

## Guillain-Barré Syndrome and Hydrocephalus in an infant with Wiskott-Aldrich Syndrome

### Síndrome de Guillain Barré e hidrocefalia en un lactante con Síndrome de Wiskott Aldrich

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#### What do we know about the subject matter of this study?

Guillain-Barré syndrome (GBS) is the most common acquired neuropathy in pediatrics, however, it has rarely been reported in infants under one year of age. Moreover, its association with Wiskott-Aldrich syndrome (WAS) has been presented previously in only two children.

#### What does this study contribute to what is already known?

This article presents the third case of an infant with associated SWA and GBS, with good response to intravenous immunoglobulins. It is important to have a high suspicion degree of GBS in infants with SWA who have acute flaccid paralysis.

#### Abstract

Guillain-Barre Syndrome (GBS) is rarely diagnosed in the first year of life. The association of GBS with Wiskott-Aldrich syndrome (WAS) is even less frequent and has been previously reported in only two children to our knowledge. Hydrocephalus is a known but rare complication of GBS. **Objective:** To describe the case of an infant in which GBS, WAS and hydrocephalus appear clinically associated. **Clinical Case:** A nine-months-old male infant with a history of WAS was admitted to our ICU with acute hypotonia and poor general condition. He developed flaccid paralysis, absent deep tendon reflexes, and respiratory failure. A lumbar puncture showed albuminocytologic dissociation. GBS was suspected and an electromyography was performed, showing a demyelinating polyneuropathy. He was successfully treated with intravenous immunoglobulins. During hospitalization, he presented intermittent bradycardia, so a brain CT scan was performed, showing acute hydrocephalus which was

#### Keywords:

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managed through an external ventricular drain achieving favorable response. In the long term, the patient underwent bone marrow transplant and had to be reoperated due to valve-related complications. However, his psychomotor development is normal, with no obvious neurological sequelae. **Conclusion:** We present the third case of GBS in a patient with WAS, which is the first infant younger than one year. Additionally, he presented acute hydrocephalus as a complication of GBS. We suggest considering these three comorbidities since their early diagnosis and prompt management allow better neurological recovery and avoid potentially lethal complications.

## Introduction

Guillain-Barré Syndrome (GBS) is the most common acquired polyradiculoneuropathy in both pediatric and adult patients, with a 0.6:100,000 incidence per year in adults<sup>1</sup> and in children under 10 years<sup>2</sup>. However, in infants under 12 months, its incidence is unknown and limited to case reports<sup>3</sup>. It is an autoimmune condition due to antibodies directed against spinal roots and peripheral nerves, often secondary to an infectious condition<sup>4</sup>. There are demyelinating, axonal, and variant forms.

Wiskott-Aldrich syndrome (WAS) is a rare x-linked primary immunodeficiency, characterized by microthrombocytopenia, eczema, infections, and an increased risk of autoimmune manifestations and neoplasms<sup>5,6</sup>. The WAS incidence has been estimated at less than 1-10 in 1,000,000 live male births<sup>6,7</sup>. This results from mutations in the Wiskott-Aldrich syndrome (WAS) gene that encodes the Wiskott-Aldrich syndrome protein (WASP), which is involved in adaptive and innate immunity processes<sup>8</sup>.

Although WAS is often associated with dysimmune disorders, there are only two previous reports of children with GBS as an associated comorbidity<sup>9,10</sup>. The following is a third child in which WAS, GBS, and additionally acute hydrocephalus were associated.

## Clinical Case

### *Perinatal and medical-surgical history:*

Male infant with WAS genetically documented by the presence of a pathogenic variant in the WAS gene (c.27\_28insC, p.Pro10Profs\*26). The patient was treated with immunoglobulin 0.5g/kg monthly and platelet transfusions as needed. He achieved sitting independently at 6 months, and his psychomotor development was normal until 8 months of age.

### *Clinical presentation, initial study, and management:*

The patient was admitted to the intensive care unit at 9 months of age on an elective basis, for the administration of his monthly immunoglobulin treatment.

