Treatment Refractory CIDP: What is the next best treatment?

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CASE 1

History of Present Illness

- 55-year-old man with a past medical history of HLD and cataracts who presents with progressive numbness and tingling for approximately one year.
- He required a walker to ambulate and had impaired fine motor tasks.
- He had increased sweating, constipation and a unintentional 20 pound weight loss
- He received influenza vaccine 2 months prior to the onset of his symptoms.

Presenting Neurologic Exam

Motor Exam: Mild distal more than proximal atrophy with normal tone. No fasciculations.

Sensory Exam: Decreased to pinprick and temperature to thighs and distal arms. Vibration decreased to the knee and elbow. Proprioception decreased up to the ankles.

Reflexes: Absent.

Gait: He is unable to stand or ambulate.

	Before Treatment		After Treatment	
	Right	Left	Right	Left
Deltoids	3	3	4+	4+
Biceps	3	3	5	5
Triceps	4	4	5	5
Wrist Extensors	3	3	4	3
Wrist Flexors	3	3	5	5
Finger Flexors	4-	4-	5	5
Iliopsoas	3	3	4+	4+
Knee Flexors	4+	5	5	5
Knee Extensors	3	4	5	5
Dorsiflexion	3	3	4	4+
Plantarflexion	4+	5	5	5

Laboratory and Diagnostic Studies

- Lumbar puncture:
  - 3 WBC, Protein 187, Glucose 66
- ANA, ESR, CRP, SPEP, ANCA, and RF non-diagnostic.
- Contactin-1 and neurofascin antibodies **positive**

Treatment Course and Results: Case 1

1. Intravenous immunoglobulin (IVIg) for 1 year.
   - No clinical improvement, patient progressively worsened.
2. Methylprednisolone 1 gram IV daily followed by oral Prednisone taper.
   - Minimal improvement, able to walk with walker and climb stairs again.
   - Still difficulty with ADLs.
3. Plasma exchange for 5 sessions.
   - No improvement in motor or sensory symptoms.
4. Rituximab 375 mg/m2 weekly for 5 treatments.
   - Minimal improvement of symptoms initially followed by regression in strength and worsened numbness and tingling.
   - Remained wheelchair-bound.
5. Cyclophosphamide 1 gram/m2 (total 2.28 grams) plus 0.4g/kg IVIg every 3 weeks.
   - Improvement in both motor and sensory symptoms.
   - Ambulatory without assistive device, able to climb stairs.

CASE 2

History of Present Illness

- 72-year-old man with a past medical history of HLD and diverticulitis who presents with a sudden onset of numbness ascending from his feet and hands that is associated weakness and instability.
- He was admitted to the hospital where he developed diplopia and significant alterations in blood pressure.
- His gait and sensory loss continued to worsen despite treatment to the point that he needed an assistive device.

Presenting Neurologic Examination

Motor Exam: Mild proximal atrophy with normal tone. Neck extensor and flexor 5/5.

Sensory Exam: Decreased to pinprick and temperature distally, mildly impaired proprioception.

Reflexes: Absent.

Gait: Unsteady, requires assistive device.

	Before Treatment		After Treatment	
	Right	Left	Right	Left
Deltoids	2	4	5	5
Biceps	4	4	5	5
Triceps	4+	4+	5	5
Wrist Extensors	4	4	5	4+
Wrist Flexors	4	4	5	5
Finger Flexors	4	4	5	5
Iliopsoas	3	3	5	5
Knee Flexors	4	4	5	5
Knee Extensors	4	4	5	5
Dorsiflexion	3	4	5	5
Plantarflexion	3	4	5	5

Laboratory and Diagnostic Studies

- Lumbar puncture:
  - 0 WBC, Protein 131, Glucose 59
- CPK 44, AST 59, ALT 80.
- Malignancy and autoimmune workup negative.
- Contactin-1 and neurofascin antibodies **negative.**

