

## Guillain-Barre syndrome associated with peginterferon alfa-2a for chronic hepatitis C: A case report

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### INTRODUCTION

An estimated 170-180 million people worldwide are chronically infected with hepatitis C<sup>[1]</sup>. These patients are at increased risk of developing cirrhosis, hepatocellular carcinoma and hepatic decompensation. Chronic hepatitis C (CHC) is the leading cause of death from liver disease and the leading indication for liver transplantation in the US<sup>[2]</sup>. The number of deaths secondary to CHC is expected to rise<sup>[3]</sup>. The current standard therapy with Pegylated interferon in combination with Ribavirin is associated with significant side effects. Almost all patients treated with Peginterferon and Ribavirin experience one or more adverse events during the course of therapy. The most common are influenza-like symptoms (fatigue, headache, fever and rigors), psychiatric symptoms (depression, suicidal ideation, irritability, and insomnia) and bone marrow suppression. Less common are weight loss, hair loss, thyroid dysfunction, pulmonary toxicity, colitis, vision loss and hypersensitivity reaction<sup>[4,5]</sup>. Significant neurological side effects such as nerve palsy and peripheral neuropathy are rare<sup>[6]</sup>. A few cases of Bell's Palsy and chronic inflammatory demyelinating po-

### Abstract

The recommended therapy for chronic hepatitis C (CHC) infection is the combination of a Pegylated interferon and Ribavirin. Almost all such patients on combination therapy experience one or more adverse events during the course of treatment. Significant neurological side effects are rare. A few cases of Bell's Palsy, chronic inflammatory demyelinating polyneuropathy and even one case of acute demyelinating polyneuropathy with atypical features for Guillain-Barre syndrome (GBS) associated with Interferon therapy have been reported but no report of GBS with typical features has been published. We present a case report of typical GBS associated with Peginterferon alfa-2a and Ribavirin used for treatment of CHC infection.

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Table 1 Time line showing the clinical course of the patient

Period 2008-09	Event	HCV RNA IU/mL	WBC × 10 <sup>3</sup> /μL	ANC/μL	Hb g/dL	Platelets × 10 <sup>3</sup> /μL	ALT IU/L	BT mg/ dL	TSH IU/mL	IFN dose/wk	RBV dose/d
Early December	Start of HCV treatment	4 275 000	5.6	3600	15.9	NC <sup>a</sup>	66	0.7	1.55	180 mcg	1000 mg
Early January	Platelets decreased	309 230	5.0	2300	14.5	31	57	1.0	NA	135 mcg	No change
Late January	Start of neurological symptoms	18 880	3.9	1400	12.7	45	38	0.8	NA	Treatment held	
Mid February	Worsening of symptoms	NA	6.4	4000	15.1	61	59	0.6	1.92	Treatment on hold	
April	F/U visit <sup>b</sup> improvement in symptoms	499 660	7.2	4400	15.8	94	61	0.6	NA	Treatment on hold	

ANC: Absolute neutrophilic count; Hb: Hemoglobin; BT: Bilirubin total; IFN: Interferon; RBV: Ribavirin; F/U: follow-up; NA: Not available; NC: Not calculated. <sup>a</sup>Due to clumping of platelets, result was not recorded. Later on repeating, platelets were found to be  $55 \times 10^3/\mu\text{L}$ ; <sup>b</sup>Last follow up to hepatology clinic but patient is being followed up regularly by the neurologist in clinic and by hepatology staff.

lyneuropathy (CIDP) and even one case of acute demyelinating polyneuropathy (AIDP) with atypical features for Guillain-Barre syndrome (GBS) associated with Interferon therapy have been reported, but no report of GBS with typical features has been published<sup>[5-9]</sup>. We present a case report of GBS that developed at wk 8 of therapy with Peginterferon alfa-2a.

