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Guillain-Barré Syndrome: Current Concepts

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Abstract

Introduction: *Guillian Barré (GBS) syndrome is the most important cause of generalized flaccid paralysis in the world, characterized by rapidly progressive and ascending muscle weakness. The association with arbourviroses has been reported in several occasions although its exact cause is still unknown.*

Objectives: *In view of the occurrence of the appearance of chikungunya and the Zika virus in recent years and the reported increase of cases of GBS and more recently the Covid 19 infection, we decided to update the new concepts regarding the syndrome.*

Methods: *A research was carried out based on papers published in English and Portuguese literature from 1997 to 2016*

Conclusions: *GBC has still several obscure aspects. The association with previous infections could be demonstrated but does not encompass all explanations regarding the disease.*

Introduction

In Brazil, in 2015, at least nine pathogenic arboviruses circulated, including three with urban circulation: The presence of dengue has been observed in the country since the mid-1980s, while the appearance of chikungunya and the Zika virus was more recent, with autochthony confirmed .respectively in 2014 and 2015.[1] Since the end of 2015, the increase in cases of Guillain Barré Syndrome (GBS) has allowed a possible relationship to be established with Zika Virus infection.[2]

Some publications reinforced this association, such as reports of the occurrence of an outbreak of Zika in French Polynesia, between October 2013 and April 2014.In the same period, an increase in cases of GBS could be observed. In the study it was identified that in 42 analyzed cases of GBS, traces of the recent presence of Zika Virus were observed in 100% of cases.[3]

We considered of interest to bring some observations regarding some current concepts about this syndrome with many aspects yet to be elucidated.

Methods

A review of articles in English from 1997 to 2016 was carried out, using Guilain Barre, arboviruses and flaccid paralysis as key words.

Epidemiology

GBS is most important cause of generalized flaccid paralysis in the world, with an annual incidence of 1-4 per 100,000 inhabitants and peak between 20-40 years of age, depending on the population series, with a slightly higher incidence in males.

It is uncommon in children under 10 and the incidence increases progressively by 20% every 10 years after that age.[4]

Pathophysiology

Although the exact cause of Guillain-Barré syndrome is unknown, recently, some countries have reported an increase in the incidence of GBS after infection with the Zika virus.[5] GBS is currently considered the most commonly acquired demyelinating neuropathy and its diagnosis must be remembered by all doctors.

The pathogenesis with clarity of the syndrome is unknown, but it is believed that the viral infectious agent induces a humoral and cellular immune response against its antigens and the condition results in the production of antibodies that can cross-react with ganglioside components on the surface of the myelin sheath due to the structural homology between bacterial and nervous tissue antigens. This cross-reaction then triggers an acute inflammatory neuropathy in 85% of cases. Of these, in 15% the cross reaction occurs with antigens present on the axon membrane, triggering the acute axonal form of the syndrome.[6]

Relationship with Arbourviruses

Arbourviruses have acquired importance due to the increased incidence in tropical regions due to rapid climatic changes, deforestation, population migration, disorderly occupation of urban areas, precarious sanitary conditions that favor viral amplification and transmission.[7]

Arbourviruses are viruses transmitted by insect bites, especially hematophagous mosquitoes. Zika virus disease is at higher risk than other arboviruses, such as dengue, yellow fever and chikunjnguya for the development of neurological complications, possibly due to its neurotropism. Among these complications encephalitis and Guillain Barré syndrome are found.

Reports in the literature prove the relationship between infection by these arboviruses and the involvement of the central and peripheral nervous system. The increase in cases of encephalitis and meningoencephalitis in patients with dengue was reported in Brasil

during the 1997 and 2002 epidemics. In addition, several studies in countries with a dengue epidemy have observed an association of this condition with other neurological manifestations, such as GBS, multiple peripheral paralysis, peripheral facial paralysis, encephalitis and myelitis.[8]

Relationship with Other Infections

The authors agree that more than 75% of GBS cases have a history of clinically evident infection or manifested by an increase in serum antibody levels, from one to three weeks before the onset of GBS.[9]

They also associate the syndrome with respiratory or gastrointestinal infections one to three weeks before the development of the syndrome, which is considered as a triggering factor for the pathology.[10]

About 2/3 of patients who develop the syndrome report symptoms of an infection within 6 weeks prior to the onset of the disease. It is assumed that these infections trigger the immune response that causes the syndrome.[11] Although several infections are classically associated with GBS, *Campylobacter* infection is considered the most common.[12] Other infections were also related: airway infection, upper respiratory tract infection, febrile syndrome of unspecified etiology, gastrointestinal infections, acute Campylobacter jejuni diarrhea, viral diseases such as dengue, cytomegalovirus Epstein Barr virus measles, Influenza A virus, hepatitis A, B, AIDS virus, rabies vaccine, metabolic stress situations such as pregnancy and surgery[14].

