Clinical Reasoning: Temporal profile of inflammatory neuropathies

Beginning to make sense of the uncertainties

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SECTION 1

A 52-year-old man presented with acute onset of weakness and paresthesias involving all 4 extremities in 2008 preceded by an episode of viral catarrh 3 weeks prior. Examination revealed symmetrical upper and lower extremity weakness (Medical Research Council [MRC] 3/5) and absent deep tendon reflexes. Sensory and cranial nerve examination was normal. CSF showed albumino-cytologic dissociation with leukocyte count of 3 and protein of 110 mg/dL. Acute demyelinating polyneuropathy (AIDP) was diagnosed based on electrodiagnostic studies (table), and IV immunoglobulin (IVIg) was commenced. Recovery was slow, taking 1 year. In 2014, he was

admitted with similar symptoms. Examination revealed normal power of the upper extremities and grade 4/5 power of the lower extremities. There was loss of vibration and proprioception over his toes. Deep tendon reflexes were absent. There was facial diplegia. Considering the clinical presentation and electrodiagnostic studies, he was diagnosed with recurrent AIDP and treated with IVIg. He continued to deteriorate and by the third week, his power was MRC grade 3/5 in his upper and lower extremities. There was no bulbar involvement.

Question for consideration:

1. What are your diagnostic considerations?

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Table Nerve conduction studies

	2008		2014	
	Right	Left	Right	Left
Motor conduction studies				
Median nerve				
Distal latency (at wrist) (4 ms)	9.45	10.00	19.25	17.50
Motor amplitude (5.2 mV)	5.1	2.8	1.5	1.8
Motor latency (elbow) (8.3 ms)	21.25	25.15	29	28.65
Motor amplitude (elbow) (5 mV)	0.1	0.1	1.1	0.6
Conduction velocity (50 m/s)	18.4	13.9	22.1	18.8
F-wave latency (28 ms)	Unrecordable	Unrecordable	60.07	70.47
Ulnar nerve				
Distal latency (3.0 ms)	5.35	5.10	6.60	6.60
Motor amplitude (6.3 mV)	3.1	4.6	5.3	5
Motor latency (below elbow) (6.5 ms)	13.90	15.45	15.80	16.65
Motor amplitude (below elbow) (5.9 mV)	1.1	2.9	2.6	2.7
Conduction velocity (below elbow to wrist) (52 m/s)	23.4	21.3	21.5	18.9
Motor latency (above elbow) (9 ms)	22.95	24.20	20.15	19.90
Motor amplitude (above elbow) (5.5 mV)	0.7	0.9	2.0	2.1
Motor conduction velocity (across elbow) (50 m/s)	16.6	16.6	23.0	33.8
F-wave latency (28 ms)	Unrecordable	Unrecordable	38.32	45.76

Continued

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Table Continued

	2008		2014	
	Right	Left	Right	Left
Motor conduction studies				
Tibial nerve				
Distal latency (ankle) (6 ms)	9.05	9.05	6.00	9.55
Motor amplitude (ankle) (4 mV)	2.3	3.3	1.3	1.6
Motor latency (knee)	27.95	23.50	24.50	24.05
Motor amplitude (knee)	0.7	1.5	0.2	0.4
Motor conduction velocity (knee to ankle) (40 m/s)	19.2	26.5	18.9	25.2
F-wave latency (50 ms)	Unrecordable	Unrecordable	Unrecordable	Unrecordable
Peroneal nerve				
Distal latency (ankle) (6 ms)	8.45	10.15	6.70	5.15
Motor amplitude (ankle) (4 mV)	1.6	1.2	0.4	0.9
Motor latency (below fibula head)	20.50	18.85	17.15	19.10
Motor amplitude (below fibula head)	0.3	0.6	0.1	0.5
Motor conduction velocity (below fibular head to ankle) (40 m/s)	27.0	34.5	24.9	21.5
Motor latency (above fibula head)	24.25	24.45	19.95	20.65
Motor amplitude (above fibula head)	0.1	0.1	0.1	0.5
Motor conduction velocity (across fibular head)	20	17.90	27.8.6	45.2
Sensory conduction studies				
Median nerve				
Sensory peak latency (3.7 ms)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Sensory amplitude (10 μ V)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Sensory conduction velocity (50 ms)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Ulnar nerve				
Sensory peak latency (3.5 ms)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Sensory amplitude (10 μ V)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Sensory conduction velocity (50 ms)	Inexcitable	Inexcitable	Inexcitable	Inexcitable
Sural nerve				
Peak latency (4.2 ms)	3.70	4.00	4.05	4.20
Amplitude (6 μ V)	10.6	3.9	8.4	5.8
Conduction velocity (40 m/s)	32.1	34.9	21.2	20.9

SECTION 2

Immune-mediated neuropathies are the commonest cause of acute neuropathies. Less common causes include vasculitic neuropathies, neuropathies mediated by toxins, and metabolic neuropathies like porphyria. Immune-mediated neuropathies are primarily classified based on the temporal profile of the disease process into Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), with occasional descriptions of the nosologically indistinct subgroups of subacute inflammatory demyelinating polyneuropathy and recurrent GBS. This time-based distinction can, however, be ambiguous.

