Guillain Barre Syndrome

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Abstract: The most common cause of acute paralytic neuropathy is known as Guillain-Barré syndrome (GBS), which consists of a number of clearly distinct subtypes. GBS's specific cause is unknown, but 50–70% of cases manifest within 1-2 weeks of a respiratory or gastrointestinal infection or another immune stimulus that sets off an abnormal auto-immune reaction that targets peripheral nerves and their spinal roots. Nothing would be known well about genes and environmental influences that affect a person's susceptibility to the disease, and it is unclear how the interactions between the microorganism and host factors control as to if and how the immune response changes towards auto reactivity. All GBS patients require close observation, can receive support from supportive care, and can gain from the early initiation of specific treatment

This study discusses the clinical characteristics and diagnostic standards for GBS and suggests a management algorithm. A review of the literature revealed that, about a century since it was described, new knowledge about its etiopathogenesis has enabled the development of new treatment strategies that should be initiated as soon as a diagnosis is made. Despite this, many patients do not respond well to the current treatments, particularly when the condition is acute inflammatory demyelinating neurological dysfunction.

Research should continue to focus on finding new biomarkers of disease severity and better ways to prevent axonal injury in order to enhance outcomes. New post-infectious forms, like the ones brought on by the Zika virus and enterovirus D68, have to be interpreted carefully.

I. INTRODUCTION

The most common cause of acute paralytic neuropathy, Guillain-Barré syndrome (GBS),[1] is an inflammatory polyneuropathy marked by an abrupt start, quick progression, symmetric muscular weakness, unstable ambulation, and hypo- or areflexia [2,3] At least at the time of initiation, the weakness is typically predominately distal, and many patients experience neuropathic pain. GBS typically manifests as ascending paralysis, weakness that first appears in the legs and then spreads to the arms, hands, and face, and total loss of deep tendon reflexes [4,5]. However, there are a few clearly distinct variants[6]. Although the precise cause of GBS is unknown, 50–70% of cases manifest within 1–2 weeks of a respiratory or gastrointestinal infection or another inflammatory stimulus that triggers an abnormal autoimmune reaction that targets peripheral nerves and their spinal roots[2,3,7]. After immunological activation, the early onset of limb weakness frequently includes sensory and cranial nerve involvement and progresses to its peak clinical deficiency in 2-4 weeks[8]. A diagnosis of Guillain-Barré syndrome should be made as soon as possible if the patient presents with rapidly progressive paralysis. Diagnosis is usually straight forward in typical cases, but many clinical and investigative factors must be considered, especially in atypical cases. Since diagnostic biomarkers aren't yet available for the majority of the syndrome's variants, the diagnosis is primarily based on clinical patterns. Identifying biomarkers and establishing their pathophysiological role, if any, in experimental models has been a major research challenge[9-10]. All Guillain-Barré syndrome patients require close observation and supportive care[11]. Intravenous immunoglobulin (IVIg) or plasma exchange should be started as soon as possible because it has been shown to be beneficial, especially in patients whose weakness is progressing quickly[12]. A large number of patients require hospitalisation in the high or critical care setting because one-fourth of patients require artificial ventilation and many experience autonomic abnormalities. The recovery phase can span months or years while the immune response degrades and the peripheral nerve goes through an endogenous repair process. Symptoms peak within 4 weeks. To better care for and treat individual patients, efforts are concentrated on the measurement and prediction of clinical course and outcome[13]. Good prognostic models have been created, but further research is required to determine whether these prognostic markers vary among illness subgroups and geographical regions. To better predict outcomes and direct action, such as individualised treatment improvements in acute management, prognostic biomarkers must now be created[14]. Patients with GBS are frequently previously healthy and free of autoimmune or systemic diseases.GBS affects men slightly more than women and has an incidence of 0.5 per 100,000 to 2 per 100,000[6,15].

II. Epidemiology

GBS is now the most frequent cause of acute and subacute flaccid paralysis, with an observed incidence rate of 0.5-2 cases per 100,000 people, thanks to the widely spread eradication of poliomyelitis. [16, 17] The annual incidence rate rises with age, and GBS in children below the age of 2 is uncommon.[18] Men are approximately 1.5 times more likely than women to be infected. [19,20,21] In some parts of the world, the incidence of GBS is greater in the winter than in the summer, which may be related to the symptomatic phases of certain infectious agents.[22] The primary etiological factors linked to GBS are summarised (Table 1). The variations in genetic susceptibility or exposure to the pathogens that cause GBS may be reflected in the differences in the incidence of the disease in various populations. Although it has been discovered that patients with GBS have a wide range of infections, case-control studies have only found associations with a minimum number of pathogens. The most commonly reported infection is campylobacter jejuni, which has been identified in 25–50% of adult patients and is more prevalent in Asian nations.[23,24] Other illnesses linked to GBS include those brought on by cytomegalovirus, Epstein-Barr virus, measles, influenza A virus, and Mycoplasma pneumoniae, [25-29] as

