ESETISMERTETÉS
CASE REPORT

Recurrent simultaneous central nervous system demyelination with possible peripheral demyelination / nodopathy in a seronegative patient

Berin INAN[1], Can Ebru BEKIRCAN-KURT[1], Fatma Gokcem YİLDİZ[1], Rahsan GOCMEN[2], Cagri Mesut TEMUCİN[1], Asli TUNCER[1], Ersin TAN[1], Sevim ERDEM-OZDAMAR[1]

[1]Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[2]Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Correspondent:
Berin INAN, MD,
Department of Neurology,
Gulhane Faculty of Medicine,
University of Health Sciences,
06010, Kecioren, Ankara,
Turkey
E-mail: berin.inan@yahoo.com
https://orcid.org/0000-0002-2758-0207

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Combined central and peripheral demyelination (CCPD) is a rare disease entity. Onset with the simultaneous central nervous system (CNS) and peripheral nervous system (PNS) involvement and its recurrence are exceptional. Anti-neurofascin antibodies have been shown to be present in up to 70% of cases, yet seronegative patients also exist. We present a case of seronegative recurrent CCPD. The PNS involvement was compatible with two episodes of recurrent Guillain-Barre syndrome (GBS), whereas the CNS involvement pattern was not typical for either multiple sclerosis (MS) or acute disseminated encephalomyelitis. The prognosis was excellent with pulse methylprednisolone, intravenous immunoglobulin, and plasmapheresis. This case highlights the varied clinical presentations of CCPD, extending beyond the realms of MS and chronic inflammatory demyelinating polyneuropathy, and underscores the potential for relapse. Importantly, to the best of our knowledge, this represents the inaugural instance of CCPD featuring PNS involvement in the form of recurrent GBS.

Keywords: combined central and peripheral demyelination, seronegative, recurrent Guillain-Barre syndrome

Visszatérő, egyidejű központi idegrendszeri demyelinisatio perifériás demyelinisatióval/nodopathiával – egy szeronegatív beteg esete

Inan B, MD; Bekircan-Kurt CE, MD, PhD-c; Yildiz FG, MD, PhD; Gocmen R, MD; Temucin CM, MD, PhD; Tuncer A, MD; Tan E, MD; Erdem-Ozdamar S, MD

A kombinált centrális és perifériás demyelinisatio (CCPD) ritka kórkép. A központi idegrendszer (CNS) és a perifériás idegrendszer (PNS) egyidejű érintettségével járó betegségkezdet és kiújulás kivételes. Az esetek 70%-ában kimutatták az antineurofascin antitestek jelenlétét, de léteznek szeronegatív betegek is. Bemutatunk egy szeronegatív recidiváló CCPD-esetet. A PNS érintettsége összeegyeztethető volt a visszatérő Guillain–Barré-szindróma (GBS) két epizódjával, míg a CNS érintettségi mintázata nem volt jellemző sem a sclerosis multiplexre (SM), sem az akut disszeminált encephalomyelitisre. A prognózis pulzáló metilprednizolon-, valamint intravénás immunglobulin-kezelés és plazmaferézis mellett kiváló volt. Ez az eset rávilágít a CCPD változatos klinikai megjelenésére, ami túlmutat az SM és a krónikus gyulladásos demyelinizáló polyneuropathia területén, és hangsúlyozza a relapszus lehetőségét. Tudomásunk szerint ez az első olyan CCPD-s eset, ami visszatérő GBS formájában jelentkező PNS-érintettséggel jár.

Kulcsszavak: kombinált centrális és perifériás demyelinisatio, szeronegatív, visszatérő Guillain–Barré-szindróma

Demyelinating disease usually affects either the central or peripheral nervous system (CNS and PNS, respectively) because their myelin content and antigenic properties are different[1]. Therefore, combined central and peripheral demyelination (CCPD) is considered an extremely rare condition[1–3]. Motor weakness, sensory and gait disturbances are common symptoms of CCPD[1, 4]. The clinical course may be monophasic or relapsing-remitting, and onset with simultaneous CNS and PNS manifestations is seen in about 20% of cases[1]. In addition, the traditional classification of neuropathies as demyelinating and axonal has been challenged with the introduction of nodo-paranodopathies[5]. Antibodies against nodo-paranodal proteins, such as neurofascin 186 (NF186), neurofascin 155 (NF155), contactin-1 (CNTN1), and contactin-associated protein-1 (Caspr1), have been described[6]. Nodo-paranodopathies present distinct clinical phenotypes, magnetic resonance imaging (MRI) characteristics, and electrophysiological findings[7]. NF155 IgG4 antibody is the most common antibody in autoimmune nodopathies. Characteristic findings include distal predominant motor weakness, tremors, cerebellar dysfunction, and autonomic disfunction. MRI studies may reveal root, plexus, and cranial nerve hypertrophies, along with contrast enhancement. Nerve conduction studies demonstrate demyelinating features and reversible conduction blocks. Denervation potentials and spontaneous activity can be found on needle electromyography[8, 9].

