UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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IMMUNOTHERAPY IN PEDIATRIC GUILLAIN-BARRÉ SYNDROME: INTRAVENOUS IMMUNOGLOBULIN, PLASMAPHERESIS OR BOTH?

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE PEDIATRIA

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JANEIRO/2020

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Trabalho final do 6ª ano do Mestrado Integrado em Medicina, com vista à atribuição do grau de Mestre em Medicina.

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Index

1. Abstract

Guillain-Barré Syndrome is an autoimmune disease of the peripheral nervous system, that affects both adults and children, causing autonomic failure, rapidly progressing and symmetric weakness, loss of reflexes and respiratory distress, leading to the need for artificial ventilation. The diagnosis of this disease arises from combining a good clinical evaluation with neuroimaging, cerebral fluid examination, nerve conduction studies and serum analysis. As an immune-mediated condition, the preferential treatment is immunotherapy combined with symptomatic care. There are two primarily used techniques, whose rationale applies to both children and adults: plasma exchange and intravenous immunoglobulin. Many studies have been conducted in severe cases, in children. Both therapies have proven to be effective in improving motor recovery, reducing the need for mechanic ventilation and hastening hospital stay. While their efficacy is comparable, plasma exchange is not used as the primary line of treatment because of its need for specialized personnel and specific equipment. So intravenous immunoglobulin is the first line treatment for pediatric Guillain-Barré Syndrome due to its accessibility, safety and efficacy. However, the results were not satisfactory in the long term, so studies combining both therapies started being developed. One of them, defining the Zipper Method, proved that intercalating both techniques may improve every outcome, when compared to each therapy on its own. So this method, pending further research, can be seen as a promising future treatment strategy in pediatric Guillain-Barré Syndrome.

Keywords

Guillain-Barré Syndrome, Immunotherapy, Plasma Exchange, Intravenous Immunoglobulin, Zipper Method.

2. Introduction

Guillain-Barré Syndrome (GBS) is an acute demyelinating polyneuropathy characterized by rapidly progressing areflexia and symmetric weakness in previously healthy individuals. This autoimmune disease is the most common form of acute flaccid paralysis in children and is normally triggered by a respiratory or gastrointestinal infection (50-70% of cases).[1] Muscle weakness starts in the distal extremities and has a proximal evolution, causing a possible failure of respiratory muscles which leads to the need for mechanic ventilation.[2]

The therapeutic approach to this disease consists of general medical care that includes respiratory vigilance and pain management and immunological treatment, such as intravenous immunoglobulin therapy and plasma exchange. However neither immunological treatment ensures a favorable long-term outcome when used separately. [1]. A recent study utilized both plasma exchange and intravenous immunoglobulin in a synergic way, which has improved the outcome in severe cases of GBS.[3] These are interesting findings, but more studies are required to attest to the reliability of such technique.

Therefore, the objective of this paper is to review what has been written about the therapeutic approach in GBS cases, particularly in children, trying to identify which seems to be the best way to treat this condition: should plasma exchange and intravenous immunoglobulin be given separately or synergistically? How can we improve the outcome of this disease? Are there any other approaches that can be used?

3. Guillain-Barré: Current Concepts

GBS is a disease of the peripheral nervous system that affects between 0.3 to 2 children out of 100,000 per year. [4] However, the incidence varies from one population to the other, reflecting genetic susceptibility and environmental exposure as the main causes for this variance. This polyneuropathy is marked by a rapidly progressing distal weakness that develops approximately 2 to 4 weeks after an acute (respiratory or gastrointestinal) infection reaching its peak of muscle weakness after 2 weeks. [1, 5]

This is an autoimmune disease that results from the activation of B-cells and T-cells by pathogenic agents, which leads to the production of autoantibodies. This immune response is triggered by immature antigen presenting cells that migrate to the lymph nodes, mature and stimulate these T-cells which will activate the B-cells, prompting a cell and humoral response to the pathogen. The inflammation results from the cytokines production, macrophages and T-cell activation, which enhances phagocytic activity and the release of several toxic substances, such as nitric oxide and metalloproteinases leading to nerve tissue damage. The mechanism most associated with this immune response is molecular mimicry, where the pathogen and the host share identical antigens and reactive T-cells recognize an antigen presented by the major histocompatibility complex II, triggering the cross reaction. The microorganism *Campylobacter jejuni* is the most common pathogen responsible for this reaction, once it has several peripheral molecules that share some of the biochemical properties of human gangliosides, thus becoming the primary target of this cross reaction. These are glycosphingolipids that are present in the nodes of Ranvier, an integral part of the human nervous system. Therefore, the production of antiganglioside antibodies causes demyelination which leads to a blockage of the electrical nerve impulses, prompting the muscle weakness, autonomic abnormalities and areflexia.[2, 6]

The clinical characteristics of this disease are marked by 3 distinct phases: an acute phase, followed by a plateau and a recovery phase with variable duration. The acute phase begins with peripheral weakness, which rapidly ascends and can lead to absence of reflexes on physical examination. In children, it can initially be detected by a change in the walking pattern of the patient, frequent falls and a refusal to walk. Cranial nerve abnormalities are usually present, especially affecting the facial nerve. Autonomic dysfunction, such as cardiac dysrhythmias, hypertension, orthostatic hypotension and bladder dysfunction are present and need to be closely monitored due to the risk of death. Pain is rarely present, which can lead to a delayed diagnosis (nevertheless, when present, it can be very difficult to tolerate neuropathic pain). This acute phase reaches

its peak in about 2 weeks after the onset of symptoms, which leads to a plateau period of variable length that is followed by the recovery phase, which can last from weeks up to months. [7]