well as those brought on by enterovirus D68, 30 and Zika virus. [31-34] Williams et al. recently reported an outbreak of atypical GBS in 10 adults that occurred more than a 3-month period (from October 2015 to January 2016) in South Wales, United Kingdom, and was probably linked to a group of four children who had acute flaccid paralysis at the time.[30] All adult cases involved males who ranged in age from 24 to 77. Seven initially had a noticeable facial diplegia. Five adults were involved in axonal activity according to available electrophysiological studies. Seven people mentioned having various respiratory issues before experiencing neurological symptoms. French Polynesia received the first reports of GBS connected to Zika virus infection between October 2013 and April 2014.31 In comparison to 54 (56%) of 98 controls, 41 (98%) of the patients with GBS seemed to have anti-Zika virus IgM or IgG and all (100%) had inhibition against the virus (p b 0.0001). 39 (93%) of the GBS patients tested positive for Zika virus IgM, and 37 (88%) of them reported having a brief illness 6 days or less prior to the initiation of neurological problems, suggesting a recent infection with the virus. Patients with GBS had rapid disease progression and electrophysiological findings consistent with the type of acute motor axonal nerve damage. 12(29%) patients needed help breathing. No patients passed away. There was anti-glycolipid antibody activity in 13 (31%) patients. (Table 1)

In a recent study, Lucchese and Kanduc looked for peptide sharing in the Zika virus polyprotein with human proteins that are linked to microcephaly and brain calcifications when altered.[33] The findings revealed significant viral and human peptide overlap, particularly with regard to centriolar and centrosomal proteins canonically categorised as microcephaly proteins, such as C2CD3, CASC5, CP131, GCP4, KIF2A, STIL, and TBG. Likewise, a greater, unpredicted level of peptide sharing was found when looking for Zika virus peptide incidences in human proteins linked to GBS. It is noteworthy that additional analyses using the Immune Epitope Database tool reveal that many of the shared peptides have immunological potential. These findings suggest that immune reactions following Zika virus infection may contribute to the neuropathologic symptoms linked to the virus.[33] These reactions may be a significant source of cross-reactions with brain-specific proteins. Subjects who had recently received vaccinations against the influenza A virus 27,36,37 and the rabies virus 36 have shown symptoms of GBS. One in 100,000 vaccine recipients who had received the A/H1N1 influenza vaccine in 1976 developed GBS,35 but this was not the case in subsequent years.[6] Hawken et al., To assess the effect of influenza vaccine vaccination on the complete risk of contracting GBS, simulation models and previously published estimates of age- and gender risks for GBS, influenza incidence, and vaccine effectiveness were used.[27] Excess GBS threat for influenza vaccination vs no vaccination was 0.36/10 lakhs vaccinations (95% credible interval, 1.22% to 0.28) for a hypothetical 45-year-old woman and 0.42/10 lakhs vaccinations (95% credible interval, 3.68 to 2.44), respectively. These flow chart show a modest absolute reduction in the risk of GBS due to vaccination. Immunization decreased the risk of GBS under typical circumstances (i.e., influenza incidence rates of N 5% and vaccine efficacy of N 60%). These results should increase patient trust in the safety of the flu vaccine and help doctors better explain the GBS risk when speaking with patients about getting vaccinated. [27] With very few exceptions, associations among vaccines and GBS have only ever been temporal, according to Haber et al. [38] The majority of vaccines are associated causally with relatively little evidence. The swine influenza vaccine used in 1976–1977 offers the strongest proof of a causal link. However, research on influenza vaccines given in subsequent years has found little to no higher risk of GBS. Recent rabies vaccine formulations derived from chick embryo cells do not appear to have an increased risk of GBS, but older rabies vaccine formulations derived from vertebrate brain tissues have now been observed to have a higher risk of GBS. In a previous analysis, the Institute of Medicine came to the conclusion that the data supported a causal relationship between the oral polio vaccine and vaccines containing tetanus toxoid and GBS. However, recent data from extensive epidemiological research and widespread immunisation drives in various nations found no connection between GBS and either the oral polio vaccine or vaccines that contain tetanus toxoid. Immediately following the release of the quadrivalent conjugated meningococcal vaccine, spontaneous reports to the US Vaccine Adverse Events Reporting System sparked worries about a potential association with GBS. Similarities with data indicate of GBS, even so, did not indicate an elevated risk, and it is difficult to infer a causal relationship in the absence of restricted epidemiological studies. Other vaccines' data are currently available, but they are based on lone case reports or very small clusters that occurred concurrently with immunizations, making it impossible to draw any conclusions about their causality. [38] In some situations, it may be prudent to exercise caution when immunising people, especially those who have a history of GBS. However, the potential risk of GBS should be weighed against the advantage of vaccines in preventing disease and reducing morbidity and mortality, especially for influenza. The benefits and risks should be discussed on a case-by-case basis, but typically the vaccination is not contra-indicated in patients who have earlier had the disease unless the infection was vaccination-related or occurred within the previous three months.6 Numerous studies conducted in 2009 revealed that there were only 1–6 extra cases of Guillain–Barré syndrome per 100,000 people who received the vaccine, a frequency that was similar to that of all seasonal flu vaccinations. [39,40] Vaccination might, in fact, decrease the probability of an individual developing Guillain- Barré syndrome after natural infection with influenza A, which is itself a potential candidate to precipitate the disorder. Whether vaccination raises the risk of Guillain-Barré syndrome recurrence in people who have already been affected is a frequently asked clinical question, but the evidence does not support this theory. [41] With the exception of patients who had the condition within the previous three months or who had Guillain-Barré syndrome associated with vaccination, there does not appear to be a general contraindication to vaccination of patients who have previously experienced Guillain-Barré syndrome. However, risk and benefit may be discussed on a case-by-case basis.