GBS is defined as a monophasic illness reaching its nadir in 4 weeks' time. However, there may be a recurrent or relapsing pattern. Recurrent GBS is defined as 2 or more episodes that fulfill the criteria of GBS, with either a minimum interval greater than 4 months between episodes if the patient has not recovered completely or greater than 2 months when there has been a complete or near complete recovery following the previous episode.¹ In addition, up to 10% of patients with GBS treated with immunotherapy may continue to worsen after a period of improvement or stabilization, a phenomenon termed treatment-related fluctuation (TRF).² This phenomenon may prolong the time course of the disease process beyond 4 weeks, leading to diagnostic confusion.

CIDP is characterized by progressive weakness of the extremities that classically evolves beyond an 8-week time course. The temporal profile can be

one of 3 patterns: a monophasic illness, a relapsing-remitting pattern, or a chronic progressive pattern. In up to 16% of patients, the initial presentation can be acute, with the tempo of evolution resembling GBS,³ often termed acute-onset CIDP. CIDP can be suspected if the patient continues to worsen beyond 9 weeks or if the patient develops 3 or more episodes of TRF following immunotherapeutic agents.⁴

The temporal profile of the illness described in our patient fits the definition of both recurrent GBS and CIDP with a relapsing-remitting course. Establishing the diagnosis at an early stage is of importance to guide the type and duration of immunomodulatory therapy. The diagnosis of CIDP entails treatment with oral steroids over a longer duration of time and initiation of other immunosuppressive agents in those who are refractory to steroids.

Clinical features can be of assistance in distinguishing GBS from acute-onset CIDP.⁵ The presence of facial weakness, bulbar symptoms, autonomic dysfunction, ventilatory compromise, and preceding infections would suggest possible GBS in comparison to prominent sensory signs and symptoms, which are seen more commonly in acute CIDP. These features, however, are not exclusively confined to one clinical entity and are not reliable. Our patient had facial diplegia with no bulbar or autonomic symptoms.

Question for consideration:

1. How would you interpret the electrodiagnostic studies and what are its limitations in the given context (table)?

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SECTION 3

Electrodiagnostic studies done on both occasions are compatible with a severe demyelinating neuropathy. Our patient demonstrated conduction velocities of less than 70% of the lower limit of normal on most of the nerves tested with prolonged distal latencies. In addition, there was prolongation of the F-wave latencies with increased chronodispersion, decreased persistence, and absence of recordable F waves in some of the nerves. Other features of an acquired demyelinating neuropathy including conduction block, temporal dispersion, and sural sparing were also observed. The absence of F waves with preserved

distal CMAP amplitude in the first study indicates a proximal conduction abnormality.

Electrodiagnostic studies may not be able to differentiate GBS from acute CIDP. Several studies have compared electrophysiologic features of GBS with acute CIDP. Typical demyelinating features of sural-sparing pattern, sensory ratio ($[(\text{sural} + \text{radial})/(\text{ulnar} + \text{median})] > 1$), and A waves are seen in both acute and chronic forms.⁵

Question for consideration:

1. What autoantibody assays would help with the differential diagnosis?

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SECTION 4

Serologic analysis for specific antibodies targeting neural antigens is evolving as a good biomarker in confirmation of the clinical subtype of inflammatory neuropathy. Autoantibodies target specific components of the peripheral nerve, like the gangliosides, myelin proteins, and the nodal or paranodal proteins. Our patient demonstrated negative titers to GM1a, GM1b, GD1a, GT1a, GQ1b gangliosides, NF155, and CNTN1.

