ECRONICON OPEN ACCESS

EC NEUROLOGY
Review Article

Breaking Down the Latest Advancements in Understanding Immune-Mediated Neuropathies: A Comprehensive Review

Ahed J Alkhatib[1,2,3]*

[1]*Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science and Technology, Jordan*

[2]*International Mariinskaya Academy, Department of Medicine and Critical Care, Department of Philosophy, Academician Secretary of Department of Sociology, Jordan*

[3]*Cypress International Institute University, Texas, USA*

***Corresponding Author:** Ahed J Alkhatib, Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science and Technology, Jordan.

Received: April 17, 2023; **Published:** May 22, 2023

Abstract

Immune-mediated neuropathies are a set of conditions that are characterized by abnormalities in the immune system's response to the peripheral nerves. The primary purpose of this investigation was to conduct a literature search focused on immune-mediated neuropathies. The information that follows is an overview of some of the most important findings that came from research on immune-mediated neuropathies. GBS is the immune-mediated neuropathy that affects the most people. Acute flaccid paralysis is typically preceded by a disease of the respiratory or gastrointestinal systems. The chronic immune-mediated neuropathy known as CIDP causes limb weakness and sensory loss to occur symmetrically. Myasthenia gravis, also known as MG, is a neuromuscular junction syndrome that is autoimmune in nature and leads to tiredness and muscle weakening. Immune-mediated neuropathies are conditions that develop when the body's T-cells and B-cells develop an abnormal immune response to the peripheral nerves. While treating immune-mediated neuropathies, corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis are often utilized treatments. In most cases, permanent nerve injury and dysfunction can be avoided by early detection and treatment. The prognosis for immune-mediated neuropathies varies depending on the type of neuropathy, its severity, and how well it responds to treatment. Immune-mediated neuropathies are complicated diseases that require prompt diagnosis, treatment, and care in order to prevent long-term harm.

Keywords: *Immune-Mediated Neuropathies; Guillain-Barré Syndrome; Chronic Inflammatory Demyelinating Polyneuropathy; Immunomodulatory Therapy*

An overview of immune-mediated neuropathies

Immune-mediated neuropathies, sometimes known as IMN for short, are a collection of neurological conditions that arise when the immune system attacks the nerves in the peripheral nervous system. Immune-mediated neuropathies include conditions such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain-Barre syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and neuropathies associated with IgM monoclonal gammopathy of unknown sig-

nificance (MGUS) [1]. It is believed that autoimmune peripheral nerve injury is caused by antibodies that are directed against myelin antigens, as well as autoreactive T cells and macrophages that breach the myelin sheath or axonal membranes. Autopsies performed on patients diagnosed with Guillain-Barre syndrome revealed segmental demyelination caused by macrophages, as well as perivascular and endoneurial inflammatory infiltrates of T cells and macrophages throughout the nerves, roots, and plexuses of the affected areas of the nervous system [2]. Autoantibodies to various gangliosides, which are abundant in axons, are found frequently in patients with the Miller-Fisher subtype (GQ1b, GT1a) or the axonal variant (GM1, GD1a) of Guillain-Barre syndrome (80 - 90%). However, these autoantibodies are found infrequently in patients with the most common demyelinating subtype of the disease (GM1, GD1a). Autoantibodies to numerous proteins found at the nodal or paranodal areas of peripheral nerves (such as CASPR1, contactin1, and NF155) that maintain axon-Schwann cell or axon-myelin binding have been found in the serum of 15 - 20 percent of CIDP patients. These autoantibodies have been identified as CASPR1, contactin1, and NF155. By activating complement and macrophages, these autoantibodies have the potential to cause axonal degeneration, demyelination, and a change in the architecture of the nodal junctions. The condition known as paraneoplastic neuropathy refers to a group of sensory neuropathies that are brought on by dorsal root ganglion pathology that is connected to antibodies against anti-Hu, CRMP5, or amphiphysin. Peripheral nerve hyperexcitability and neuropathic pain can be brought on by antibodies directed against CASPR2. Anti-Hu antibodies have been associated to both severe gastrointestinal mobility issues and enteric autonomic involvement. Plasmapheresis, intravenous immunoglobulin, and/or immunosuppression are all frequent treatments for these diseases [3,4].