The GBS can be classified in six different subtypes: Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP), Acute Motor-Sensory Axonal Neuropathy (AMSAN), Acute Motor Axonal Neuropathy (AMAN), Miller-Fisher Variant, Pharyngeal-Cervical-Brachial Variant and Acute Pandysautonomia. [6] The AIDP is the most common form of GBS, representing about 75% of all cases in Western countries.[1] This variant mainly targets the sensory and cranial nerves, which is not the case in other subtypes, where the motor nerves are the most affected. Demyelination is the main characteristic of this variant, due to the damage caused to the Schwann cells. [1, 4, 7] The AMSAN is a variant that targets both motor and sensory nerves, which gives it a worse prognosis than the subtype already discussed by having a severe effect on the respiratory system. [4, 7] The AMAN is a form of GBS that is similar to AIDP, but targets the motor nerves as opposed to the sensory nerves. This variant has been mostly associated with gastroenteritis caused by *Campylobacter jejuni*, because the lipo-oligosaccharides induce the production of IgG, IgA and IgM autoantibodies, causing a cross reaction with the human gangliosides. This phenomena is, as stated earlier, explained by a mimicry hypothesis. [1, 4, 6]. The Miller-Fisher variant is characterized by ophthalmoplegia, ataxia and areflexia. Muscular strength is usually spared. This particular subtype is associated with a specific antibody, the anti-GQ1b, whose production is usually triggered by *Campylobacter jejuni* and has a high sensitivity and specificity for this particular clinical variant. [1, 6] The Pharyngeal-Cervical-Brachial Variant distinguishes itself from the other subtypes, because the muscular weakness is proximal and descending, instead of being distal and ascending. [7] Finally, the Acute Pandysautonomia is the least specific variant and is characterized by sympathetic and parasympathetic failure that affects the entire body. [6]

The diagnosis of GBS is essentially the result of a good clinical evaluation of the patient, but it may require an integration of several data coming from neuroimaging, cerebral fluid evaluation, nerve conduction studies and serum analysis. Regarding clinical characteristics, it is important to evaluate the presence of a progressive distal weakness in arms and/or legs for no more than 6 weeks, diminishing or absence of reflexes, autonomic abnormalities, pain, respiratory complications and, depending of the subtype, sensory symptoms. [8, 9] In neuroimaging, gadolinium enhancement of the *cauda equina* and nerve roots can be very suggestive of the diagnosis, particularly in children. However, this pattern is not specific for this condition and it is particularly useful

when it may add something to the information coming from other tests, in specific clinical contexts. [1, 6, 7, 8] When analyzing the cerebrospinal fluid through a lumbar puncture, it is important to evaluate the levels of proteins and cells. In this particular disease there is a dissociation between these two, protein levels increase, while cell count remains normal (mononuclear cell count <50 cells/mm^3). However, it is important to state that the cerebrospinal fluid parameters might be normal during the first week of the disease, so it is essential to repeat the analysis never disregarding what appears to be normal, when there is a high degree of suspicion. [7, 9] Electromyography is a relevant test used not only to diagnose this disease (and exclude other important differential diagnoses), but mainly for establishing an early prognosis, since it has in consideration neurophysiological aspects related with the degree of nerve fiber damage. This exam shows that after 2 weeks of illness the sensory and/or motor nerve conduction, depending on the subtype, begins to decrease and there is an increase latency and conduction blocks (defining a demyelinating pattern), which attests to the clinical manifestations of weakness and areflexia. [5, 6, 7, 8] An axonal lesion, characterized by a great reduction in the amplitude of nerve potentials, may preclude for a difficult functional recovery. Nevertheless, in children, the utility of the electromyogram may be overcome by technical difficulties related with exposing children to such painful stimuli and recordings. In terms of serum examination, it is important to test for antiganglioside antibodies, which are present in about 50% of all pediatric GBS cases. The study of these antibodies takes extra importance, particularly in cases where the presentation of the disease is atypical or when doubts subsist about the diagnosis. [1, 6, 8]

GBS, being a disease that affects the peripheral nervous system, has clinical similarities to other diseases that target the peripheral nerves, namely: vasculitic neuropathies, lymphomatous neuropathy or heavy metal intoxication. Besides nerve damage, the disorders of the neuromuscular junction can also be a differential diagnosis, such as myasthenia *gravis* or Eaton-Lambert syndrome. Disorders like inflammatory myopathies, periodic paralysis, hypokalemia or hypophosphatemia that target the muscle fibre can also be considered as possible differential diagnoses, due to their similarities, in terms of motor symptoms. There are also some diseases of the central nervous system that have similar clinical features to GBS, like stroke involving the brainstem or brainstem encephalitis, being this another relevant variable to take into consideration, when defining the differential diagnosis. [1, 5, 6]

The therapeutic approach to this syndrome is complex, because there is no immediate cure, therefore, it requires a combination of general medical care and immunological treatment, trying to overcome what is known in pathophysiological terms.

One of the most important factors to monitor in this disease is its impact on the respiratory system (15-20% of children require mechanic ventilation) and on cardiac rhythm, since dysautonomia may preclude serious medical complications, on GBS. Psychological support may also be relevant, due to the impact that this condition may have on children's daily routine, but also because of the impact this transition may have on parents. [1, 2, 6] If only supportive treatment is given, the recovery process begins 2-4 weeks after the disease has stopped progressing. [10]

Mechanical ventilation is used in this syndrome when the disease is rapidly progressive and difficult to control, when the patient cannot flex arms or head, when there is bulbar weakness or an inability to cough, when there is autonomic abnormalities or when the cerebral fluid protein level is >800mg/L. There are factors which are indications for intubation in this syndrome, like oropharyngeal paresis, autonomic failure or respiratory malfunction, threatening life. [10]

Due to the need for continuous monitoring, some children must be admitted to a pediatric Intensive Care Unit, if any of the following are present: flaccid tetraparesis, autonomic instability, rapidly progressive condition, reduced vital capacity that requires ventilation or symptomatic bulbar palsy. [11]

In theory, steroids should be beneficial because of their effect on inflammatory processes. However, it appears that they are ineffective in GBS. A meta-analysis of four trials that used oral corticosteroids showed that there was no improvement of the condition of patients that used the steroids, as opposed to those who did not. [12, 13] Furthermore, a study tested the effect of intravenous immunoglobulin with methylprednisolone and without it, to see if it improved patients' outcome. No significant differences were found, so it warrants more investigation on the association between steroids and other immune-directed treatment. [14] The reason why steroids are not effective in this disease is not clear, but studies reveal that macrophages are primarily active in the recovery phase of the disease, instead of the acute one, therefore, limiting their action with the steroids might hinder the healing of the nerves and delay patients' full recovery. [12] Complement inhibitors are a treatment currently under investigation, because the pathophysiology of this disease depends on the complement activation, therefore targeting it might be a new step towards a better treatment for patients with this syndrome. [1, 6]

There are two so-called "immunological treatments" that have documented efficacy in GBS: intravenous immunoglobulin therapy and plasma exchange.[1] The basis of

these therapies and current advancements are going to be discussed in the latter part of this paper.