III. Pathogenesis

It is now known that there are different phenotypes of GBS, which include acute inflammatory demyelinating polyneuropathy (in which the immune-related injury affects the myelin sheath and associated Schwann cells) and acute motor axonal nerve damage, in which the membranes of nerve axons are the primary target).[6] Previously, GBS was thought to be a homogeneous disorder whose severity was related to the extent of axe. GBS can occur in healthy individuals and is not frequently linked to autoimmune or other

systemic disorders. In this context, acute motor axonal nerve damage has seemed as an antibody-mediated attack driven by molecular mimicry between microbial (i.e., glycans) and axolemmal surface molecules (i.e., GM1 and GD1a gangliosides).[42,43] It is primarily a humoral- rather than T-cell-mediated disorder.[44] In contrast, due to the variety of immune stimulants that can cause acute inflammatory demyelinating polyneuropathy and the lack of specific antibody biomarkers, the immunological mechanisms underlying this condition are less clear.[6,43] The boundaries with both acute motor axonal nerve damage and acute inflammatory demyelinating polyneuropathy appear to be conceptually distinct, but they are less so in practise. Electrophysiological findings are frequently unclear because they can be indicative of both acute motor axonal neuropathy and acute inflammatory demyelinating polyneuropathy at the same time. [45] The T cell epitope redundancy mentioned by Moise et al. [46] represents an intriguing mechanism that might be involved in GBS. While Certain of these epitopes only affect T effectors, others also affect regulatory T cells. The molecular mimics are glycans (i.e., sugars) expressed on the lipooligosaccharides (LOS) of previous pathogenic organisms, particularly C jejuni, which are able to trigger immune reactions against these carbohydrate antigens. [47] It is thought that anti-carbohydrate antibody responses are largely T cell independent. Then, glycans found on nerve gangliosides that are structurally identical to anti-LOS antibodies can bind to them. In acute motor axonal neuropathy, complement-fixing anti-ganglioside antibodies of the IgG1 and IgG3 subclass primarily bind to the GM1 and GD1a gangliosides.[48] By fixing complement, enlisting macrophages, and depositing membrane attack complex in the axolemmal membrane, they cause axonal injury in animal models.[49] In nerve terminals and nodes of Ranvier, this immunological cascade compromises the anatomical and physiological integrity of exposed nerve membranes, resulting in a nerve conduction blockade that can either be reversed or, in more extreme cases, lead to severe, widespread axonal degeneration with poor recovery. The GQ1b ganglioside, which is disproportionately enriched in the motor nerves that innervate extraocular muscles, is the antigenic target in a model that is similarly put forth for Miller Fisher syndrome linked to anti-GQ1b antibodies. [50,51]

IV. Clinical features

The French neurologists Guillain, Barré, and Strohl wrote about two soldiers who suddenly recovered from acute paralysis with areflexia in 1916. The cerebrospinal fluid (CSF) was discovered to have an elevated protein concentration and a normal cell count. [52] The GBS was coined from the confluence of these clinical and laboratory characteristics. However, it has recently become evident that GBS includes a range of acute idiopathic peripheral neuropathies that are typically monophasic. [53] Pain, paresthesia, numbness, and rapidly progressing bilateral limb weakness are the initial symptoms of classic GBS.[6,54,55] Patients typically experience "rubbery legs," or legs that have a propensity to buckle, whether or not they are numb or tingly. Bulbar weakness and breathing problems result from the weakness, which typically begins in the distal lower extremities and progresses upward over a period of hours or days to affect the arms and facial muscles as well. [56] It is possible for the muscle weakness to develop simultaneously in the legs and arms or descendingly in the arms first (descending type). Facial, oculomotor, or bulbar weakness may result from the disease's weakness in some forms of it, such as Miller Fisher syndrome. [57] 2-4 weeks after the onset of the symptoms, the weakness reaches its height. Paraparesis may persist throughout the course of the disease in a small amount of patients. [58] Patients may also exhibit sensory symptoms, ataxia, and autonomic dysfunction in addition to weakness.[6] Another common initial sign is muscle pain or radicular pain, which in about 30% of patients occurs before weakness.6 Initial stages of pure motor and axonal reflexes can be common or even hyper-reflexic. [59] Up to six weeks can pass before the disease progresses [6] ; 20–30% of patients encounter complications during this time, such as respiratory distress requiring mechanical ventilation. [61] pneumonia from aspiration, sepsis, and cardiac arrhythmia (such as tachycardia or bradyarrhythmia with asystole), arterial hypertension or hypotension, unusual sweating, and gastrointestinal dysmotility are additional complications.[11] Diarrhoea and urinary retention are uncommon at the beginning of the disease but frequently appear when it is at its worst.[11] Patients with severe weakness and respiratory failure are more likely to exhibit signs of autonomic dysfunction. [11] Acute inflam- matory demyelinating polyradiculoneuropathy (AIDP) is to blame for the majority of cases in North America and Europe. [61] Acute motor axonal neuropathy (AMAN),62 which affects only the motor system, and acute motor and sensory axonal neuropathy (AMSAN),[63] which affects the sensory system, are the two axonal forms that are more common in Asia and Japan. Miller Fisher syndrome (MFS),[64] which typically displays the triad of ophthalmoplegia, areflexia, and ataxia, Bickerstaff brainstem encephalitis (BBE),[65] which begins with cranial nerve dysfunction and can progress to BSE, pharyngocervico-brachial pattern, and pure sensory form are other uncommon variants of the GBS spectrum. In Europe, the MFS variant of GBS accounts for 5% of cases; in Japan and Taiwan, the proportions are higher.[66]

