

## Guillain-Barré Syndrome vs acute onset CIDP – a clinical dilemma for the neurologist

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### ABSTRACT

The most common acquired immune mediated polyneuropathies are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a form of Guillain-Barré syndrome (GBS), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Sixteen percent of cases ultimately diagnosed as CIDP may present acutely and be indistinguishable initially from AIDP. While GBS is typically thought of as a monophasic illness, 10% may show treatment related fluctuations. Therefore, distinguishing acute onset CIDP (A-CIDP) from GBS with treatment-related fluctuations may be difficult early in the disease course but it's important to distinguish between the two entities to guide further treatment strategies. We present 2 illustrative cases of A-CIDP, diagnosed as GBS who eventually required long term immunosuppression for sustained recovery.

### Introduction

Guillain-Barré syndrome (GBS) is an acute immune mediated polyradiculoneuropathy that presents with acute flaccid paresis. Although GBS is considered to be monophasic, recurrences are reported in 2 to 5% of patients.<sup>[1,2]</sup>

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a subtype of GBS, is characterized by its acute onset and progression up to four weeks and is often preceded by an infection. However chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) progresses slowly over weeks to months or in a relapsing remitting manner<sup>[3,4]</sup>. Five percent of patients initially diagnosed with GBS may evolve into CIDP and 16% of patients with CIDP present with an acute GBS-like illness<sup>[5]</sup>. Distinguishing between GBS, GBS with treatment related fluctuation (TRF) and A-CIDP is important as patients with A-CIDP require long-term immunotherapy. Treatment related fluctuation in GBS is defined as worsening by at least one grade in the GBS disability scale or by at least 5 points in MRC sum score after initial improvement or stabilization with the initial treatment with immunotherapy by either plasmapheresis or intravenous immunoglobulin therapy, not occurring more than 2 times and within the first two months of onset of symptoms. A-CIDP should be considered when a patient

with GBS deteriorates after 9 weeks of onset or deterioration occurs more than 3 times<sup>[5,6]</sup>.

Here we present 2 cases: one presenting as recurrent GBS and the other one as GBS with TRF and relapses which posed a diagnostic dilemma of A-CIDP vs GBS. Both required initiation of immunosuppression and achieved remission after rituximab infusion.

### Case 1

A 17-year-old girl presented to the emergency department with a history of low-grade fever lasting for 1 day followed by rapidly progressive weakness of all four limbs over the next 2 days. On examination she had bilateral lower motor neuron facial nerve palsy, absent gag reflexes, strength 0/5 (MRC grade) in all 4 extremities. She developed bulbar and severe respiratory weakness requiring mechanical ventilation. She had a previous history of similar illness on two occasions.

The first episode of weakness was in 2016 when she was diagnosed with Guillain-Barré Syndrome. She was treated with intravenous immunoglobulin (IVIG) followed by plasmapheresis due to no response to IVIG. A second episode of GBS occurred in 2020 where she again received IVIG in an outside hospital. This was followed by plasmapheresis with improvement. In between the above episodes, she had complete recovery and was walking independently. This was treated as recurrent GBS. Nerve conduction studies (NCS) revealed absent F responses in bilateral median, ulnar and common peroneal nerves with mildly prolonged latency in the peroneal motor nerve and a sural sparing pattern. Cerebral spinal fluid (CSF) examination showed albumino-cytological dissociation. Serum acetyl choline receptor binding antibody was negative. Urine porphobilinogen was negative.

In the current episode she was treated with plasmapheresis due to no response to IVIG in previous two episodes. Since she had no response by the fifth session, we she received two more sessions of plasmapheresis. Over the next 3 weeks she showed gradual improvement and was weaned off the ventilator. She showed complete improvement in weakness over one month and could walk independently at discharge. In view of this third episode of severe GBS-like presentation, she was treated with rituximab infusion 1000 mg followed by another 1000 mg 2 weeks apart with premedication. Since she had three GBS episodes, CIDP was considered and a neuropathy panel was sent which was positive for NF-155 and NF-186 antibodies. She received maintenance dose of 500 mg rituximab at 6 months follow up. She is in remission with minimal left facial weakness.