Pediatric GBS is usually less severe than in adults. Pain and bulbar dysfunction are more frequent in children. Pediatric cases have a more acute onset than adults and are more prevalent in the summer. However, respiratory paralysis and autonomic abnormalities have a similar incidence in children and adults. Unlike in adult cases, autonomic dysfunction is an independent factor for mechanic ventilation in childhood GBS. In terms of treatment efficacy, no significant differences were found.[15, 16]

The outcome of this disease is primarily influenced by respiratory insufficiencies, autonomic abnormalities and ventilation residual complications. As previously stated, pediatric GBS is usually less severe, so older age correlates with worse outcomes. Besides this factor, others such as mechanic ventilation, diarrhea and *Campylobacter jejuni* infection are associated with a worse outcome. [1, 6, 8, 16]

The prognosis is usually good. After 6 months, the majority of children completely recover. However, 15-20% of children need mechanic ventilation and 20-25% show weakness and slightly impaired reflexes. After the acute phase of the disease, 30-40% of children are able to walk, as opposed to only 19% of adults. [15, 16, 17, 18]

This disease has a mortality rate of 3-7% and it is associated with pulmonary complications or autonomic failure. However, with prompt treatment, the majority of patients will be able to recover their functional capacity. [1, 6, 8, 18] The Hughes Functional Grading Scale is used in many clinical trials to attest clinical disability and functional outcome (Table 1). [9, 19]

Table 1 - Hughes Functional Grading Scale

Score	*Functional Status*
0	Healthy
1	Minor symptoms, able to run
2	Can walk 5 meters without help
3	Can walk 5 meters with a walker or support
4	Confined to chair or bed
5	Requires mechanic ventilation
6	Death

Adapted from Ref. 19

4. Methods

An online research was conducted using *Pubmed* as the preferred database and using as MESH terms: Pediatric Guillain-Barré Syndrome, pediatrics, immunotherapy, plasma exchange, plasmapheresis, intravenous immunoglobulin, IV immunoglobulin and immunomodulation. The following research equations were used: Guillain-Barré Syndrome AND pediatrics; Guillain-Barré Syndrome AND pediatrics AND immunotherapy; Guillain-Barré Syndrome AND pediatrics AND immunotherapy AND plasma exchange; Guillain-Barré Syndrome AND pediatrics AND immunotherapy AND plasmapheresis; Guillain-Barré Syndrome AND pediatrics AND immunotherapy AND intravenous immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND immunotherapy AND IV immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND plasmapheresis; Guillain-Barré Syndrome AND pediatrics AND plasma exchange; Guillain-Barré Syndrome AND pediatrics AND intravenous immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND IV immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND intravenous immunoglobulin AND plasma exchange; Guillain-Barré Syndrome AND pediatrics AND intravenous immunoglobulin AND plasmapheresis; Guillain-Barré Syndrome AND pediatrics AND intravenous immunoglobulin NOT plasma exchange; Guillain-Barré Syndrome AND pediatrics AND intravenous immunoglobulin NOT plasmapheresis; Guillain-Barré Syndrome AND pediatrics AND plasma exchange NOT intravenous immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND plasmapheresis NOT intravenous immunoglobulin; Guillain-Barré Syndrome AND pediatrics AND immunomodulation.

After this research, 682 articles were found. After excluding articles based on the language (English was the only language admitted for this study), we defined the type of article as another exclusion criteria. The following types of article were considered: case report, clinical study, clinical trial, controlled clinical trial, meta-analysis, randomized controlled trial, review, systematic review and observational study. After the application of these filters, 387 articles remained. An analysis of the abstract was then conducted and repetitive information was deleted from the database. After that, 60 articles remained and were used in this review.

Besides *Pubmed*, the *Cochrane Library* was also used as a reference database. Due to the rarity of this medical condition and to the little research done in children, there was no temporal cut-off, in terms of online research.

5. Results

The treatment of pediatric GBS is based on general medical care and on the usage of immune-directed interventions, aiming to restore the normal functioning of the immune system, which is strongly implicated in the pathophysiology. This approach consists of plasma exchange and intravenous immunoglobulin, separately or combined. Based on the report of the quality standards subcommittee of the American Academy of Neurology in 2004, both immunological treatments are used in severe Pediatric GBS, as opposed to steroids, that are not recommended. [2, 10]

5.1 Plasma Exchange

Plasma exchange consists of extracting plasma from the blood of the patient by utilizing centrifugal separators. This technique allows the removal of neurotoxic antibodies, inflammatory mediators, complement factors and immune complexes that might be responsible for the disease. After this removal, the plasma is reinjected into patient´s bloodstream alongside a solution of 5% albumin, in order to compensate the lost proteins. [1, 6, 9]

This therapy should be started within 7-14 days of the onset of the disease. As stated earlier, this approach is used in severe cases, frequently associated with the necessity of mechanic ventilation. The administration protocol of 5 plasma exchanges in a 2-week span proved to provoke less damage to nerves and showed a better clinical improvement. [2, 9] In total, the exchanges should mount to approximately 250 ml/kg. This technique is usually safe for children above 10 kg, because their total blood volume should support this invasive procedure. [1, 10]

Plasma exchange has proved effective since the 1980s in adults, and its results have been, in part, extrapolated to children. One study, in 1990, divided 23 children with the mean age of 8.8 years old into two groups: 9 treated with 220 ml/kg of plasma exchange and 14 as a control group. After the exchange, the first group needed 24-49.4 days to recover independent mobility, as opposed to the control group, which required from 60.2-103.8 days to reach the same outcome. [20]

One of the earlier studies regarding the efficacy of plasma exchange in pediatric GBS submitted 4 children to different procedures. The sessions varied from 4 to 8 and from 8 to 24 days. The plasma removed varied from 2888 to 8500 grams. Three out of 4 children showed motor improvement during the sessions. The other child did not improve as quickly, which was attributed to a *Campylobacter jejuni* infection during the sessions.