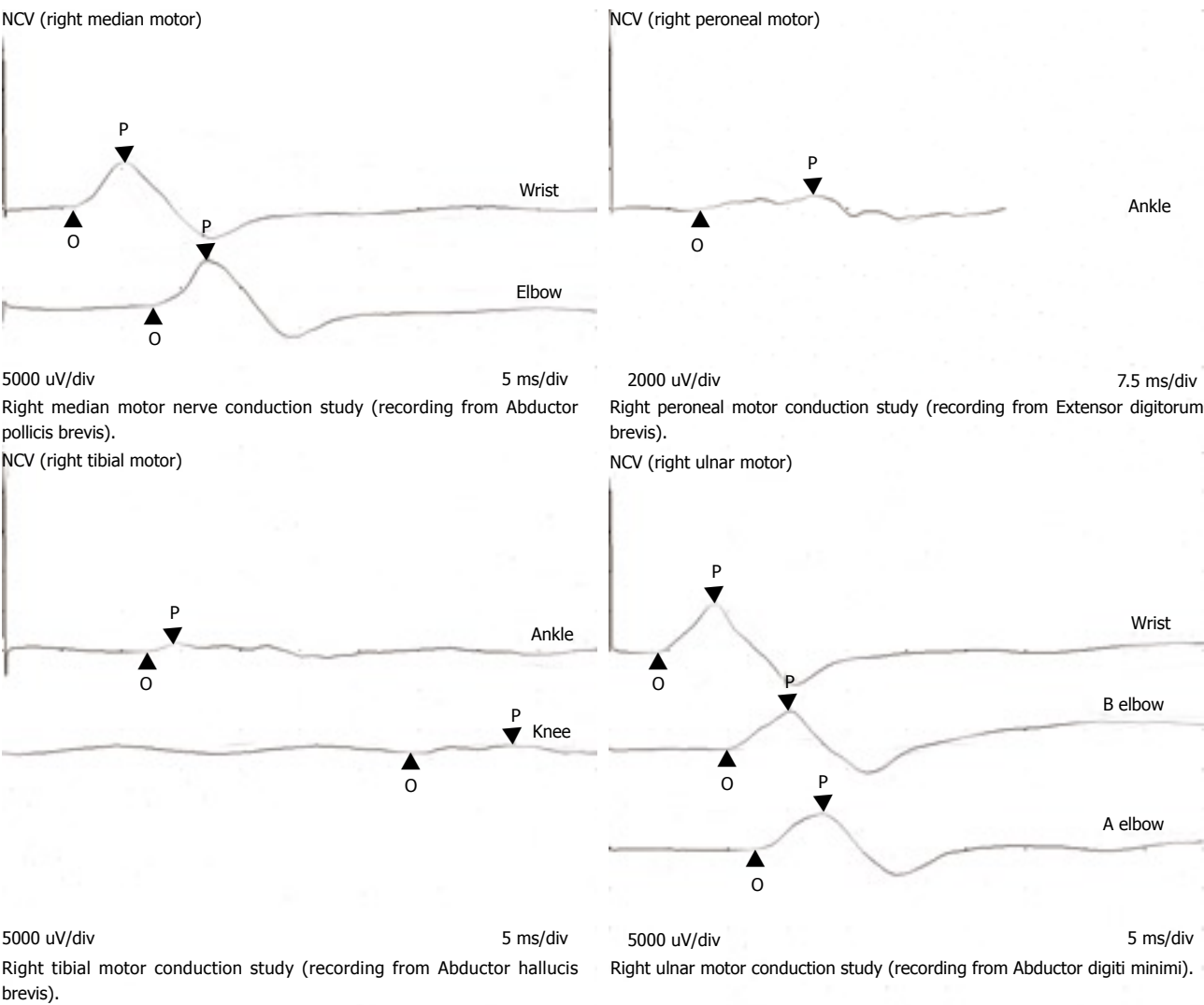
## CASE REPORT

A 55-year-old Caucasian male was referred to our center for treatment of CHC. The patient had a long-standing history of hepatitis C virus (HCV) infection, which was diagnosed 20 years earlier when he tried to donate blood. He was treatment naive. His risk factor for acquiring CHC was cocaine sniffing when he was young although he denied any intravenous drug use, unprofessionally made tattoos, body piercing or blood transfusions. The patient denied any history of jaundice, confusion or gastro intestinal bleeding. His only complaint was mild fatigue. A history of smoking (one pack per day) and social drinking was present. Family history revealed one brother with HCV infection. Physical examination showed no stigmata of advanced liver disease although the patient had grade 3 varices on EGD. The timeline of his clinical course is summarized in Table 1.

