Optic Nerve Demyelination in IgG4 Anti–Neurofascin 155 Antibody–Positive Combined Central and Peripheral Demyelination Syndrome

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ABSTRACT

Optic nerve demyelination is one of the clinical features of combined central and peripheral demyelination (CCPD), an entity with heterogenous immunopathogenesis and clinical characteristics, overlapping between multiple sclerosis (MS) and chronic inflammatory demyelinating polyneuropathy (CIDP). Of interest, earlier studies among patients with CIDP prior to discovery of antibodies against paranodal protein neurofascin 155 (anti–NF 155) also reported optic nerve dysfunction. We aimed to evaluate optic nerve demyelination among anti–NF 155 CIDP patients. We studied 2 patients with anti–NF 155 CIDP using visual-evoked potentials (VEP) and optical coherence tomography (OCT). Both patients had distal acquired demyelinating symmetric (DADS) subtype CIDP. Other common features were prominent sensory ataxia, hand tremors, significantly elevated cerebral spinal fluid protein, high titre anti–NF 155 antibodies and poor response to corticosteroid and intravenous immunoglobulin (IVIg). No central nervous system neuroradiological abnormality detected. Both had normal visual acuity and colour vision, but one had subclinical right relative afferent pupillary defect (RAPD). VEP of both showed bilateral prolonged P100 latencies. OCT for patient with RAPD demonstrated moderate to severe retinal nerve fibre layer (RNFL) thinning. Identification of optic nerve demyelination among subclinical CIDP with anti–NF 155 antibodies expanded the spectrum of demyelination within the subset of CCPD.

KEYWORDS: combined central and peripheral demyelination, optic nerve demyelination, chronic inflammatory demyelinating polyneuropathy, neurofascin 155, paranodopathy

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Introduction and Aims

Combined central and peripheral demyelination (CCPD) is an entity with heterogenous immunopathogenesis and clinical characteristics, overlapping between multiple sclerosis (MS) and chronic inflammatory demyelinating polyneuropathy (CIDP).[1] The underlying immunopathogenesis remains unknown and no biomarkers have been found. A common manifestation of the 2 contributing entities is optic nerve demyelination. Although predominantly seen among MS patients, optic nerve demyelination was also reported previously among patients with peripheral demyelination.[2-5] To confirm this association, a recent study conducted from Germany using enhanced multifocal VEP technique found no difference in VEP latencies and amplitude as well as low-contrast visual acuity between treatment responsive CIDP patients and controls, refuted earlier findings.[6] However, previous studies on optic pathway dysfunction on among CIDP patients were prior to discovery of autoantibodies against paranodal/nodal proteins and visual sensory impairment among CIDP with autoantibodies was not specifically investigated.[2-4] One recently published case series from Japan investigating the involvement of cranial nerves among 13 CIDP patients with anti–neurofascin 155 antibody (anti–NF 155) found that up to 76.9% of the patients had abnormal VEP findings but only 23.1% had apparent visual impairment.[5] Of interest, antibodies against neurofascin 155 were subsequently detected among subset of patients with CIDP and MS, and therefore, also found among patients with CCPD but clinical distinction between CCPD with and without these antibodies remains unclear.[7,8] Likewise, whether optic nerve demyelination in CCPD belongs to part of MS or an extension of a greater spectrum of CIDP remains uncertain.

We report 2 male patients who presented initially with chronic progressive distal acquired demyelinating symmetric neuropathy (DADS), with subsequent identification of subclinical optic nerves demyelination and detection of high titre IgG4 anti–NF 155 antibodies, unveiling a subset of antibody-mediated CCPD syndrome with predominant peripheral nerve paranodopathy.

