LETTER TO THE EDITOR

To The Editor

NF-155 IgG in Acute-onset Inflammatory Neuropathy: Two Cases with Relapses and Recovery

Keywords: Neurofascin-155, AIDP, CIDP, IVIg, Rituximab

IgG4 autoantibodies to neurofascin-155 (NF-155) have recently been described in a subset of patients with chronic inflammatory demyelinating polyneuropathy (CIDP). CIDP with autoantibodies to NF-155 is usually characterized by a younger age of onset, more severe disease, tremor, prominent distal weakness, ataxia, and poor response to IVIG.[1,2] While reports suggest an acute onset is more likely than in antibody negative CIDP,[3–5] little literature exists around the subsequent course of NF-155 positive cases that originally presented with an acute inflammatory demyelinating polyneuropathy (AIDP) phenotype. Herein, we describe two NF-155 positive cases with an AIDP phenotype and a relapsing disease course more consistent with acute-onset CIDP, but with excellent recovery.

The first case is of a 51-year-old male with medical history notable for hypertension and obstructive sleep apnea. He presented with a 2-week history of progressive proximal weakness without preceding infection. On initial exam, he had absent reflexes and symmetric quadriparesis with at least antigravity power. Cerebrospinal fluid showed elevated protein without leukocytes. Initial nerve conduction studies (NCS) demonstrated only a prolonged median F-wave latency (36.3 msec; normal < 33). He was diagnosed with AIDP and prescribed IVIg 2 g/kg. His weakness improved, and he went home.

Three days after discharge and 3 weeks since onset, he returned with recurrent weakness. A treatment-related fluctuation was suspected. An additional 1 g/kg of IVIg was administered without improvement. Follow-up NCS (Table 1) demonstrated prolonged F-wave latencies. Motor power continued to decline. Thus plasmapheresis was started. Additional investigations were ordered to rule out potential mimics and were noncontributory. Despite ongoing plasmapheresis, he deteriorated developing bulbar dysfunction and respiratory failure necessitating intubation. NCS in the intensive care unit 6 weeks into his illness showed interval worsening and clear features of a demyelinating neuropathy (Table 1).

At the nadir of his illness, the patient was nearly locked in with only flickers of facial and trapezius muscle activation. Steroids were added and 8 weeks into his illness, the patient began to recover. At 12 weeks, his exam showed at least 4/5 power in all limbs and return of some of his reflexes.

After completing rehabilitation, he was discharged on a 9-month prednisone taper. Four months after prednisone was stopped, the patient developed a bladder infection, fatigue, and paresthesia. His motor examination was normal including retained reflexes. NCS were normal. One month later, he returned unable to ascend stairs. Motor examination showed mild distal upper extremity and proximal lower extremity weakness with absent reflexes. NCS showed slowing of his ulnar and median motor velocities and prolonged F-waves (Table 1). Prednisone 20 mg daily and monthly IVIg 2 g/kg were initiated with subsequent improvement. Testing through Washington University Neuromuscular Laboratory returned positive for IgG4 antibodies directed against NF-155. With attempts to wean steroids, the patient experienced recurrent symptoms, leading to a trial of azathioprine and then rituximab. Since starting rituximab, he has recovered full power while tapering off prednisone and IVIg completely.

The second case is a 59-year-old healthy male who presented with a 1-week history of limb paresthesia, lower extremity weakness, and gait instability. Examination showed mild weakness of all four limbs, reduced distal sensation, and absent reflexes. Cerebrospinal fluid showed elevated protein and one leukocyte. Initial NCS were significant for mild prolongation of minimal latencies in multiple F-waves (Table 1). He was diagnosed with AIDP, started on IVIg 2 g/kg, and he improved markedly with a normal exam 3 months later in follow-up.

Six months after admission and shortly after a viral illness, he noticed ascending paresthesia in his hands and feet followed by weakness. Examination showed mild symmetric arm weakness (MRC grade 4/5) with absent or reduced reflexes. Follow-up studies (Table 1) showed improvement in the prolonged F-wave latencies without new findings of demyelination. He improved spontaneously over the next several weeks without treatment. Serum testing was positive for NF-155 IgG4 antibodies through Washington University Neuromuscular Laboratory.

NF-155 is expressed by glial cells located at paranodes where it is necessary to form septate-like axo-glial junctions.[2,6] IgG4 is the predominant autoantibody type implicated in clinical disease.[7] While the typical distinguishing clinical characteristics of NF-155 IgG4 seropositive CIDP have been described,[7] there is a lack of detailed reports on the subsequent disease course in acutely presenting NF-155 IgG4 positive neuropathies. Only three other reports[3-5] describe an acute-onset CIDP with a similar course of initial improvement followed by progressive deterioration (Table 2). In contrast to previously published reports suggesting poorer prognosis and lack of IVIg response in NF-155 CIDP, both of our patients had an initial response to IVIg and eventually had complete recovery despite relapse.