Due to the atypical ways that young children present their complaints, GBS can be difficult to diagnose in these patients.67 The differential diagnosis is very broad, so it's important to rule out alternative causes like brainstem or spinal cord lesions, defects in the neuromuscular junction, or abnormalities of the muscles.[53] Once GBS is ruled out as the primary cause of an acute peripheral neuropathy, the clinician should also take other conditions like toxic neuropathy, porphyria, vasculitis, tick paralysis, and metabolic disturbances into account.

Overall, GBS is a fatal illness with a 3-7% mortality rate.[68,69] Patients typically pass away from pulmonary complications, autonomic dysfunction, or inadequate ventilation. Remaining complaints and deficits frequently affect those who survive and significantly affect their everyday tasks and quality of life.[70] Although patients may continue to improve even three years or longer after GBS onset, improvements primarily take place during that first year. An older age (40 years), diarrhoea or C. jejuni infection in the four weeks prior to the disease, and a high degree of disability at the time the weakness is maximal are all associated with poor outcomes.[6]

V. Diagnostic algorithm

The criteria for a diagnosis of GBS are outlined in Table 3, which are primarily based on the findings of a clinical examination, though additional investigations may be needed for confirmation.[71] A lumbar puncture is typically performed on patients with

suspected GBS. They typically have cyto-albuminological dissociation in their cerebrospinal fluid (CSF), which is defined as a normal cell count with elevated protein levels.[72] In the first week after onset, CSF protein concentration is frequently normal, but by the end of the second week, it has risen in more than 90% of patients.[6] 15% of patients have a CSF cell count that is slightly elevated (10–30 cells/L) .[11] Early in the course of the disease, nerve conduction studies (NCS) are typically normal, but this does not rule out a diagnosis of GBS [73,74] as nerve conduction abnormalities are most noticeable two weeks after the weakness begins. The axonal and demyelinating subtypes of GBS can sometimes be distinguished by NCS findings: individuals with axonal neuropathy have decreased motor and/or sensory amplitudes, However, those who have demyelinating polyneuropathy display symptoms like prolonged distal motor latency, decreased nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conductivity blocks. Insofar as patients with demyelination need mechanical ventilation more frequently and low compound muscle potentials are the most reliable findings indicating a poor outcome, they may also be related to prognosis. [6,75] In cases of suspected GBS, neuroimaging has emerged as a useful complement to NCS. On spi- nal magnetic resonance imaging (MRI) scans of up to 95% of patients, post-gadolinium enhancement of peripheral nerve roots and the cauda equine can be seen, though it is not specific.[76,77] A para-sagittal cerebral lesion or structural myelopathy can also be ruled out using MRI. Approximately 50% of patients have anti-ganglioside antibodies, which are very helpful in confirming a diagnostic test, especially in cases where patients have atypical presentations.[78]

VI. Therapeutic approach

A multidisciplinary strategy including general medical care and immunological treatment is necessary for the treatment of GBS (Table 3). In order to prevent or manage complications, it is necessary to monitor respiratory, cardiac, and hemodynamic function.6 Additionally, prophylaxis for deep vein thrombosis, the management of potential bladder and bowel dysfunction, the early beginning of physiotherapy and rehabilitation, and psychosocial support should all be taken into consideration.[6, 79, 80] Additionally, it is crucial to manage pain with opioids or non-steroidal anti-inflammatory drugs. [84]

Although there isn't a specific medication for GBS, a variety of medications were used to focus on the immune response's various components. Plasma exchange (PE) and intravenous immunoglobulin (IVIg) therapy have both been shown to be effective immuno modulating therapies for accelerating healing and improving outcomes. [81] As soon as possible, before irreversible nerve damage has occurred, IVIg and PE should both be started. Whether a total IVIg dose of 2 g/kg over two days is preferable to a dose of 0.4 g/kg per day over five days is unknown. The usual recommendation is for five PE sessions spread over two weeks, but IVIg therapy is preferred in many centres due to its widespread availability and good tolerability, despite being more expensive than PE. There is no proof to support a second course of IVIg, and combining PE and IVIg is no better than PE or IVIg alone. [6]

Patients with GBS have not been found to benefit from oral or intravenous steroids, either on their own or in combination with IVIg or PE. [82]

There are some novel immunological therapeutic approaches being researched right now. These include the use of interferon (IFN)-beta therapy, which reduces the frequency of multiple sclerosis relapses but whose effects on GBS patients are still debatable.[6] According to two case reports, using IFN-beta and IVIg together may have therapeutic advantages. [83] In an animal model, the immunomodulator cyclophosphamide (CY) appears to improve the clinical and histological characteristics of GBS. However, prolonged CY treatment has been linked to infections and neoplastic diseases. [82] A different strategy relies on humanised monoclonal antibodies, such as eculizumab, which has a strong affinity for complement factor C5, and rituximab, which is an antibody against CD20 that can cause targeted B cell depletion. [6, 84] However, there hasn't been a clinical trial to confirm the effectiveness and security of monoclonal antibodies in GBS patients.