Initial laboratory findings before initiating the HCV treatment included, Aspartate Transaminase of 60 (0-40) IU/L, Alanine Transaminase of 62 (0-55) IU/L, total bilirubin 0.6 mg/dL, albumin 3.8 g/dL, and International Normalized Ratio was 1.0. Anti smooth muscle, antimicrobial, anti alpha-one antitrypsin and antineutrophilic antibodies were normal. Hepatitis B virus serology was negative and iron studies were normal. The patient's HCV RNA viral load was 1 352 000 IU/mL. His genotype was 1a. Liver biopsy revealed stage 3 bridging fibrosis with mild macro vesicular steatosis and severe inflammation. The patient was started on Pegylated interferon alfa-2a 180 mcg/mL subcutaneously per week

and Ribavirin 1000 mg/d in divided doses. Because of thrombocytopenia, the interferon dose was decreased to 135 mcg/mL weekly. He responded to the treatment with a more than 2 log<sub>10</sub> drop in HCV RNA at wk 8. At that time, he visited a local hospital complaining of numbness of the face, difficulty eating, loss of taste sensation and facial diplegia. The work up for stroke was negative and magnetic resonance imaging (MRI) of the brain was normal. He was seen by a neurologist, who made the diagnosis of Bell's Palsy and started the patient on oral steroids. Peginterferon was discontinued at that time, and the patient was advised to follow up with the neurologist.

Subsequently, the patient developed back pain, progressive weakness and neuropathic pain in both lower extremities, leading to difficulty in ambulation. Computerized tomography scans and MRI of the lumbar and thoracic spine were normal. These symptoms progressed over two weeks and the patient became wheelchair bound. He was then admitted to a local hospital where physical examination revealed bilateral weakness involving both upper and lower facial muscles, normal muscle strength in upper extremities but decreased in the lower extremities. There were decreased deep tendon reflexes (DTRs) in both upper extremities, absent DTRs at the knees bilaterally and at the right ankle and decreased at the left ankle. The patient underwent an electromyography study (EMG), nerve conduction study and lumbar puncture for cerebrospinal fluid (CSF) analysis. EMG and nerve conduction studies (Figure 1 and Tables 2, 3) showed that the right radial sensory distal latency was prolonged (2.8 ms; normal < 2.6 ms) with a diminished amplitude response (11 uV; normal > 20 uV) and the right sural sensory response was absent (technically difficult). The right median motor distal latency was markedly prolonged (6 ms; normal < 4.4 ms) with a slow conduction velocity (37 m/s; normal > 49 m/s) and prolonged F-wave latency (33 ms; normal < 31 ms). The right ulnar motor distal latency was prolonged (4.1 mV; normal < 3.5 ms); the conduction velocity was slowed both in the forearm



The waveforms correspond with the data in the table below:

Site	NR	Onset (ms)	Norm onset (ms)	O-P Amp (mV)	Norm O-P Amp	Site 1	Site 2	Delta-0 (ms)	D (cm)	Velocity (D/Delta) (m/s)	Norm velocity (m/s)
Right median motor (Abductor pollicis brevis)											
Wrist		6.0	< 4.2	5.6	> 4.4	Elbow	Wrist	6.7	25	37	> 49
Elbow		12.7		5.6							
Right peroneal motor (Extensor digitorum brevis)											
Ankle		11.4	< 5.7	0.7	> 2.2						
Below fibular	NR										
Right tibial motor (Abductor hallucis brevis)											
Ankle		12.1	< 5.7	1.0	> 2.8	Knee	Ankle	22.3	43	19	> 41
Knee		34.4		0.9							
Right ulnar motor (Abductor digiti minimi)											
Wrist		4.1	< 3.5	6.1	> 5.6	B elbow	Wrist	5.9	24	41	> 49
Below elbow		10.0		4.8		A elbow	B elbow	2.3	11	48	> 49
Above elbow		12.3		4.4							

NR: No response; Norm: Normal; O-P: Onset-Peak; Amp: Amplitude; Vel: Velocity; D: Distance; A: Above; B: Below.

