Atypical Presentation of Guillain-Barré Syndrome in a 38-year-old Previously Healthy Male

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Abstract

Guillain-Barré is an acute immune-mediated polyneuropathy characterized by acute, acquired weakness that can affect all myelinated nerves, usually triggered by an immune response to preceding infection.

This case presents a 38-year-old previously healthy male presenting with new peripheral weakness rapidly progressing over the course of 24 hours.

Per neurology recommendations, extensive infectious workup was completed to isolate the cause of his particular presentation of Guillain-Barré syndrome, all leading to negative findings.

Patient was given IVIg therapy for 5 days and began extensive physical and occupational therapy to recover weakness, showing improvement by time of discharge to an acute rehabilitation center.

This case is a unique presentation of Guillain-Barre syndrome without clear etiology.

Introduction

- First reported in 1916, Guillain-Barré syndrome (GBS) is an acute postinfectious polyneuropathy characterized by symmetric and ascending flaccid paralysis. Usually caused by an immune reaction to an antecedent infection, cross-reactive autoantibodies attack the host's own axonal antigens, resulting in inflammatory and demyelinating polyneuropathy.

- There are 1-2 cases of GBS per 100,000 every year, more commonly in males than females (1.5:1), and incidence increases 20% with each 10-year increase in age after 10 years.

Introduction

There are two types of GBS: demyelinating and axonal loss.

- **Demyelinating GBS**, the most common type being acute inflammatory demyelinating polyneuropathy (AIDP), is caused by a focal inflammatory response against Schwann cells or peripheral myelin, leading to decreased saltatory conduction along the nerve, and resulting in muscle weakness.

- **Axonal Loss GBS**, including acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), present with prominent axonal loss without lymphocytic infiltration but rather an immune reaction against the axonal membrane, particularly the nodes of Ranvier, leading to blocked conduction.

Introduction

- Laboratory findings reveal albuminocytologic dissociation, characterized by elevated protein levels and normal cell counts in cerebrospinal fluid (CSF), a hallmark finding of GBS. Additionally, muscle and nerve electrophysiology are used to diagnose demyelinating processes.
- Symptomatic and supportive treatment results in disease remission in about 70% of cases.
- In severe cases or patients who do not respond to treatment, intravenous immunoglobulin (IVIg) administration and/or plasmapheresis may be used. Potentially acute life-threatening complications such as respiratory insufficiency, pulmonary embolism, and/or cardiac arrest increase mortality.
- Although GBS is associated with a good prognosis overall, up to 20% of patients remain severely disabled and approximately 5% of cases are fatal, despite immunotherapy.

Introduction

- About two-thirds of GBS patients experience symptoms of an upper respiratory or gastrointestinal (GI) tract infection 1-4 weeks prior to onset of GBS.
- Campylobacter Jejuni is the most common antecedent in GBS and the most common associated virus is cytomegalovirus (CMV).
- Other associated pathogens include, HIV, influenza, Mycoplasma pneumoniae, Zika virus, Epstein-Barr virus, and SARS-CoV-2.
- There are also cases of vaccination-associated GBS, seen in the influenza, meningococcal, recombinant zoster, and more recently, the COVID-19 vaccine (J&J, AstraZeneca).
- Other antecedents include surgery, trauma, Hodgkin lymphoma, lupus, sarcoidosis, and therapies such as TNF-alpha inhibitors, tacrolimus, and isotretinoin.

Case Presentation

Patient is a 38-year-old previously healthy male presenting to Kaiser Permanente Fontana Medical Center on 6/28/22 with new weakness for three days. He first noticed this 3 days prior, when he felt excessive fatigue the day after doing heavy yard work and donating blood.

The next day he had difficulty exercising, feeling too weak to tolerate his normal previous workout and having trouble opening a bottle cap. He also mentions that ten days prior to presentation, he had a bout of diarrhea and cramping, which resolved 5 days later.