Patients with acute motor axonal neuropathy (AMAN), the regional variants of GBS, Miller Fisher syndrome, and acute ataxic neuropathy have antibodies targeting gangliosides that are located on the axonal surface. These gangliosides have specific topographical and fiber type localization and hence the regional phenotypes.⁶ Miller Fisher syndrome is associated with antibodies against GQ1b, which is strongly expressed on the oculomotor, trochlear, and abducens nerves and the muscle spindles, which probably explains the ophthalmoplegia and ataxia. The

pharyngeal-cervical-brachial variant of GBS has antibodies against GT1a, which are strongly expressed on the glossopharyngeal and vagus nerves. Anti-GM1 and anti-GD1 antibodies are commonly associated with AMAN and anti-GD 1a antibodies are commonly associated with the paraparetic variant of GBS.

In contrast, antibodies directed against axonal gangliosides do not have a direct implication in the pathogenesis of AIDP and CIDP. The antigenic targets in the demyelinating neuropathies are presumed to be in the myelin components or within the nodal, paranodal, and juxtaparanodal proteins. These include myelin protein zero, P2 basic protein, or peripheral myelin protein 22, which are localized within the compact myelin, or several other cell adhesion molecules located within the node or paranode like the gliomedin, NF186, Gjb1, Contactin-1, and NF155.

Serologic studies in our patient were inconclusive.

Question for consideration:

1. Would you consider any further investigations?

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SECTION 5

Nerve ultrasound revealed diffuse thickening of the peripheral nerves and of the cervical roots (figure).

The role of nerve ultrasound in inflammatory neuropathies is evolving, with several articles highlighting its usefulness in the evaluation of inflammatory neuropathies looking at measures such as nerve cross-sectional area, nerve size variability, vascularity, and nerve echogenicity. Limitations of nerve ultrasound include the high degree of technical expertise required to assess morphologic neural changes and difficulty in the evaluation of deeper nerves, especially in those who are obese. CIDP is invariably associated with neural enlargement and changes in the echogenicity of the fascicles. There are several patterns of nerve enlargement depending on the timing of the ultrasound studies.⁷ Those very early in the disease process tend to have large nerves with enlarged fascicles that are hypoechoic and associated with loss of fascicular

architecture. With variability in the disease severity and effect of therapy, the enlarged nerves demonstrate a variable echotexture, with some of the fascicles being hypoechoic and others hyperechoic. A third pattern of hyperechoic nerves with normal cross-sectional area can be seen in later stages. Most patients with CIDP also demonstrated enlargement of the cervical roots that tended to decrease with disease duration.

Recent studies have also shown nerve ultrasound to be of value in distinguishing acute from chronic demyelinating neuropathies. The main distinguishing feature is the distribution of nerve enlargement, with CIDP showing a more widespread pattern of enlargement compared to GBS. Kerasnoudis et al.^{8,9} in a retrospective chart review and prospective study demonstrated nerve ultrasound to be superior to electrodiagnostic studies in distinguishing the 2 entities and also demonstrated it to be the most specific

Figure Nerve ultrasound of the cervical roots and the peripheral nerves (circled in yellow and numbered)

(A) Grossly enlarged cervical roots C5 (1) with cross-sectional area (CSA) of 0.18 cm² (normal <0.07 cm²), C6 (2) with CSA of 0.20 cm² (normal <0.12 cm²), and C7 (3) with CSA of 0.20 cm² (normal <0.14 cm²). (B) Enlarged median (1) 0.24 cm² and ulnar (2) 0.18 cm² nerves in the arm (normal <0.10 cm²). (C) Ulnar nerve in the forearm 0.09 (normal <0.07 cm²). (D) Median nerve in the forearm 0.10 (normal <0.08 cm²).

parameter when evaluated prospectively in a group of 10 patients when compared to electrodiagnostic studies and clinical features. Grimm et al.¹⁰ analyzed the regional variation of nerve enlargement across different subtypes of inflammatory neuropathies. Patients with CIDP tended to have predominant enlargement of sensorimotor nerves of the extremities and the sural nerve in comparison to GBS, where the enlargement predominantly involved the cervical roots and vagal nerve.

Our patient had an acute onset of CIDP with a relapsing and remitting course. The absence of cranial nerve and autonomic symptoms during his first admission with predominant sensory symptoms and signs on his second admission makes the diagnosis of CIDP more likely. Electrodiagnostic studies were noncontributory. Nerve ultrasound showed diffuse swelling of both the peripheral nerves and cervical roots, in keeping with CIDP. He was started on long-term oral steroids, on which he improved. Follow-up ultrasound studies showed decreased nerve enlargement.

AUTHOR CONTRIBUTIONS

C. Bharatendu, J. Vijayan, and A. Therimadasamy performed the initial diagnostic assessment and initial investigations. C. Bharatendu, J. Vijayan, N. Yuki, and E. Wilder-Smith helped in compilation of the text, literature search, and editing of the manuscript.

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