However, he presented a 1-month history of poor general condition, sitting ability loss, decrease in weight and height increase, and decreased food intake. During this period, he consulted a dietitian, who requested videofluoroscopic swallowing study and catheterized specimen urine culture, increased caloric intake and set a date for his check-up. Due to persistent symptoms in the check-up, it was suggested to hospitalize him for study and intensive management, which was postponed due to lack of available beds.

In the admission evaluation to the intensive care unit, the patient was in poor general condition, irritable, dehydrated, with polypnea, tachycardia, and toxic appearance, and he had lost 230 grams five days before hospitalization. Due to his severe condition, septicemia was suspected, thus laboratory tests were performed showing white blood cells count 20,620/ul, C-reactive protein 91mg/L, and negative direct viral immunofluorescence (respiratory syncytial virus, adenovirus, parainfluenza viruses 1, 2, and 3, and influenza type A and B). In addition, cultures of blood, urine, and cerebrospinal fluid were requested and broad-spectrum antibiotic treatment was indicated with ceftriaxone and vancomycin due to suspected bacterial meningitis.

On the first day of hospitalization, his clinical condition worsened, highlighting on neurological examination global hypotonia, reduced head control and sitting ability, and deep tendon reflexes with active response, which was attributed to ongoing sepsis. Due to ventilatory impairment, the patient required invasive mechanical ventilation. Lumbar puncture was performed showing clear liquid, but with increased pressure, no leukocytes, Gram staining without bacteria, glucose 70 mg/100 ml, and protein 2.27 gr/L. Initially, these high CSF protein concentrations were interpreted as encephalitis and a CT scan was requested where ventriculomegaly was observed due to brain atrophy (Figure 1-A). The cultures requested at admission were negative.

Due to the improvement in ventilatory parameters, the patient was extubated on the 4th day of hospitalization and sedation was suspended. However, he developed poor respiratory mechanics, requiring reintu-

bation. At the same time, there was a reduction of the deep tendon reflexes of the upper limbs and areflexia in the lower ones, therefore, the lumbar puncture was repeated. There was a clear colorless liquid, glucose 83 mg/ml, protein 2.56 grams/L, 3 leukocytes/ml, and Gram staining without bacteria. In this scenario, GBS was suspected, starting treatment with immunoglobulins 1 g/kg/day for two days.

Because of intermittent bradycardia, a control CT scan was performed on the 7th day of hospitalization, which showed increased ventriculomegaly and sulcal effacement, diagnosing acute hydrocephalus associated with GBS (Figure 1-B). External ventricular drain (EVD) was placed, and the next day, a new control CT scan showed a well-placed drain, smaller ventricles, and more prominent sulci.

Regarding ventilatory aspects, he progressed favorably, extubating on the 9th day and changing to BiPAP system. Brain MRI was performed showing secondary hydrocephalus without changes since the last CT scan (Figure 1-C).

Once the patient was extubated and without sedation, a neurological evaluation was performed on the 10th day of hospitalization, showing severe hypotonia and weakness. He could only move extremities in the horizontal plane but not against gravity and presented global areflexia. An electrophysiological study was performed showing demyelinating polyradiculoneu-

