REVIEW ARTICLE

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Guillain-Barré syndrome in childhood – what we know and where we are? A therapeutically difficult problem

Magdalena Chrościńska-Krawczyk[1,F] ✉, Aleksandra Ziółkiewicz[1,D], Aleksandra Jartych[1,D], Ilona Jastrzębska[1,D], Karolina Jankowiak[1,D], Agata Miecznikowska[1,D], Dominika Michalska[1,D], Agnieszka Cichocka[1,D]

[1] *Department of Child Neurology, University Children's Hospital, Lublin, Poland*
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Abstract

Introduction and Objective. Guillain-Barré syndrome (GBS) is a complex clinical entity with an autoimmune basis. It is considered the most common cause of acute neuromuscular paralysis in children. The incidence of GBS is approximately 0.34 per 100 000 cases annually, with a higher prevalence in the male population. The cause of the incidence is considered to be a complication of infection or vaccination.

Review Methods. The studies cited in the presented review were selected from PUBMED. The key words used for the search included: 'Guillain-Barré syndrom', 'Guillain-Barré treatment', and 'Guillain-Barré therapeutic methods'. Articles not written in English, conference abstracts only and duplicated papers were excluded.

Brief description of the state of knowledge. In the 19th century, abnormalities in albimuno-cytological dissection were considered to be the cause, but today diagnostic criteria have evolved. The most important element in the diagnosis of patients is the analysis of cerebrospinal fluid and nerve conduction studies. Possible pathogens that may cause symptoms of the disease include viruses such as Epstein-Barr virus, varicella, cytomegalovirus, and SARS-CoV-2. GBS manifests itself with numerous neurological and cardiovascular symptoms, including bilateral limb weakness, facial paralysis or cardiac arrhythmias. Patient treatment includes immunotherapy immediately after diagnosis.

Summary. GBS is a rapidly progressive and difficult to treat clinical entity. It is important to make a timely diagnosis and immediately implement therapy to reduce the risk of death. Further clinical research is needed to find new therapeutic options for young patients.

Key words

immunotherapy, Guillain–Barré syndrome (GBS), autoimmunology

INTRODUCTION

Guillain-Barré syndrome (GBS) is an immune-mediated disease and is considered the most common cause of acute neuromuscular paralysis in children since the elimination of poliomyelitis [1]. GBS disease was first described in 1859 from the cases of two soldiers. At that time, the emphasis was on ascending paralysis and abnormalities of albumin-cytological dissociation. Since then, the diagnostic criteria have been significantly developed and are based on clinical analysis, cerebrospinal fluid findings, and nerve conduction findings [2]. Currently, the global annual incidence of GBS ranges from 0.34/100,000/year to 1.34/100,000/year. The disease is slightly more common in males [3, 4].

No clear cause of GBS infection has been established, but patients have been shown to report frequently after infection (usually six weeks after infection) or vaccination. There are also pathogens that are considered to trigger GBS, among which can be distinguished: Epstein-Barr virus, chickenpox, cytomegalovirus, SARS-CoV-2, Mycoplasma Pneumoniae, and Campylobacter jejuni [4, 5]. GBS can occur in people at any age. In children, in most cases, GBS has a self-limiting course and recovery occurs spontaneously [3]. The main symptoms that can be observed in small patients are bilateral limb weakness, sensory deficits, hyporeflexia, facial paralysis, ophthalmoplegia and ataxia, allodynia [6]. In addition, there are cardiac symptoms in this arrhythmia [3]. The first symptoms that can be observed are on the hands and feet, and then include the upper body and shoulders [7, 8]. Patients have a rapid progression of symptoms which peak within the first two weeks. After that, patients enter a plateau phase (which can last up to six months) and then begin to recover [9]. However, some patients experience treatment-related fluctuations [3]. During the acute phase of the disease, about 15% of patients develop respiratory muscle attacks and may require artificial mechanical ventilation [7, 10].

Symptoms. The most common cause of acute flaccid paralysis in children is Guillain-Barré syndrome [11]. There are reported cases of the disease progressing quickly, leading to a complete destruction of the body within 14 days. Until now, it has been thought to be a demyelinating disease, but numerous studies have shown that it has both axonal and

✉ Address for correspondence: Magdalena Chrościńska-Krawczyk, Department of Child Neurology, University Children' Hospital, Gębali 6, 20-093 Lublin, Poland; E-mail: magdalenachk@wp.pl

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focal variants. Clinical and neurophysiological criteria enable division of the Guillain-Barré syndrome into two subtypes:
1) Subtype AIDP – acute inflammatory demyelinating polyradiculoneuropathy, in which demyelination of nerve fibres and neuritis occurs.
2) Subtypes AMAN and AMSAN – acute axonal motor neuropathy, acute motor sensory neuropathy; demyelination and axonal damage features accompanied by generalised weakness [13].