He first was seen in Urgent Care, where he was treated for a cut on his leg, he had from a few days prior and was given Tdap. The following morning, on the day of admission, he had no strength in his hands, with noted weakness with squeezing objects, and could not walk on his toes.

Case Presentation

- On examination, cranial nerves 2-12 were intact, sensation in all four extremities were normal, motor function of proximal joints were normal, but finger abduction/adduction and plantarflexion/dorsiflexion were impaired.
- CT head was normal without acute changes, cervical MRI was normal, and CSF labs from lumbar puncture were unremarkable.
- Neurology recommended admission for close management with evolving symptoms, and IVIg course for 5 days was initiated as a precaution per neurology recommendation.
- Extensive infectious workup was completed to elucidate the etiology of GBS including viral, bacterial and autoimmune causes, however all results were negative.

Case Presentation

- During the first days of admission, weakness progressively worsened throughout all four extremities. He was only able to receive one dose of IVIg due to supply shortages, and therefore treatment was shifted to plasmapheresis therapy per hematology recommendations.
- Patient's weakness progressed with some noted respiratory difficulty, and he was transferred to the ICU for acute management. Patient did not require intubation for respiratory drive failure. After plasmapheresis and 1 unit cryoprecipitate, the patient noted improved strength, and was downgraded for remaining IVIg doses.
- Patient worked with Physical Therapy and Occupational Therapy on a daily basis and had great strides of improvement in weakness throughout the latter part of admission. Patient was discharged to an acute care rehabilitation center for intensive physical therapy and occupational therapy.

Discussion – Guillain Barre Syndrome

- Guillain Barre syndrome is an acute postinfectious polyneuropathy characterized by symmetric and ascending flaccid paralysis via cross-reactive autoantibodies that attack the host's own axonal antigens, resulting in inflammation and demyelination.
- GBS is classically differentiated from other polyneuropathies by a preceding viral infection, typically a gastrointestinal or respiratory pathogen, that leads to rapid onset upper and lower neuron paralysis. With two-thirds of cases presenting in this fashion, diagnostic testing typically is used to confirm the etiology.
- Albuminocytologic dissociation within the cerebrospinal fluid (CSF) is a hallmark finding of GBS. Additionally, muscle and nerve electrophysiology are used to further diagnose demyelinating processes.

Discussion – Guillain Barre Syndrome

- This case demonstrates the rarer subtype of GBS where diagnostic testing is negative, despite strong evidence of clinical symptoms with a preceding viral infection. In this case, treatment was guided by an empiric approach. In this patient, initial laboratory testing helped screen out other causes of acute weakness, leading to a diagnosis of GBS.

- Due to his atypical findings, further testing was done to support the diagnosis of GBS. In addition, autoantibody testing can suggest axonal loss GBS. This patient in particular had a completely negative workup, requiring neurology specialists to treat the patient per disease gold standard protocol and without specific clinical direction.

Discussion – Guillain Barre Syndrome

- Studies as of late particularly investigated GBS due to infectious etiologies such as dengue (1) and Zika virus (2) primarily in pediatric patients, however lab work would indicate positive findings for these infections. With the recent coronavirus pandemic, more atypical cases of GBS were presented after inoculation with the COVID-19 vaccine or even after COVID-19 infection. A recent systematic review showed the broader age range of GBS presentation with COVID-19, but most patients presented with symptoms and positive tests (3).

- This patient's case was not confounded with recent COVID-19 or other respiratory infection, but rather had gastroenteritis-like symptoms. However, the testing for ganglioside (GM1) antibodies was negative. Due to this patient's unusual findings being pan-negative for most infectious and autoimmune workup, his case presents an interesting consideration for further studies to elucidate other noninfectious or autoimmune causes of GBS.

Discussion – Treatment Modalities

- Studies have shown that IV immunoglobulin (IVIg) and plasmapheresis (PLEX) are the mainstays of therapy for treating immune-mediated neurological conditions. Although not curative, these modalities help shorten disease progression by up to 50% and minimize further neuron and myelin destruction.

