6% of patients with GBS required mechanical ventilation for more than two months. The prolonged mechanically ventilated patients had a median (range) length of stay at the ICU of 101 (97–126) days and at hospital of 129 (104–162) days, followed by 252 (177–403) days of clinical rehabilitation and 198 (183–502) days of outpatient rehabilitation. At 11 years follow-up, only 58% had regained ambulation and the median time to regain ambulation was

548 (270–730) days. This emphasizes the need for more effective treatment in GBS. Recently, small clinical studies have indicated that monoclonal antibodies against complement proteins given in the early phase of the disease could have some benefit in GBS; however, larger studies are needed to confirm this [20, 21]. It is important to underline that there are currently no evidence-based pharmacological treatments available to prevent muscle atrophy or muscle weakness in GBS [22].

Multidisciplinary rehabilitation. Most patients with moderate to severe GBS are offered multidisciplinary rehabilitation, which means two or more coordinated interventions under medical supervision by a neurologist or rehabilitation physician. Multidisciplinary rehabilitation aims at regaining autonomy with the ability to perform all activities of daily living. This may include physiotherapy or occupational therapy and exercise programs, but also nursing, dietary advice, psychotherapy, speech therapy, and social rehabilitation depending on the needs of the individual patient. The individualized approach to multidisciplinary rehabilitation as well as a considerably variability in facilities between countries and hospitals compromise the possibility to design research trials to assess the efficacy of a multidisciplinary rehabilitation intervention. In a systematic review of rehabilitation interventions in patients with GBS [23], only five original studies could be identified evaluating the effectiveness of multidisciplinary rehabilitation. These studies include only one good quality randomized controlled study comparing high and low intensity rehabilitation in patients with remaining disability more than one year after GBS [24]. In this study, 79 adult patients were included 1–12 years after the GBS diagnosis and randomized to receive either individualized outpatient-based high-intensive rehabilitation (intervention, n = 40) or a lower intensity home-based program (control, n = 39). The intervention comprised three one-hour individualized sessions weekly for 12 weeks. Sessions included physical and occupational therapy for strengthening, endurance and gait training as well as specific rehabilitation tasks to improve everyday life activities as well as community and work functions. The control group completed a 30-minute maintenance training program twice weekly and was also allowed to perform other rehabilitation activities if needed. Outcome was assessed one year after the intervention and included measurements of activity level, participation, and perceived impact of disease-related problems. Based on the total and the motor scales of the Functional Independence Measure (FIM) in an intention to treat analysis, there was a small but statistically significant improvement in the high intensity rehabilitation group compared to the controls. Furthermore, 80% of the patients complying with the high intensity protocol had a clinically meaningful improvement in the FIM motor score (at least 3 points) compared with only 8% of controls. Adverse effects were not reported; however, only 22 (55%) of the 40 patients assigned to high intensity rehabilitation completed the study due to loss to follow up or inability or unwillingness to comply with the protocol. This low number of follow-up reduces the applicability and external validity of the study suggesting that applicability of the intervention is challenging. Other original studies have included: (1) one case control study (n = 34) of inpatient rehabilitation with a control group of healthy subjects [25], (2) one prospective case series (n = 35) of inpatient rehabilitation followed by a home-based training program [26], and (3) two retrospective case series (n = 39 and 24) of inpatient rehabilitation [27, 28]. In these studies, patients with GBS improved during multidisciplinary rehabilitation but the studies were not designed to distinguish between spontaneous recovery and the effect of the rehabilitation intervention.

Despite several limitations, the authors of the review concluded that there is good evidence (Grade level II) to support ambulatory, outpatient multidisciplinary

rehabilitation to obtain long-term improvements in levels of activity and participation in patients with GBS in the later stages of recovery. Further, the authors concluded that there is satisfactory (Grade level III) evidence to support (1) inpatient rehabilitation followed by outpatient rehabilitation thereby inducing functional recovery and (2) physical therapy and exercise to reduce joint contractures and muscle weakness. In another more recent case series of 51 patients with GBS, motor recovery following the acute pharmacological treatment response was assessed during the acute inpatient care as well as after outpatient and homebased rehabilitation [29]. A description of the intervention was not provided, but it included physical therapy for 61 ± 58 (mean ± SD) days for inpatients, 96 ± 70 days for outpatients, and 75 ± 15 days during home rehabilitation. Again, the natural history with spontaneous improvement after GBS and the lack of a control group impairs the possibility to draw any final conclusions based on this study regarding the effectiveness of rehabilitation. However, it was shown that muscle strength measured with a MRC sum score [30] and ambulation assessed with the GBS disability score [31] continue to improve beyond the first six months of rehabilitation.