This study concluded that plasmapheresis is a successful treatment in children with this clinical condition, even though a standardized protocol still needed to be studied and implemented. [21]

In 1993, a group of 19 children were enrolled in a study in which the efficacy of plasmapheresis was tested in severe GBS (grade 3 or higher in the Hughes scale). Of these 19 children, 11 served as a control group and 8 were subjected to plasmapheresis 4.6 days on average after the onset of symptoms. The total of plasma removed varied from 74-415 ml/kg and the duration of the treatment was an average of 7.3 days. One week after the end of the procedure, all of the patients submitted to plasma exchange improved by 1 grade or more. Furthermore, the average duration of mechanic ventilation in children subjected to plasmapheresis was 9.0 days, as opposed to 25.0 days of children that served as controls. [22]

A French Cooperative Group studied the use of plasma exchange on GBS and the correlation between the gravity of the disease and the number of exchanges needed to treat the patient. In order to participate in this study, the patient had to be at least 16 year old. The subjects were divided into 3 groups depending on the severity of the disease: mild, moderate and severe (although the majority of the patients recruited for this study were adults and late adolescents, the main conclusions can be extrapolated from this protocol for pediatric populations). In the severe cases, the patients were given either 4 or 6 plasma exchanges. In terms of recovery and ability to walk, there were no differences between 4 and 6 plasma exchanges, although 4 exchanges slightly shortened the motor recovery, when compared to 6. In regards to side effects, the patients which were submitted to 6 exchanges suffered more systolic pressure instability than the patients that were given 4. This finding attests to the current treatment of a maximum of 5 plasma exchanges implemented in actual protocols, always regarding the side effects of this treatment. [2, 9, 23]

A study where 40 pediatric patients over a one-and-a-half year span were submitted to a total of 122 plasma exchange procedures showed a significant improvement from complete paralysis to the possibility of movement. This study showed that plasma exchange reduced hospital stay, mortality and morbidity, proving that this therapy can be used as a first line approach or as an adjuvant. [24]

There are 6 controlled trials containing 649 patients, which compared plasma exchange with supportive treatment. After 4 weeks, the patients treated with plasmapheresis fared better, in terms of recovering of mobility, walking without aid and necessity of mechanic ventilation. One of those trials showed that there was a real cut-

off of 7 days that affected how well the patients responded and recovered. Other studies contradict this one, by saying that even after 7 days of onset of the disease, patients' response was the same. [25]

Plasma exchange is not generally the first line of treatment, in this disease. This arises from the fact that in pediatric patients there is low blood fluid, no adequate vascular access and worse collaboration than in adults. Furthermore, this technique is limited to major centers, due to the need for trained professionals and proper equipment. [2, 23] There is still a lack of controlled randomized trials in children, to effectively measure the benefits and risks of this technique in children, at least when comparing with adults. There are a number of studies revealing the short-term effect of plasmapheresis, but there are no reports of its efficacy after 1 year. [26, 27]

5.2 Intravenous Immunoglobulin

Intravenous immunoglobulin (IgIV) acts by inhibiting antibody production, by targeting B and T cells, leading to a faster catabolism of the referred antibodies. This technique also prevents the phagocytic activity of macrophages, by blocking the gamma receptors, complement activity, the formation of membrane attack complex and leads to a decrease of cytokines and other adhesion molecules responsible for the inflammatory process, which diminishes nerve damage. [1, 6, 11, 18, 28, 29] IgIV has been suggested to improve peripheral remyelination in GBS. This proposition arises from the study of a monoclonal antibody (IgMk), which has been proved to promote the myelination process and, at the same time, to suppress the inflammatory responses that this disease provokes, expecting to improve patients recovery. [18]

IgIV is said to be the preferred method for GBS treatment, because of its ease of administration and less hemodynamic impact. This therapy has its maximum efficacy when given within 2 weeks of the onset of the disease. [1, 28]

The use of this therapeutic approach in children has its controversies. On one hand, it is advised to only use in mild cases, in order to prevent the progression of the disease. However, other authors defend that it should only be given in severe cases, especially in ventilated children, because of its effect on the reduction of the number of days in which the child needs mechanical support and on the shortening of hospital stay. [17] The dosage of this drug has fluctuated through the years. The research done in order to find the best dose came to different conclusions, from 400 mg/kg to 1 or 2 g/kg,

from 1 single dose to 2-5 days of treatment. Current studies point towards 2 g/kg for 2-5 days as the best dose to use in this disease. [1, 30]

One of the first studies involving children with this condition came in 1990, when 3 children with severe GBS were submitted to 1 g/kg of IgIV for 2 days. At the time of the study, only plasma exchange was used in this disease, but was only available in some centers and needed trained personnel and appropriate equipment. Therefore, the need of something else that could help patients was clinically relevant. IgIV became the solution with results in the short term, reducing hospital stay and signs of nerve damage after 6-18 months of follow-up. [31]

A 1994-study involved 4 children with GBS that were submitted to 400 mg/kg for 5 days (patients 1 and 2) and 400 mg/kg every 3 weeks for 3 months (patients 3 and 4). All of the patients had ascending paralysis and were unable to walk independently. After 6 weeks, all patients were able to walk unaided with no relevant adverse effects from the treatment. This small study laid the foundations for the systematic use of this intravenous therapy. [32]

Nine children diagnosed with GBS and a Hughes score of 3 or 4 were subjected to a single dose of 1 g/kg of IgIV. Motor improvement came after, on average, 3.5 days as opposed to 5.7 days without the treatment and ambulation came after 11.2 days. Full mobility came after 14.5 months. The progression of the disease stopped in all children, which attests to the efficacy of early usage of this technique. [33]