It is also mentioned that patients with other conditions such as lymphoma and systemic lupus erythematosus have a higher incidence of GBS than the general population.[14]

Clinics

Progressive weakness is the most noticeable symptom, generally occurring in this order: lower limbs, arms, trunk, head and neck.[15] About 5% -15% of patients develop ophthalmoparesis and ptosis.[16]

The sphincter function is, in most of cases, preserved, while the loss of myotactic reflexes can precede the sensory symptoms even in little affected muscles. Neuropathic lumbar or leg pain can be seen in at least 50% of cases.[15] Different degrees of aggression, causing from mild muscle weakness in some patients to total paralysis of the four limbs are reported.[17]

The disease usually progresses for 2 to 4 weeks. At least 50% -75% of patients reach their peak in the second week.[18] It is important to mention that the progression of signs and symptoms for more than 8 weeks excludes the diagnosis of SBG, suggesting then chronic inflammatory demyelinating polyneuropathy.[19]

Autonomic dysfunction is a sign of poor prognosis, reflecting a manifestation of failure of mechanisms of nervous self-regulation of blood pressure and cardiac function causing orthostatic hypotension, labile blood pressure and cardiac arrhythmias.[20]

The evolution of paralysis can affect the respiratory muscles. Such occurrence reflects a more serious

picture. Cardiac musculature is also usually affected in this condition, whose association often determines fatal evolution.[20]

Anamnesis and Physical Examination

The importance of a detailed anamnesis and physical examination for the presumptive diagnosis of GBS is of paramount importance, with subsequent confirmation with complementary tests, especially examination of the CSF (from the fifth day of evolution).

Important elements such as pattern of weakness, pattern of progression and distribution, interrogation of sensitive symptoms, history of immunosensitizing factors and previous infections are of fundamental importance. The investigation of the differential diagnosis should not be neglected even when the clinical picture is typical of GBS.

The diagnostic criteria are well established by the National Institute of Neurological Disorders and Stroke (NINDS), and these criteria are used worldwide. More recently, the World Health Organization (WHO) recommends the use of the Brighton Criteria for the definition of suspected cases in countries affected by the Zika virus.

The diagnosis for GBS must be based on the set of clinical and laboratory findings, since no single observation is pathognomonic for the syndrome and no laboratory exam is specific to the pathology.

Analysis of cerebrospinal fluid is essential (the principal exam): It consists of an increase in proteins accompanied by few mononuclear cells. This is the characteristic laboratory finding, evident in up to 80% of patients after the second week.

Complementary Exams

The diagnosis of GBS is primarily clinical. However, additional tests are needed to confirm the clinical impression and exclude other causes of flaccid paraparesis.

Electrophysiological: GBS is a dynamic process with variable rate of progression.[22] The ideal would be to examine the patient after the first week of symptom onset when electrophysiological changes are more evident and better established. It is important to note that the absence of electrophysiological findings in this period does not exclude the hypothesis of GBS. However, electrophysiological exploration is necessary to exclude other neuromuscular diseases that cause acute flaccid paraparesis.[23]

Currently, the ultrasound image of peripheral nerves may reveal an increase in the volume of cervical nerve roots, indicating inflammation of the spinal root.

This technique can help establish a diagnosis early in the course of the disease.[24] Magnetic resonance imaging can be used, especially in children whose electrophysiological evaluation can be difficult to perform. The presence of nerve root enhancement after gadolinium injection is a non-specific but sensitive feature.[25]

Discussion

(GBS) was described by Guillain, Barré and Strohl (1916), being characterized by rapidly progressive and ascending muscle weakness, which can lead the patient to quadriplegia[26], constituting acquired peripheral polyradiculoneuropathy of immunomediated origin.[27]

The myelin sheath is composed of bimolecular layers of lipids interspersed with proteins. It has the same composition as cell membranes, that is, 70% lipids and 30% proteins, with a high concentration of cholesterol and phospholipids in its composition

It is a structure of fundamental importance in neuronal integrity that covers and protects peripheral nerves, guaranteeing the speed of nerve transmission.[28]

GBS can be considered an autoimmune disease in which the immune system recognizes and attacks the nervous system leading to damage to the myelin sheath due to a acute inflammation of the nerves, losing the normal transmission of afferent and efferent nerve stimuli making the impulse extremely slow.[29]

The exact cause of GBS syndrome is unknown, however recently, some countries around the world have reported an increase in the incidence of GBS after infection with the Zika virus.