Damage to the myelin sheath, axonal degeneration, or both can be seen in patients suffering from several illnesses. IMN encompasses a number of separate clinical entities, some of which are the Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN). The incidence of IMN ranges from 48,000 to 82,000 cases per 100,000 persons and can strike people of any age or gender [5].

Clinical features

The clinical manifestations of IMN can vary significantly from patient to patient and are highly dependent on the particular subtype. GBS is characterized by characteristic symptoms such as fast progressing weakness and sensory abnormalities, frequently accompanied by autonomic dysfunction. In most cases, CIDP manifests itself with a more gradually progressing course of weakening and sensory loss, frequently accompanied by pain and other sensory abnormalities. MMN often manifests itself clinically as asymmetric weakness and atrophy of particular muscular groups, frequently accompanied by accompanying cramping or fasciculations [6].

Diagnosis

In order to arrive at a diagnosis of IMN, it is required to first conduct a clinical examination, followed by electrophysiological testing, and finally a laboratory analysis. Electrophysiological testing is the only method that can discriminate between the demyelinating and axonal subtypes of neuropathy. This distinction can only be made between the two types. Studies in the laboratory may include a serological search for specific antibodies, such as anti-ganglioside antibodies in the case of GBS or anti-MAG antibodies in some instances of CIDP. These antibodies may be found in select cases [7].

Treatment

Treatment for IMN is dependant on the particular subtype of the disease as well as the severity of the symptoms. Treatment for GBS typically consists of intravenous immunoglobulin or plasmapheresis, both of which have been demonstrated to enhance patient outcomes. Corticosteroids, intravenous immunoglobulin, or plasma exchange are all potential treatments for chronic inflammatory demyelinating polyneuropathy (CIDP). However, some patients will require long-term immunosuppressive therapy. Intravenous immunoglobulin is a treatment option for MMN, but patients' responses to the medication can vary [8]. When taken as a whole, IMN describes a range of conditions that arise as a consequence of the body's immune system attacking its own peripheral nerves. These conditions are characterized by a diverse set of clinical symptoms and can only be accurately diagnosed through a combination of clinical evaluation, electrophysiological

testing, and laboratory research. Treatment options are contingent on the particular subtype of the condition as well as the severity of the symptoms and may include immunomodulatory treatments. More studies are required if we are to increase our understanding of the pathophysiology of these ailments as well as the appropriate treatment for them.

Guillain-Barré syndrome

Guillain-Barré syndrome, sometimes known as GBS, is an acute form of immune-mediated neuropathy that causes progressively worsening motor weakness as well as sensory abnormalities. The illness, which is often brought on by infections that came before it, can result in a large amount of morbidity and mortality [2].

Clinical features of GBS

The clinical appearance of GBS is defined by quickly progressing, symmetric, ascending motor weakness and sensory disruption. This presentation can be seen in patients at any stage of the disease. Alterations in blood pressure and heart rate, as well as tachycardia and bradycardia, are also possible for patients who have autonomic dysfunction. The clinical manifestations of GBS can range from quite moderate to extremely severe, with some patients requiring mechanical breathing due to weakening in their respiratory muscles [9].

Etiology of GBS

The Guillain-Barré Syndrome, sometimes known as GBS, is an autoimmune condition that affects the peripheral nerve system. It causes muscle weakness and, in more severe cases, paralysis. It is widely held that a faulty immunological response to an infection or vaccine is the root cause of GBS, despite the fact that its root cause has not been pinpointed with absolute certainty [2]. The following are some of the infections that are most frequently associated with GBS:

