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## Case Report

# Guillain-Barré syndrome spectrum as manifestation of HIV-related immune reconstitution inflammatory syndrome: case report and literature review

José E. Vidal <sup>a,b,c,\*</sup>, Bruno F. Guedes <sup>b</sup>, Hélio R. Gomes <sup>b</sup>,  
Rodrigo Holanda Mendonça <sup>b</sup>

<sup>a</sup> Instituto de Infectologia Emilio Ribas, São Paulo, SP, Brazil

<sup>b</sup> Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil

<sup>c</sup> Instituto de Medicina Tropical da Universidade de São Paulo, São Paulo, SP, Brazil

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## ABSTRACT

A 34-year-old man presented with a history of 21-days of gait unsteadiness and diplopia. Ten days before presentation, he developed limb weakness and in the last three days reduced consciousness. HIV infection was diagnosed three months ago (CD4+ = 160 cells/mm<sup>3</sup>; viral load HIV-1 = 144.000 copies/mL), and antiretroviral therapy was initiated. Impaired consciousness, ophthalmoplegia, limb weakness, ataxia, areflexia, and Babinsky's sign were noted. At that moment, CD4+ count was 372 cells/mm<sup>3</sup> and viral load HIV-1 <50 copies/mL. The clinical, laboratory and neurophysiological findings suggest overlapping Guillain-Barre syndrome (GBS) and Bickerstaff brainstem encephalitis as manifestation of HIV-related immune reconstitution inflammatory syndrome (IRIS). Here, we review and discuss 7 cases (including the present report) of GBS spectrum as manifestation of HIV-related IRIS.

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## Introduction

Peripheral neuropathies have been documented since the early years of the HIV epidemic<sup>1</sup> and distal sensory neuropathy is the most common presentation of peripheral neuropathy in people living with HIV/AIDS (PLWHA).<sup>2</sup>

Guillain-Barré syndrome (GBS) has typically been described early in the natural history of HIV infection as part of the acute retroviral syndrome or early infection.<sup>3</sup> However,

as the combined antiretroviral therapy (cART) era emerged, rare and challenging cases of immune reconstitution inflammatory syndrome (IRIS)-related GBS were described.<sup>4</sup>

Herein, we present a case of the GBS spectrum as a manifestation of HIV-related IRIS and a review of the literature on this topic.

## Case report

A 34-year-old man who has sex with men presented with progressive gait unsteadiness and diplopia in the past 21 days. He developed limb weakness 10 days before presentation and

\* Corresponding author.

E-mail address: [josevibe@gmail.com](mailto:josevibe@gmail.com) (J.E. Vidal).

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reduced consciousness level in the last three days. HIV-1 infection had been diagnosed three months before (CD4+ cell count = 260 cells/mm<sup>3</sup> and viral load HIV-1 = 140,000 copies/mL) and cART was then initiated.

Neurological examination revealed consciousness impairment, complete ophthalmoplegia, generalized weakness and areflexia, truncal and limb ataxia, and bilateral Babinsky response. Brain magnetic resonance imaging (MRI) showed diffuse and symmetric atrophy, ventricular enlargement and symmetric and confluent periventricular and deep white matter T2 hyperintensity with no mass effect and no enhancement. Spinal cord MRI was normal. CSF examination showed 2 cells/mm<sup>3</sup>, protein level 109 mg/dL, and glucose rate 48 mg/dL. Cryptococcal latex agglutination test was negative as well as cultures for bacteria, fungi, and mycobacteria. CSF DNA amplification was negative for HSV-1/2, Varicella zoster virus, Cytomegalovirus, *Toxoplasma gondii*, and *Mycobacterium tuberculosis*. CSF HIV viral load was <50 copies/mL. DNA amplification in blood was negative for cytomegalovirus. CD4+ cell count was 372 cells/mm<sup>3</sup> and HIV viral load was <50 copies/mL. Serum anti-GQ1b and AQP4-IgG were negative. Electroencephalogram revealed general slightly slowed cortical activity. GBS spectrum was considered and the patient received a 5-day intravenous immunoglobulin (IVIG) course.