Case Report

Case 1

25-year-old male patient presented with progressive symmetrical distal lower and upper limb weakness in August 2015, one month following yellow fever vaccination. Distal power (abductor pollicis brevis, first dorsal interossei, abductor digiti minimi and wrist extensors) was 4/5 on MRC grading with wasting and areflexia. There was prominent sensory ataxia and bilateral fingers tremor. Cerebral spinal fluid (CSF) protein was elevated (900 mg/dL) with zero cell count. Nerve conduction study (NCS) showed diffuse symmetrical sensorimotor polyneuropathy of demyelinating range, fulfilling definite European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP. Treatment with regular high dose intravenous immunoglobulins (IVIg) treatment over the next 18 months in addition to corticosteroid maintenance therapy proved unhelpful. Upon referral to our centre, he had subtle right relative afferent pupillary defect (RAPD) but otherwise normal visual acuity and colour vision. Other cranial nerves were normal. Brain and whole spine MRI were normal. Serum IgG 4 against NF 155 was positive with titre 1:24 300. Visual-evoked potentials (VEP) showed prolonged P100 latencies suggestive of bilateral optic nerve demyelination (right 124.0 ms, left 132.0 ms) (Figure 1(a)). Optical coherence tomography (OCT) showed normal retinal nerve fibre layer (RNFL) at all quadrants (average thickness right 101 µm and left 96 µm). Following that, he received IV rituximab maintenance with stabilisation of disease.

Case 2

26-year-old male patient presented in April 2012 with progressive onset numbness and weakness in all limbs following an episode of febrile illness. Over the next 2 months, he developed tremor at both hands. Similarly, he had predominantly distal weakness. There was generalized areflexia with sensory loss in a stocking distribution and ataxia. Cranial nerves examination was normal. NCS showed diffused demyelinating changes in upper limbs and absent of motor responses in lower limbs. CSF protein was elevated (610 mg/dL). His serum IgG 4 against NF 155 was positive with titre 1:8100. MRI Brain and spine was normal while VEPs showed prolonged P100 latencies bilaterally (right 118.2 ms, left 119.4 ms) Figure 1(b). Assessment by neuro-ophthalmologist revealed normal visual acuity, colour vision but abnormal OCT demonstrated moderate RNFL thinning in the right nasal and severe thinning over the left superior and inferior quadrant (average thickness right 82 µm and left 75 µm) (Figure 2). He received oral corticosteroid and azathioprine for more than 3 years, however, with no sustainable improvement. Treatment with high dose IVIg therapy did not demonstrate positive response. Following that, he received 1 cycle of plasma exchange, followed by rituximab maintenance for 2 years, with stabilisation of disease.

Discussion

We characterized optic nerve demyelination among CIDP patients with positive anti–NF 155 antibodies without CNS involvement, unveiling an underlying CCPD.

Before the description of CCPD and discovery of IgG4 paranodal/nodal antibodies, evidence of optic nerve involvement among CIDP patients was conflicting.[2-6] One study reported close to half of CIDP patients had increased latencies on VEP despite largely subclinical.[2] However, up to 23% had significant T2-hyperintense lesion on brain MRI. Another study using enhanced multifocal VEP technique has, however, refuted the involvement of optic nerve in treatment responsive CIDP.[6] Newer report from another CIDP cohort continues to produce inconsistent conclusion.[9] Despite that, occurrence of optic nerve pathway dysfunction among CIDP patients with paranodal/nodal antibodies which can be found in up to 20% of patients has not been specifically studied.[10] Whether previously reported cases of CIDP with optic nerve abnormalities were subset of CCPD with predominantly MS manifestation or in association with anti–NF155 antibodies remained uncertain.

Table 1 shows the comparison of visual symptoms, MRI optic lesion and VEP findings in relation to anti–NF 155 antibodies among CCPD/CIDP patients from major published cohorts. Following characterization of central and peripheral criteria defining CCPD among 40 Japanese patients, visual disturbance was reported in 19 (47.5%) patients, in which 14 also had abnormal VEP from a subgroup of 30 patients (73.3% fulfilled McDonald's