- *Campylobacter jejuni* is the most commonly found pathogen that is linked to GBS. It is responsible for up to forty percent of all cases. An infection caused by the bacterium *C. jejuni*, which is widely present in contaminated food and water, can lead to gastroenteritis, which is a form of stomach flu. GBS can develop as a result of the immune system's reaction to germs in some instances [10].
- Cytomegalovirus (CMV): CMV is a type of herpes virus that can produce a variety of symptoms, ranging from a mild illness that is similar to the flu to a serious condition in those who have compromised immune systems. Although it is linked to GBS a smaller percentage of the time than *C. jejuni*, CMV is also a known trigger for the condition [11].
- Epstein-Barr virus (EBV): EBV is a different type of herpes virus that is responsible for infectious mononucleosis, also known as "mono". Although the majority of people who catch EBV will only suffer moderate symptoms, the virus has been associated in certain cases to the development of GBS [12].
- *Mycoplasma pneumoniae* is a strain of bacterium that has been linked to the development of respiratory diseases including pneumonia. Infection with *M. pneumoniae* has been linked to GBS, despite the fact that it is quite uncommon [13]. GBS has been documented to be associated with a wide number of additional disorders, in addition to these infectious triggers, which include the following:
- Surgery: Giant cell arteritis can develop after undergoing surgical operations, despite the fact that the risk is typically quite low [14].
- Physical trauma: In some cases, Guillain-Barré syndrome has been linked to physical trauma, such as a head injury or an injury to the spinal cord [15].
- Drug exposure: Certain antibiotics, such as fluoroquinolones and macrolides, as well as vaccines, such as the influenza vaccine, have been associated to the development of Guillain-Barré syndrome (GBS). This association has been found in several studies [16].

In general, even if the specific reason behind GBS is still unknown, researchers believe that it is the result of a complicated interaction between genetic and environmental variables.

Diagnosis

Clinical characteristics, electrophysiological testing, and laboratory tests are the primary pillars on which the diagnosis of Guillain-Barré Syndrome (GBS) is founded. Ascending weakness and areflexia are two of the clinical signs that are diagnostic of GBS. These symptoms can get progressively worse over the course of several days or weeks. In order to differentiate between axonal and demyelinating subtypes of neuropathy, electrophysiological testing is an essential part of the diagnostic workup that is performed. In demyelinating neuropathies, nerve conduction tests, also known as NCS, might reveal a slower nerve conduction velocity, prolonged distal motor delay, and conduction block. Axonal neuropathies, on the other hand, are distinguished by lower compound muscle action potential (CMAP) amplitudes and normal or very slightly slowed nerve conduction velocities. Analysis of the cerebrospinal fluid (commonly known as CSF) is another important diagnostic tool in GBS since it has the ability to show higher protein levels in the majority of patients. In addition, serological testing for certain antibodies, such as anti-ganglioside antibodies, could be a part of the laboratory investigations. Anti-ganglioside antibodies are discovered in a fraction of people who have been diagnosed with GBS. The presence of these antibodies may assist in the identification of particular subtypes of the disease [11].

Treatment

Patients diagnosed with GBS need to get their condition diagnosed as soon as possible so that they can begin immunomodulatory treatment as soon as possible. Care that is supportive and treatment that modulates the immune system are normally what are involved in GBS management. Patients diagnosed with GBS have been proven to fare better when they undergo treatment with intravenous immunoglobulin (IVIg) and plasmapheresis [17]. IVIg is associated with less problems than plasmapheresis does, and as a result, it is the initial treatment of choice in the majority of instances [17]. IVIg is able to exert its therapeutic effects because it binds to the Fc region of antibodies, thereby limiting the capacity of those antibodies to activate the complement cascade and foster inflammation [17]. In plasmapheresis, the patient's blood plasma is drawn out and replaced with a protein solution. This procedure is performed on a continuous basis. Plasmapheresis is believed to be effective because it eliminates potentially harmful antibodies and complement components from the circulation [17]. Plasmapheresis and intravenous immunoglobulin (IVIg) are both effective therapies for GBS; however, IVIg is more commonly used since it requires less side effects and is simpler to administer [18].

