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Case Study
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Plasmapheresis and Guillain–Barré Syndrome: Desperate Therapy for Desperate Patient? A Case Report

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Abstract

Introduction: Guillain-Barre syndrome is a rare disorder in which our body's immune system attacks nerves determining weakness and tingling of extremities as first symptoms. It can also be associated to respiratory failure and require mechanical ventilation during hospitalization (up to 30% of patients). Nowadays patient's hyper-reactive immune responses benefits from immunotherapies such as Intravenous Immunoglobulin (IVIg), Therapeutic Plasma Exchange (TPE) and new biological drugs.

Case Study: We report our experience with the case of a 64-year-old woman who presented a symmetric progressive flaccid paralysis after a week of mild cold symptoms. The respiratory and neurological symptoms worsened despite immunoglobulin infusions and intensive supportive care. She gradually improved with TPE, but we didn't respect schedules of the American Society for Apheresis (ASFA) and we decided to extend the number of TPE treatments to sixteen.

Conclusion: Although the first case of Guillain-Barre syndrome was described a century ago, there are still many dark sides about its etiology, pathogenesis, clinical variants and therapeutic strategies. Further studies are necessary to find answer too many still unanswered questions. The management of these patients must include a high index of clinical suspicion, a prompt diagnosis and adequate therapy without mistakes.

Keywords: Guillain-Barre syndrome; Intravenous immunoglobulin; Plasma exchange; Acute motor axonal neuropathy; Acute motor and sensory axonal neuropathy; Miller-Fisher syndrome

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Introduction

Guillain-Barre Syndrome (GBS) is an acute polyradiculoneuropathy, often symmetrical, and typically ascending. GBS affects more males than females and has a mean age of onset of 40 years. GBS has an annual incidence of 0.81 to 1.89 cases (median, 1.11) per 100,000 persons worldwide [1]. GBS is usually preceded by infectious immune stimulation that induces an abnormal acute inflammatory response targeting peripheral nervous system. The favored pathogenesis of GBS is autoimmune antibody-mediated damage to peripheral nerve myelin. Up to 75% of cases of GBS are preceded by an infection, fifteen to thirty days prior to the onset in most cases [2]. GBS cases have often a prodromal upper respiratory or gastrointestinal tract infection without any specific organism identified [3]. The major mechanism behind the development of this disease seems to be the molecular mimicry between germ and nerve antigens, as suggested by the increase of GBS incidence in regions with association with *Campylobacter jejuni* outbreaks. How and why the immune response is shifted towards unregulated auto-reactivity is not still clear. Spontaneous recovery may occur, but neurologic reliquates persist in up to 20% of patients [4]. GBS severely affected patients have to be referred as soon as possible to a specialized neurological Intensive Care Unit (ICU) and those cases that progress to respiratory failure need intensive supportive care. This is the most important element of clinical management of these patients. A multidisciplinary team should provide intensive care for severe GBS cases to avoid multiple complications.

GBS has an in-hospital mortality rate of approximately 2.7%. Negative prognostic factors are old age, severity of disease at entry, time to peak disability and respiratory failure [5].

Case Study

We report the case of a 66-year-old woman with a 3 days history of weakness and increasing

difficulty walking; she also referred a mild cold, a transient pruriginous dorsal rush and cough one week before. Fever went to spontaneous resolution after a few days and she didn't refer gastrointestinal symptoms. Her medical history was not relevant; she only suffered of mild hypertension treated with beta-blockers. First on clinical evaluation she was alert and conscious, no autonomic disorders (tachy/bradycardia, hyper/hypotension), no respiratory fatigue (respiratory rate of 16 bpm and oxygen saturation of 99%); her vital signs revealed body temperature 36.5°C. The systemic examination was normal. First she was admitted to neurological departmental. On neurological examination, she was para-paretic with a rapidly progression to paraplegia. She denied any facial numbness, swallowing inability, and blurred vision but she subsequently developed distal weakness in the upper limbs and diffuse areflexia, without clear sensory deficits. She underwent lumbar puncture. The Cerebrospinal Fluid (CSF) puncture didn't reveal abnormalities of glucose and cell count, but 139 mg/dL protein. Albuminocytologic dissociation in the CSF is a laboratory typical feature of the disease that is evident in up to 90% of all patients during the third week of the GBS course [6]. CSF viral serology and bacterial cultures were negative. No routine laboratory testing is helpful to diagnose GBS.