A 18-month old boy was submitted, inadvertently, to a continuous infusion of 2.4 g/kg of IgIV over a 25-hour period. After the end of the procedure, the clinical improvement started after 36 hours. The patient did not experience side effects, which were expected, like thromboembolism due to the increase viscosity of the serum. In comparison to the standard procedure, which has been object of more studies, this single dose technique turned out interesting, inclusively in terms of savings for patients and for health systems. [34]

A study involving 9 children with GBS grades 3 and 4 on the Hughes scale were submitted to one single dose of 2 g/kg of immunoglobulin 10 days after symptom onset. This pilot study had a small sample size, but can be considered as the beginning of the discovery of the correct dose of this therapy. In all children, the progression of the disease was stopped, hospital stay shortened and all recovered complete mobility. Infusion rate was variable, but this dose proved to help the recovery of all patients with no adverse effects. This study concluded that this dosage is effective in improving the

clinical progression of children with GBS, even though further trials are needed to clarify the correct therapeutic regimen. [35]

In a different study, 7 children with a mean GBS score of 3.7 were subjected to a treatment of IgIV (0.4 g/kg/day) divided in 4-5 days. Six of the children received the dosage for 5 days as opposed to one of them, which only received for 4 days. The treatment was started from 4-22 days after the onset of symptoms. Five children improved 1 grade with the first week of treatment. The 3 children with grade 3 were walking without aid after 1 day of therapy. The other 4 children had a higher grade, so started to walk unaided on average 12.5 days after treatment initiation. Five children left the hospital with a score of 3 or less. Only one experienced a disease relapse. This child was submitted to the therapy 22 days after the onset of symptoms, as opposed to the other children, which were treated much faster. This study revealed the fact that quick intervention improves the efficacy of the treatment and also the outcome of patients. [36]

A study involving 23 children with severe GBS who had a grade 4 or higher on the Hughes functional grading scale, separated the patients into 2 groups: one group of 15 children that were submitted to a protocol of 1 g/kg of IgIV for 2 days; a second group of 5 were given supportive treatment and 3 of them received steroids. The group submitted to the immunological treatment needed between 4-35 days to improve one grade in the Hughes scale. On the contrary, the group that was not given such therapy needed between 40-60 days to achieve the same outcome. Furthermore, in the first group, patients were able to walk independently after 4-90 days, as opposed to 30-200 days of the group with no immunological therapy. [37]

A different study aimed to understand the effect of IgIV on GBS progression. A total of 18 children were studied and 9 were submitted to a 4-6 hours infusion of 1 g/kg of IgIV for 2 days. The other 9 children served as the control group. All the patients submitted to the treatment were able to walk independently after 7 days, as opposed to the control group, which took about 12 days. No side effects were reported, what points to the fact that this procedure is effective in changing the progression of this disease and is safe. [38, 39]

Thirty-three children admitted to the intensive care unit were studied, in order to understand if this intravenous therapy would help in their recovery process. Twenty-two children were given 0.4 g/kg of IgIV for 5 days, while 11 were used as a control group. After treatment, there was a reduction of the number of children that needed mechanical ventilation and intubation in the group receiving IgIV. Furthermore, 16 out of 22 children were able to improve one grade on the Hughes scale after 1 month and 15 were able to

walk after 3 months, compared with 2 and 4 in the controls respectively. This study showed the marked improvement of intensive care unit patients, which led to the shortening of their hospital stay. [40]

A study compared two different regiments in 50 children, divided in two groups: one of them received 0.4 g/kg of IgIV for 5 days and the other 1 g/kg for 2 days. There were no significant differences between these groups, which means that the dosage of 2 g/kg is the most important aspect, regardless of if a 2 day or 5 day protocol is implemented. [39, 41, 42]

One hundred and one children with Guillain-Barré Syndrome were studied over a 40-month period. All of them, except 8, were submitted to 2 g/kg of IgIV over a 2- or 5-day period. Sixteen experienced mild transitory effects, particularly fever, leukopenia and allergic reaction. Seven children suffered from a transitory limitation few weeks after the treatment. The follow-up had a duration of 288 days. By the end of that period, 75% of patients were symptom-free. When comparing with supportive treatment, patients which received IgIV had a faster recovery time. The time needed to walk unaided was affected by the maximum severity of the disease. The protein concentration on the cerebral spinal fluid and electrophysiological data did not have impact in the recovery time. Younger children and those infected with Coxsackievirus were symptom-free faster than other patients. [43]

A study published in 2009 discovered a correlation between serum IgG levels and the time to recovery of patients. More specifically, if the IgG levels after the first dose of treatment with IgIV were elevated, the recovery of the patient would be slower, comparing to the other patients, leading to a poorer outcome. So maybe a second dose of the therapy could improve the outcome in these individuals. This hypothesis is still being studied and investigated, but it could prove useful in the future, particularly in patients that do not respond to the first dose of treatment. [44]

A review compared the efficacy of IgIV and the timing of its administration. Thirty-four patients of mean age of 5.1 years were selected to enter the study. Of these, 11 only received supportive treatment, 3 received plasma exchange and 10 IgIV. The 10 patients submitted to immunoglobulin were divided into subgroups with two different time cut-offs. Initially, the study compared the efficacy of the treatment if given before or after 7 days of symptoms onset. Seven children were given the therapy within 7 days of the beginning of symptoms, while 3 were given after 7 days. Patients with early treatment improved faster in every category, when compared with patients submitted to the late treatment regimen. The 7 children needed on average 7.7 days to improve one grade,

as opposed to 9.0 days of children with the late treatment protocol. Furthermore, with early treatment children left the hospital on average after 17.4 days, as opposed to the 47.5 days needed by the other patients. Another time cut-off was tested, being early treatment defined as within 10 days of symptom onset and late treatment of that was implemented after 10 days. The early treatment group was formed by 8 children and the late by 2. The 8 children needed an average of 7.1 days to improve one grade, as opposed to 11.5 days by the other 2 children. Furthermore, the mean length of hospital stay in the early treatment group was 17.4 days, as opposed to 47.5 in the other group. In both definitions, the early treatment has proven to improve the motor recovery, while shortening the hospital stay, which confirms the necessity of giving treatment as soon as the symptoms appear. However, it is not clear if the optimal time of action is before 7 or 10 days. [45]

