Concurrence of Guillain-Barré syndrome and primary biliary cholangitis not related to SARS-CoV-2: Case report

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Citation
Segura-Chávez D, Tagle-Lostaunau I, Sifuentes-Monge J, Aquino-Peña F. Concurrence of Guillain-Barré syndrome and primary biliary cholangitis not related to SARS-CoV-2: Case report. *Medwave* 2023;23(3):e2663

DOI
10.5867.medwave.2023.03.2663

Submission date
Sep 23, 2022
Acceptance date
Mar 21, 2023
Publication date
Apr 27, 2023

Keywords
Guillain-Barré syndrome, primary biliary cholangitis, autoimmune hepatitis, autoimmune diseases

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Abstract

Introduction

Guillain-Barré syndrome is a polyradiculoneuropathy of autoimmune origin, considered the most frequent cause of acute flaccid paralysis. Various associations of Guillain-Barré syndrome with other non-neurological autoimmune diseases have been reported, some of them extremely rare, such as that which occurs with primary biliary cholangitis, a chronic disease of autoimmune etiology whose diagnosis is also supported by the clinical picture. , in the alteration of liver enzymes and the presence of anti-mitochondrial antibodies.

Clinical case

A 38-year-old male patient, with no history of previous comorbidities, who, after presenting with diarrheal disease two weeks prior, developed subacute onset ascending weakness associated with paresthesias in four extremities that progressed to quadriplegia and respiratory distress. Cerebrospinal fluid cytochemistry was performed, which showed albuminocytological dissociation and electromyography, which showed findings compatible with acute motor axonal neuropathy, for which he received treatment with intravenous immunoglobulin at 0.4g/kg/day, achieving improvement in the neurological condition. Since admission and during hospitalization, he presented persistent changes in liver enzymes which followed a cholestatic pattern, in addition to mild abdominal pain and generalized itching, for which he was evaluated by gastroenterology, who requested anti-mitochondrial antibodies that were positive. Concluding in the diagnosis of primary biliary cholangitis.

Conclusion

The present case shows an extremely rare association of two autoimmune diseases Guillain-Barré syndrome and primary biliary cholangitis, so much so that it represents the first case reported, not linked to SARS-CoV-2.

Main messages

- Guillain-Barre syndrome is an autoimmune polyradiculoneuropathy, which can be associated with other neurological and non-neurological autoimmune diseases.
- The concurrence of Guillain-Barré syndrome and autoimmune liver diseases is rare. There is only one reported case with primary biliary cholangitis, and it was associated with SARS-CoV-2 infection.
- The present case is the first reported case of concurrence of Guillain Barré and primary biliary cholangitis not associated with SARS-CoV-2. Additionally, this case was part of the Guillan-Barre syndrome outbreak in Peru in 2019, in which most cases were linked to *Campylobacter jejuni* infection.

Introduction

Guillain-Barré syndrome is an autoimmune polyradiculoneuropathy, considered the most frequent cause of acute flaccid paralysis [1].

Several associations of Guillain-Barré syndrome with other non-neurological autoimmune diseases have been reported, such as systemic lupus erythematosus, Graves' disease, autoimmune hemolytic anemia, and idiopathic anemia thrombocytopenic purpura, and rarely with autoimmune hepatitis, primary biliary cholangitis, among others [2–4].

Primary biliary cholangitis is a chronic autoimmune disease characterized by damage to the intrahepatic bile ducts leading to cholestasis, fibrosis, and potential cirrhosis, which can manifest with generalized pruritus, mild jaundice, and in some cases, abdominal pain. This clinical condition, together with altered liver enzymes and the presence of anti-mitochondrial antibodies, confirm the diagnosis [5].

Our case is the first report of concurrence of Guillain-Barré syndrome with primary biliary cholangitis before the emergence of SARS-CoV-2. This case belongs to the Guillain-Barré syndrome outbreak in Peru in 2019, in which most cases were linked to an atypical variant of *Campylobacter jejuni*.

Case report

Anamnesis

A 38-year-old male patient with no previous comorbidities reported a four-day history of symptoms. He developed subacute weakness starting in the lower limbs and ascending to the upper limbs, associated with paresthesias. The weakness progressed to quadriplegia and respiratory distress, for which he was intubated and connected to mechanical ventilation.

The patient reported that two weeks before the onset of the neurological symptoms, he presented diarrhea that self-limited after three days.

Physical examination

On the admission clinical examination, he was awake, connected to mechanical ventilation, responding to simple commands, facial diparesis, and quadriplegia with absent reflexes.