### Case 2

A 35-year-old female presented to the hospital with a history of tingling in hands and feet for 4 days prior to admission. She also had imbalance on walking. This was

preceded a week prior with fever and upper respiratory infection. She was admitted with a clinical diagnosis of GBS with proximal and distal weakness in the lower extremities (MRC grade 3) and upper extremities (MRC grade 4-/5 in proximal and distal muscles). No sensory impairment was present. There was generalized hypo/areflexia. An NCS was performed (table 1). Examination of CSF revealed albuminocytological dissociation. Treatment was initiated with IVIG 2g/kg divided over 5 days. However, on the second day of IVIG she developed bulbar symptoms with dysphagia, diplopia and strength in the upper and lower extremities worsened to grade 0-1/5. She progressed rapidly to respiratory failure requiring mechanical ventilation. There was an initial slight improvement after IVIG but she deteriorated again to grade 1/5 in arm strength. Hence, she received another course of IVIG. However, there was no improvement and she remained dependent on ventilator at week 3 of illness. A repeat NCS was performed at week 3 (table 1). Since there was no improvement after IVIG, she underwent plasmapheresis 2 weeks after IVIG. She showed remarkable improvement and after the fourth session of plasmapheresis, she was weaned off the ventilator, strength

in the upper extremities improved to 4-/5 and was shifted out of the intensive care unit. However, four days after the initial response, strength in shoulder abduction worsened to 2/5. She underwent two more sessions of plasmapheresis in view of this treatment related fluctuation. She was also started on oral prednisolone 40 mg once a day with azathioprine 50 mg twice a day and physiotherapy were continued. Strength in the upper extremity gradually improved. She was discharged in a week and started walking 2 months later. Prednisolone was gradually tapered off over next 2 months. She developed pancytopenia at that time which was thought to be due to azathioprine. Hence it was stopped at 3 months from the onset of her illness.

However, one month after stopping immunosuppression, (5 months from initial symptom onset) she noticed worsening of gait imbalance, diplopia with weakness in both lower (MRC grade 2/5) and upper extremities (MRC grade 4-/5). She was treated with plasmapheresis. This was the first relapse after the initial episode of GBS like presentation.

2 months later, she presented for the third time with gait imbalance, this time with predominant sensory ataxia,

**Table 1:** Case 2: Nerve conduction study at week 1 (day2) and week 3 of illness

	Recording site	Peak Latency (ms)		Amplitude (microV)		Velocity (m/s)		F wave latency (ms)	
		Week 1	Week 3	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
SENSORY									
R Sural	Lateral malleolus	2.60	2.86	54.6	11.9				
R Superficial peroneal	Lower leg	2.60	2.70	27.2	13.0				
R Median	Digit II	2.76	NR	15.3					
R Ulnar	Digit V	2.40	NR	23.4					
R Radial	Thumb	2.03	2.40	42.8	11.8				
MOTOR	Recording site	Distal latency (ms)		Amplitude (mV)		Velocity (m/s)		F wave latency (ms)	
		Week 1	Week 3	Week 1	Week 3	Week 1	Week 3	Week 1	Week 3
R Peroneal Ankle	EDB	9.17	22.86	2.6	0.9			45.10	Absent
Fibular head		15.31	30.36	2.5	0.5	48.8	40.0		
Pop fossa		17.45	34.79	2.3	0.4	42.1	20.3		
R Tibial Ankle	AH	7.40	14.90	5.7	1.1			47.10	Absent
Pop fossa		16.46	30.57	5.1	1.1	40.8	22.3		
R Median Wrist	APB	8.07	24.38	1.1	2.6			Absent	Absent
Elbow		12.71	31.82	1.1	2.5	49.6	30.9		
R Ulnar Wrist	ADM	4.43	14.74	2.0	2.5			Absent	Absent
B elbow		7.92	20.00	1.8	2.1	54.4	36.1		
A elbow		9.84	28.07	1.4	1.5	51.9	12.4		

areflexia, and weakness in her extremities (MRC grade 4-/5 in the upper and 2/5 in the proximal lower extremities). She responded to IVIG with improvement in the strength, sensory symptoms and gait. She received rituximab infusion 1000 mg followed by another dose of 1000 mg after 2 weeks in view of these frequent relapses. Since then, her disease is in remission for last 3 years with no neurological deficit.

## Discussion

Guillain-Barré syndrome (GBS) is an acute immune mediated polyradiculoneuropathy affecting 0.8–1.9 subjects per 100,000 every year worldwide<sup>[7]</sup>. A preceding infection can be identified in about 70% of cases. GBS represents a model for post-infectious auto-immune disorders<sup>[7]</sup>. The most common preceding infection causing GBS has been shown to be *Campylobacter jejuni* enteritis, responsible for 50% of cases. Recurrences of GBS are rare, reported in 2-5% of patients.