All variants are characterised by symmetrical weakening or loss of pro-prioceptive muscle reflexes, which progress rapidly and intensify over time [13].

Focal forms of Guillain-Barré syndrome, which are extremely rare in childhood, include Miller Fisher syndrome (MFS) and the throat-neck-shoulder variant. Miller Fisher syndrome is characterised by lower palsy of the cranial nerves and facial nerve, ataxia and areflexia, while pharyngeal-cervical-shoulder weakness is predominant in pharyngeal and cervical area [13].

Guillain-Barré syndrome is an autoimmune disease characterised by the acute onset of symmetrical flaccid paralysis, often accompanied by respiratory and autonomic dysfunction, which can be fatal. Early treatment can shorten the duration of the disease and reduce the mortality rate. The correct diagnosis of Guillain-Barré syndrome in children is difficult due to the need for more complex and precise neurological examination. Diagnosis is further complicated by less pronounced symptoms in younger children. In addition, young children are often unable to describe symptoms, such as weakness, especially when pain appears before weakness and can mask the underlying symptom[11].

Guillain-Barré syndrome is associated with a previous infection that the patient had a few weeks earlier [11,12,13,15]. Illnesses peak in the second year of life, which may be due to campylobacteriosis, a risk factor for Guillain-Barré syndrome. There is also a possible relationship between age and the axonal form of the disease. Reported infections also include Mycoplasma pneumoniae and cytomegalovirus [13,16]. Vaccinations against Rabies and Polio increase the risk of falling ill. New studies also report a possible increased risk after vaccination against COVID-19 [12].

One of the most common symptoms in children, often requiring treatment, is pain. This includes muscles, joints and neuropathic pain, localised in the lower extremities and back. Differential diagnosis should take into account other possible causes, including orthopaedic or rheumatological, as well as neurological (meningitis and myositis) causes [11]. In most patients, the first symptom is neuropathic pain, which includes numbness of the distal limbs, hypersensitivity and hypoaesthesia. Another important symptom is weakness. Due to weakness in the peak period of the disease, 3/4 of paediatric patients are no longer able to walk, and 1/3 suffer from tetraparesis. The gait of young children may be unstable and make it difficult to diagnose the syndrome [11, 14, 15]. Symmetrical, progressive flaccid paralysis first affects the lower extremities and then proceeds to the shoulders. Other types of nerves, such as sensory, cranial and autonomic, may also be affected. In a small number of children with Guillain-Barré syndrome, normal or increased tendon reflexes can be observed [17].

Although autonomic disorders are rarely diagnosed, they are common in children and include hypertension, arrhythmias, orthostatic hypotension, urination disorders and constipation. For this reason, it is necessary to monitor the functioning of these organs, as well as blood pressure and pulse. Patients also complain of excessive sweating. In about half of the patients, cranial nerve involvement occurs in the form of paralysis, facial nerve palsy, and epididymal weakness. This is associated with severe muscle weakness in children with this syndrome [16]. Some patients have difficulty breathing and even require invasive mechanical ventilation. Some require tracheostomy [17].

Miller-Fisher syndrome may include acute atactic neuropathy, acute ocular paralysis, acute eyelid drooping and acute mydriasis. Patients who have been tested for additional involvement of the reticular system causing altered consciousness and hypersomnolence have a subtype of central nervous system known as Bickerstaff's brainstem encephalitis. However, there is no weakness of the limbs [17].

The pharyngeal-neck-arm variant of Guillain-Barré syndrome is characterised by weakness of the neck, laryngeal and arm muscles. There are problems swallowing food, nasal intonation of the voice, the vomiting reflex may be impaired, difficulty in breathing and speaking [10]. It is possible that the subtypes of Guillain-Barre syndrome overlap [18].

The Erasmus GBS Outcome Score (EGOS) and Modified EGOS Scale (mEGOS), as well as the Erasmus GBS Respiratory Insufficiency Score (EGRIS), are used to determine prognosis in order to select appropriate therapy for patients with Guillain-Barré syndrome. The EGOS and mEGOS are used to predict independent fitness at six months, and the EGRIS is used to predict the need for mechanical ventilation within a week [15,19].