An Indian study compared the outcome of IgIV with supportive treatment at 3 and 6 months. In terms of motor recovery, mechanic ventilation and duration of hospital length, there were no significant differences between the two groups. So, this study states that, even though this immunological therapy is important in the short term, it has not proven to improve the outcome in the long term, arising the need for further research. [46]

Another study compared the efficacy of IgIV and of supportive treatment. This retrospective study selected 55 children, where 25 received the immunotherapy and 30 only a supportive intervention. The 25 patients received 0.4 g/kg/day for 5 days. Contradictory to other studies, there were no significant differences between the time of recovery of the two groups. Furthermore, the treatment group had a higher rate of mortality and of mechanic ventilation dependence. [47]

It is of the upmost importance to avoid over exposing the patient with IgIV. A 12-year-old child, diagnosed with GBS, was submitted to the standard course of intravenous immunoglobulin. After this procedure, the patient was transferred to another hospital, where 2 extra cycles took place. This led to treatment-related acute lung injury, which only improved with high-flow oxygen therapy. The overdose of IgIV could lead to iatrogenic respiratory failure, so it has to be monitored carefully in order to avoid similar events. [48]

5.3 Comparison between plasma exchange and intravenous immunoglobulin

After presenting each therapeutic strategy independently, it is important to review the literature comparing both, in order to understand which could be the best treatment approach for children diagnosed with GBS

A retrospective study which studied 35 children that were diagnosed with GBS over a 20 year span used both plasmapheresis and IgIV as a therapeutic option for the treatment of that condition. Of all the children that were treated with plasma exchange as a first line, 88% of them showed improvement. This therapy had a greater success rate than IgIV, with whom 70% of children showed improvement. This study´s result contradicts others, where IgIV is considered a better option or, at the very least, of equal efficacy than plasma exchange. [49]

A retrospective study was conducted with 62 children in order to determine which of the two immunological therapies could be the most favorable. Thirty children received a dose of 0.4 g/kg of IgIV for 5 days and 32 were submitted to 200-250 ml/kg of plasma exchange for 7-10 days. After the procedures were concluded, the patients treated with plasma exchange had a lesser need for ventilation and their hospital stay was inferior to the patients treated with immunoglobulins. Furthermore, complete recovery was achieved in patients treated with plasma exchange after 6 months and less side effects were reported, when compared with IgIV-treated patients. [50]

A study conducted over a period of 3 years submitted a group of 44 children with severe GBS, in need of mechanic ventilation, to either plasma exchange (21 children) or IgIV (20 children). The used protocols for the techniques were: 1 plasma exchange a day for 5 days and 0.4 g/kg of IgIV for 5 days. In terms of recovery of the motor function, there were no significant differences between the 2 groups. However, the patients submitted to plasma exchange revealed a shorter hospital stay and less need for mechanic ventilation. Both therapies did not provoke relevant side effects, highlighting the safety of these procedures. [39, 51]

A different study, published in 2001, compared the action of plasma exchange and IgIV in children. Even though the specific outcome measures for this study were not available, the children that received the immunoglobulin had a faster recovery of bulbar and respiratory functions than children that were submitted to plasma exchange, 17 and 30 days respectively. [39, 52] An adult study conducted in 1992 had the same objective of determining the efficacy of plasma exchange and IgIV in GBS. The authors submitted 2 groups of patients to either plasma exchange or IgIV. The first group received 200-250 ml/kg of plasma in 5 sessions between 7-14 days; the other group received 0.4 g/kg/day

of IgIV over a 5 day period. After the study, which analyzed 100 patients, 30% of plasma exchange-exposed patients took 4 weeks to improve 1 or more grades in the functional scale. Regarding the group exposed to the immunoglobulin, about 51% of patients took 4 weeks to improve 1 or more grades on the functional scale. After analyzing 150 patients, the plasma exchange group improved to 34% and the immunoglobulin group to 53%. The median time of recovery of 1 grade in the plasma exchange group was 27 days and in the immunoglobulin group was 41 days. In terms of independent walking, it took 55 days for the immunoglobulin patients to achieve that milestone and 69 for the plasma exchange group to do so. Another important outcome measure was the need for mechanic ventilation. In this study, 27% of immunoglobulin-treated patients and 42% of plasma exchange needed this artificial help. This directly contradicts other studies where plasma exchange patients had a lesser need for artificial ventilation. [48, 49, 51] Even though this study was conducted in adults and not in children, it is a study that compares in a randomized and controlled way the two main techniques that are used in this disease. This study ultimately concludes that IgIV is at least as effective as plasma exchange, if not more, in the treatment of GBS and is a very safe procedure. So, this conclusion can correlate with the effect that these therapies can have in children, making that article a true reference concerning the therapeutic approach of pediatric GBS. [53]

Few studies have been published in which there was a poor response to an initial treatment with plasma exchange or IgIV. A retrospective study identified 116 children diagnosed with GBS, in which patients received standard plasma exchange or IgIV, but 20 children did not recover their motor capacity and required another set of treatment. Of these 20, 7 received immunoglobulins 0.4 g/kg/day for 5 days and 13 received 5 exchanges of plasma over 1-2 weeks. Nineteen children served as the control group. These children were evaluated in terms of their Hughes score and length of hospital stay. The treatment group improved in the Hughes scale after 1 month of follow-up, when compared with the control group, but not after 3 and 6 months. Furthermore, the treatment group left the hospital, on average, after 55 days when compared with 11 days in the control group. Nearly 41% of children in the treatment group had a score of 4 or 5 after the rescue treatment. So, a second line of treatment is still not well established, if the first course of treatment proves to be unsuccessful. [54]

5.4 Combination of plasma exchange and intravenous immunoglobulin

After understanding the effects of plasma exchange and intravenous immunoglobulin, it is important to understand if the two combined can further improve the prognosis and recovery of patients with GBS. It is established that immunotherapy is an effective treatment, but there are still questions that need answering, primarily on the dose and timing of treatment in severe cases with poor outcome. Thus, if these two therapies have different mechanisms of action, shouldn´t they work even better if combined, in severe cases?