Our clinical suspect of GBS was endorsed by the demonstration of a typical albumin-cytological dissociation; subsequently we decided to confirm the diagnosis with electrophysiologic studies which were essential to exclude GBS's mimics. The differential of pure motor syndrome includes: Diseases associated with quadriparesis/paralysis (myasthenic crisis), acute presentation of idiopathic inflammatory myopathies. Associated clinical features can be useful in distinguishing these from GBS. Although on the diagnosis of GBS prompted initiation of Intravenous Immunoglobulin (IVIg, 0.4 g/kg for 5 days), her condition quickly deteriorated and in a few days she became quadriplegic despite the completion of immune-therapy. By this time, she had complete right-sided ptosis with a normal left eye. On hospital day 6, the patient also developed tachycardia and blood pressure instability (dysautonomic features) and bulbar involvement (she was unable to swallow and presented a severely slurred speech). Clearly, the patient did not benefit from immunoglobulin therapy. Respiratory muscle weakness and inefficient cough in our patient contributed to the loss of airway protection and desaturation. Progressively gas exchanges worsened so intubation was required and ICU admission, where treatment started with Therapeutic Plasma Exchange (TPE).

GBS patients should be admitted to the ICU when one or more of these criteria are identified: (a) Rapid evolution of respiratory fatigue; (b) tachycardia and blood pressure instability severe or difficulty swallowing; (c) progression of respiratory distress; (d) Erasmus GBS Respiratory Insufficiency Score (EGRIS) >4 [7].

The Erasmus GBS outcome score is a 1 to 7 score that predict the probability of respiratory insufficiency within the first week of admission, in patients with Guillain-Barre syndrome. According to Erasmus GBS score number of days between onset of weakness and hospital admission, presence of facial and/or bulbar weakness and severity of muscle weakness at hospital admission, were independently associated with the probability to develop respiratory insufficiency within the first week of admission.

Because a prolonged MV (>3 weeks) was predicted, we considered tracheostomy immediately and we performed it on the third day. Early tracheostomy could help GBS patients in several ways: Earlier enteral feeding, accurate oral hygiene facilitated oral communication, easier out-of-bed mobilization. Complications during MV and ICU stay are negative prognostic factors for GBS patients. We prevented complications such as decubitus ulcers *via* frequent repositioning. She gradually improved with TPE. The first to improve was ptosis and autonomic feature, she returned to blood pressure stability on the sixth day (three TPE performed). Five days later her cough was turning to be effective and respiratory muscles were less weak; then we started weaning from mechanical ventilation, but she was still quadriplegic (six TPE performed). Her motility gradually improved over the next week and lower limbs muscle strength slowly improved, upper limbs' weakness reduced few days later (eleven TPE performed). Respiratory weaning was very slow and difficult. She reached spontaneous breathing with tracheostomy 24 h a day on the 25th day. Over the next week we started oral feeding.

TPE was performed removing 3 to 6 liters of plasma over six-eight hours and replacing it with albumin. We performed TPE with continuous flow machines. We usually used hemodialysis catheter inserted through internal jugular or femoral venous access. No complications occurred (hemo/pneumothorax, hypotension, and hemorrhage from vein puncture). For our patient the total exchange volume was approximately 15,000 cc. During TPE, we monitored blood pressure, heart rate, oxygen saturation, and amount of fluids exchange. We obtained daily hemochrome, calcium, coagulation pattern and hold apheresis one to two days. Nosocomial complications such as Hospital-Acquired Pneumonia (HAP), Ventilator Acquired Pneumonia (VAP) and hyponatremia were considerable factors in prolonging MV (>21 days) and hospitalization (>36 days) and causing death. Blessedly our patient didn't have any nosocomial complications and she was transferred to rehabilitation department where stayed over several months.