In this report, we present a patient with recurrent simultaneous central demyelination and possible peripheral demyelination / nodopathy.

Case report

An eighteen-year-old male was presented with progressive weakness and respiratory compromise. He had complaints for a week and was deteriorating. The motor strength was bilaterally 2/5 proximally and 3/5 distally in all extremities according to Medical Research Council (MRC) scale. Sensory examination was normal, deep tendon reflexes (DTR) were absent. His medical history and blood workup were unremarkable, with no reported infections or other precipitating factors. The cerebrospinal fluid (CSF) protein level was high (288 mg/dl), IgG index was normal, and oligoclonal band (OCB) was type-4 positive. Distal motor latencies (DML) of right median, ulnar, tibial, and peroneal nerves, and F-wave latencies of right median and ulnar nerves were prolonged. F-waves of right tibial and peroneal nerves could not be obtained. Right median, tibial, and peroneal compound muscle action potential (CMAP), median and ulnar sensory nerve action potential (SNAP) amplitudes were decreased, while right sural SNAP was spared. The median, tibial, and peroneal motor, the median and ulnar sensory nerve conduction velocities (NCV) were mildly slowed. There was a severely reduced recruitment pattern in tibialis anterior (TA) muscle in needle electromyography (EMG). The results were compatible with acute inflammatory demyelinating polyneuropathy (AIDP). The patient was intubated because of rapidly progressive respiratory insufficiency on the day of hospital admission. Intravenous immunoglobulin (IVIg) was initiated (0.4 g/kg/day). He was extubated after IVIg treatment. However, he experienced sudden central visual loss in the left eye. Brain and orbital MR images are presented in **Figure 1A–G**. The cervical, and thoracic spinal MRIs were normal. Visual evoked potentials showed no response in the left eye, and normal P100 latency and amplitude in the right. He completely recovered, and contrast enhancement of demyelinating lesions decreased after five days of pulse methylprednisolone (1000 mg/day) treatment.

Twelve years later, he presented with severe headache, generalized weakness, and respiratory insufficiency. There were no clinical relapses during 12-year yearly neurological follow-ups. There was no history of infections or vaccinations. Bilateral shoulder abduction was 2, elbow flexion and extension were 3, hip flexion was 3, and foot dorsiflexion was 4 according to the MRC motor scale. DTRs were hypoactive. Vibration sensation was diminished bilaterally in the toes. Left peripheral facial paralysis and decreased gag reflex were also noted. The NCS revealed mildly reduced SNAP amplitudes, and F-wave latencies of right ulnar and median nerves were close to upper limit. Again, right sural SNAP was spared. Severely reduced recruitment patterns were observed in the biceps brachii and first dorsal interosseous muscles on needle EMG. CSF protein (305 mg/dl) and IgG index (1, normal:0.30-0.85) were high, and OCB was type-4 positive. NF155, NF186 IgG antibodies, myelin oligodendrocyte glycoprotein, and aquaporin-4 antibodies were negative. Brain MR images are shown in **Figure 1H–J.** Cervical MRI was normal, and thoracolumbar MRI revealed thickening and contrast enhancement of the cauda equina nerve roots **(Figure 1K)**. IVIg was initiated. Three days later the patient was intubated due to carbon dioxide retention. He underwent seven sessions of plasmapheresis. NCSs repeated on the tenth day of admission revealed prolonged DMLs in right median, tibial, and peroneal nerves, and prolonged F-wave latencies in median and ulnar nerves. The F-waves of peroneal and tibial nerves were absent. The median, ulnar, and peroneal CMAP amplitudes, and right sural SNAP amplitudes were reduced. A probable conduction block was observed in the right tibial nerve. All motor and sensory NCVs were normal. Needle EMG revealed mild fibrillation potentials, positive sharp waves, and a reduced recruitment pattern at the TA and vastus medialis (VM). None of the NCSs of the patient met temporal disper-

sion criteria: temporal dispersion in the peroneal nerve increased from 3% to 19% and from 3% to 28% in the tibial nerve within ten days. However, with delayed DMLs and CMAP duration prolongation on second EMG, we classified the patient as AIDP without conduction failure.

He was extubated after seven plasmapheresis sessions. Maintenance treatment was planned as twice-weekly IVIg and daily methylprednisolone (0.8 mg/kg/day). Two months later motor strength was 4/5 in upper extremities bilaterally and 4/5 in proximal and 5/5 in distal lower extremities according to the MRC scale. The CSF protein was 87.21 mg/dl, IgG index was normal, and OCB was negative. After six months, the patient completely recovered, maintenance treatment was stopped. Brain MRI showed only sequela T2 hyperintense lesions, and electrophysiological parameters significantly improved.

