CASE REPORT

Worsening Guillain-Barré syndrome: harbinger of IRIS in HIV?

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SUMMARY

We report an HIV patient aged 38 years with acute inflammatory demyelinating polyradiculoneuropathy subtype of Guillain-Barré syndrome (GBS) as the only manifestation of seroconversion and worsening of GBS being the harbinger of immune reconstitution inflammatory syndrome (IRIS). To date, only 5 cases of GBS during IRIS are reported. They manifested either during the third week or later after starting highly active antiretroviral therapy (HAART). Our patient witnessed worsening weakness by fifth day after starting HAART, even before the occurrence of *Pneumocystis jirovecii* pneumonia, cautioning one of the impending serious complications of IRIS and helped us initiate steroids at an early date.

BACKGROUND

HIV infection can affect various sites in the neuraxis—peripheral nerve, spinal cord and brain. Peripheral neuropathy can present during all stages of HIV infection and cause considerable morbidity and disability. Symptomatic neuropathies occur in approximately 10%–15% of HIV population, the most common being distal sensory polyneuropathy. Toxic neuropathy, radiculoneuropathy (acute inflammatory demyelinating polyradiculoneuropathy (AIDP), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)), progressive polyradiculopathy, mononeuritis multiplex and autoimmune neuropathy are among others.

Guillain-Barré syndrome (GBS) presenting as AIDP is infrequently associated with HIV infection. Its incidence in HIV infection is not known. It can complicate HIV infection anytime during the course of the disease but more commonly presents at seroconversion and in the early asymptomatic stages, wherein there is high viral load along with low CD4 counts.¹ The proposed mechanisms for GBS in HIV infection include autoimmune with generation of antimyelin antibodies secondary to immune dysregulation or direct invasion of nerves by neurotropic HIV strains.

GBS has also been noted as one of the several different immune reconstitution illnesses associated with highly active antiretroviral therapy (HAART), although rarely. To date, there are very few such cases reported in the literature and these patients manifested either during the third week or later on after starting HAART.^{2–5} Puthanakit *et al*, in his study on 153 symptomatic HIV Thai children, described one more case of GBS during

immune reconstitution inflammatory syndrome (IRIS).⁶

Ours is the first of its kind in literature, wherein we report a case of GBS as the only manifestation of HIV seroconversion and worsening of GBS being the earliest manifestation of IRIS even before the infectious complication of IRIS had set in.

CASE PRESENTATION

A man aged 38 years had progressive quadriparesis with distal sensory symptoms over 5 days. He met a local doctor where he was provisionally diagnosed as GBS. Preliminary evaluation including complete blood picture, liver function tests, renal function tests, random blood sugar, serum electrolytes, serum vitamin B12 levels, vasculitic profile, HIV and hepatitis serology were normal. As the disease remained static thereafter, he went back home despite being offered treatment. He arrived at our hospital 20 days after the onset of the disease because of persistent disability and functional handicap.

On examination, he had areflexic flaccid quadriparesis with 3/5 power in both upper and lower limbs proximally and distally, bilateral lower motor neuron facial weakness and distal sensory loss involving hands and feet. Electrophysiological studies revealed demyelinating sensorimotor polyradiculoneuropathy (table 1). Cerebrospinal fluid (CSF) analysis showed albuminocytological dissociation and he was found to be HIV reactive with a CD4 count of 90 cells/mm³ and 1 57 000 copies/mL of HIV RNA. Infections which are known to cause radiculoneuropathy—cytomegalovirus, Epstein-Barr virus, varicella zoster virus, herpes simplex 1 and 2, influenza, West Nile, Zika virus, syphilis, mycobacteria, toxoplasma, brucella, borrelia, *Campylobacter jejuni*, *Mycoplasma pneumoniae* and carcinomatous infiltration due to lymphoma were excluded. Final diagnosis of retroviral disease and AIDP subtype of GBS was made. The Medical Research Council (MRC) sum score (the sum of MRC power grades of six muscle groups—shoulder abductors, elbow flexors, wrist dorsiflexors, hip flexors, knee extensors and foot dorsiflexors, on both sides, score ranging from 60 (normal) to 0 (quadriplegic)), which has a predictive value for prognostication in GBS was 32.