After two weeks hospitalization and mild improvement, the patient was discharged home with the guidance of a rehabilitation program. Six weeks later, the patient was hospitalized again because of consciousness level impairment. He was disoriented and lethargic, presented bulbar dysarthria, maintained ophthalmoplegia and areflexia. Nerve conduction studies showed reduction in the amplitude of compound muscle action potentials (CMAP) in the distal muscles of the upper limbs and lower limbs, with normal nerve conduction velocities and normal distal latencies; sensory amplitude responses (SNAP) were reduced without slowing of sensory conduction velocities, prolonged F waves and hyperactive H reflexes, which was consistent with a diagnosis of Acute Motor Sensory Axonal Neuropathy (AMSAN). Needle electromyography showed a neurogenic pattern in distal muscles with acute denervation activity (fibrillation, positive acute wave and fasciculations). Due to clinical condition, a second 5-day IVIG course was given. However, the patient continued to evolve with a worsening level of consciousness until he was in coma, two weeks after the second hospitalization.

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## Discussion

Herein we describe a patient with GBS spectrum as manifestation of HIV-related IRIS. Clinical and neurophysiological findings were compatible with overlapping GBS and Bickerstaff brainstem encephalitis (BBE).

Seven cases (including the present report) of GBS spectrum as manifestation of HIV-related IRIS could be identified. Main characteristics of these cases are showed in Table 1. All but one patient presented chronic stage of HIV infection. In contrast, HIV-related GBS has been classically reported as an early manifestation of HIV infection.<sup>4–11</sup> In this scenario, the occurrence of GBS in HIV is thought to be due to an autoimmune response against myelin sheath due to dysregulation

triggered by the primary infection. This potential mechanism also can explain IRIS-related GBS. However, it is unknown whether this phenomenon is HIV-specific or self-reactive immune response.<sup>12</sup> Probably IRIS-related GBS is a HIV-driven disease whose clinical expression depends on the susceptibility of the host, the intensity and quality of the antiretroviral induced immune response, and the nature and characteristics of the HIV.<sup>13</sup>

Clinical and electrophysiological features of all but one patient of the present case series (Table 1) do not differ from that observed in HIV-related GBS and in non-HIV-infected patients.<sup>14</sup> Only the case presented here showed compatible findings with overlapping GBS and BEE. MRI is usually normal in BBE and unspecific findings of our patient probably were secondary to HIV-1 itself. The presence of anti-GQ1b antibodies is a feature of BEE in common with Miller-Fisher syndrome, suggesting that these two entities have similar pathophysiological mechanisms. However, anti-GQ1b antibodies are present in up to 75% of BBE cases.<sup>15</sup> Considering the neurological findings, negative anti-GQ1b antibodies, and exclusion of other conditions, our case was classified as probable BBE.<sup>15</sup> BBE with negative anti-GQ1b antibodies suggest the presence of undetermined anti-ganglioside antibodies or alternative pathophysiological mechanisms (i.e direct viral damage; activated macrophages, targeting either the myelin sheaths or the nodes of Ranvier).<sup>15,16</sup> The possibility of direct HIV damage is low in the case of IRIS, as demonstrated by the undetectable HIV viral load in serum and CSF in our patient. The exact inflammatory mechanisms of IRIS-related overlapping GBS and BBE are unknown as suggested by the absence of both pleocytosis and findings suggestive of encephalitis on neuroimaging.

Most patients had baseline severe immunosuppression and all had high HIV-1 viral load (Table 1) as typically expected in IRIS cases.<sup>12</sup> Cerebrospinal albumin-cytological dissociation was described in all patients with IRIS-related GBS spectrum (Table 1). This profile is similar with most cases of GBS in immunocompetent patients but different to mild lymphocytic pleocytosis usually described in HIV-related GBS.<sup>17</sup> The absence of pleocytosis in IRIS-related GBS likely reflects the control of viral replication in the context of cART use.

Recommended treatment of HIV-related SGB is IVIG or plasmapheresis, similar to non-HIV-infected patients and outcomes seems to be similar in both groups.<sup>14</sup> All but one patient with available information received IVIG and only two patients had total recovery (Table 1). Corticosteroids are the mainstay of central nervous system IRIS therapy,<sup>18</sup> but there is no information in IRIS-related SGB spectrum.