VII. Conclusion

New treatment approaches for GBS have been created and should be started as soon as a diagnosis is made thanks to new knowledge about the etiopathogenesis that has emerged about a hundred years after it was first described. Nevertheless, the available therapies are insufficient in many patients, particularly in the presence of acute inflammatory demyelinating polyneuropathy. In order to improve patient outcomes, research should continue to focus on identifying new biomarkers of disease severity and better ways to prevent axonal injury. New post-infectious forms, like those brought on by the Zika virus and enterovirus D68, also need to be carefully analyzed.

Take-home messages

Guillan-Barré syndrome (GBS) is the most common cause of acute paralytic neuropathy.

When patients present with rapidly progressive paralysis, GBS needs to be diagnosed as soon as possible.

All patients with GBS need meticulous monitoring, and can benefit from supportive care and the early start of specific treatment.

Available therapies are not sufficient in many patients, especially in the presence of the acute inflammatory demyelinating polyneuropathy.

In order to improve patient outcomes, research should continue to aim at identifying new biomarkers of disease severity and better means of avoiding axonal injury.

Figures and Tables

Table 1: Main etiological factors associated with Guillain Barre Syndrome

Infections	Bacteria • Campylobacter jejune • Mycoplasma pneumoniae
	Viruses • Cytomegalovirus • Epstein-Barr virus • Influenza A virus • Enterovirus D68 • Zika virus
Vaccines	Rabies vaccine Influenza A virus/H1N1 vaccine

Table 2: Diagnostic criteria of Guillain–Barré syndrome.

Clinical features -	Progressive weakness over a period of up to 6 weeks in legs and arms (sometimes only in arms) Hypo- or areflexia (sometimes normal or even hyper-reflexia) Relative symmetry Mild sensory symptoms or signs Pain Autonomic dysfunction Complications like aspiration pneumonia, sepsis, cardiac arrhythmia, hypertension, hypotension, and urinary retention as well as respiratory failure requiring mechanical ventilation
Lumbar puncture	Cytoalbuminological dissociation (i.e. normal cell count with increased protein levels) in cerebrospinal fluid.
Nerve conduction studies	Evident after 2 weeks, showing decreased motor and/or sensory amplitudes In the case of demyelinating polyneuropathy, prolonged distal motor latency, reduced nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conduction blocks
Magnetic resonance imaging	Post-gadolinium enhancement of the peripheral nerve roots and cauda equine
Serum	Anti-ganglioside antibodies (in about 50% of patients)

Table 3 Therapeutic approaches to Guillain–Barré syndrome.

General medical care	Monitoring of respiratory, cardiac and hemodynamic function Prophylaxis for deep vein thrombosis Management of possible bladder and bowel dysfunction Early initiation of physiotherapy and rehabilitation Psychosocial support Pain management using opioids or non-steroidal anti-inflammatory drugs
Immunological treatment with documented efficacy	Intravenous immunoglobulin therapy Plasma exchange
New treatments under evaluation	Interferon-beta Cyclophosphamide Rituximab Eculizumab

REFERENCES

[1] SejvarJJ,BaughmanAL,WiseM,MorganOW.PopulationincidenceofGuillain–Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011;36: 123–33.

[2] Ropper A. The Guillain–Barré symptom complex. N Engl J Med 1992;17:1130–6.

[3] Schessl J, Luther B, Kirschener J, Mauff G, Korinthenberg R. Infections and vaccina- tions preceding childhood Guillain–Barré symptom complex: a prospective study. Eur J Pediatr2006;165:605–12.

[4] Ho T, Griffin J. Guillain–Barré syndrome. Curr Opin Neurol 1999;12:389–94.

[5] Alter M. The epidemiology of Guillain–Barré syndrome. Ann Neurol 1990;27:S7–12.

[6] Willison HJ, Jacobs BC, van Doorn PA. Guillain–Barré syndrome. Lancet 2016;388: 717–27.

[7] Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early rec- ognition of poor prognosis in Guillain–Barré syndrome. Neurology 2011;76:968–75.

[8] Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain 2014; 137: 33–43.

[9] Lim JP, Devaux J, Yuki N. Peripheral nerve proteins as potential autoantigens in acute and chronic inflammatory demyelinating polyneuropathies. Autoimmun Rev 2014; 13: 1070–78.

[10] Willison HJ. Biomarkers in experimental models of antibody-mediated neuropathies. J Peripher Nerv Syst 2011; 16 (suppl 1): 60–62.

[11] Hughes RA, Wijdicks EF, Benson E, et al, for the Multidisciplinary Consensus Group. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol 2005; 62: 1194–98.

[12] Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev 2014;9: CD002063.