Exercise. In a systematic review, Simatos and colleagues evaluated the available literature on exercise as an intervention in the rehabilitation of adult patients with GBS [32]. Studies between 1951 and 2016 were identified in PubMed searches and the quality of the studies was assessed and classified according to a modified version of the Centre for Evidence-Based Medicine level of evidence. Seven studies with exercise as the main intervention were identified, including four uncontrolled single cases with a low evidence level, one trial including multidisciplinary rehabilitation (reviewed in the previous section), [24], and two Dutch studies of a case series in an open label standardized exercise protocol (evidence level 5) [33, 34]. In the Dutch study, 16 patients were included between six months and 15 years after their GBS diagnosis as well as four patients with stable chronic inflammatory demyelinating polyradiculoneuropathy. All patients were ambulatory and reported fatigue as a major complaint. The exercise intervention consisted of three 45-minute bicycling sessions every week for 12 weeks. During the 12-week period, training intensity was gradually increased. The target heart rate increasing from 65% to a maximum of 90% of maximal heart rate and an increasing workload was applied on the bicycle home trainer. The intervention resulted in lower fatigue levels, increased isokinetic muscle strength and a higher peak oxygen uptake. Further, patients improved on a handicap scale and on the physical components score of the SF36 Quality of Life scale. Two patients did not complete the study for non-study related reasons, and 25% reported mild and transient muscle cramps, paresthesia, or pain. Overall, exercise as an intervention in patients with late disabilities and fatigue in GBS is feasible and may benefit some patients.

Neuromuscular electrical stimulation (NMES). In the acute phase of severe GBS, rehabilitation exercise is challenged by limited patient participation due to severe weakness or even paralysis. For practical reasons, exercise may also be challenged if patients are in the ICU, intubated and on ventilator support. Inactive and denervated muscles will indisputably and fast degenerate and muscle atrophy will develop [35, 36]. NMES is a method to induce muscle contractions without patient participation. This may be an alternative therapeutic approach in the acute phase of GBS, which can minimize inactivation and denervation wasting until patients have recovered to a level where a multidisciplinary rehabilitation effort can be initiated [37, 38]. In a small proof of concept study this has proven feasible with satisfactory safety. There was also a trend for an effect of

NMES on muscle wasting as an add on to established standard of care in the acute and subacute phases of GBS [39]. Seventeen patients with moderate to severe GBS were randomized to receive an hour of NMES on weekdays on the right or left quadriceps femoral muscle with the non-stimulated muscle serving as control. Stimulation was initiated within two weeks after the first sign of weakness and was continued through the acute hospital admission and the following inpatient rehabilitation. The median (range) time of participation was 27 days (10–95) and included 17 (4–53) stimulation sessions. During the study, each patient had a mean loss of lean body mass (muscle) of 3.4 kg, establishing that patients with GBS will experience substantial muscle wasting. NMES was found to be safe and feasible as an add on to standard supportive therapy and rehabilitation in the acute and subacute phases of GBS. There was a trend towards a preventive effect of NMES on muscle atrophy, but the study was not designed to explore effect on patient disability.

Virtual Motor Rehabilitation System. Virtual Motor Rehabilitation (VMR) is a new technology combining novel rehabilitation software with low cost commercially available devices such as the Nintendo® Wii platform. To be effective, multidisciplinary rehabilitation in GBS is very time demanding including several daily sessions for as long as 6, 12 and 18 months [40]. Often the rehabilitation offered is limited due to lack of time and resources, and patients may find training tedious and monotonous, resulting in lack of compliance. Therefore, VMR could be an attractive supplement to the established rehabilitation regimen. The method is still under development and so far only one study has been published, describing VMR applied four and five months after admission in two patients with severe GBS as an add on to the conventional multidisciplinary rehabilitation [41]. In this study, the Nintendo® Wii Balance Board and a virtual environmental tool were applied in 20 rehabilitation sessions consisting of 30 minutes of traditional therapy and 30 minutes of VMR. Compliance was good and patients' status improved. VMR could be developed further to include more aspects of the rehabilitation process in the future.