Diagnostic process. The basis for a well-established diagnosis is a properly and thoroughly performed physical and physical examination of the patient and the performance of additional tests. The Brighton collaboration has developed diagnostic criteria for Guillain Barré syndrome, which include limb weakness with symmetrical symptoms on both sides of the body with additional loss of deep tendon reflexes. According to the criteria, the course of GBS should be monophasic. The result of a diagnostic lumbar puncture in this disease shows an elevated protein level in the cerebrospinal fluid (CSF) without abnormalities in the number of CSF cells, known as albuminocytologic dissociation [20]. A normal CSF protein level is not a factor in ruling-out a diagnosis of GBS, as it is normal in up to 50% of patients in the first week of illness [21]. Patients with GBS should have nerve conduction examinations that show abnormalities consistent with demyelinating polyneuropathy [20]. Electrodiagnostic studies may show pathological changes, such as decreased conduction velocity, reduced evoked amplitudes (both sensory and motor), various temporal dispersions, partial conduction blocks and a 'sagittal nerve sparing pattern'.

During the first week of illness, measurements may be normal. The results of a test repeated after two weeks can help make the diagnosis. In some clinical variants of GBS, electrodiagnostic test results may be normal regardless of when the test was performed. Some subtypes of GBS can be distinguished based on this test [21]. According to the Bringhton criteria, it is necessary to exclude alternative causes of such symptoms. The onset of GBS may be preceded by a gastrointestinal infection, upper respiratory tract infection or vaccination [20].

It is speculated that under the influence of an abnormal immune response, molecular mimicry results in cross-reactivity with gangliosides present in nerve axons. In laboratory tests, AGA (anti-ganglioside antibodies) are found in the blood serum of some GBS patients, especially in AMAN (acute axonal motor neuropathy), AMSAN (acute axonal motor-sensory neuropathy) and MFS (Miller-Fisher syndrome). These antibodies can be detected by enzyme-linked immunosorbent assay (ELISA) or line/dot test [22]. Other laboratory tests are helpful in the differential diagnosis, such as glucose, electrolytes or complete blood count.

Additional criteria to confirm the diagnosis according to National Institute of Neurological Disorders and Stroke (NINDS) include:
– disease progression lasting several to 28 days;
– minor sensory symptoms;
– symptoms suggestive of canial nerve involvement;
– autonomic system dysfunction [21].

Based on the Brighton criteria, four degrees of diagnostic certainty were distinguished. Patients meeting all diagnostic criteria were classified in the first degree of diagnostic certainty. According to a study involving 67 participants, almost all children with a diagnosis of GBS met the criterion of limb weakness in the form of tetraparesis or lower limb paresis. In each case, it was eventually accompanied by decreased reflexes, and the monophasic course of GBS occurred in 97% of cases. Full manifestation of the disease developed within four weeks of the onset of symptoms. The average time from onset of symptoms to lumbar puncture was four days. Cerebrospinal fluid samples showed elevated protein levels in 77% of children and mild pleocytosis (mainly up to 20 leukocytes/μl) in 47%.

Nerve conduction studies showed changes characteristic of polyneuropathy in 91% of the patients. In 60% of cases, the results suggested acute inflammatory demyelinating polyneuropathy [23]. Typical changes for AIDP include slowed motor and sensory nerve conduction, and high F-wave latency or conduction block [24]. The average time from onset of symptoms to nerve conduction study was nine days. Most children met the Brighton criteria and had similar symptoms to adults [23].

In addition to the standard procedure according to the guidelines, studies have been conducted on the use of other diagnostic methods. These may be helpful, especially in children in whom nerve conduction studies are not possible. Further observations on larger groups of patients are needed in connection with these studies.

An additional test that can be performed in patients with GBS is nerve ultrasonography. Ultrasound examinations of the ulnar nerve and median nerve were performed on a group of 21 patients which showed enlargement of the nerve in at least one location in 50% of GBS patients during the acute phase of the disease, and in 60% of patients after the acute phase. Diffuse nerve enlargement was observed in only one patient. In 43% of cases, the enlarged nerve site was the proximal part of the median nerve. Most patients with GBS do not have enlarged nerves or have only mild enlargement. Ultrasound changes may persist despite treatment. This test has the potential to help diagnose and control the course of the disease [25].