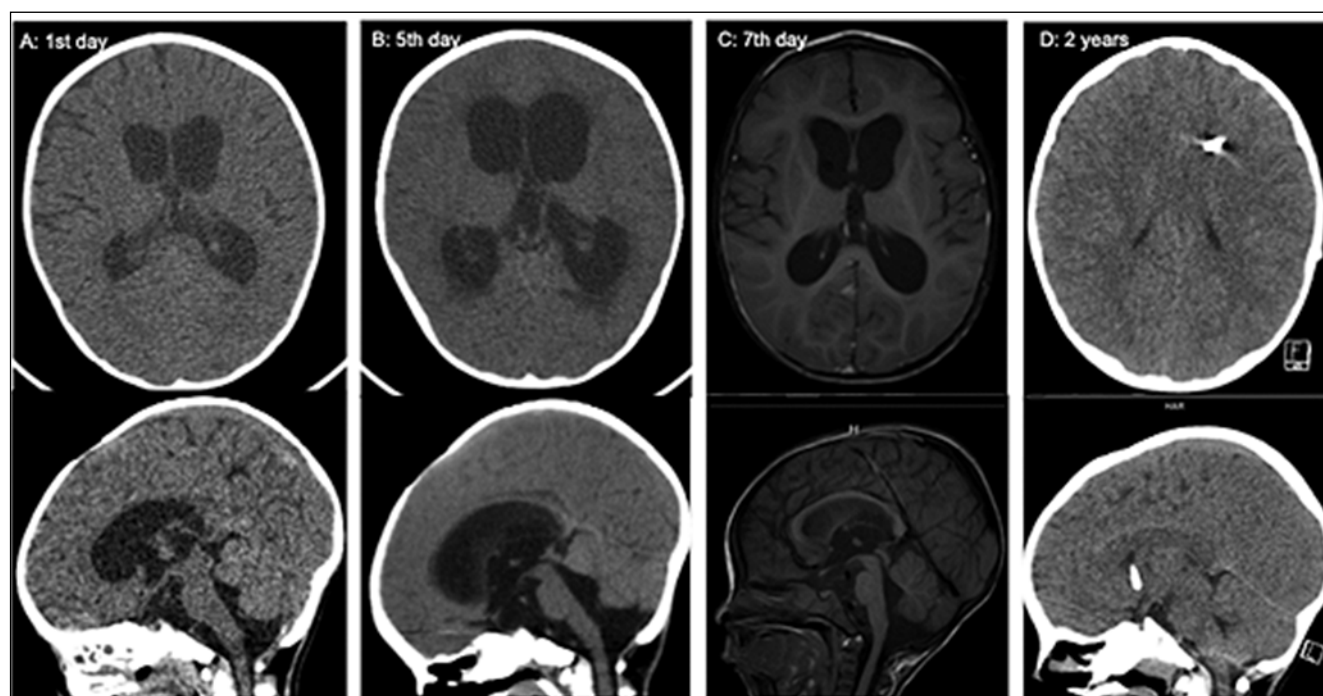
ropathy (Figure 2, Table 1). Due to persistent weakness and dependence on non-invasive ventilation, immunoglobulin dose was repeated with the same previous scheme.

#### *Short-term follow up:*

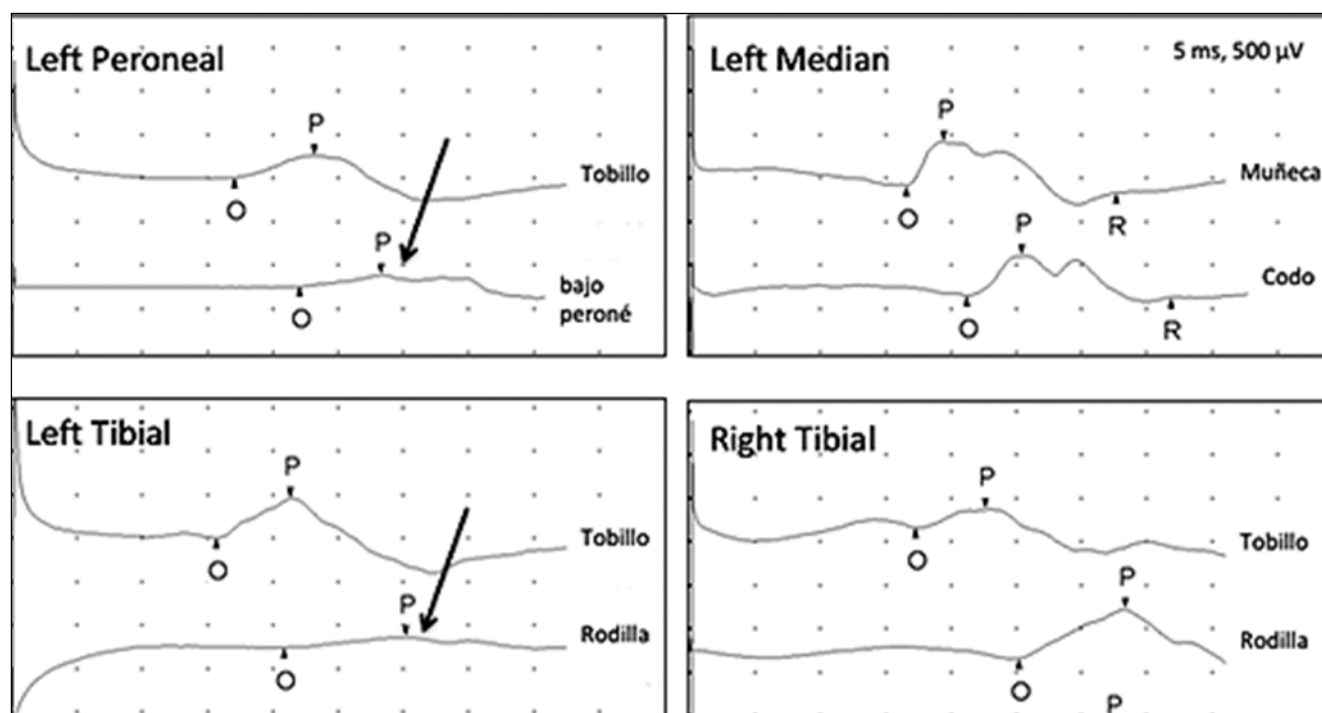
Ventilation continued to improve during the third week of evolution, withdrawing BiPAP and oxygen administration. The patient underwent internalization of EVD and a control CT scan was performed which showed less ventricular dilatation.