[13] Rajabally YA, Uncini A. Outcome and its predictors in Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 2012; 83: 711–18.

[14] Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology 2011; 76: 968–75.

[15] Esposito S, Longo MR. Guillain-Barre´ syndrome. Autoimmun Rev 2017;16(1): 96Y101.

[16] Winner SJ, Evans JC. Age-specific incidence of Guillain–Barré syndrome in Oxford- shire. Q J Med 1990;77:1297–304.

[17] Halls J, Bredkjaer C, Friis ML. Guillain–Barré syndrome; diagnostic criteria, epidemiology, clinical course and prognosis. Acta Neurol Scand 1998;78:118–22.

[18] Beth AR. Guillain–Barré syndrome. Pediatr Rev 2012;33:164–70.

[19] Hughes RA, Cornblath DR. Guillain–Barré syndrome. Lancet 2005;366:1653–66.

[20] van Koningsveld R, van Doorn PA, Schmitz PI, Ang CW, van der Mechè FG. Mild forms of Guillain–Barré syndrome in an epidemiologic survey in The Netherlands. Neurology 2000;54:620–5.

[21] Bogliun G, Beghi E. Incidence and clinical features of acute inflammatory polyradiculoneuropathy in Lombardy, Italy. Acta Neurol Scand 2004;110:100–6.

[22] Webb AJ, Brain SA, Wood R, Rinaldi S, Turner MR. Seasonal variation in Guillain-Barré syndrome: a systematic review, meta-analysis and Oxfordshire cohort study. J Neurol Neurosurg Psychiatry 2015;86 (11):1196–1201

[23] Jasti AK, Selmi C, Sarmiento-Monroy JC, Vega DA, Anaya JM, Gershwin ME. Guillain– Barré syndrome: causes, immunopathogenic mechanisms and treatment. Expert Rev Clin Immunol 2016:1–15 [Epub Jun 21].

[24] Loshaj-Shala A, Regazzoni L, Daci A, Orioli M, Brezovska K, Panovska AP, Beretta G, Suturkova L. Guillain Barré syndrome (GBS): new insights in the molecular mimicry between C. jejuni and human peripheral nerve (HPN) proteins. J Neuroimmunol 2015;289:168–76.

[25] Orlikowski D, Porcher R, Sivadon-Tardy V, Quincampoix JC, Raphaël JC, Durand MC, Sharshar T, Roussi J, Caudie C, Annane D, Rozenberg F, Leruez-Ville M, Gaillard JL, Gault E. Guillain–Barré syndrome following primary cytomegalovirus infection: a prospective cohort study. Clin Infect Dis 2011;52:837–44.

[26] Tselis AC. Epstein–Barr virus infections of the nervous system. Handb Clin Neurol 2014;123:285–305.

[27] Hawken S, Kwong JC, Deeks SL, Crowcroft NS, McGeer AJ, Ducharme R, Campitelli MA, Coyle D, Wilson K. Simulation study of the effect of influenza and influenza vac- cination on risk of acquiring Guillain–Barré syndrome. Emerg Infect Dis 2015;21: 224–31.

[28] Ghaderi S, Gunnes N, Bakken IJ, Magnus P, Trogstad L, Håberg SE. Risk of Guillain– Barré syndrome after exposure to pandemic influenza a(H1N1)pdm09 vaccination or infection: a Norwegian population-based cohort study. Eur J Epidemiol 2016; 31:67–72.

[29] Meyer Sauteur PM, Huizinga R, Tio-Gillen AP, Roodbol J, Hoogenboezem T, Jacobs E, van Rijn M, van der Eijk AA, Vink C, de Wit MY, van Rossum AM, Jacobs BC. Myco- plasma pneumoniae triggering the Guillain–Barré syndrome: a case–control study. Ann Neurol 2016 [Epub Aug 4].

[30] Williams CJ, Thomas RH, Pickersgill TP, Lyons M, Lowe G, Stiff RE, Moore C, Jones R, Howe R, Brunt H, Ashman A, Mason BW. Cluster of atypical adult Guillain–Barré syn- drome temporally associated with neurological illness due to EV-D68 in children, South Wales, United Kingdom, October 2015 to January 2016. Euro Surveill 2016; 2016:21.

[31] Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, Dub T, Baudouin L, Teissier A, Larre P, Vial AL, Decam C, Choumet V, Halstead SK, Willison HJ, Musset L, Manuguerra JC, Despres P, Fournier E, Mallet HP, Musso D, Fontanet A, Neil J, Ghawché F. Guillain–Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case–control study. Lancet 2016;387: 1531–9.

[32] BroutetN,KrauerF,RiesenM,KhalakdinaA,AlmironM,AldighieriS,EspinalM,Low N, Dye C. Zika virus as a cause of neurologic disorders. N Engl J Med 2016;374: 1506–9.

[33] LuccheseG, KanducD. Zikavirus and autoimmunity: from microcephaly to Guillain– Barré syndrome, and beyond. Autoimmun Rev 2016;15:801–8.

[34] Lucchese G, Kanduc D. Reply concerning the article "Zika virus and autoimmunity: from microcephaly to Guillain–Barré syndrome, and beyond". Autoimmun Rev 2016;15:854.

