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Case Report

Case Report of a Severe Presentation of Anti-Contactin-1 Nodopathy

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Abstract

A 46-year-old, previously healthy woman presented via telemedicine with 14 months of progressive asymmetrical weakness, numbness, paresthesias and tremors. History and clinical exam findings suggested a peripheral etiology resembling a variant CIDP presentation. Electrodiagnostic testing identified only one motor nerve with signs of demyelination; the remainder of motor and sensory nerves were unable to be evoked. MRI showed diffuse enhancement of the trigeminal nerve and cauda equina. CSF revealed albuminocytologic dissociation. The patient was treated empirically with methylprednisolone for a clinically suspected variant of CIDP, more specifically a nodo-paranodopathy. Two weeks after initiation of steroid treatment, cerebrospinal fluid and serum yielded antibodies to contactin-1 which coincided with our clinical suspicion for an autoimmune nodo-paranodopathy, which is known to be refractory to IVIG. Rituximab was added given the patient's severe presentation at the time of diagnosis. The autoimmune nodo-paranodopathies are treatable,

even in the case of a severe presentation. Lack of clinician awareness and delay in diagnosis can be detrimental as in the case of our nearly paralyzed patient. It is important to raise awareness of the disease, its presentation and therapeutic management since early diagnosis and correct treatment is paramount for neurological recovery.

Keywords
Chronic inflammatory demyelinating polyradiculoneuropathy; IgG4 antibodies; anti-contactin-1 antibodies; rituximab

1. Introduction

Autoimmune nodo-paranodopathies were officially recognized as their own entity in 2003 and account for 10% of CIDP cases. IgG4 antibodies targeting the nodal and paranodal cell adhesion proteins cause axonal degeneration and pathological studies do not show the expected changes that are seen in typical CIDP such as demyelination and inflammation with histological findings of "onion bulbing" [1]. This makes sense since the IgG4 antibodies are not targeting myelin and they are not able to activate the complement cascade. In the nodo-paranodaopathies, electrodiagnostic findings include early axonal degeneration, reduced CMAPs, conduction blocks and prolonged distal latencies while histology shows widened nodes, detached myelin loops and axonal degeneration [1]. Diagnosing autoimmune nodo-paranodaopathies can be difficult if the specific antibody is not detected in serum or CSF; clinicians must rely on history, electrodiagnostic testing, nerve biopsy results and response to therapies [2].

The patient in this case report presented with rapidly progressive sensory loss and associated distal and proximal extremity weakness. This classical pattern of weakness and sensory symptoms localized best to the peripheral nerves and nerve roots; it is the typical pattern observed in inflammatory demyelinating polyradiculoneuropathies, e.g. Guillain Barre syndromes, chronic inflammatory demyelinating polyneuropathy (CIDP), etc. Although the patient was initially seen by telemedicine, due to the COVID pandemic, her pattern of weakness and sensory loss could be observed virtually. Due to the chronic, progressive and severe, 14-month course of this illness, the differential diagnosis included: CIDP and variants, infectious radiculoneuropathies (e.g. Lyme, HSV), CIDP mimics (e.g. POEMS neuropathy), peripheral nerve vasculitis and autoimmune nodo-paranodopathies. While severe classic CIDP remained high on the differential, the patient's rapid decline and early severe weakness raised concern for IgG4 antibody syndromes and CIDP mimics like POEMS disease. This patient has granted permission to submit this manuscript for publication so that her disease process and treatment gains greater awareness.

2. Case

A 46-year-old woman was seen via telemedicine after 14 months of rapidly progressive weakness and numbness. She was previously a healthy nursing director with a reported history of multiple remote episodes of viral meningitis. Her symptoms began with tingling and numbness in her toes that rapidly progressed up her legs, necessitating a cane within 2 weeks and a walker at 6 weeks. For the next year she progressively lost function of both her upper and lower extremities. At the

time of the telehealth visit she required a wheelchair for mobility and a Hoyer lift for transfers. She also reported diffuse numbness, lancinating pain, burning paresthesias, myoclonic jerks/tremor, trouble sleeping, changes to her voice, mild dysphagia, new hypertension, migraines, as well as distal extremity edema. On telehealth video exam, cranial nerves were intact, distal upper extremity bulk was reduced but confounded by edema. Strength was symmetric: 3/5 shoulder abduction, elbow flexion and extension, 2/5 wrists and with finger extension, 1/5 hip flexion and 1/5 knees extension and 0/5 ankle dorsiflexion and great toe extension. Cold sensation was reduced up to the knees and forearms.