Figure 1 Electromyography/nerve conduction studies.

segment and across the elbow whilst the F-wave was normal. The right peroneal motor distal latency was markedly prolonged with a low amplitude dispersed response and absent proximal response. The right tibial motor distal latency was markedly prolonged with a low amplitude dispersed waveform and slow conduction

velocity. Concentric needle examination of selected distal right lower extremity muscles demonstrated a reduced number of voluntary motor units in right tibialis anterior without any spontaneous activity or motor unit changes. The CSF analysis revealed markedly elevated protein levels of 405.8 mg/dL, (normal: 15.0-45.0 mg/

Table 2 Electromyography studies

Side	Muscle	Nerve	Root	Insertional activity	Fibrillations	Psw	Amp	Dur	Poly	Interphase pattern
Right	MedGastroc	Tibial	S1-2	Nml	Nml	Nml	Nml	Nml	0	Nml
Right	AntTibialis	Deep br peroneal	L4-5	Nml	Nml	Nml	Nml	Nml	0	25%

Nml: Normal; Psw: Positive sharp waves; Amp: Amplitude; Dur: Duration; Poly: Polyphase activity. Electrical activity of the muscles at rest (Insertional activity, Fibrillations, Psw) and with voluntary activation (Amp, Dur, Poly, Interphase) showing that most of the results were normal, reflecting that patient had an acute event of neurological symptoms and did not have a chronic ongoing muscle disease.

Table 3 Nerve conduction studies

	Distal latency (m/s)	Conduction velocity (m/s)	Amplitude sensory (uV) motor (mV)
Sensory			
Right radial	2.8 (NML < 2.6)		11 (NML > 20)
Right sural	Absent <sup>a</sup>		Absent <sup>a</sup>
Motor			
Right median	6.0 (NML < 4.4)	37 (NML > 49)	5.6 (NML > 4.2)
Right ulnar	4.1 (NML < 3.5)	41 (NML > 49)	6.0 (NML > 5.6)
Right peroneal	11.4 (NML < 5.7)		0.7 (NML > 2.2)
Right tibial	12.1 (NML < 5.7)		1.0 (NML > 2.8)
F wave			
Right median	33 (NML < 31)		
Right ulnar	27.6 (NML < 31)		
Right peroneal	Absent		
Right tibial	Absent		

<sup>a</sup>Technically difficult; NML: Normal.

dL), normal glucose level of 67 mg/dL (normal: 40-70 mg/dL), 3 white blood cell (WBC)/ $\mu$ L and 3 red blood cell/uL. Based upon these clinical and laboratory findings, the patient was diagnosed with AIDP (GBS) and was started on intravenous immunoglobulins (IVIG). Other laboratory tests included normal complete blood count, blood chemistry (chemistry-8 panel), thyroid stimulating hormone, normal CSF Lymes antibodies and normal CSF immunoglobulin A level. Thereafter, the patient was transferred to a rehabilitation center.

As per the last follow up at the hepatology clinic, the patient was able to walk short distances with a walker, with left sided facial strength improvement and right sided weakness. However, as per the latest follow up visit to the neurology clinic, he does not even require a walker. The patient still shows some neurological deficit although he is back at work. The neuropathic pain has improved significantly and the patient demonstrates improved muscle strength. Interferon therapy is still on hold.

## DISCUSSION

GBS is a heterogeneous condition with several variant forms. It is an acute monophasic progressive disease presenting with symmetric muscle weakness and absent or decreased deep tendon reflexes<sup>[10]</sup>.