Safety. In anecdotal case reports and experimental animal studies it has been indicated that over-exercising during rehabilitation after GBS may damage motor units and cause paradoxical weakening, which has led to hesitation concerning the recommendation to do intensive and strenuous exercise [16]. The clinical data to support this concern are negligible and overall, it is reasonable to believe that the benefit of exercising weakened muscles after GBS excess the risk of harm. However, systematic registration of safety and complications should always be included in future studies.

3. Conclusions

Neuromuscular rehabilitation after GBS is important for the functional outcome of each individual patient. Studied rehabilitation interventions in the acute, subacute/intermediate, and chronic/long-term phase are summarized in **Figure 1**. However, the quality of the present evidence of rehabilitation efficacy is low, rehabilitation is both complex, time consuming and expensive, and there is currently no standardized care for patients with neuromuscular disabilities after GBS. Therefore, the rehabilitation effort may lack necessary resources and expertise. Because the monophasic course and spontaneous recovery in GBS challenge the interpretation of non-controlled studies, future large controlled studies and standardized sensitive efficacy outcome measures are needed to improve the interpretation of neuromuscular rehabilitation trials in GBS.

Acute phase (1-8 weeks) **Patients are at risk of deteriorating and to suffer complications**	Rehabilitation focus (no grade 1 or 2 evidence)
Patients are at hospital for acute care including respiratory and autonomic monitoring and support, thromboprophylaxis, pain treatment etc.	* Physiotherapy to prevent muscle shortening and contractures. * Neuromuscular electrical stimulation. Safe and feasible, efficacy still to be explored.
Intermediate phase (weeks to several months) **Patients improve gradually**	Rehabilitation focus: Regain autonomy and ability to perform activities of daily living. (no grade 1 or 2 evidence)
Patients are at rehabilitation centers or outpatient rehabilitation facilities.	* Multidisciplinary rehabilitation * Task specific training * Neuromuscular electrical stimulation. Safe and feasible, efficacy still to be determined. * Cardiovascular and strengthening exercises
Chronic phase (months to years) **Patients are stable with residual disabilities**	Rehabilitation focus: Further improve or maintain function
Patients are exercising and performing rehabilitation training at home, at outpatient facilities or fitness centers.	* High intensity multidisciplinary rehabilitation improves functional independence **(grade level 2)**. * Multidisciplinary rehabilitation * Task specific training * Exercise cardiovascular and strength * Virtual Motor Rehabilitation

Figure 1.
Neuromuscular rehabilitation in three phases of Guillain Barré syndrome. Rehabilitation focus and studied interventions in three phases of Guillain Barré syndrome, the acute, subacute/intermediate, and chronic/long-term phase. Level of evidence is indicated using the following grade system: Level 1, meta-analysis of multiple well designed randomized controlled trials; level 2, at least one randomized controlled trial; level 3–5, non-randomized controlled trials, descriptive studies or case series.

4. Policy and procedures

Neuromuscular Electrical Stimulation Protocol.
Stimulation of the quadriceps muscle was performed using a STIWELL med4 stimulation unit, https://www.ottobock.co.th/neurorehabilitation/solutions/solutions-with-functional-electrical-stimulation/stiwell-med-4/(Otto Bock, Konigsee, Germany) and two large stimulation pads (6 × 8 cm). The intensity of electrical stimulation was titrated individually at entry and weekly during the study to the point of maximal contraction or the highest tolerable intensity. During the first session of stimulation, the skin under the pads was inspected every five minutes for redness or other signs of tissue damage. Trained physical therapists attached the equipment and titrated the stimulation intensity, but after being attached to the patient the individualized stimulation protocol ran automatically.

Direct muscle fiber stimulation (MFS). With MFS, contraction is induced directly through the muscle fiber membrane independent of the neuromuscular junction, which means that complete distally denervated muscle fibers can be activated. The disadvantage is that higher intensity stimulation, especially in atrophic muscle, is needed which may cause discomfort and skin irritation. MFS was applied by placing two pads over the proximal and distal part of the muscle (**Figure 2**) with triangular dual-phase stimulation pulses. The initiation protocol was 1 Hz frequency,