Due to the severity of the patient's presentation, we admitted her that day to the general neurology inpatient service for expedited work-up and treatment. The admission exam confirmed the presence of severe upper and lower extremity proximal and distal muscle weakness, dramatic small and large fiber sensory loss with areflexia throughout. An EMG/nerve conduction study was performed to confirm localization and to evaluate for axonal vs. demyelinating physiology. Only the spinal accessory nerve could be evoked with nerve conduction testing (Table 1); the remainder of limb sensory and motor nerve response could not be evoked. Spinal accessory nerve conduction findings indicated demyelination due to a prolonged distal motor latency (8.28 ms) and low amplitude CMAP (2.5 mV) [3, 4]. EMG showed widespread upper/lower extremity denervation and chronic reinnervation, with less involvement of the spinal accessory innervated trapezius (Figure 1). The severity of the nerve conduction findings highlighted the principle of continuing to check more proximal nerves until either no additional nerves can be examined, or a normal nerve is observed. In this case, the spinal accessory nerve findings were critical to understanding this patient's presentation. Lumbar puncture demonstrated albuminocytologic dissociation (CSF Total Protein: 152 mg/dL, normal <25 mg/dL) typical of immune mediated radiculoneuropathies. No white blood cells were present in the CSF to support an infectious etiology. MRI of the brain and lumbosacral spine demonstrated diffuse contrast enhancement of the trigeminal nerve and cauda equina. Together, these findings supported the working diagnosis of an immune mediated radiculoneuropathy such as CIDP. Due to the severity and rapidity of her presentation there was ongoing concern for autoimmune nodopathies and mimcs. POEMS was excluded due to a normal SPEP with immunofixation, serum free light chains, and a VEGF level. Serum Lyme, serum HIV, TSH, B12, A1c and CT chest abdomen pelvis were also normal. A serum demyelinating neuropathy panel from The University of Washington came back positive only for IgM vs Histone H3. Serum and CSF evaluation at Mayo Clinic's Neuroimmunology Laboratory for neural specific autoantibodies was positive for contactin-1 autoantibodies on cell-based assay (transfected HEK293 cells; Euroimmun), reaffirming the clinical suspicion for a nodo-paranodopathy [5].

Table 1 Motor nerve conduction.

Nerve/Sites	Muscle	Latency ms	Amplitude mV	Rel Amp %	Duration ms	Segments	Distance mm	Lat Diff ms
R Median - APB								
Wrist	APB	**NR**	**NR**	**NR**	**NR**	Wrist - APB	80	
Palm	APB	**NR**	**NR**	**NR**	**NR**	Palm - APB		

R Ulnar - ADM								
Wrist	ADM	**NR**	**NR**	**NR**	**NR**	Wrist - ADM	80	
B.Elbow	ADM	**NR**	**NR**	**NR**	**NR**	B.Elbow - Wrist		**NR**
						A.Elbow - Wrist		**NR**
R Peroneal - EDB								
Ankle	EDB	**NR**	**NR**	**NR**	**NR**	Ankle - EDB	80	
Fib head	EDB	**NR**	**NR**	**NR**	**NR**	Fib head - Ankle		**NR**
Pop fossa	EDB	**NR**	**NR**	**NR**	**NR**	Pop fossa - Fib head		**NR**
						Pop fossa - Ankle		**NR**
R Tibial - AH								
Ankle	AH	**NR**	**NR**	**NR**	**NR**	Ankle - AH	80	
R Peroneal - Tib Ant								
Fib Head	Tib Ant	**NR**	**NR**	**NR**	**NR**	Fib Head - Tib Ant		
R Accessory (spinal) - Trapezius								
Neck	Trapezius	8.28	2.5	100	18.75			
Facial - Nasalis (Bilateral)								
R Postauricular	Nasalis	**NR**	**NR**	**NR**	**NR**			
R Femoral - Vastus Med								
B. Ing Lig	Vastus Med	**NR**	**NR**	**NR**	**NR**	B. Ing Lig - Vastus Med		