Our cases along with the previously reported cases (Table 2) suggest that in patients with an AIDP-like presentation, NF-155 IgG4 autoantibodies could be a marker of disease recurrence but do not necessarily predict a poor outcome. The first case presented here satisfies both clinical and electrophysiologic EFNS criteria for CIDP. The second case is less clear as his recurrent weakness resolved without treatment. Whether this represented a self-limited relapse in CIDP or recurrent AIDP is unclear. Regardless, both of our NF-155 positive cases had an initial AIDP-like presentation, followed by a relapsing course and excellent eventual recovery.

The clinical utility of screening acutely presenting demyelinating neuropathies for NF-155 IgG4 antibodies remains

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Table 1: Selected nerve conduction study results

Nerve studied	Case 1 – Readmission	Case 1 – In ICU	Case 1 – Relapse	Case 2 – Initial	Case 2 – Relapse	Normal values
Median Digit 2 Sensory Amplitude (uV)	28.8	NR	25.6	NR	21.6	>19
Ulnar Digit 5 Sensory Amplitude (uV)	20.0	5.2	17.0	5.2	8.4	>14
Superficial Radial Sensory Amplitude (uV)	30.9	19.4	16.2	11.7	18.9	>11
Superficial Peroneal Sensory Amplitude (uV)	16.5	8.7	8.0	1.2	3.2	>7
Sural Sensory Amplitude (uV)	8.9	7.7	13.4	7.5	7.0	>4
Median APB DML (ms)	4.3	5.6	4.1	4.8	4.1	<4.6
Median APB CMAP at Wrist (mV)	10.4	2.4	11.0	7.4	8.6	>5.9
Median APB CMAP at Elbow (mV)	10.0	1.7	10.2	7.0	8.5	
Median APB CV in Forearm (m/s)	48	39	45	50	50	>47
Ulnar ADM CMAP at Wrist (mV)	10.1	1.8	9.5	6.0	9.1	>7.9
Peroneal EDB CMAP at Ankle (mV)	5.9	2.0	5.1	7.3	6.1	>2.5
Tibial AH CMAP at Ankle (mV)	12.2	5.6	8.8	8.3	9.4	>5.3
Median Minimal F-Wave Latency (ms)	42.3	NR	39.5	37.6	32.8	<33
Peroneal Minimal F-Wave Latency (ms)	70.0	NR	58.3	57.9	56.6	<59
Tibial Minimal F-Wave Latency (ms)	71.4	NR	65.6	64.9	62.9	<61
Ulnar Minimal F-Wave Latency (ms)	41.6	NR	38.6	37.7	36.5	<36

ADM = abductor digiti minimi; AH = abductor hallicus brevis; APB = abductor pollicus brevis; CMAP = compound muscle action potential; CV = conduction velocity; DML = distal motor latency; EDB = extensor digitorum brevis; ICU = intensive care unit; NR = no response.

Table 2: Literature presenting cases with NF-155 IgG positive acute or subacute neuropathy

Paper	Patients with acute, AIDP-like, or subacute onset (out of total reported)*	IgG, G4 subtype	IVIg response	Relapse
Case series including acute and/or AIDP-like presentations				
Querol et al., 2014	1/4	Yes	No	Yes
Demichelis et al., 2018	1/1	Yes	Initial response, but not at relapse	Yes
Caetano et al., 2019	1/1	IgG positive, subtype not stated	Initial response, but not at relapse	Yes
Ng et al., 2012	2/8	Acute patients not IgG4 positive	Not described	Not described
Zhang et al., 2019 [8]	1/6	Yes	No	Not described
Case series with subacute presentations				
Ogata et al., 2015	1/13	Yes	4/13†	Not described
Devaux et al., 2016	12/38	Yes	5/25†	1/38†
Burnor et al., 2018	1/4	Yes	No	3/4†

*acute onset includes presentations peaking within 4 weeks or authors describing the presentation as such. AIDP-like onset includes presentations diagnosed as AIDP or GBS or authors describing the presentation as such. Subacute includes presentations peaking between 4 and 8 weeks.
†IVIg responsive patients and patients that relapsed were not stratified by presentation type.

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uncertain. A previous study testing for NF-155 antibodies in AIDP found positive antibodies in only 2/65 patients.[6] The sensitivity of such testing is therefore likely low. However, when clinical follow-up was available, all other reported cases with an acute or AIDP-like initial phenotype and positive NF155 eventually relapsed (see Table 2) suggesting the recurrence risk is high. Nonetheless, it is unclear if chronic immunosuppressive therapy would have an effect on outcome, especially in light of the excellent recovery in both cases presented here. Further studies looking not only at the prevalence of antibody positivity in acute inflammatory neuropathies but also the risk of recurrence and long-term prognosis in this patient group would be important to determine if widespread screening could result in meaningful changes in management.

Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

Authorship Statement

MH and AJA drafted the initial version of the manuscript and the first table. CH created the second table. MH, AJA, and CH all participated critical revisions of the manuscript.

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