Cytochemical analysis of cerebrospinal fluid showed albumin-cytological dissociation, and electromyography showed findings compatible with acute motor axonal neuropathy, for which he was treated with intravenous immunoglobulin at a dose of 0.4 grams per kilogram per day, after which he presented improvement of his neurological symptoms, achieving extubation and improvement of limb strength.

Since his admission and during hospitalization, the patient presented persistent alteration of liver enzymes, which followed a cholestatic pattern. As a result, he also experienced abdominal pain in the right hypochondrium and generalized pruritus, for which the gastroenterology service evaluated him. These physicians requested additional tests, including anti-mitochondrial and anti-centromere B antibodies, which were positive. Therefore, the diagnosis of primary biliary cholangitis was confirmed.

He received prednisone at a dose of 1 milligram per kilogram and then 100 milligrams per day of azathioprine, which he has received as maintenance treatment until the writing of this report.

The patient completely recovered his limb strength; he walks and performs all his basic activities without assistance (modified Rankin 2). Regarding the primary biliary cholangitis, the patient persists with mild jaundice, being monitored and treated by the gastroenterology service.

Auxiliary testing

Upon admission:

1) Glucose: 138 micrograms per deciliter.
2) Aspartate aminotransferase (AST): 169 units per liter.
3) Alanine aminotransferase (ALT): 210 units per liter.
4) Alkaline phosphatase: 1,055 units per liter.
5) Total bilirubin: 1.17 micrograms per deciliter.
6) Direct bilirubin 0.42 micrograms per deciliter.

Table 1. Motor electrophysiological study.

	Distal motor latency (ms)		Amplitude (mV)		Conduction velocity (m/s)	
Nerve	**Normal value**	**Value at 1 month of illness**	**Normal value**	**Value at 1 month of illness**	**Normal value**	**Value at 1 month of illness**
Median, right/ left	< 3.8	NR/NR	> 3.5 mV	NR/NR	> 50	NR/NR
Ulnar, right/left	< 3.8	NR/NR	> 3.5 mV	NR/NR	> 50	NR/NR
Peroneal, right/left	< 5.5	NR/NR	> 2.5 mV	NR/NR	> 40	NR/NR
Tibial, der/izq	< 5.5	NR/NR	> 2.5 mV	NR/NR	> 40	NR/NR

NR: no response. m/s: meters per second. mV: millivolts. ms: milliseconds.
Source: Prepared by the authors from the results of the study.

During hospitalization:

1) Gamma-glutamyl transpeptidase (GGTP): 666 normal value (11 to 50) units per liter.
2) Abdominal ultrasound: hepatomegaly and chronic diffuse hepatopathy.
3) Anti-mitochondrial antibodies-M2: reactive (+++).
4) Centromere B: reactive (+++).
5) Cerebrospinal fluid study: proteins: 184 milligrams per deciliter; cells: 02 cells per cubic millimeter.
6) Electromyography: acute motor axonal neuropathy (tables 1 and 2).

Discussion

Our patient presented with two simultaneous autoimmune diseases, Guillain-Barré syndrome and primary biliary cholangitis [1,5].

The diagnosis of Guillain-Barré syndrome was based on albumin-cytological dissociation and evidence of acute motor axonal neuropathy [1]. Meanwhile, primary biliary cholangitis diagnosis was confirmed by persistent elevation of liver enzymes with cholestatic pattern and anti-mitochondrial antibodies [5].

The association of Guillain-Barré syndrome with autoimmune hepatopathies, specifically with primary biliary cholangitis, as occurred in our patient, is extremely rare, and reports are scarce [6,7].

Only one case of concomitant Guillain-Barré syndrome and primary biliary cholangitis linked to SARS-CoV-2 infection has been reported [8]. This case, like ours, was classified as acute motor axonal neuropathy, presented elevation of liver enzymes after the development of neurological symptoms, and responded adequately to treatment with immunoglobulin. However, unlike ours, it also presented Hashimoto's thyroiditis, which suggested a certain predisposition to developing autoimmune diseases [8].

Multiple mechanisms may result in loss of tolerance to axonal-myelinic autoantigens in Guillain-Barré syndrome and mitochondrial autoantigens in primary biliary cholangitis. However, viral and bacterial infections are probably one of the main pathways [1,9].

SARS-Cov-2 and other infectious agents are potential triggers of Guillain-Barré syndrome. This virus, in turn, being of the ribonucleic acid (RNA) type, and because of its similarity to the mouse mammary tumor-related human β-retrovirus RNA, a known inducer of primary biliary cholangitis, could also induce it by a similar mechanism [8,9].

Bacterial and fungal agents have also been linked to the development of primary biliary cholangitis, including *Escherichia coli, Novosphingobium aromaticivorans,* and *Lactobacillus delbrueckii* [9].