In the management of GBS, immunomodulatory medication is an important component, but supportive care is also an essential part of the treatment process. Patients may receive physical and occupational therapy as part of their supportive care. These therapies are intended to assist patients in regaining their function and prevent problems such as deep vein thrombosis and pneumonia [17].

To summarize, Guillain-Barré syndrome is an acute form of immune-mediated neuropathy that has the potential to cause considerable morbidity and mortality. In most cases, the condition is brought on by infections that occurred in the patient's past and can bring about fast progressing motor weakness as well as sensory problems. Patients who have GBS really need to have a diagnosis as soon as possible and begin immunomodulatory treatment, such as IVIg, as soon as possible in order for their outcomes to improve. The provision of supportive care is also an essential part of the management of GBS.

The pathogenesis of GBS

It is not fully understood how GBS develops, although it is believed to include molecular mimicry between the pathogen and peripheral nerve antigens, which results in the development of autoantibodies that cross-react with the peripheral nerves. The exact etiology of GBS is not fully understood. A respiratory or gastrointestinal infection caused by a variety of pathogens, such as *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and the Zika virus, is typically the initial trigger for Guillain-Barré syndrome, as stated in a review article that was published in the *Journal of Neurology, Neurosurgery, and Psychiatry*. Antibodies are produced as a result of the immune response to the infection. These antibodies are able to detect the infectious agent as well as components of the

myelin sheath that surrounds the peripheral nerves. Following this step, the cross-reactive antibodies bind to the myelin sheath and cause damage to it. This leads to demyelination, which in turn leads to nerve dysfunction. Other mechanisms, such as the activation of complement, the recruitment of inflammatory cells, and the production of cytokines and chemokines, have been postulated to play a role in the pathogenesis of GBS. This is in addition to the production of autoantibodies, which is already known to play a role [19].

The treatment of GBS

It includes immunomodulatory medications to lessen the severity of the disease and shorten its duration, as well as supportive care to manage symptoms and prevent complications. Both intravenous immunoglobulin (IVIG) and plasmapheresis have been shown to be equally beneficial in the treatment of GBS, according to a meta-analysis that was recently published in the *Cochrane Database of Systematic Reviews*. It has been demonstrated that both treatments cut the amount of time needed for recovery, reduce the number of days spent in the hospital, and enhance outcomes overall. On the other hand, intravenous immunoglobulin (IVIG) is more commonly used since it is simpler to administer, carries a lower risk of problems, and is more widely available. On the other hand, the use of corticosteroids is not advised for the treatment of GBS. Corticosteroids did not enhance patient outcomes and may even increase the risk of complications, such as sepsis and gastrointestinal bleeding, according to the findings of a systematic review and meta-analysis that was recently published in the journal *Neurology*. As a result, corticosteroids should not be utilized as the primary treatment for GBS. Pain management, breathing support (such as mechanical ventilation), and physical therapy to avoid muscle atrophy and enhance recovery are some of the other supportive interventions that may be used for GBS patients. It is essential to keep in mind that the treatment of GBS should be customized depending on the specific symptoms of the patient, the degree of disease severity, and any other relevant circumstances. Thus, decisions regarding treatment should be made in cooperation with a neurologist or another healthcare provider who has experience with GBS [11,20,21].

Chronic inflammatory demyelinating polyradiculoneuropathy

Inflammatory demyelinating polyradiculoneuropathy, also known as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), is a chronic immune-mediated neuropathy that mostly affects the peripheral nerve system. It can either have a relapsing-remitting course or a progressive one, and it can cause symmetric or asymmetric sensorimotor polyneuropathy. The disease's progression can be either slow or rapid. The incidence of CIDP is believed to be between one and two instances per one hundred thousand persons each year. This is significantly lower than the incidence of GBS. Those in their forties and sixties are more likely to be affected by it, and men are more likely to be affected than women.