Treatment

The Ministry of Health of Brazil is responsible for the treatment of GBS cases. Human immunoglobulin is the preferred treatment. In some cases of greater severity, the procedure called plasmapheresis is recommended.[1]

For the correct indication of treatment, it is necessary to determine the clinical severity proposed by Hughes et al, being considered a mild disease of 0-2 and moderate-severe of 3-6:

1 - Healthy

2 - Minor signs and symptoms of neuropathy, but able to perform manual tasks

3 - Able to walk without the aid of a cane, but unable to perform manual tasks

4 - Able to walk only with a cane or support

5 - Confined to bed or wheelchair

6 - Needs assisted ventilation

The use of glucocorticoids is not indicated. Human intravenous immunoglobulin (IVIG) has been the treatment of choice in most countries, although the mechanism of action is poorly understood.[30]

Its short- and long-term efficacy is similar to that of plasmapheresis, avoiding complications inherent to the second modality (hypotension, need for venous catheter, thrombophilia).

Prior assessment of renal function should be performed, especially in diabetic patients, prior hydration, control of clinical signs for anaphylaxis and adverse effects, such as moderate chest, hip or back pain, nausea and vomiting, chills, fever, malaise, fatigue, feeling weak or slightly dizzy, headache, hives, erythema, chest tightness and dyspnea.[31]

Immunoglobulins are relatively safe, with side effects in 1-15% of cases, headache, nausea, myalgia and fever with or without chills.[32]

In case of new outbreaks of the disease, according to what was exposed by Cecatto et al. (2003)[33], the same treatment as the first episode is generally used, however, the risk of remaining sequelae becomes greater.

Prognosis

Several studies show that the majority of patients with GBS have elevated serum levels of tumor necrosis factor alpha (TNF-α), a cytokine highly toxic to the myelin sheath and Schuwan cell. This increase is directly correlated with the severity of the disease, because when the circulating levels of TNF-α fall, clinical improvement is observed in most patients.[34]

GBS progresses in three phases that are called progression, stabilization and regression, which is only completed in three to six months.[35] Approximately 95% of cases recover completely, and some patients may experience moderate muscle weakness, with the most favorable recovery results when remission of symptoms begins within three months of the onset of the syndrome.[36]

These factors are associated with the poor prognosis of GBS: age over 60 years, rapid progression of the disease (less than seven days), extent and severity of axonal damage, persistent cardiorespiratory disease and late treatment.[37] Added to these factors is the history of diarrhea due to by Campylobacter jejuni, the presence of anti-ganglioside antibodies, clinically severe disease and the absence of adequate immunomodulatory treatment, according to Tavares et al. (2000).

Only 15% of patients will remain without any residual deficit 2 years after the onset of the disease and 5% -10% will remain with disabling motor or sensory symptoms. GBS patients have mortality rates of approximately 5% -7%, usually resulting from respiratory failure, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias and hospital sepsis.[38,39]

he motor prognosis is better in children, as they need less ventilatory support and recover faster. Recurrence of the episode can be observed in up to 3% of cases, with no relation to the form of treatment used in the acute phase, as was believed.[40]

The early recognition of GBS should be done with the aim of allowing the treatment to be carried out in a timely manner to increase the speed of recovery and for the patient to be monitored for complications and rehabilitated from the functional point of view.

Recovery can last from six to one year, rare cases last for up to 3 years.

Conclusions

GBS has been shown, even after decades since its initial description, a syndrome with several obscure aspects. Their knowledge, especially in recent years, when an increase in arborvirosis in urban centers has been reported, and now, the report of some cases related to the Covid 19 infection, takes an important place in medical practice. We believe that over the next years new aspects related to the syndrome will provide a better understanding of this syndrome.

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