Animal studies and molecular mimicry analysis between the E2 subunit of the human and *Escherichia coli* pyruvate dehydrogenase complex showed that infection by the latter bacterium is a key factor in breaking immune tolerance against the mitochondria, resulting in the production of anti-mitochondrial antibodies, the specific autoantibodies of primary biliary cholangitis [9].

Our case was part of the outbreak in Peru in 2019, before the emergence of SARS-CoV-2 worldwide. Although the specific infectious agent in our case was never determined, most of the cases in this outbreak were linked to an atypical variant of *Campylobacter jejuni* [10], an agent that has not been associated so

Table 2. Sensitive electrophysiological study.

	Distal sensory latency (ms)		Amplitude (mV)		Conduction velocity (m/s)	
Nerve	**Normal value**	**Value at 1 month of illness**	**Normal value**	**Value at 1 month of illness**	**Normal value**	**Value at 1 month of illness**
Median, right/ left	< 3.2	2.4/2.0	> 20 mV	37.1/42.4	> 50	51.1/61.5
Ulnar, right/left	< 3.2	1.8/1.7	> 20 mV	32.3/28.6	> 50	68.6/70.6
Sural, right/left	< 4.0	3.8/3.6	> 20 mV	30.8/28.1	> 40	40.2/41.4

NR: no response. m/s: meters per second. mV: millivolts. ms: milliseconds.
Source: Prepared by the authors from the results of the study.

far as an inducer of primary biliary cholangitis, but whose ability to induce it should be observed in further studies, even more so when phylogenetically similar enterobacteria such as *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus*, *and Salmonella Minnesota*, have shown cross-reactivity with anti-mitochondrial antibodies [9].

Conclusions

The present case shows an extremely rare combination of two autoimmune diseases, Guillain-Barré syndrome, and primary biliary cholangitis. Representing the first reported case unrelated to SARS-CoV-2 in the literature.

Notes

Contributor roles

DSCH, FAP: conceptualization, methodology, research, manuscript preparation, review, and editing of the manuscript. ITL, JSM: review and editing of the manuscript.

Conflictos de intereses

The authors have completed the ICMJE conflict of interest declaration form and declare that they have not received funding for the report; have no financial relationships with organizations that could have an interest in the published article in the last three years; and have no other relationships or activities that could influence the published article. The forms can be requested by contacting the corresponding author.

Funding

The authors declare no external sources of funding.

Ethics

The patient signed an informed consent form; a copy was sent to the journal's editorial office.

Provenance and peer review

Not commissioned. Externally peer-reviewed by two reviewers, double-blind

Language of submission

Spanish.

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Concurrencia de síndrome de Guillain-Barré y colangitis biliar primaria no vinculado a SARS-CoV-2: reporte de caso

Resumen

Introducción

El síndrome de Guillain-Barré es una polirradiculoneuropatia de origen autoinmune, considerada la causa más frecuente de parálisis flácida aguda. Se han reportado diversas asociaciones del síndrome de Guillain-Barré con otras enfermedades autoinmunes no neurológicas, algunas de ellas extremadamente raras, como la que ocurre con la colangitis biliar primaria, una enfermedad crónica de etiología autoinmune cuyo diagnóstico se sustenta, además del cuadro clínico, en la alteración de las enzimas hepáticas y la presencia de anticuerpos anti-mitocondriales.

Caso clínico

Paciente varón de 38 años, sin antecedente de comorbilidades previas, quien luego de presentar enfermedad diarreica dos semanas antes, desarrolló debilidad ascendente de inicio subagudo asociado a parestesias en cuatro extremidades que progresó hasta generar cuadriplejia y dificultad respiratoria. Se le realizó examen citoquímico de líquido cefalorraquídeo que evidenció disociación albumino-citológica y electromiografía que mostró hallazgos compatibles con neuropatía axonal motora aguda. Recibió tratamiento con inmunoglobulina intravenosa a dosis de 0,4 gramos por kilogramo al día, logrando mejoría del cuadro neurológico. Desde su ingreso y durante la hospitalización, presentó alteración persistente de las enzimas hepáticas que seguía un patrón colestásico. Además, se agregó dolor abdominal de leve intensidad y prurito generalizado, por lo cual fue evaluado por gastroenterología, quienes solicitaron anticuerpos anti-mitocondriales que resultaron positivos. Con esta prueba, se comprobó el diagnóstico de colangitis biliar primaria.

Conclusión

El presente caso muestra una asociación extremadamente rara de dos enfermedades autoinmunes; síndrome de Guillain-Barré y colangitis biliar primaria, tanto así que representa el primer caso reportado, no vinculado a SARS-CoV-2.