A randomized trial submitted 128 patients to a regimen of 5 plasma exchanges of 50 ml/kg followed by 5 days of 0.4 g/kg of IgIV after the last exchange. This had the intent of understanding if the two techniques combined prove to be better than each one alone. The primary outcome was to see if this combination was better in reducing the disability after 4 weeks of treatment. After the trial and subsequent follow-up period, this combination gave only a small advantage when comparing with the therapies alone. There were 3 secondary measures studied, time to independent walking, time to discontinuation of mechanic ventilation and rate of recovery. Of these 3, only time to independent walking did not reveal an advantage of the combined treatment This trial showed that combining both therapies does not seem to confer a significant advantage in GBS treatment. [55]

Nevertheless, there are some published case reports in which this concept of combination therapy is emphasized. A 3-year-old girl with suspected brainstem encephalitis was submitted to 400 mg/kg/day of IgIV. Three days after the admission, the patient experienced hemodynamic instability and the diagnosis of fulminant GBS was established. Despite the use of immunoglobulin, the patient did not improve. Plasmapheresis was initiated for the following 3 days with a replace rate of 30 ml/min. After the conclusion of the plasma exchange, a steroid therapy with methylprednisolone (20 mg/kg/day) was initiated for a period of 3 days. After this intervention, the patient was subjected to 400 mg/kg/day of IgIV for 5 days. The steroid therapy was repeated for 3 days from day 23 and 5 days of IgIV were given again from day 30. The clinical improvement of the patient started after the tenth day and by day 55 there were no neurological symptoms. So, a combination of supportive and immunological therapies was essential for the management of a fulminant case of GBS. [56]

In 2019, a new technique was presented in the treatment of severe GBS, the Zipper Method. Over the course of 7 days, 9 children were submitted to an alternate program of plasma exchange and IgIV. They received an exchange of 1.5 their plasma

volume on the first day. After this exchange was finished, they would receive right away 0.4 g/kg of IgIV. The second exchange had to be given 24 hours after the end of the immunoglobulin and not immediately. This process was conducted 5 times. This method was applied to children with poor outcome. In this study, children left mechanic ventilation after 7 days of treatment. If immunoglobulin was used alone, the mean time required for ventilation withdrawal was 26 days. In terms of plasma exchange, the time ascended to 29 days and with both combined (not using the Zipper Method) to about 18 days. Regarding the duration of hospital stay, if immunoglobulin was used alone, this period was on average 53 days. With plasma exchange it ascended to 63 days and in combination to about 51 days. With the Zipper Method, the hospital discharge was obtained after 18 days, on average. Besides hospitalization, nerve damage was an important outcome to be evaluated. In terms of ability to walk without help, the plasma exchange group took 49 days to do so, the IgIV group took 51 days and the combination of both, without using the Zipper Method, took 40 days. With the Zipper Method, patients were able to walk unaided after 24 days, on average. Furthermore, all patients submitted to this novel treatment approach were able to walk independently. On the contrary, after 48 weeks, 16.7% of patients only given plasma exchange were not able to walk unaided. In the group that received IgIV, 16.5% were also not able to walk without help after 48 weeks. When combining both (not using the Zipper Method), 13.7% of patients were not able to walk unaided after 48 weeks of follow-up. [3, 50] In this study there was no mortality observed. The mortality in pediatric patients is under 10%. Even though this study had a small sample size, the fact that there was no mortality is an encouraging sight and a good omen for the future of this therapeutic approach. The only potential negative effect associated with this technique is the cost of using both interventions. However, it can be stated that by increasing the time of recovery and decreasing the need for mechanic ventilation, it may limit the cost of hospitalization and be more cost-effective that each one of the techniques alone. [3]

5.5 Immunomodulation and alternative treatments

During the acute phase of GBS, there is a decrease of TGFß-1 and this points to the possibility of an immunomodulation approach to this disease, since agents like Interferon-beta can be used to stimulate the production of this cytokine. [8, 57]

A 51-year-old man who suffered from motor impairment was diagnosed with GBS and started immediately the treatment with IgIV (0.4 g/kg between day 3 and 8). During this period, the neurological condition of the patient deteriorated, so a dose of Interferon-beta was started on the 14th day. On the 21st day, there was no clinical response, so was initiated a course of immunoglobulin and Interferon-beta at the same time during 5 days. After this process, the condition of the patient dramatically improved and Interferon-beta was stopped after 52 days. After 66 days, the patient revealed a full recovery. This is, of course, a small sample size, but it suggests that the combination of an immunotherapeutic approach with Interferon-beta may have positive results in the outcome and recovery of patients. [57] However, more studies are required, in order to fully understand how this therapeutic approach may fit in the paradigm of GBS treatment.

And this is also true for a different intervention, which is illustrated by a different case report, in which a 58-year-old man developed a GBS after an allogenic transplantation of stem cells. After the diagnosis, the patient was submitted to a treatment with 500 mg/kg/day of IgIV for 4 days. However, his condition worsened and he developed quadriplegia, needing to be ventilated. A month later, he repeated the process, but still with no results. Forty days after the diagnosis, an infection by Epstein Barr virus was detected, which was treated with a dose of 375 mg/m^2 of Rituximab once a week, for 4 weeks. After this treatment, the patient regain some muscle strength and, after the second dose, his muscle strength was 3/5. By the last dose, his strength was 4/5. Shortly after, the patient was removed from the mechanical ventilation. This therapy is said to be effective, because it prevents the action of antiganglioside antibodies, by removing B-cells and not allowing axon damage. [58]

A review published in 2017 comprised the biological approach to the treatment of this disease including studies in animals and humans. Animal studies proved that by modulating the complement, T-cells, monocytes, cytokines and autoantibodies there was an improvement in clinical manifestations of the disease. However, in adult studies not all the drugs tested proved to be efficient in dealing with T-cells activation (Anti-T cell monoclonal Ab (OK3) or cytokine production (Interferon β + IgIV). There are no studies exploring these possibilities in children. [59]