He was treated with HAART (regimen—tenofovir 300 mg, lamivudine 300 mg and efavirenz 600 mg), cotrimoxazole double strength tablet (trimethoprim 160 mg, sulfamethoxazole 800 mg) once a day and intravenous immunoglobulins (IVIg)

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Table 1 Nerve conduction studies at day 20 of illness

Motor nerves	Lat (ms)	Amp (μV)	CV (m/s)	Amp% (%)	F Lat (ms)
Right median					—
Wrist—APB	7.3	3.8			
Elbow-wrist	13.8	2.9	36.9	−23	
Left median					—
Wrist—APB	8.2	3.2			
Elbow-wrist	13.8	2.5	46.4	−21	
Right ulnar					35.8
Wrist—ADM	3.0	5.9			
Elbow-wrist	7.5	4.8	53.3	−19	
Left ulnar					—
Wrist—ADM	4.0	2.4			
Elbow-wrist	9.1	2.1	52.9	−11	
Left tibial					—
Ankle—AHL	7.3	5.0			
Knee-ankle	24.7	2.6	25.3	−48	
Left peroneal					—
Ankle—EDB	8.8	3.4			
Fibula-ankle	15.2	1.3	48.4	−61	
Abfibul-fibula	22.2	0.9	14.3	−35	
Sensory nerves	Lat (ms)	Amp (μV)	CV (m/s)	Amp% (%)	
Right median					
Digit 2—wrist	—	—			
Left median					
Digit 2—wrist	—	—			
Right ulnar					
Digit 5—wrist	2.2	2.1	54.5		
Left ulnar					
Digit 5—wrist	1.90	3.2	63.2		
Left sural					
Stim 2—Rec 2	2.8	29	42.9		

at a dose of 2 g/kg body weight over 5 days. On the fifth day of HAART, while on day 5 of IVIg, after 19 days of static disease, his limb weakness further worsened with new onset of severe bulbar palsy (MRC sum score was 22) and the same was reflected on electrophysiology. As the nadir of weakness was still under 4 weeks from the onset of illness, worsening of AIDP as a part of IRIS was considered. CD4 count, HIV RNA were assessed and they were 175 cells/mm³, 590 copies/mL, respectively. The serum IL-6 level was elevated to 14.18 pg/mL (normal range: 0–7 pg/mL).

IRIS was confirmed and he was started on 5-day pulse therapy with intravenous methylprednisolone. The limb power, bulbar weakness started improving on third day after starting steroids (MRC sumscore was 26). With the completion of steroid pulse, his MRC sumscore increased to 30. He was started on oral prednisolone 60 mg once a day. The next day, he developed sudden respiratory distress with respiratory rate of 30/min. Chest auscultation revealed fine inspiratory crepitations in the basal lung fields. Phrenic nerve conduction studies, ECG and 2D echocardiogram were normal. Arterial blood gas analysis showed hypoxaemia and normocapnoea (pO₂ 67 mm Hg, Pco₂ 35 mm Hg and percentage O₂ saturation of 91%). Chest X-ray revealed bilateral, diffuse, mainly perihilar, fine reticular interstitial opacities suggestive of *Pneumocystis jirovecii* (PCJ) pneumonia (figure 1). As the patient was not willing for further investigation, he was treated presumptively for PCJ pneumonia with O₂ inhalation

Figure 1 Chest X-ray—PA view—*Pneumocystis jirovecii* pneumonia. PA, posteroanterior.

via face mask and optimal dose of cotrimoxazole for 21 days. Steroid dose was tapered to 40 mg once daily after 2 weeks of treatment with oral prednisolone 60 mg/day. He was discharged on HAART and secondary prophylaxis for PCJ pneumonia along with oral steroids. At discharge, his upper and lower limb power were 4/5 and facial and bulbar weakness improved (MRC sum score of 48). Oral steroids tapered and stopped over 1 month.

OUTCOME AND FOLLOW-UP

He regained normal power in the limbs with no residual facial or bulbar weakness by the end of 3 months.