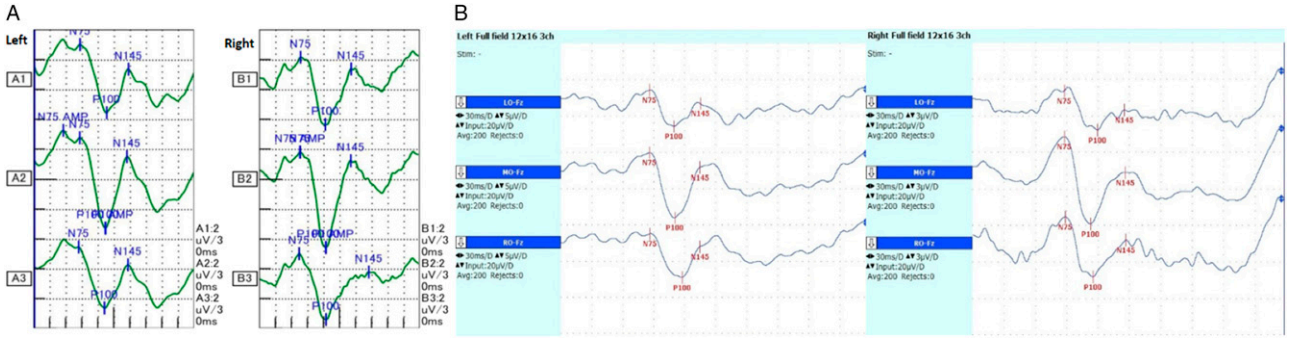

Figure 1. (a) Visual-evoked potentials (VEPs) showed prolonged P100 latencies suggestive of bilateral optic nerve demyelination (right 124.0 ms, left 132.0 ms), (1) (right 118.2 ms, left 119.4 ms).