Discussion

Acroparesthesia is the most common initial symptom of GBS associated to upper and lower limbs weakness which ensues commonly in a symmetric "rapidly ascending pattern" [8]. Clinical

Table 1: Diagnostic criteria of Guillain Barre Syndrome (adapted and modified from reference 4).

Required	Supportive	Exclusionary
Progressive symmetric weakness of >1 limb	Sensory symptoms or signs	Other causes excluded (toxins, botulism, porphyria, diphtheria)
Hyporeflexia or areflexia	Cranial nerve involvement especially bilateral VII	
Progression <4 weeks	Autonomic dysfunction	
Symmetric weakness	CSF cell count< 10/mm^3	
	CSF protein elevation	
	Electrophysiologic features of demyelination	
	Recovery	

Table 2: ASFA category indications*.

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment
III	Optimal role of apheresis therapy is not established. Decision making should be individualized
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken

*Suspect HIV; Lyme; Sarcoidosis; Lymphoma

Table 3: Grading Recommendations*.

Recommendation grade	Description	Methodological quality of supporting evidence	Implications
1 A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1 B	Strong recommendation, moderate- quality evidence	RCTs with important limitations or exceptional strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1 C	Strong recommendation, low-quality evidence	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2 A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances
2 B	Weak recommendation, moderate- quality evidence	RCTs with important limitations or exceptional strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances
2 C	Weak recommendation, low-quality evidence	Observational studies or case series	Very weak recommendation; other alternatives may be equally reasonable

*Suspect HIV; Lyme; Sarcoidosis; Lymphoma

status is then characterized by neuropathic or radicular back pain, acute flaccid paralysis, sensory or autonomous neuropathy, hypo- or areflexia [9]. GBS's main symptom is weakness, which reach its nadir within twenty eight days in 90% of cases [3]. Facial nerve is frequently involved, dysphagia occurs in 40%, and rarely (5%) patients may develop ophthalmoplegia, ptosis [3].

Poor prognostic factors in GBS

- Older age (>50–60)
- Rapid onset prior to presentation (<1 week)
- Ventilator dependency
- Preceding infection with CMV
- Preceding diarrheal illness/*C. Jejuni*

The revised diagnostic criteria are well established and include clinical, cerebrospinal fluid and electrophysiologic criteria. They go back to several years ago (Table 1).

TPE is the extracorporeal technique by which we can remove toxic substances and replace lost plasma elements; it represents an important device for the management of several disorders [10].

It is performed in an apheresis device where patient's plasma is separated from whole blood and removed without depleting the patient of other blood constituents (such as red blood cells) and returning the rest to the patient's circulatory system. Literature available data confirm that TPE is a safe and effective device. Currently, to assist physicians in the decision of using apheresis as a treatment modality, the American Society for Apheresis (ASFA) regularly publishes updated evidence-based treatment guidelines, with the most recent edition being published in 2019. The role of TPE in the treatment of diseases and indications in the Guidelines are categorized in accordance with the ASFA categories (Table 2).

Additionally, a recommendation grade based on the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system (Table 3) is also provided along with the ASFA category for each TA indication.

TPE for GBS is primary treatment, category I, GRADE IA and should be initiated within a week of disease onset [10]. TPE has beneficial effect in sever and mild GBS patients, increasing proportion of patients able to walk after one month. TPE mainly functions *via* removing extra antibodies, abnormal proteins, or other harmful substances from the blood [10]. The usual TPE strategy is to exchange 1 to 1.5 plasma volumes 5 to 6 times over one-two weeks, but some patients may need additional treatments. How to manage the severe GBS patients who don't improve two weeks after TPE or Immunotherapy is a hot topic. Our patient didn't improve in standard time, so we decided to extend the number of TPE treatments to 16. We didn't use corticosteroids because they are not beneficial in the disorder. Dramatic improvement within days of beginning treatment is not typical and if this happens, it may have happened regardless of treatment.