The diagnosis of CIDP

Clinical characteristics, nerve conduction investigations, and an examination of cerebrospinal fluid (CSF) all contributed to the conclusion. Clinical symptoms of chronic inflammatory demyelinating polyneuropathy (CIDP) include weakness, sensory impairments, and areflexia, as stated in a review that was published in the *Journal of Clinical Medicine*. Nerve conduction investigations often indicate evidence of demyelination. A study of the cerebrospinal fluid can reveal increased protein levels or lymphocytic pleocytosis. It is essential to keep in mind that CIDP can be difficult to diagnose because many different illnesses, including diabetic neuropathy and genetic neuropathies, can present with symptoms that are very similar to those of CIDP. As a result, the diagnosis of CIDP should only be made after consulting a neurologist or another healthcare provider who is experienced in the diagnosis and treatment of peripheral neuropathies [22].

The pathogenesis of CIDP

Although it is not fully understood, it is believed to include a synergistic interaction between humoral and cellular immunity processes. Autoantibodies against myelin proteins, including myelin-associated glycoprotein (MAG), were discovered in a subset of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), according to a review that was recently published in the *Journal of Clinical Medicine*. These autoantibodies have the potential to harm the myelin sheath and the axons of the peripheral nerves. On the other

hand, not every patient diagnosed with CIDP has detectable autoantibodies, which suggests that there may be additional immunological processes at play. There is some speculation that T-cell-mediated immune responses against myelin antigens are also involved in the development of chronic inflammatory demyelinating polyneuropathy (CIDP). Patients who suffer from CIDP have been shown to have an increased number of T cells and other immune cells infiltrating their peripheral nerves. These immune cells have the potential to release cytokines that are pro-inflammatory, which can cause inflammation as well as damage to the myelin sheath and axons. It is also likely that genetic factors have a role in the development of CIDP. A higher risk of CIDP has been related with particular human leukocyte antigen (HLA) alleles, therefore it is plausible that genetic factors play a role. A complicated interaction between immune cells, autoantibodies, and genetic factors is likely involved in the development of chronic inflammatory demyelinating polyneuropathy (CIDP), which suggests that the cause of CIDP is multiple [22-24].

The treatment of CIDP

Immunomodulatory treatments, such as intravenous immunoglobulin (IVIG), corticosteroids, and immunosuppressants are used in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). IVIG and corticosteroids are both considered to be effective first-line therapy, whereas immunosuppressants are utilized as second-line medicines for patients whose conditions do not respond to the first two treatments. Plasma exchange is yet another possibility that could be looked into in certain circumstances. In addition, the monoclonal antibody rituximab, which is used to specifically target B cells, has also been utilized in the treatment of CIDP. The appropriate course of treatment is determined by a number of factors, including the severity of the patient's condition, their reaction to any prior treatments, and any potential adverse effects [25-28].

Summary

Immune-mediated neuropathies result from aberrant immunological responses to peripheral nerves. Immune-mediated neuropathies research findings are summarized below.

GBS is the most frequent immune-mediated neuropathy. A respiratory or gastrointestinal illness precedes acute flaccid paralysis. Chronic immune-mediated neuropathy CIDP causes symmetric limb weakening and sensory loss. Immune-mediated neuropathies are caused by aberrant T-cell and B-cell immunity against peripheral nerves. Corticosteroids, IVIG, and plasmapheresis are often used to treat immune-mediated neuropathies. Early detection and treatment prevent permanent nerve damage and impairment. Immune-mediated neuropathies vary in prognosis depending on kind, severity, and therapy response. Immune-mediated neuropathies are complex illnesses that require rapid diagnosis, treatment, and prevention of long-term damage.

Bibliography

1. Querol L., *et al*. "Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications". *Nature Reviews Neurology* 13 (2017): 533-547.
2. Yuki Hartung H-P. "Guillain- Barre syndrome". *The New England Journal of Medicine* 366 (2012): 2294-2304.
3. Alkhatib AJ. "Autoimmunity and Diseases". In: The Role of Microbes in Autoimmune Diseases. Springer, Singapore (2022).
4. Alkhatib AJ. "The Role of Microbes in Autoimmune Diseases". Springer, Singapore (2022).
5. Wakerley BR and Yuki N. "Infectious and noninfectious triggers in Guillain-Barré syndrome". *Expert Review of Clinical Immunology 9*.7 (2013): 627-639.
6. Gorson KC. "Immune-mediated neuropathies". *CONTINUUM: Lifelong Learning in Neurology* 25.5 (2019): 1286-1309.