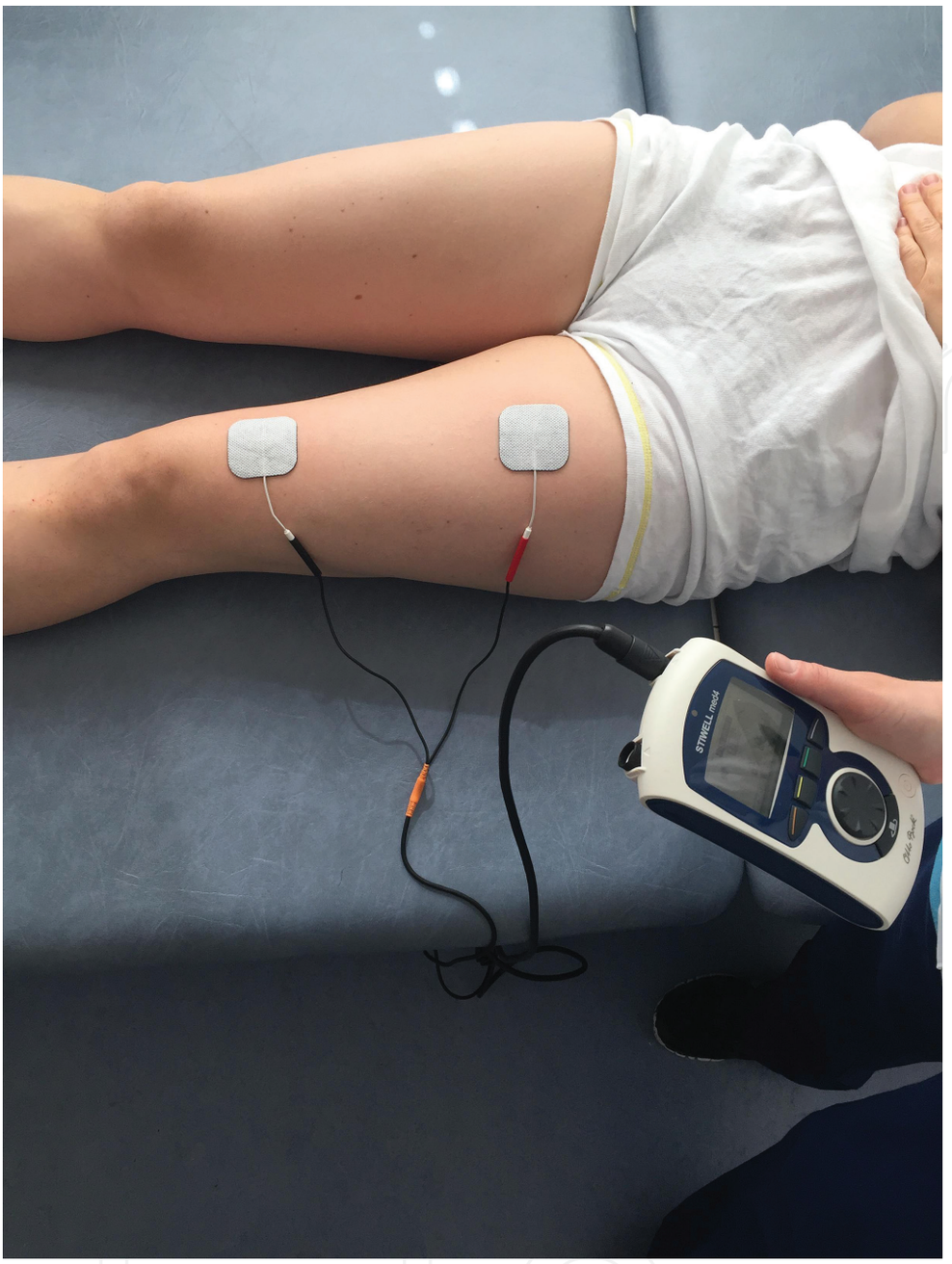

Figure 2.
Electrical muscle stimulation. A healthy control subject with electrodes in place for direct muscle fiber stimulation of the left quadriceps femoris muscle by the STIWELL med4 stimulation unit.

250 ms pulse width, and 3/6 on/off ratio. The lowest pulse width with maximal contraction was chosen and frequency was increased to the highest tolerated level.