All patients affected by autonomic dysfunction should be monitored carefully because they remote susceptible to intravascular volume exchange TPE. Relapses may occur in up to 5% to 10% of patients 2 to 3 weeks following either treatment with TPE or IVIG [11,12].

IVIg is a therapeutic preparation containing antibodies and especially IgG antibodies obtained from the pooled blood plasma of usually thousands of blood donors [13,14]. High-dose IVIg [ranging from 1000 to 3000 mg/kg Body Weight (BW)] have immunomodulatory actions in autoimmune and inflammatory conditions. Their actions are highly complex and differ in different diseases. In general, they lead to a reversal of their effects, as opposed to their actions at replacement doses, resulting in a more immunosuppressive and anti-inflammatory phenotype. The benefit of a second course of IVIg is still matter of debate [13].

We closely monitor patients during the first infusion, starting very slowly and increasing progressively. Mild reactions (headache, nausea, chills, myalgia, chest discomfort, back pain) are uncommon and solved when slowing the infusion rate. Acute renal failure is rare and related to patient hydration [15]. Treatment decisions are made on a case-by-case basis but IVIG is usually used as initial therapy; the dose is 0.4 g/kg for 5 consecutive days. TPE scavenges pathogenic

inflammatory mediators [10], so can accelerate motor recovery and decrease time on the ventilator but a priori combining of TPE and IVIG in sequential order is not recommended [16-20].

Conclusion

GBS patients are usually admitted to neurological department for close and frequent monitoring of clinical signs and symptoms of the disease. A rapid decline of the vital capacity <15 ml/kg BW, hypoxemia (PaO_2<7.5 kPa), hypercarbia ($PaCO_2$>6.4 kPa), or intolerable respiratory fatigue indicate the need for urgent intubation and mechanical ventilation. Ideally a multispecialty team should assist these patients above all for the decision-making of support of vital functions (MV if respiratory failure, nasogastric tubes for feeding if severe dysphagia). Tracheostomy should be considered in those patients with expected mechanical ventilation for more than two weeks.

In the management of patient's with dysautonomic features it is important to avoid aggressively treating blood pressure fluctuations and long-term anti-hypertensives. Deep venous thrombosis prophylaxis with subcutaneous heparin is mandatory for bed-ridden patients and, whenever possible, motion can help prevent muscle contractures in paralyzed patients.

Despite IVIg and TPE are still incurring controversies due to high cost, potential adverse events and incompletely known mechanisms; these immunotherapies have an efficacy validated in the treatment of GBS by extensive investigations.

TPE is strongly recommended for severe GBS patients, in the acute phase with impaired independent walking capacity or requiring or tracheal intubation. Patients with GBS usually benefit from a standard TPE schedule (5 sessions with 40 ml to 50 ml plasma/kg per session within 1 to 2 weeks). TPE is routinely performed every other day to allow the redistribution of pathogenic mediators in both extra vascular and intravascular compartments and its efficacy depends on the speed of production and clearance of these mediators.

Optimization of the procedure of TPE is a hot topic. The routine frequency of TPE is of four sessions for moderate to severe GBS cases, while two sessions for those with mild disease. TPE can also be conducted with albumin instead of fresh frozen plasma but when albumin is used, dilution of the anti infectious immunoglobulins is an important feature.

Before initiating TPE or IVIG, every patient should know that it takes a long time to walk without aids. TPE is generally safe although many complications may occasionally occur.

GBS is a rare and clinically variable disease, as a consequence diagnose is not always easy and its treatments are often empirical. Observational data are often used to guide clinical practice of severe GBS in the ICU. We need documented investigations with large sample size to address treatment doubts like mild cases, variant forms of GBS, when the onset of weakness was more than 15 days ago, or when patient doesn't improve or even progresses after initial treatment.

Actually, TPE and IVIg are the cornerstone of GBS treatment, despite no evidence supports the combinational use of IVIg and TPE for severe GBS patients as well. Research is still displaying new approaches like small-volume TPE, double filtration plasmapheresis, a second dose of IVIg, and very early use of steroids.

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