In the 4th week, he regained muscle strength, progressively lifting all four limbs. In the reassessment at the 5th week, he achieved movement against gravity and resistance, and deep tendon reflexes presented a positive reaction, although hypotonia persisted in lesser degree.

The patient was discharged after six weeks of hospitalization and in good general conditions. The neurological examination showed that the patient was alert, well-connected with reality, able to focus and visually track stimuli, had normal cranial nerves, with minimal trunk hypotonia but without weakness. He had recovered complete head control but did not yet recovered independent sitting. He had globally diminished deep tendon reflexes, plantar flexors reflexes, without clonus, and absence of lateral and forward parachute reflexes.



**Figure 1.** Axial (upper) and coronal sections (lower) of the brain images of the patient. **A:** CT scan at admission shows moderately large ventricles. **B:** Control CT scan shows larger ventricles. **C:** Magnetic resonance imaging after external ventricular drain placement shows smaller ventricles. **D:** CT scan after two years of follow up shows normal ventricles and drain in situ.



**Figure 2.** Motor nerve conduction of left peroneal, tibial and median nerves, and right tibial nerve: there are longer proximal latencies and smaller amplitudes in all nerves. Arrows show conduction blocks. O: onset, P: peak..

**Table 1. Electrophysiology study**

Nerve	Distal latency proximal (ms)	Amplitude (mV)	Conduction velocity (m/s)
Right ulnar and median	No response		
Left median	16.6	0.5 (VN > 1)	16 (VN > 34)
Left peroneal	17.1	0.3 (VN > 1,5)	26 (VN > 32)
Right tibial	17.3	0.5 (VN > 5)	14 (VN > 32)
Left tibial	15.7	0.2 (VN > 5)	27 (VN > 32)

Distal latencies are longer and amplitudes are smaller in all nerves. Conduction velocity is severely diminished in left median and right tibial nerves. ms: milliseconds, mV: millivolts, m/s: meters per second, NV: normal value.

#### *Long-term follow up:*

Cord blood stem cell transplantation from an unrelated donor was performed at 12 months of age and progressed without significant complications. On two occasions, at 28 and 37 months of age, he had to be re-intervened due to valve dysfunction with satisfactory outcome (Figure 1-D).

The patient did not present any new significant intercurrent illness and his psychomotor development improved progressively over the coming months, presenting sitting recovery at 12 months and gait at 18 months. His last neurological evaluation was carried out at 3 years 2 months of age, highlighting a normal psychomotor development and motor skills examination. In his last check-up, it was possible to observe that he was well-connected with reality, related well to his

peers, understood complex instructions, elaborated sentences of up to five words, fed and dressed partially independently, and controlled his sphincters. Also, his gait was normal, he ran and climbed stairs, and he had no residual symptoms such as fatigue, gait disturbances, or sensory abnormalities.