In low-income countries, where plasmapheresis and IgIV might be of difficult access, exchange transfusion was implemented as an alternative treatment. This process consists of replacing red blood cells of the patient that are saturated with immune complexes with red blood cells of donors. A 6-year old boy was admitted with progressive motor weakness on the lower and upper limbs. Due to the unavailability of standard procedures, he was submitted to 60 ml/kg of exchange transfusion. Motor limitation started to improve after 2 days and independent walking came after 8 months. However, 16 months after the first episode, the patient experienced similar symptoms and was subjected to 2 exchange transfusions. The patient motor response started after 36 hours and independent walking came after 7 months. So, even though the success was not the same as with standard techniques, exchange transfusion proved to be an alternative to standard procedures, when unavailable. [60]

6. Discussion

GBS is an autoimmune disease that targets the peripheral nervous system, leading to demyelination and alteration of peripheral nerve conduction. As such, this will cause reflexes abnormalities, muscle weakness, autonomic failure and respiratory complications that can lead to death. [1, 2, 4, 6] Thus, it requires an assertive treatment approach that can eliminate the produced autoantibodies or block the B-cells responsible for their production. In this context, 2 techniques are available: plasma exchange and IgIV administration.

Plasma exchange emerged in the 1980s and has proven to be an effective treatment in severe cases of childhood GBS, by accelerating motor recovery, reducing hospital stay and the need for mechanic ventilation. [20, 21, 22, 23, 24, 25] The ideal dosage for this therapy is stated in several articles as 5 exchanges of a total of 250 ml/kg for 7-14 days. [1, 2, 9, 10, 23] The amount of exchanges is a critical point, because more exchanges than necessary may lead to hemodynamic instability. [1, 2, 23] Regarding treatment initiation, the timing is still not clearly defined, because some studies state that it should be given within 7 days of the onset, but other reports say that 7 days is not a strict timepoint. [25] This technique has proved to be effective, however it is not the first line of treatment, due to the necessity of trained personnel and specific equipment. Furthermore, this therapy is not safe for children under 10 kg of weight, due to their low blood volume, which can lead to hemodynamic instability. [26, 27] At this time, this therapy is used in severe cases, in which it proved its efficacy. However, more research is needed to shed a better light on the subject, particularly on the matter of safety of this therapy, with the goal of preventing hemodynamic instability (particularly in children) [1, 6, 28]

IgIV is the first-line treatment for this disease, because of its efficacy, accessibility and safety. Even though an early study [33] showed the effectiveness of a single dose of 1 g/kg of immunoglobulin, several studies state that the dosage determined to be the most effective is 2 g/kg, for 2-5 days. This can be administered as a single dose of 2 g/kg or 0.4 g/kg for 5 consecutive days. Thus, the dosage is set, independently of the duration of the treatment. This technique proved to improve motor recovery, to shorten hospital stay and the need for mechanic ventilation. [31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42] In terms of safety, it has proven to cause less side effects and hemodynamic instability. For maximum effectiveness, it should be given within 2 weeks of the onset of symptoms. [1, 30, 31] The several studies presented prove that this therapy is a good treatment option in pediatric GBS, particularly in severe cases, being safe and accessible. One study [47]

contradicted these findings, however, being only one study, results should be interpreted with caution. This treatment has to be carefully monitored, in order to prevent iatrogenic lung injury and several minor complications associated, mainly due to hemorheological effects of immunoglobulins. [48] More studies are required in the future, in order to determine how this treatment can further improve the outcome of children, in the long term. [46]

Regarding the comparative effectiveness of the two approaches, it appears that both treatments are effective in speeding the motor recovery process of these patients. However, it is not clear which therapy is more effective, because different studies present different conclusions. Equally, there is not a unanimous conclusion regarding the need for mechanic ventilation. Most articles state that plasma exchange reduces the need for artificial ventilation [49, 50], which is contradicted in the van der Meché et al 1992 article. One thing in that all articles agree is that IgIV is a very safe treatment option, as well as very accessible. On the contrary, plasma exchange is a more expensive method, which requires trained personnel and technical support. Furthermore, this technique is not as safe as immunoglobulins, especially in children under 10 kg, due to their low blood volume and potential hemodynamic instability, which makes the exchanges a very difficult process. [1, 6, 30, 53] One point that needs to be clarified is when the first line of treatment is not successful, what should be the correct approach. A study [54] states that the patients submitted to a second course of therapy had a lengthier hospital stay and slower motor recovery.

There are not many studies where both plasma exchange and IgIV are used simultaneously. In one of the few early articles [56] there were no significant differences between using each technique alone or in combination. However, in fulminant GBS, the combination of both immunological therapies and supportive treatment are essential in the management of the disease. [56] In 2019, an innovative article was published, where it was stated that using both therapies intercalated would be a better option than using each one alone. In this study, patients had better results in every parameter, when comparing with each therapy alone. This suggests that using this method might be the best way to treat children with severe GBS, because it will accelerate their recovery and ability to walk, reduce their hospital stay, nerve damage and necessity for mechanic ventilation. [3] However, more studies are required in order to implement this protocol as the standard procedure in children with severe cases of GBS.

Immunomodulation in GBS is still an area where there is little research, particularly in children, but studies in adults and animals reveal what it could be a

possible treatment, in the future. [57, 58, 59] In low-income countries, exchange transfusion has presented some results as a good alternative method. However, more studies are required in order to better characterize this therapeutic approach. [60]

7. Conclusion

Plasma exchange and IgIV infusion are two interesting, effective and generically safe therapeutic approaches in pediatric GBS. There are no data suggesting a clear superiority of one of them in children, so their use in clinical practice is essentially related to the greater or lesser experience of clinical teams in the field. However, it has recently been pointed out that both techniques may be used interchangeably in the same patient, with better results than if they were used separately. Further studies will be needed to fully demonstrate this, but it may be a solution, at least to the more dramatic cases of GBS we encounter in daily clinical practice.

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