[35] Gadre G, Satishchandra P, Mahadevan A, Suja MS, Madhusudana SN, Sundaram C, Shankar SK. Rabies viral encephalitis: clinical determinants in diagnosis with special reference to paralytic form. J Neurol Neurosurg Psychiatry 2010;81: 812–20.

[36] Martín Arias LH, Sanz R, Sáinz M, Treceño C, Carvajal A. Guillain–Barré syndrome and influenza vaccines: a meta-analysis. Vaccine 2015;33:3773–8.

[37] Bardenheier BH, Duderstadt SK, Engler RJ, McNeil MM. Adverse events following pandemic influenza a (H1N1) 2009 monovalent and seasonal influenza vaccinations during the 2009–2010 season in the active component U.S. military and civilians aged 17–44 years reported to the Vaccine Adverse Event Reporting System. Vaccine 2016;34:4406–14.

[38] Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain–Barré syndrome. Drug Saf 2009;32:309–23.

[39] Lehmann HC, Hartung HP, Kieseier BC, Hughes RA. Guillain-Barré syndrome after exposure to influenza virus.Lancet Infect Dis 2010; 10: 643–51.

[40] Salmon DA, Proschan M, Forshee R, et al, for the H1N1 GBS Meta-Analysis Working Group. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. Lancet 2013; 381: 1461–68.

[41] Guillain-Barré syndrome common concerns. http://www.cdc.gov/ vaccinesafety/Concerns/gbs.html (accessed Feb 1, 2016).

[42] Sudo M, Miyaji K, Späth PJ, Morita-Matsumoto K, Yamaguchi Y, Yuki N. Polyclonal IgM and IgA block in vitro complement deposition mediated by anti-ganglioside antibodies in autoimmune neuropathies. Int Immunopharmacol 2016;40:11–5.

[43] KuwabaraS.Guillain–Barrésyndrome.Epidemiology,pathophysiologyandmanagement. Drugs 2004;64:597–610.

[44] Soliven B. Animal models of autoimmune neuropathy. ILAR J 2014;54:282–90.

[45] DiCapua DB, Lakraj AA, Nowak RJ, Robeson K, Goldstein J, Patwa H. Relationship between cerebrospinal fluid protein levels and electrophysiologic abnormalities in Guillain–Barré syndrome. J Clin Neuromuscul Dis 2015;17:47–51.

[46] Moise L, Beseme S, Tassone R, Liu R, Kibria F, Terry F, Martin W, De Groot AS. T cell epitope redundancy: cross-conservation of the TCR face between pathogens and self and its implications for vaccines and autoimmunity. Expert Rev Vaccines 2016;15: 607–17.

[47] Willison HJ, Goodyear CS. Glycolipid antigens and autoantibodies in autoimmune neuropathies. Trends Immunol 2013; 34: 453–59.

[48] Jacobs BC, Koga M, van Rijs W, et al. Subclass IgG to motor gangliosides related to infection and clinical course in Guillain-Barré syndrome. J Neuroimmunol 2008; 194: 181–90.

[49] McGonigal R, Rowan EG, Greenshields KN, et al. Anti-GD1a antibodies activate complement and calpain to injure distal motor nodes of Ranvier in mice. Brain 2010; 133: 1944–60.

[50] Plomp JJ, Willison HJ. Pathophysiological actions of neuropathy-related anti-ganglioside antibodies at the neuromuscular junction. J Physiol 2009; 587: 3979–99.

[51] Liu JX, Willison HJ, Pedrosa-Domellöf F. Immunolocalization of GQ1b and related gangliosides in human extraocular neuromuscular junctions and muscle spindles. Invest Ophthalmol Vis Sci 2009; 50: 3226–32.

[52] Guillain G, Barre J, Strohl A. Sur un syndrome de radiculo-nevrite avec hyperalbuminose du liquide cephalorachidien sans reaction cellulaire. Remarques sur les caracteres cliniques et graphiques desrefl exes tendineux. Bull Mem Soc Med Hop Paris 1916;28:1462–70.

[53] EldarAH, ChapmanJ. Guillain Barré syndrome and other immune mediated neuropathies: diagnosis and classification. Autoimmun Rev 2014;13:525–30.

[54] Korinthenberg R, Schessl J, Kirschner J, Mönting JS. Intravenously administered im- munoglobulin in the treatment of childhood Guillain–Barré syndrome: a random- ized trial. Pediatrics 2005;116:8–14.

[55] HughesRA, SwanAV, vanDoornPA. Intravenous immunoglobulin for Guillain–Barré syndrome. Cochrane Database Syst Rev 2014;9, CD002063.

[56] Anand B, Nimisha K. Guillain–Barré syndrome. Pharmacol Rep 2010;62:220–32.

[57] Hahn AF. Guillain–Barré syndrome. Lancet 1998;352:635–41.

[58] van den Berg B, Fokke C, Drenthen J, van Doorn PA, Jacobs BC. Paraparetic Guillain–Barré syndrome. Neurology 2014;82:1984–9.

[59] Yuki N, Kokubun N, Kuwabara S, Sekiguchi Y, Ito M, Odaka M, Hirata K, Notturno F, Uncini A. Guillain–Barré syndrome associated with normal or exaggerated tendon reflexes. J Neurol 2012;259:1181–90.