CIDP is a chronic progressive or relapsing condition that develops over at least 2 months. Studies have shown that up to 16% of CIDP patients may present acutely like AIDP, developing in <8 weeks.<sup>[8]</sup> This entity is defined as acute-onset CIDP (A-CIDP) which presents acutely like GBS but followed by a chronic course beyond 2 months.

Treatment-related fluctuations (TRF) may be observed during the course of GBS, during which clinical deterioration after treatment is observed but <8 weeks after symptom onset. Acute onset with more than three fluctuations after treatment and progression beyond 9 weeks was considered as A-CIDP as against GBS with TRF.<sup>[5]</sup>

A-CIDP patients in Dionne et al. and Alessandro et al. studies<sup>[8,9]</sup> were significantly more likely to have prominent sensory signs with proprioceptive disturbances and sensory ataxia, which was noted in both our patients. Cranial nerve involvement including bulbar weakness (defined as dysphagia, dysarthria), and respiratory tract involvement are atypical features of CIDP, which was however present in both our patients.

A sural-sparing pattern or elevated sensory ratio, when observed, might be useful to differentiate a length-dependent axonal polyneuropathy from an acquired demyelinating and potentially treatable polyneuropathy. According to the study by Dione et al., this pattern is observed with similar frequency in both AIDP and CIDP, at least when studied acutely. None of the electrophysiological parameters studied could reliably differentiate between AIDP and A-CIDP. [9,10]

Kerasnoudis et al. observed that nerve ultrasound score called Bochum ultrasound score could be a useful tool in distinguishing CIDP from AIDP. The score includes measurement of cross-sectional area of (a) the ulnar nerve in Guyon's canal, (b) the ulnar nerve in upper arm, (c) the radial nerve in spiral groove and (d) the sural nerve between the lateral and medial head of the gastrocnemius muscle.<sup>[11]</sup>

The spectrum of CIDP is expanding and patients with

antibodies against nodal or paranodal antigens seem to constitute a distinct group, referred to as the autoimmune nodopathies<sup>[2]</sup>. Antibodies against CNTN1 have been reported in these patients, they may present acutely as GBS, have a severe disease course with predominant distal weakness and sensory ataxia, with no or poor response to IVIG. Antibodies against NF155 have been observed mainly in young adults with a subacute or chronic disease course, distal more than proximal weakness, sensory ataxia, tremor, and poor response to IVIG. CIDP with anti-Caspr1 antibodies had more frequent respiratory failure and cranial nerve involvement.<sup>[2]</sup>

Plasma exchange after initial IVIG in GBS was not associated with improved short-term outcomes but rather with increased cost and hospital stay<sup>[13]</sup>. However, we believe there is a subgroup of patients who do not respond to IVIG may benefit with plasmapheresis. These may be A-CIDP as in our patients or nodopathies. We need prospective studies to identify this subgroup of patients.

Our first patient clinically behaved like recurrent AIDP. However, this was the third relapse of weakness with severe illness each time requiring ventilatory support with prolonged recovery. She received IVIG despite non-responsiveness to initial IVIG at an outside hospital. Given the 3 relapses of GBS-like presentation, and non-responsiveness to IVIG she was treated at our hospital with plasmapheresis. She had dual positive Neurofascin NF-155 and NF-186 antibodies and was given Rituximab to prevent further relapses. Hence, her clinical presentation was that of A-CIDP.

The second patient presented as GBS, with prominent cranial nerve and respiratory involvement at the onset. In her subsequent relapses there was prominent proprioceptive impairment with sensory ataxia in addition to severe proximal and distal weakness. With more than 3 relapses and progression beyond 9 weeks, she was also treated as CIDP. Given the severe clinical course with sensory ataxia, GBS-like presentation and poor response to IVIG, nodopathy was considered. Neurofascin NF-155, anti-contactin and anti-CASPR antibodies were negative.

Both the patients had poor response to IVIG and responded well to plasmapheresis and rituximab raising the possibility of nodopathies which show poor response to conventional IVIG treatment<sup>[14]</sup>. They both showed improvement with remission after treatment with rituximab.

## Conclusion

Patients presenting as GBS with treatment related fluctuations or recurrent relapses may be A-CIDP. IVIG unresponsive patients with a fluctuating clinical course may benefit with aggressive treatment with plasmapheresis. It is important to recognize this subgroup of patients while treating them as GBS as they may require long term immunosuppressive treatment.

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