Neuromuscular electrical stimulation (NMES). With NMES the muscle is activated through the muscle spindle and neuromuscular endplate. As a result, the contraction is more physiological and less electrical stimulation is needed. NMES was applied by one pad placed on the middle of the muscle bulk, where the neuromuscular transmission is located with rectangular dual-phase stimulation pulses. The protocol included four phases of 5, 15, 15, and 5 minutes, with frequencies of 10, 40, 60, 3 Hz, with a pulse width of 0.3 ms. Intensity could be adjusted from 0 to 100 mA and was increased to the highest tolerated level.

The intention was to stimulate patients five to seven days a week including 20 minutes of MFS followed by 40 minutes of NMES. Also, the NMES was applied to patients where no visible contraction could be observed.

5. Mini-dictionary of terms

Neuromuscular Electrical Stimulation: A method to induce muscle contraction by applying an electrical impulse to the neuromuscular endplate by an electronic device.

Multidisciplinary rehabilitation: Two or more coordinated interventions for disabled patients to regain autonomy and functions of daily living. Usually, multidisciplinary rehabilitation is performed by physical therapists and occupational therapists but may include other professions.

Motor dysfunction: Several methods are used to describe motor dysfunction in GBS. Muscle weakness is a main feature of GBS, which develops quickly in the acute phase. Weakness can be assessed manually with the MRC score on a scale from 0 to 5. (0, paralysis with no visible contraction; 1, visible contraction but no limb movement; 2, limb movement only with gravity eliminated; 3, active movement against gravity; 4, active movement against gravity and resistance but reduced strength; 5, normal strength). Weakness may be quantified on a linear scale using a dynamometer [42]. In addition to weakness, chronic muscle dysfunction can result in muscle wasting, and muscle and joint contractures and shortening, which is very disabling.

Impairment and disability: Impairment is the direct damage caused by the disease, for example weakness of leg muscles (as described above) or loss of sensation, while disability is the loss of the function caused by the impairment, for example loss of ambulation. Often, the GBS disability score is used to describe the severity of the disease concerning the level of disability. (0, healthy; 1, minor symptoms and capable of running; 2, able to walk 10 m without assistance but unable to run; 3, able to walk 10 m across an open space with help; 4 bedridden or chair bound; 4, requiring assisted ventilation for at least part of the day; 6, death).

6. Key facts of neuromuscular rehabilitation in GBS

Neuromuscular rehabilitation in Guillain Barré Syndrome can include

- Physical therapy to prevent muscle and joint shortening and contractures.
- Multidisciplinary rehabilitation with two or more coordinated interventions for disabled patients to regain autonomy and functions of daily living.
- Exercise and training to improve or maintain physical functioning.
- Neuromuscular electrical stimulation to prevent muscle wasting.

The prognosis of Guillain Barré Syndrome

- Guillain Barré Syndrome is a heterogenous disorder with a monophasic course.
- Clinical severity ranges from mild impairment to complete paralysis combined with respiratory and autonomic failure.
- In 20 to 30% of patients, mechanical ventilation is required at nadir of GBS.
- The most severely affected patients have a long recovery phase and a poor prognosis.
- More than half of all mechanically ventilated patients are unable to walk unassisted at one year follow up.

7. Summary points of neuromuscular rehabilitation in GBS

- Most commonly, GBS is preceded by an infection, therefore, the incidence of GBS can increase during outbreaks of infectious diseases, which was most recently observed during the Zika Virus outbreak in the French Polynesia and Latin America with a high increase in the incidence of GBS in several countries.

- Despite optimal evidence-based treatment with immunoglobulin and plasma exchange, a large proportion of patients with GBS will have substantial neuromuscular disabilities more than one year after disease onset. Among patients receiving mechanical ventilation, more than half will be able to walk unassisted.

- In the acute phase of GBS, physical therapy is important to prevent muscle shortening and joint contractures.

- Patients may still improve their physical function several years after onset of GBS.

- There is evidence to support high intensity multidisciplinary rehabilitation and exercise which improves level of activity and participation in the late and chronic stages of GBS.

- New approaches like Neuromuscular Electrical Stimulation and Virtual Motor Rehabilitation seem to be feasible methods in the acute and late stage recovery of GBS, but efficacy needs to be explored in future studies.

Abbreviations

FIM	functional independence measure
GBS	Guillain Barré syndrome
ICU	intensive care unit
IVIG	intravenous immunoglobulin
MFS	muscle fiber stimulation
NMES	neuromuscular electrical stimulation
PE	plasma exchange
VMR	virtual motor rehabilitation

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