DISCUSSION

GBS is an acute inflammatory polyneuropathy that is autoimmune in nature. Both cellular and humoral mechanisms are thought to be involved. GBS is most commonly seen during early stages of HIV infection or seroconversion. The occurrence of GBS in HIV is thought to be because of an autoimmune response against myelin due to immune dysregulation triggered by the primary infection. It can also occur during IRIS.^{2–6}

IRIS refers to a disease or pathogen-specific inflammatory response in HIV-infected patients that is triggered after initiation of antiretroviral therapy or change to a more active regimen. French *et al* have laid down the criteria to aid in the diagnosis of IRIS. Atypical presentation of opportunistic infections or tumours in patients on antiretroviral therapy and decrease in plasma HIV RNA level by at least 1 log₁₀ copies/mL are the major criteria. Increased blood CD4+ T-cell count after HAART, increase in immune response specific to the relevant pathogen, spontaneous resolution of disease without specific antimicrobial therapy or tumour chemotherapy with continuation of antiretroviral therapy are included as the minor criteria. Our patient fulfilled two major criteria (had a precipitous fall in plasma HIV RNA copies and acquired *Pneumocystis jirovecii* infection) and one minor criterion (CD4 count raised to 175 cells/mm³ from 90 cells/mm³) for the diagnosis of IRIS. He presented with GBS—AIDP subtype during seroconversion and worsened during immune reconstitution. We presume that he presented to us during seroconversion because the patient who was initially HIV seronegative elsewhere, became seropositive with CD4

count of 90 cells/mm³ when tested 15 days later in our hospital. The duration of CD4 decline after the onset of acute illness was 20 days in our patient, whereas it was 9 days in the study determining the T-cell response to primary HIV infection by Cooper *et al.*⁷ Even a single CD4 count <350 cells/mm³ within 6 months of seroconversion is an early indicator of high risk of disease progression which applies to the case in discussion as well.

The frequency of IRIS among HIV-infected patients starting antiretroviral therapy is estimated at 16% (11.1%–22.9%), of which 4.5% cases are fatal. HIV-infected people with high viral load and low baseline CD4 count (<50 cells/mm³) are prone for IRIS. Approximately 60% of cases occur within the first month of starting HAART, but this interval may range from less than a week to several months.^{8,9} Lymphopenia together with numerical or functional defects in regulatory T cells might compromise the mechanisms that normally serve to maintain host tolerance, thereby promoting the initiation and exacerbation of immune responses.⁸ IRIS is coherent with a dysregulated host immune response provoked by either pathogen-derived antigens or auto-antigens that cause disproportionate tissue damage.

Neuroinflammatory diseases driven by IRIS (neuro-IRIS) are estimated to occur in 0.9%–1.5% of patients initiating antiretroviral therapy.⁸ The neurological manifestations of IRIS, in addition to GBS, include sarcoidosis, central nervous system (CNS) vasculitis, demyelination, progressive multifocal leukoencephalopathy, meningoencephalitis, CNS tuberculosis, toxoplasmosis, etc.⁸

Makela *et al* reported recurrent GBS as a complication of immune reconstitution in HIV in an old man aged 56 years with first episode of GBS during seroconversion and the recurrence with immune reconstitution 5 weeks after starting HAART.²

Piliero *et al* reported a case of GBS with immune reconstitution occurring 26 days after initiation of HAART in an old man aged 58 years on a background of long-standing moderate-to-severe peripheral neuropathy and HIV-associated dementia.³ The first patient had a demyelinating variant and the second had evidence of both demyelination and axonal involvement on nerve conduction studies. Electrophysiology in the other two cases described by Fantauzzi *et al* and Teo *et al* who presented after 2 months of initiation of HAART, was of demyelination while there was no mention of electrophysiology in the case by Puthanakit *et al.*^{4–6} The Thai child in the study by Puthanakit *et al* was started on HAART 3 weeks prior to the weakness.

In our patient, IRIS occurred by fifth day after starting HAART which is very early as compared with the published case reports. And worsening of AIDP was the harbinger of IRIS. The worsening paralysis cautions one of the impending serious complications of IRIS and help in initiating steroids at an early date.

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Learning points

- ▶ Guillain-Barré syndrome (GBS) in HIV is uncommon, occurring mostly during seroconversion or early asymptomatic stages. Nevertheless, it does occur as a part of immune reconstitution inflammatory syndrome (IRIS).
- ▶ IRIS is to be suspected in HIV patients with GBS whose weakness worsens after a plateau phase, especially when it is temporally related to initiation of highly active antiretroviral therapy.
- ▶ Clinical suspicion aids in early diagnosis and directed treatment in such patients, avoiding considerable morbidity.

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