[60] FokkeC,vandenBergB,DrenthenJ,WalgaardC,vanDoornPA,JacobsBC.Diagnosis of Guillain–Barré syndrome and validation of Brighton criteria. Brain 2014;137(Pt 1):33–43.

[61] Van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain–Barré syndrome. Lancet Neurol 2008;7:939–50.

[62] McKhann GM, Cornblath DR, Griffin JW, Ho TW, Li CY, Jiang Z, et al. Acute motor ax- onal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333–42.

[63] Griffin JW, Li CY, Ho TW, Tian M, Gao CY, Xue P, Mishu B, Cornblath DR, Macko C, McKhann GM, Asbury AK. Pathology of the motor–sensory axonal Guillain–Barré syndrome. Ann Neurol 1996;39:17–28.

[64] van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain– Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014;10:469–82.

[65] Al-Din AS, Jamil AS, Shakir R. Coma and brain stem areflexia in brain stem encephalitis (Fisher's syndrome). Br Med J 1985;291:535–6.

[66] Roodbol J, de Wit MC, Walgaard C, de Hoog M, Catsman-Berrevoets CE, Jacobs BC. Recognizing Guillain–Barré syndrome in preschool children. Neurology 2011;76: 807–10.

[67] Roodbol J, de Wit MC, Aarsen FK, Catsman-Berrevoets CE, Jacobs BC. Long-term out- come of Guillain–Barré syndrome in children. J Peripher Nerv Syst 2014;19:121–6.

[68] Hughes RA, Swan AV, Raphaël JC, Annane D, van Koningsveld R, van Doorn PA. Im- munotherapy for Guillain–Barré syndrome: a systematic review. Brain 2007;130: 2245–57.

[69] Živković S. Intravenous immunoglobulin in the treatment of neurologic disorders. Acta Neurol Scand 2015 [Epub May 21].

[70] Darweesh SK, Polinder S, Mulder MJ, Baena CP, van Leeuwen N, Franco OH, Jacobs BC, van Doorn PA. Health-related quality of life in Guillain–Barré syndrome patients: a systematic review. J Peripher Nerv Syst 2014;19:24–35.

[71] Ryan MM. Pediatric Guillain–Barré syndrome. Curr Opin Pediatr 2013;25:689–93.

[72] Wong AH, Umapathi T, Nishimoto Y, Wang YZ, Chan YC, Yuki N. Cytoalbuminologic dissociation in Asian patients with Guillain–Barré and Miller Fisher syndromes. J Peripher Nerv Syst 2015;20:47–51.

[73] Agrawal S, Peake D, Whitehouse WP. Management of children with Guillain–Barré syndrome. Arch Dis Child Educ Pract Ed 2007;92:161–8.

[74] Walgaard C, Lingsma HF, Ruts L, Drenthen J, van Koningsveld R, Garssen MJ, van Doorn PA, Steyerberg EW, Jacobs BC. Prediction of respiratory insufficiency in Guillain–Barré syndrome. Ann Neurol 2010;67:781–7.

[75] Ho TW, Mishu B, Li CY, Gao CY, Cornblath DR, Griffin JW, Asbury AK, Blaser MJ, McKhann GM. Guillain–Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 1995;118: 597–605.

[76] Yikilmaz A, Dogonay S, Gumus H, Per H, Kumandas S, Coskun A. Magnetic reso- nance imaging of childhood Guillain–Barré syndrome. Childs Nerv Syst 2010; 26:1103–8.

[77] Zuccoli G, Panigrahy A, Bailey A, Fitz C. Redefining the Guillain–Barré spectrum in children: neuroimaging findings of cranial nerve involvement. Am J Neuroradiol 2011;32:639–42.

[78] Willison HJ, Goodyear CS. Glycolipid antigens and autoantibodies in autoimmune neuropathies. Trends Immunol 2013;34:453–9.

[79] Liu J, Wang LN, McNicol ED. Pharmacological treatment for pain in Guillain–Barré syndrome. Cochrane Database Syst Rev 2015;4, CD009950.

[80] Ruts L, Drenthen J, Jongen JL, Hop WC, Visser GH, Jacobs BC, van Doorn PA, Dutch GBS Study Group. Pain in Guillain–Barré syndrome: a long-term follow-up study. Neurology 2010;75:1439–47.

[81] Vitaliti G, Tabatabaie O, Matin N, Ledda C, Pavone P, Lubrano R, Serra A, Di Mauro P, Cocuzza S, Falsaperla R. The usefulness of immunotherapy in pediatric neurodegen- erative disorders: a systematic review of literature data. Hum Vaccin Immunother 2015;11:2749–63.

[82] Pithadia AB, Kakadia N. Guillain–Barré syndrome. Pharmacol Rep 2010;62: 220–32.

[83] Schaller B, Radziwill AJ, Steck AJ. Successful treatment of Guillain–Barré syndrome with combined administration of interferon-beta-1 and intravenous immunoglobu- lin. Eur Neurol 2001;46:167–8.

[84] Ostronoff F, Perales MA, Stubblefield MD, Hsu KC. Rituximab-responsive Guillain– Barré syndrome following allogeneic hematopoietic SCT. Bone Marrow Transplant 2008;42:71–2.