High-resolution sonography can also be potentially useful in the diagnosis and appropriate treatment of polyneuropathy as an inexpensive, simple and non-invasive procedure. In a study of 17 patients with GBS, 86% had enlargement of peripheral nerves – either the ulnar nerve or the median nerve [26]. In addition to swelling in the affected nerves, activation of the complement system and increased numbers of macrophages can be observed [20].

Another test that can help with the diagnosis is gadolinium-enhanced spinal magnetic resonance imaging (MRI). In seven of eight children with GBS studied, the test showed spinal nerve root enhancement after gadolinium. The effectiveness of the results was comparable to that of CSF and nerve conduction studies (NCS) analysis. In addition, MRI allows visualisation of some diseases from the differential diagnosis, such as spinal cord compression. Unfortunately, anaesthesia is often required to perform MRI in children [27].

The differential diagnosis of GBS should include diseases of the central and peripheral nervous system (such as inflammation, infection, malignant neoplasm, compression), anterior horn cell dysfunction, nerve root injury, neuromuscular junction or muscle disease, and vitamin deficiency.

Admission to the intensive care unit may be necessary when:
– limb weakness progresses rapidly;
– the patient has great difficulty swallowing, or severe autonomic dysfunction;
– respiratory failure develops;
– EGRIS >4 (Erasmus Guillain-Barré Syndrome Respiratory Insufficiency) [20].

Treatment. According to current knowledge, there are only two clinically supported treatment options for children with GBS – plasma exchange (PE) and intravenous immunoglobulin infusions [28]. The indication for starting treatment with either of these options is the patient's inability to walk 10 meters on his own [29]. Such immunomodulatory treatment is appropriate for any GBS subtype, even focal variants [28]. Undoubtedly, supportive treatment should also be considered, especially in severe cases with rapid progression or respiratory involvement, when patients may also require mechanical ventilation and initial therapy [1,3].

Plasma exchange is effective due to the removal of circulating auto-antibodies and inflammatory factors that are responsible for neuronal damage. As a result of this process, immune molecules and essential plasma components are eliminated, which can cause numerous side-effects, such as hypocalcaemia, haemodynamic instability, dilutional coagulopathy and allergic reactions [30]. However, its effectiveness outweighs its potential risks, especially when used for strict indications and under special control. The recommended treatment regimen is 200–250 ml/kg body weight in five sessions, and should be implemented within four weeks of the onset of symptoms [6, 31].

An alternative treatment for PE is intravenous immunoglobulins (IVIg), the mechanism of action of which affects the immune response by blocking circulating plasma auto-antibodies, modulating the action of B lymphocytes, NK cells and macrophages, and reducing the production of inflammatory cytokines [29]. Standard treatment includes immunoglobulin infusions at a dose of 04 g/kg for five days and should be started within two weeks of the onset of symptoms [6]. Studies show that IVIg speeds-up recovery, but there is a need for further testing in children [29].

Corticosteroids are not an appropriate treatment for GBS because there is insufficient evidence of their effectiveness

Table 1. Table of GB syndrome.docx (26.13 kB)

	AIDP	AMAN	ASMAN	Miller-Fisher syndrome
Pathogenesis	demyelination of nerve fibres and neuritis	axonal demyelination features	axonal demyelination features	lower cranial nerves and facial nerve palsy
Main symptoms	symmetrical weakness of the muscles of the lower limbs with impaired or absent deep reflexes muscular paresis of a flaccid nature involvement of the facial area - facial nerve palsy in 25%, the phrenic and intercostal nerves were involved surface sensation disorders in the form of paresthesia of the toes autonomic disorders (usually arrhythmia)	clinical picture similar to AIDP respiratory failure more common in the axonal type of the disease, rarely, cranial nerve involvement. no sensory disturbances.	clinical picture similar to AIDP respiratory failure more common in the axonal type of the disease, rarely, cranial nerve involvement. sensory disturbances..	external ophthalmoplegia limb and gait ataxia areflexia weakness of the face and bulbar muscles (impaired facial expressions, speech and swallowing disorders)
Process	clinical symptoms increase within 1 - 4 weeks from the first signs of the disease; peak of severity in the first 2 weeks	severe course of the disease	severe course of the disease	mild course of the disease

[1]. In addition, there are studies that have shown that corticosteroids do not significantly speed-up recovery [3]. Due to the high impact on the immune system and the many possible consequences of its use, this form of therapy should not be considered standard treatment. Interferon-beta 1a has also been considered as a possible form of treatment, but its efficacy is similar to corticosteroids [28].