- Based off literature alone, IVIg has been commonly used as first-line therapy due to its ease of administration and limited adverse effects. The mechanism of action of IVIg in neurological disorders centers around the interference of antigen presentation, autoantibody modulation, cytokine production, and complement activation.
  - Therapy is administered at 2g/kg over 2-5 days.
  - Side effects include generalized systemic side effects, such as headache, nausea, chills, and back pain. Rare severe reactions include anaphylaxis, MI, stroke, or PE.

Discussion – Guillain Barre Syndrome

- Plasmapheresis has also been used based off availability and improved cost-analysis from new techniques in centrifuge technology. PLEX works by directly removing humoral factors from the blood, such as cytokines, autoantibodies, immune complexes, and complement.
- Complications included hypotension, sepsis, PE, hemorrhage, thrombocytopenia, pneumothorax, or hypocalcemia. PLEX is performed over several hours over the course of 5-10 days, replacing 3-6 liters of plasma with FFP or albumin in each exchange.

PLEX after IVIg vs IVIg after PLEX

- Both treatment modalities are similarly efficacious with preference focusing mainly on availability. However, with national IVIg shortages limiting the access of immunomodulatory therapy by around 30%, the courses of IVIg have been shortened, disjointed, or replaced with PLEX out of necessity.

- In this case, the patient received only a single dose of IVIg before switching to PLEX due to national shortages of IVIg. His symptoms began to improve concurrently with supply refills, and he was transitioned back to IVIg after a single dose of PLEX. The challenges of interchanging IVIg and PLEX based off institutional supply has demonstrated varied effects in treatment efficacy.

PLEX after IVIg vs IVIg after PLEX

- One retrospective study of 46 patients demonstrated that PLEX administered after IVIg led to longer hospitalizations and worsened GBS disability grades at discharge. The reasons for this phenomenon remain unclear; however, the researchers hypothesized that PLEX washes out IVIg, preventing the therapeutic outcomes of IVIg. Alternatively, they also theorized that the longer hospitalizations could be reflective of worsening disease course in patients receiving two different treatment modalities.

- Alternatively, one randomized trial compared the efficacy of IVIg after PLEX in 379 affected patients, along with testing the efficacy of IVIg and PLEX alone. This study demonstrated no significant differences between the administration of IVIg after PLEX compared the IVIg or PLEX alone. In addition, this study also compared IVIg and PLEX head-to-head and demonstrated no added neurological improvement in patients with either treatment modality.

Healthcare Access Affecting Treatment

For years, the use of IVIg was first-line over PLEX due to the easy of accessibility, cost, and limited side-effect profiles. However, over the last 15 years, new data suggests the contrary. Recent supply chain delays have led to nationwide shortages of IVIg since 2018. What was once a readily available drug has become increasingly difficult to acquire, with a 30% reduction in supply since 2018.

The treatment course of IVIg has also been historically more favorable due to a shorter time course of administration. However, the use of central access is still commonplace and harbors procedural risk with each administration. Advances in PLEX technology have allowed treatment of patients via peripheral venous access, leading to lessened procedural risks and limited invasive procedures. This added benefit is compounded with new data suggesting that PLEX and IVIg have comparable adverse event profiles.

- IVIg's central access being limited to membrane filters, cost per exchange is estimated at $954 dollars
- PLEX peripheral access and new centrifuge technology, recent cost-minimization analysis studies of 44 GBS patients have highlighted an average **annual cost savings for PLEX over IVIg of $343,362.**

Healthcare Access Affecting Treatment

Overall, the advantages of IVIg have become more limited over the last decade secondary to the advancements of PLEX technology and supply chain shortages of IVIg.

Although the treatment time course of IVIg still proves superior, the arguments for using PLEX as a first-line treatment have been justified.

With new technologies continuing to improve access to PLEX, it is possible that PLEX becomes the new widely-accepted first-line therapy for GBS management. It is still unclear if PLEX or IVIg in sequence proves to be beneficial, harmful, or insignificant; however, new studies could shed further light on this subject in the future.

Resources

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