Treatment Course and Results: Case 2

1. Intravenous Immunoglobulin (IVIg) for 10 days.
   - Mild clinical improvement in weakness.
   - Discharged to rehabilitation stable until symptoms acutely worsened.
2. Additional 7 days of IVIg given plus 3 days of IV methylprednisolone upon acute worsening of symptoms.
   - Minimal improvement, but still required assistive device.
   - Persistent numbness, weakness, and gait instability.
3. Readmitted and given four sessions of plasmapheresis.
   - Minimal improvement in symptoms.
4. Cyclophosphamide 1 gram/m2 monthly for 3 to 6 months with hydration and mesna plus IVIg plus prednisone taper.
   - Improved balance, tingling resolved.
   - Ambulating with minimal assistance.

Electrodiagnostic Studies Before and After Treatment: Case 1

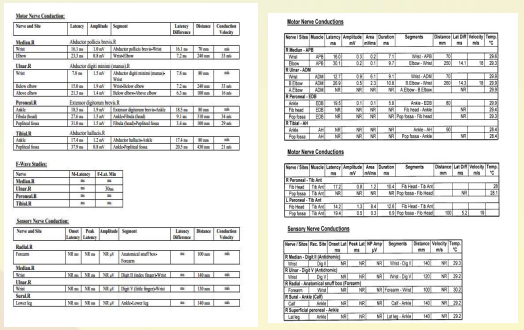

Figure 1. Serial nerve conduction studies for a patient with treatment refractory CIDP showing lack of improvement following standard treatment. Improvement is documented with initiation of Cyclophosphamide both clinically and on nerve conduction studies.

Electrodiagnostic Studies Before and After Treatment: Case 2

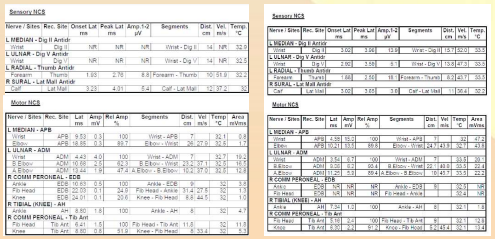

Figure 2. Serial nerve conduction studies for a patient with treatment refractory CIDP showing lack of improvement following standard treatment and improvement with subsequent treatment with Cyclophosphamide

RESULTS

- Two patients were clinically diagnosed with CIDP on the basis of CSF studies showing cytoalbuminogenic dissociation, electrophysiological testing consistent with a demyelinating sensorimotor polyneuropathy, and all CIDP mimics were excluded.
- Both patients were treated with IVIg, methylprednisolone and plasma exchange.
- Both patients had minimal response to worsening of their symptoms.
- Serology for contactin-1 and neurofascin antibodies was obtained.
- Antibodies present in one and absent in the other.
- Both patients responded to cyclophosphamide with near complete resolution of symptoms.

CONCLUSIONS

- Most cases of CIDP are responsive to conventional therapy with steroids, IVIg, or plasmapheresis.
- Treatment refractory CIDP is rare and only includes a small subset of patients with CIDP (approximately 20%).
- Cyclophosphamide should be considered in patients refractory to conventional therapies.
- Further studies are needed to determine superiority compared to Rituximab.

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- Good JL, Chehrenama M, Mayer RF, Koski CL Neurology. 1998;51(6):1735. Fifteen patients with chronic inflammatory demyelinating neuropathy (CIDP) were treated with pulse intravenous cyclophosphamide (IVCY) monthly for up to 6 months. Eleven patients reached a complete remission; only one patient worsened. Complications included nausea, vomiting, anemia, and hair loss. This case series suggests that monthly IVCY is beneficial in the treatment of CIDP and warrants a controlled study.
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- Four patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who were refractory to conventional treatment were treated with high-dose cyclophosphamide (200 mg/kg over 4 days). All improved in functional status and muscle strength. Nerve conduction studies improved in three of four. Other immunomodulatory medications have been discontinued. High-dose cyclophosphamide can be given safely to patients with CIDP and patients with disease persistence after standard therapy may have a response that lasts for over 3 years and results in long-term disease remission.
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