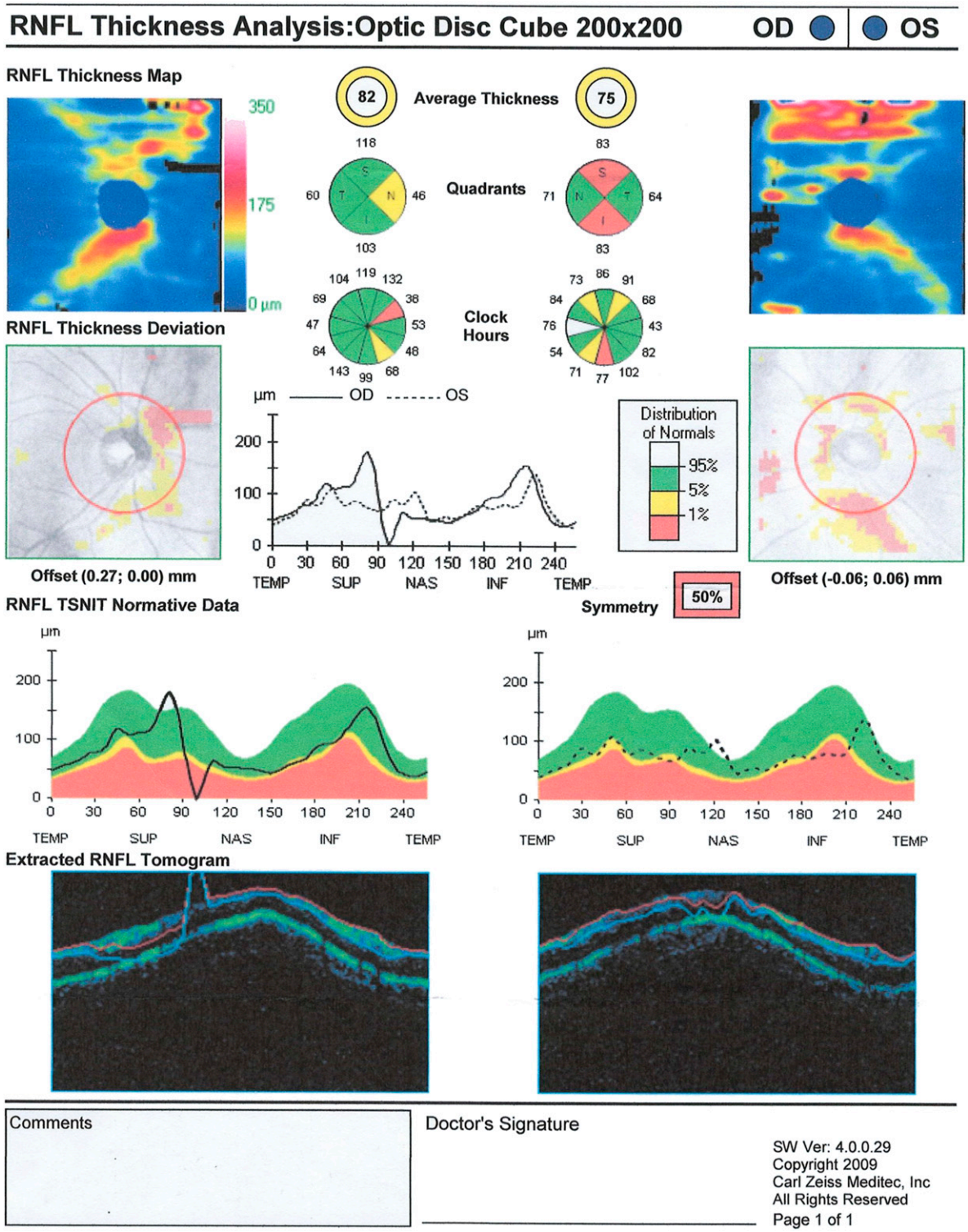

Figure 2. Abnormal OCT demonstrated moderate RNFL thinning in the right nasal and severe thinning over the left superior and inferior quadrant (average thickness right 82 µm and left 75 µm).

criteria for MS) with separated onset of central and peripheral nervous system manifestations. In contrast, only one from the simultaneous onset group of 8 patients (50% fulfilling MS criteria) had subclinical abnormal VEP. Abnormal optic nerve lesions on MRI were much lower (7/38, 18.4%).[1] Only five of 11 patients were tested positive for NF 155 antibody, but detailed analysis on their visual pathway involvement in this subgroup was not performed. From a recent analysis of 22 Chinese CCPD patients, 50% had abnormal VEPs study but only 18% were reported to have visual symptoms, all diagnosed under primarily CNS demyelinating group.[11] Likewise, 9/14 (64.3%) CCPD patients from a cohort of 31 Italian patients were mostly

Table 1. Visual symptoms, MRI optic lesion and VEP findings in relation to anti-NF 155 antibodies among CCPD/CIDP patients from major published cohorts.

	OGATA H ET AL, 2016	CORTESE A ET AL, 2016	WANG YQ ET AL, 2018	OGATA H ET AL, 2020
Number of patients	40	31	22	13
Neurofascin 155	5/11 (45.5%)	N/A	N/A	13
Visual disturbance	19 (47.5%)	N/A	4 (18.2%)	2 (15.4%)
Unilateral	9 (47.4%)	—	2 (9.1%)	N/A
Bilateral	10 (52.6%)	—	2 (9.1%)	N/A
MRI optic lesion	7/38 (18.4%)	N/A	0	0
VEPs	15/21 (71.4%)	9/14 (64.3%)	11 (50%)	10 (76.9%)
Unilateral	7 (46.7%)	0	N/A	3 (23.1%)
Bilateral	8 (53.3%)	9/14 (64.3%)	N/A	7 (53.8%)

N/A, Not available; VEP, visual-evoked potentials; CCPD, combined central and peripheral demyelination; CIDP, chronic inflammatory demyelinating polyneuropathy.

asymptomatic despite abnormal VEPs bilaterally.[12] Anti–NF 155 was not tested among the Chinese and Italian cohorts. No OCT result was presented in any of the studies above despite significant number of patients with optic nerve demyelination. Nonetheless, these studies indicated a significant number of CCPD with optic pathway dysfunction were asymptomatic at the time of assessment, consistent with findings among our patients. Large majority of CCPD patients with visual pathway dysfunction had primarily CNS demyelination.

From predominant CIDP perspective, most recent case series investigating cranial nerves involvement among 13 CIDP patients with anti–NF 155 positive found a high frequency of subclinical VEP abnormalities of up to three-fourth in addition to abnormal blink reflexes.[5] Only 2 of the patients had T2-hyperintense ovoid lesions suggestive of demyelination. These findings are consistent with the presentation in our patients, suggesting the frequent involvement of optic nerves in patients with anti–NF 155 antibodies.

In conclusion, there may be a subset of patients with anti–NF 155 within the spectrum of CCPD exhibiting optic nerve dysfunction without apparent visual manifestation. A better classification and refinement of the clinical definition of this unique multifaceted disease entity is needed in relation to the pathogenicity role of antibody to paranodal/nodal protein.

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