### Pathophysiology and causes

An immune response to a preceding infection that can

cross-react with peripheral nerve components is the proposed mechanism of GBS. This immune response can be directed against the myelin or the axon of the peripheral nerve, resulting in demyelinating and axonal forms of GBS. Campylobacter Jejuni infection is the most commonly identified precipitant of GBS<sup>[11]</sup> although our patient did not have any gastrointestinal symptoms making, C Jejuni highly unlikely. Other infections such as Haemophilus influenzae, Mycoplasma pneumoniae and Cytomegalovirus are the most commonly identified precipitant of GBS. However, our patient did not show any evidence of flu-like symptoms or systemic signs and symptoms of infection and there was no evidence of pneumonia on chest x-ray<sup>[12]</sup>. CSF pleocytosis is common in patients who have GBS and concurrent HIV infection<sup>[13]</sup> but our patient had only 3 WBCs. Certain vaccinations such as Influenza vaccination<sup>[14]</sup> and Meningococcal vaccination have also been associated with GBS but our patient did not receive any of these vaccines. Industrial toxins and drugs can also cause demyelinating neuropathies. Our patient had no exposure to any of toxins or drugs other than Pegylated interferon alpha 2-a and Ribavirin.

### Diagnosis

The typical findings with lumbar puncture in patients with GBS are an elevated CSF protein with a normal WBC count. AIDP is the most common form of GBS in the United States and Europe, representing approximately 85 to 90 percent of cases. Clinical neurophysiology studies (i.e. electromyography and nerve conduction studies) show evidence of an AIDP. The earliest abnormalities seen on clinical neurophysiology studies in patients with AIDP are prolonged or absent F waves, reflecting demyelination at the level of the nerve roots<sup>[10,15]</sup>. Sensory nerve conduction studies reveal absent responses or slowed conduction velocities. Typically, the sural sensory response is normal, while median and ulnar sensory responses are affected (sural sparing).

### Treatment

Treatment of GBS according to the American Academy of Neurology recommendation<sup>[16]</sup> is with plasma exchange or IVIG. Both hasten recovery from GBS. The beneficial effects of plasma exchange and IVIG are equivalent. Steroid treatment alone is not beneficial. Plasma exchange is recommended for nonambulatory adult patients with GBS who start treatment within

four weeks of the onset of neuropathic symptoms or for ambulatory patients who start treatment within two weeks of the onset of neuropathic symptoms. IVIG is recommended for nonambulatory adult patients with GBS who start treatment within two or possibly four weeks of the onset of neuropathic symptoms. Overall, about 80 percent of patients with GBS either recover completely or are left with only minor deficits which do not interfere with activities of daily living.

Neurological side effects of interferon are rare. However, a variety of peripheral neuropathies have been reported such as Bell's palsy, optic neuropathy, sensory and autonomic neuropathy, CIDP and more recently AIDP (atypical GBS)<sup>[6-9,11]</sup>. We did not test for IFN antibodies (that could possibly cross-react), did not rule out all the GBS related infectious causes definitely and did not check autoimmune markers at the time of onset of neurological symptoms. However, our patient did not have any clinical signs of any other autoimmune disorder. This is the second reported case of AIDP and the first case of typical GBS that was associated with treatment for chronic hepatitis C with Pegylated interferon alpha 2. Although a few cases of Bell's palsy have been reported with HCV therapy<sup>[6]</sup>, only one atypical GBS has been reported after 16 wk of HCV treatment<sup>[7]</sup>. Our case is unique in the way our patient first developed Bell's palsy, and was then subsequently diagnosed with GBS. Unlike the prior atypical GBS reported, our patient had all the required cardinal features of GBS. Another notable observation is that these findings were reported within only 8 wk of initiation of treatment.

We think it is important for clinicians, and in particular hepatologists to keep this association with GBS in mind when prescribing Peginterferon alfa-2a for HCV treatment. Close attention should be paid to any neurological symptoms developing during the course of treatment. Prompt referral to a neurologist is warranted if these symptoms develop. In addition, patients should have a close and regular follow up with the Hepatologist where the treatment was initiated.

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