#### **Discussion**

We present the case of a 9-month-old infant, carrier of WAS, who presented with acute flaccid paralysis, areflexia, albuminocytologic dissociation, and electrophysiological findings compatible with a demyelinating variant of GBS. This is associated with acute hydrocephalus, considered a complication of GBS.

GBS is rare in infants, especially before one year of age, but cases have been reported since neonatal age<sup>11</sup>. In young children, clinical suspicion is usually lower than at older ages, due to its lower frequency and because history and neurological tests are more difficult to carry out, as well as performing an EMG by a neurophysiologist with experience in this age group<sup>12</sup>. For this reason, a significant delay in diagnosis has been reported in young infants<sup>3</sup>. The treatment used for infants has been intravenous immunoglobulin administration in most cases<sup>12,13</sup>. One article even describes the successful use of plasmapheresis<sup>13</sup>, however, the experience is very limited in this age group, its safety has not yet been clarified, and due to its potential complications, its routine use is not recommended<sup>14</sup>.

Despite being an immunodeficiency, autoimmune disorders are common in WAS, found in 22 to 72% of patients<sup>15</sup>. Also, the presence of autoimmune hemolytic anemia, vasculitis, arthritis, neutropenia, inflammatory bowel disease, and IgA nephropathy have been described<sup>15</sup>. At the same time, the association of GBS with infections related to immunodeficiencies such as HIV<sup>16</sup> and with dysimmune conditions such as rheumatoid arthritis<sup>17</sup>, Sjögren's syndrome<sup>18</sup>, and celiac disease<sup>19</sup> has been reported.

International literature reports two 2-year-old children with WAS associated with GBS<sup>9,10</sup>. The first one had demyelinating GBS and the second one had axonal GBS. The first child, consulted due to difficulty in walking and a one-week history of lower extremities weakness, during prolonged coughing, highlighting areflexia in the neurological examination at admission, thus GBS was suspected<sup>10</sup>. The second child presented sepsis with negative cultures, requiring mechanical ventilation. After one week, despite hemodynamic stability, he presented mildly altered consciousness, he did not follow instructions, and deep tendon reflexes presented positive response. Initially, an encephalopathy was suspected, thus brain MRI and lumbar puncture were performed, finding albuminocytologic dissociation, which increased the suspicion of GBS<sup>9</sup>. Both cases were confirmed through albuminocytologic dissociation and electrophysiological study and were treated with intravenous immunoglobulin, with good response. This third case of GBS in a child carrier of WAS suggests that there is an association between both pathologies since given the low frequency of both entities, it is unlikely that they appear in the same patient, which would be explained by the underlying physiopathological mechanisms due to the immune disorders shared by both pathologies.

The increase in CSF protein concentrations has been reported in isolated cases with the use of immunoglobulin, which is secondary to aseptic meningitis<sup>20</sup>. We believe that high CSF protein concentrations in this

patient are mainly explained by the nerve root inflammation of GBS. Chronic treatment with immunoglobulin may have had a minor role in the high CSF protein concentrations that our patient presented.

The association between GBS and acute hydrocephalus is rare. It is believed that the etiopathogenesis is an obstruction of the cerebrospinal fluid circulation due to high CSF protein concentrations or decreased absorption of it<sup>21,22</sup>. In our patient, high CSF protein concentrations reached very high levels, therefore, it probably played a fundamental role in its etiopathogenesis.

The long term progression of GBS tends to be favorable in children, with complete recovery of motor function in most of them, as in our case. Despite this, the reported motor sequelae, although infrequent, are important since they are associated with disability, including gait loss and facial diplegia<sup>23,24</sup>. In addition, the persistence of less severe residual symptoms has been reported such as paresthesia, gait instability, feet and hands pain, and fatigue in up to 65% of children<sup>23</sup>.

## Conclusion

We present the third patient with WAS associated with GBS, which, at the same time, is worsened by acute hydrocephalus. We suggest keeping in mind the GBS diagnosis in children with WAS who have flaccid paralysis and remember that hydrocephalus is a complication in patients with GBS. Early detection and management of these complications will allow changing the vital and neurodevelopmental prognosis, as it happened in this child.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.



## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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