DISCUSSION

Since the elimination of poliomyelitis, GBS has become the predominant cause of acute flaccid paralysis in all age groups. However, it is important to state that the incidence of GBS increases with age, with a recent study showing a 20% increase in GBS cases with each additional 10 years of a person's age [31,32]. Several studies have shown that GBS in children peaks at two years of age [11,33,34].

GBS infection causes an increase in prevalence in males that is non-specific for autoimmune diseases. Studies suggest that this prevalence may be due to gender-related heterogeneous differences, such as in immunopathogenic mechanisms and immunosenescence. In the paediatric population, there is less disproportion associated with the predominant gender prevalence of the disease, and is related to the pre-pubertal age of the patients [13,36]. However, most studies show no significant correlation between gender and the course, complications, and mortality of the disease [33,35].

Among the symptoms of GBS, a distinction is made between axonal and focal forms.

AIDP is the predominant GBS variant in North America, Europe, the Middle East, Oceania and, in some studies, Asia [36]. It accounts for up to 90% of all paediatric GBS cases in Europe and North America and 32–67.4% in Asia [36,38]. Although AMAN is widely recognized as the second most common form of GBS in the Western world, it has historically been associated as the most common form in Asia, particularly in China (60–86% of all paediatric GBS cases) [39].

Based on the variable history, symptoms, course of disease and differences in required treatment, it is crucial to perform an appropriate diagnosis and identify the GBS variant in each patient. AIDP is more commonly associated with upper respiratory tract infection and in the axonal variants [38, 40]. The axonal forms, on the other hand, occur in gastrointestinal infections and are characterised by rapid onset, variable recovery time and hyperreflexia [38, 39, 41]. In the adult population, there are other causes of GBS, such as cancer or previous surgery [11]. Previously, it has been speculated that vaccinations such as influenza, polio, human papillomavirus (HPV), measles, mumps and rubella (MMR), rabies and COVID-19 may cause GBS [42, 43].

Axonal forms of GBS are thought to be more severe than AIDP or MFS. Children with the axonal variant are more likely to require admission to an intensive care unit, the use of a ventilator and a longer hospital stay [1, 33,36]. Chiu et al. report that the prospect of full motor recovery was 75% for patients with AMAN/AMSAN, compared to 87.1% for AIDP and 100% in MFS [36]. This observation is consistent with studies conducted in other clinical centres [37,40]. Reports have suggested that residual syndromes were observed only in patients with AIDP [38]. However, most studies indicate that the overall recovery rate in GBS in children is quite good for all subtypes, and significantly higher than in adults [14,36,38]. The estimated mortality rate among children is 3–4% [44].

It has been suggested that the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) are more appropriate for diagnosing GBS because they include both typical and atypical GBS variants [21,23]. The EGOS, mEGOS and EGRIS scales have been shown to be reliable in predicting the outcome of paediatric GBS in one study in China, but further studies are needed to confirm these findings [45].

A thorough performance and evaluation of numerous laboratory tests is necessary to make a correct diagnosis. Protein and pleocytosis levels on CSF examination remain important in the diagnosis of GBS, even if abnormalities are not always present. Electrodiagnostic methods, although included in the Brighton criteria, are not considered crucial in the diagnostic process. It should be mentioned that it is difficult to perform such tests, especially in children, and in the case of MFS, the results are often normal. Blood AGAs level tests are known for their limited usefulness; positive results are helpful for diagnosis, but negative results do not rule out GBS [20]. Positive results are usually found in MFS (90–100% of cases) [20,35]. Gadolinium-enhanced MRI and nerve ultrasound appear to be new, non-invasive diagnostic methods, but both require further study [21,25,26].

In the currently known treatment options, IVIG – intravenous immunoglobulins – appears to be a better first-line method for treating GBS in children, as it causes less discomfort and complications than plasmapheresis, although both methods have been shown to be safe and effective. The standards used in adults are also applicable in children [20]. There are reports of IVIG-resistant patients with a positive response to plasma exchange, corticosteroids or rituximab, but these are isolated cases or small-group studies [14].

CONCLUSIONS

Guillain-Barrė syndrome is a diagnostically complex clinical entity with a difficult treatment process in which the prognosis of the patient varies from case-to-case. Careful adherence to international guidelines is essential throughout the clinical care of the patient. However, more thorough clinical research is needed to improve the treatment model for patients.

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