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## Conclusion

IRIS-related overlapping GBS and BBE is a possible manifestation in HIV-infected patients. Negative anti-GQ1b antibodies suggests the presence of alternative mechanisms. Pleocytosis was absent in all reported IRIS-related GBS spectrum and IVIG seems to be effective in these cases but BBE can complicate the outcome.

**Table 1 – Reported and present cases of people living with HIV/AIDS and Guillain-Barre Syndrome Spectrum as a complication of immune reconstitution inflammatory syndrome.**

Patient [Ref.]	Age / Sex	Stage of HIV infection	Time of initiation or optimization of ART	Neurological diagnosis /EMG	Form of IRIS	CD4 (cells/ $\mu$ L) / HIV VL (copies/mL) before current ART	CD4 (cells/ $\mu$ L) /HIV VL (copies/mL) at GBS diagnosis	CSF WBC (cells/mm <sup>3</sup> ) / CSF protein (mg/dl) / CMV-PCR / Antiganglioside antibodies	Treatment	Outcome
1 <sup>5</sup>	56 / M	Chronic	1 month	Recurrent GBS / Acute acquired demyelinating polyneuropathy with axonal damage	Paradoxical	86 / 217.075	510 / < 50	0 / 139 /Not performed /Negative	IVIG	Subsequent relapse, use of corticosteroids, and partial improvement
2 <sup>6</sup>	58 / M	Chronic	26 days	GBS /Mixed axonal and inflammatory demyelinating polyneuropathy*	Unmasking	31 / 867.736	602 / 2.685	4 / 58 /Negative /Not performed	Plasmapheresis	Initial stabilization but eventually dead due to hospital pneumonia
3 <sup>7</sup>	2 / F	Chronic	3 weeks	GBS /Compatible with GBS	Unmasking	12 / 5.9 log <sub>10</sub>	26 / 3.5 log <sub>10</sub>	CSF WBC and protein compatible with GBS /Negative /Not available	Not available	Total recovery in 4 weeks
4 <sup>8</sup>	26 / M	Early	6 weeks	GBS /Demyelination	Unmasking	~125 / ~ 200.000	~ 150 / Undetectable	3 / 3 /Not performed / Negative	IVIG	Partial improvement and discharged to home after 1 month of hospitalization
5 <sup>9</sup>	36 / M	Chronic	2 months	GBS /Demyelinating polyradiculoneuropathy	Unmasking	545 / 212.000	517 / 116	0 / 97 /Negative /Not performed	IVIG	Rapid clinical improvement and complete improvement by 3 months
6 <sup>10</sup>	38 / M	Chronic	5 days	GBS /Demyelinating sensorimotor polyradiculopathy	Paradoxical	90 / 157.000	175 / 590	Albuminocytological dissociation /Negative /Not available	IVIG	Subsequent worsening, use of corticosteroids, and partial improvement by 3 months
7 Present Case	34 / M	Chronic	12 weeks	GBS Spectrum (overlapping GBS and EBB)	Unmasking	260 / 140.000	372 / < 50	2 / 109 /Negative / Negative	IVIG	Initial mild improvement and later worsening. Vigil coma by 4 years of follow-up.

Note. M: male; F: female; ART: antiretroviral therapy; CMV: cytomegalovirus; CSF: cerebrospinal fluid; VL: viral load; PCR: polymerase chain reaction; EMG: electromyography; IVIG=intravenous immunoglobulin; GBS: Guillain-Barré syndrome; BBE: Bickerstaff brainstem encephalitis; IRIS: immune reconstitution inflammatory syndrome; Early infection:  $\leq$  6 months after primary HIV infection; Chronic infection:  $>$  6 months after primary HIV infection; "Unmasking" IRIS: flare-up of an underlying, previously undiagnosed infection soon after ART is started; "paradoxical" IRIS worsening of a previously treated infection after ART is started.

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## Conflicts of interest

The authors declare no conflicts of interest.

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