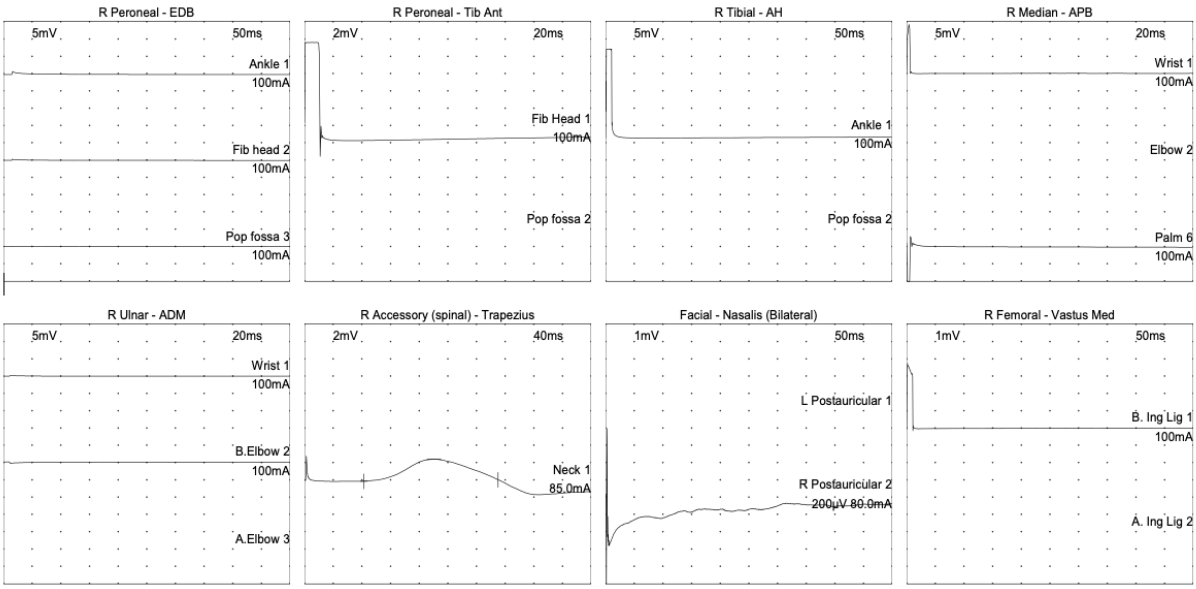

Figure 1 Motor nerve conduction studies showing no responses except for a right accessory spinal nerve with prolonged distal motor latency of 8.28 ms and low amplitude CMAP of 2.5 mV.

While waiting for the specialized demyelinating neuropathy panels, the patient was treated empirically with IV methylprednisolone 1g daily for 5 days. She was treated empirically with steroids since her clinical presentation correlated strongly to the autoimmune nodopathies and fact that nodopathies do not respond to IVIG. On Day 3 of corticosteroid treatment, she reported improved sensation. By day 9 she was able to flex and extend her knees with elimination of gravity. Upon discovery of Mayo's cell-based assay results and her severe presentation she was treated with rituximab 375 mg/m^2 IV for 4 weeks and continued the patient on methylprednisolone 1 gm IV weekly. Four weeks after initiating treatment she was able to extend one wrist, both hips and her knees with elimination of gravity. At her six-month follow-up visit, with continued methylprednisolone weekly, she was able to crochet and stand on her own.

3. Discussion

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common immune mediated radiculoneuropathy with a prevalence of 1-9 cases per 100,000. Patients with typical CIDP have progressive symmetric distal and proximal weakness in all extremities, areflexia and sensory ataxia that nadirs after 8 weeks. The immune mediated process is believed to be related to a combination of humoral and/or cellular immunity [6]. Patients with typical CIDP improve following treatment with IVIG, corticosteroids or plasma exchange [7, 8]. Oral cell-based immunosuppressant medications, e.g. mycophenolate and azathioprine, are less well studied in CIDP but are also likely effective in treating CIDP [7]. Mimics of CIDP should be considered in patients with suspected CIDP who do not respond to first line treatment and who have an atypical presentation at onset, such as the rapidly progressive weakness, tremor, or cranial nerve involvement, as observed in the described patient [1, 9]. These cases should be screened for autoimmune nodo-paranodopathies and POEMS syndrome with a demyelinating neuropathy panel, antibodies to nodal and paranodal markers (using a cell based assay with mammalian expression

vectors for NF155, CNTN1, CF186/NF140 and Caspr1), serum free light chains, VEGF levels, and if suspicious, a skeletal bone survey. POEMS has distinctive lab and electrodiagnostic findings that can be helpful [10, 11]. If a diagnosis of typical CIDP is confirmed after a negative work-up for mimics, typical CIDP patients will often improve with the switch to a second immunotherapy, e.g. replacement of IVIG with IV methylprednisolone [8].