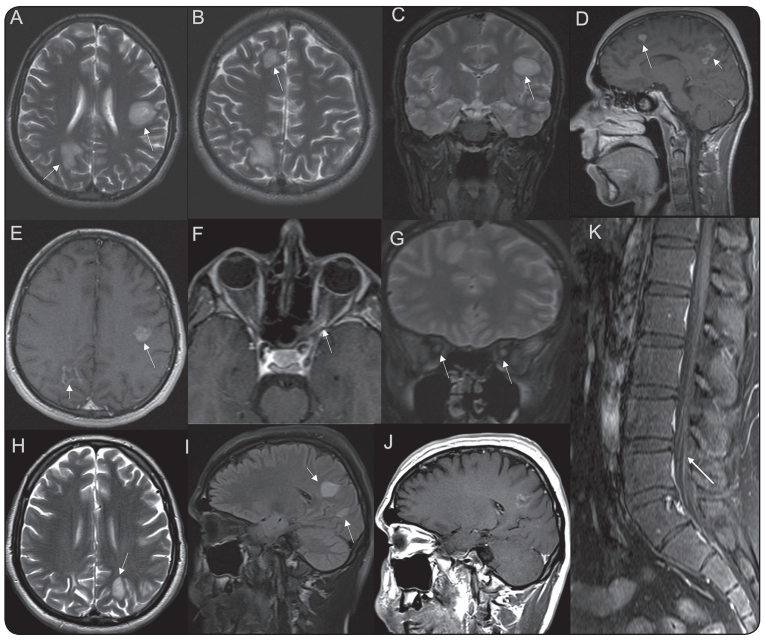

Figure 1. *Magnetic resonance imaging (MRI) of the patient in 2003* **(A–G)** *and in 2015* **(H–K).** *Axial* **(A, B)** *and coronal* **(C)** *T2-weighted images show multiple juxtacortical T2-hyperintense inflammatory-demyelinating lesions (arrows). The sagittal* **(D)** *and axial* **(E)** *post-contrast T1-weighted images depict open-ring (short arrow) and solid nodular (long arrow) contrast enhancement of the lesions. Orbit MRI (F, G) reveals contrast enhancement* (**F**, *arrow*) *and T2-hyperintensity* (**G**, *arrows*) *of the left optic nerve consistent with optic neuritis. Brain MRI performed during the second attack shows new juxtacortical T2-lesions* (**H, I**; *arrows*)*, and contrast enhancement in T1-weighted* **(J)** *images. Post-contrast sagittal T1-weighted image reveals cauda equina nerve root contrast enhancement* (**K**, *arrow*)

Discussion and conclusion

We presented a case of recurrent simultaneous CCPD. CCPD is a distinct disease entity rather than a mere coincidence of specific demyelinating diseases[1, 2]. Although anti-neurofascin antibodies are present in 45.5 – 71.4% of patients with CCPD[1, 2], seronegative cases also exist[3, 10–12].

There are few reports of patients with simultaneous Guillain-Barre syndrome (GBS) and acute disseminated encephalomyelitis (ADEM). The reported patients are from the pediatric population and generally have poor outcome[4]. In our case, especially in the second episode, one might consider distinguishing between nodopathy and AIDP without conduction failure. In the second EMG of the second episode, distal motor latencies in the median, tibial, and peroneal nerves, and F-wave latencies of the median and ulnar nerves were prolonged. The F-waves of the peroneal and tibial nerves were absent. The median, ulnar, and peroneal CMAP amplitudes and right sural nerve SNAP amplitudes were reduced. However, NCVs were still within the normal range for all nerves. Temporal dispersion may also aid in distinguishing conduction failure in demyelinating neuropathy from conduction failure in nodopathies[13]. In our patient, none of the NCSs met the temporal dispersion criteria. It has been shown that nodopathies have a favorable prognosis, axonal degeneration does not develop, and nodal and motor functions rapidly recover[14]. However, motor recovery of our patient took approximately six months. Therefore, considering the delayed distal motor latencies and CMAP duration prolongation on the second EMG, lack of conduction blocks, long recovery time, and the absence of well-known antibodies related to nodopathies, we classified the patient as having AIDP without conduction failure. Moreover, the CNS involvement pattern was not typical for either multiple sclerosis (MS) or ADEM. The prognosis was favorable, unlike in pediatric cases[4]. We diagnosed the patient with recurrent GBS rather than CIDP because of acute onset, facial nerve involvement, severe autonomic instability, and respiratory failure requiring mechanical ventilation. Besides, electrophysiological testing was almost normal between the two attacks[15].

Simultaneous demyelination of the CNS and PNS is rare, and recurrence of this phenomenon is even more exceptional[16]; thus, our patient is unique in this respect. The treatment response was excellent in both attacks similar to former report[16].

In conclusion, CCPD may manifest with clinical pres-

entations different from those of MS and CIDP. Some cases may be negative for anti-neurofascin antibodies. In these instances, biobanks play a crucial role in advancing neuroimmunology research by providing a diverse collection of biological samples from individuals with neurological disorders. This enables the identification of novel antibodies and biomarkers associated with neuroimmunological conditions, contributing to the development of more accurate diagnostic tools and targeted therapies. However, being unable to test for antibodies, other than anti-neurofascin, directed against nodal/paranodal proteins was a limitation of our case. Nevertheless, we believe that our case contributes to the understanding of the scope of CCPD.

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