7. Dalakas MC. "Advances in the diagnosis, pathogenesis and treatment of CIDP". *Nature Reviews Neurology* 10.5 (2014): 267-277.

8. Kaku M and Simpson DM. "Neuropathy in the immune-mediated disorders". *CONTINUUM: Lifelong Learning in Neurology* 20.5 (2014): 1344-1364.

9. Van den Berg B., *et al*. "Guillain-Barré syndrome: Pathogenesis, diagnosis, treatment and prognosis". *Nature Reviews Neurology* 10.8 (2014): 469-482.

10. Yuki N. "Infectious origins of, and molecular mimicry in, Guillain-Barré and Fisher syndromes". *The Lancet Infectious Diseases* 12.4 (2012): 281-297.

11. Van Doorn, P. A., *et al*. "Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome". *The Lancet Neurology* 7.10 (2008): 939-950.

12. Lehmann HC and Hartung HP. "Guillain-Barré syndrome". *Current Opinion in Neurology* 26.5 (2013): 496-505.

13. Alshekhlee A., *et al*. "Guillain-Barré syndrome: incidence and mortality rates in US hospitals". *Neurology* 74.7 (2010): 581-587.

14. Hughes RA and Cornblath DR. "Guillain-Barré syndrome". *The Lancet* 366.9497 (2005): 1653-1666.

15. Kuwabara S., *et al*. "Guillain-Barré syndrome after traumatic injury: an analysis of 16 cases". *Journal of Neurology, Neurosurgery, and Psychiatry* 75.5 (2004): 678-682.

16. Vellozzi C., *et al*. "Safety of influenza vaccines in adults with Guillain-Barré syndrome". *Vaccine* 32.37 (2014): 4711-4716.

17. Hughes RA., *et al*. "Intravenous immunoglobulin for Guillain-Barré syndrome". *Cochrane Database of Systematic Reviews* 7 (2012): CD002063.

18. Yuki N., *et al*. "Guillain-Barré syndrome". *New England Journal of Medicine* 366.24 (2012): 2294-2304.

19. Willison HJ., *et al*. "Guillain-Barré syndrome". *Lancet* 388.10045 (2016): 717-727.

20. Hughes RA., *et al*. "Intravenous immunoglobulin for Guillain-Barré syndrome". *The Cochrane Database of Systematic Reviews* 9 (2014): CD002063.

21. Walgaard C., *et al*. "Prediction of respiratory insufficiency in Guillain-Barré syndrome". *Annals of Neurology* 75.2 (2014): 327-334.

22. Mahdi-Rogers M., *et al*. "Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): An Overview". *Journal of Clinical Medicine* 10.3 (2021): 376.

23. Mathey EK., *et al*. "Prevalence and clinical features of chronic inflammatory neuropathies in an Australian population". *Annals of Neurology* 80.1 (2017): 89-100.

24. Willison HJ and Yuki N. "Peripheral neuropathies and anti-glycolipid antibodies". *Brain* 125.12 (2002): 2591-2625.

25. Gajdos P., *et al*. "Plasma exchange for CIDP". *Cochrane Database of Systematic Reviews* 1 (2009).

26. Van Den Bergh PY and Hadden RD. "European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society-First Revision". *European Journal of Neurology* 19.2 (2012): 356-359.

27. Mahdi-Rogers M. "Current and emerging treatments for the management of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review". *Clinical Neurology and Neurosurgery* 115.8 (2013): 1293-1302.

28. Cortese A., *et al*. "Chronic inflammatory demyelinating polyradiculoneuropathy: immunological features of typical and atypical forms". *Journal of Neurology, Neurosurgery and Psychiatry* 90.10 (2019): 1127-1134.

Volume SP15 2023