CIDP variants are clinically suspected when the presentation is predominantly distal, multifocal, focal, pure motor or pure sensory [12]. To further clarify, variants of CIDP are considered variants since they are similar to CIDP in that they are demyelinating in nature and they share similar treatment strategies as typical CIDP but they clinically present differently typical CIDP. While patients can be diagnosed with CIDP, the nodo-paranodopathies (antibodies against contactin-1, contactin-associated protein-1, and neurofascin 155, 140, 186) are not considered variants of CIDP per the second revision of the EAN/PNS consensus guidelines on diagnosis and treatment of CIDP [12]. CIDP patients who have nodal and paranodal antibodies have a unique clinical presentation and therefore autoimmune nodopathies are considered a unique entity by the 2021 EAN/PNS consensus guidelines. The anti-contactin-1 nodopathy presents with an aggressive onset of subacute progressive predominantly motor weakness, neuropathic pain, nephrotic syndrome and sensory ataxia which does not respond or has a poor response to IVIG. The 2021 EAN/PNS consensus guidelines suggest to consider testing for nodal and paranodal antibodies in all patients with a clinical suspicion for CIDP. The guidelines also advise to conduct nodal and paranodal antibody testing in CIDP patients that are refractory to IVIG and corticosteroids, those who had an acute or subacute aggressive onset of symptoms, have a low frequency tremor, ataxia disproportionate to sensory involvement or cerebellar features, respiratory failure and cranial nerve involvement, nephrotic syndrome or very high CSF protein levels.

4. Conclusion

It is crucial for clinicians to be familiar with the autoimmune nodo-paranodopathies and variants of CIDP because treatment strategies should target the underlying pathophysiology. IVIG which is often used as first line treatment for typical CIDP does not work for treating the nodo-paranodopathies because IgG4 has a low affinity for the Fc**γ** receptor on macrophages so blocking that receptor with IVIG is an ineffective therapy [1]. Patients with autoimmune nodo-paranodopathies often respond to IV methylprednisolone and rituximab [13, 14]. While there have been reported non-responders to IV methylprednisolone, immediate treatment with high dose corticosteroids and/or plasmapheresis is indicated in clinically suspected or antibody positive patients [1]. Long term treatment is recommended with a B cell depleting therapy such as rituximab or cyclophosphamide [2, 15]. Prognosis in autoimmune nodopathies is highly dependent on early recognition of the disease since patients with prolonged disease courses and delayed treatment have poorer responses to therapy [1, 13]. Our patient was able to walk with a walker 7 months after initiation of treatment and at 15 months was ambulating independently with ankle foot orthotics but without other assistive devices.

Author Contributions

Dr. Zerebiec: Data collection, data analysis, and manuscript composition and revision. Ms. Carey: Data collection, data analysis, and manuscript composition. Dr. Kolb: Data collection, data analysis,

and manuscript composition. Ms. LaMoy: EMG/Nerve Conduction data collection, critical revision manuscript. Dr. Dubey: Laboratory data collection and critical revision manuscript. Dr. Hehir: Data collection, data analysis, and manuscript composition and revision.

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Competing Interests

Dr. Zerebiec has stock options in Squarex LLC and IGF Oncology LLC. Dr. Carey: No disclosures. Dr. Kolb: Alexion pharmaceuticals, disarm therapeutics, abalone bio, NIH Lake Champlain Cancer Research Organization, Expert witness for Ralston, Pope and Diehl. Ms. LaMoy: no disclosures. Dr. Dubey: Dr Dubey has received research support from Center of Multiple Sclerosis and Autoimmune Neurology and Grifols pharmaceuticals. He has consulted for UCB, Immunovant and Astellas Pharmaceuticals. All compensation for consulting activities is paid directly to Mayo Clinic. Dr Dubey has patents pending for Kelch-like protein 11 (KLHL11) IgG and Leucine Zipper 4 (LUZP4) IgG as markers of neurological autoimmunity. Dr. Hehir has consulted for Alexion and Argenx for unrelated myasthenia gravis projects and UCB pharma.

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