

## DEMYELINATION OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM: A CASE REPORT

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Inflammatory demyelinating diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), acute inflammatory demyelinating polyradiculoneuropathy (AIDP), and chronic inflammatory demyelinating polyneuropathy (HIDP) are autoimmune diseases that affect the peripheral or central nervous system. In rare instances, demyelination may damage simultaneously the peripheral and central nervous system. Peripheral and central myelin have different protein components, but they also have some common ones such as myelin basic protein (MBP), myelin-associated glycoprotein (MAG), and neurofascin. Therefore, abnormal autoimmune responses against common antigens are suspected in the pathogenesis of demyelinating diseases with simultaneous central and peripheral nervous system involvement (1-3).

In this paper, the case of a female patient was presented, whose neurologic finding showed the signs of peripheral and central nervous system damage existent at the same time, which was confirmed using electroneuromyography and magnetic resonance imaging of the brain. In terms of differential diagnosis, we took into consideration AIDP, HIDP, and other acquired demyelinating polyneuropathies that can occur concurrently with central nervous system demyelination and are very rare entities.

In our female patient, the final diagnosis was made of a rare form of acute inflammatory demyelinating polyneuropathy with central nervous system demyelination. Establishing the final diagnosis was a key step in the management of the patient, since treatment protocols differed in the above demyelinating diseases.

Further research should focus on autoantibodies targeting directly the common myelin epitopes in the Schwann cells of the peripheral nervous system and oligodendrocytes of the central nervous system (21). *Acta Medica Medianae* 2017;56(1):39-43.

**Key words:** demyelination, central, peripheral, nervous, system

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### Introduction

Inflammatory demyelinating diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy (HIDP) are all autoimmune diseases that affect and damage the peripheral or central nervous system.

In chronic, immune-mediated polyneuropathies, the presence of IgM antibodies against neural antigens such as myelin-associated glycoprotein (MAG), sulfatide and ganglioside GM1, GM2, GD1, GD1b has been documented (1-3).

In patients with Guillain-Barre syndrome, antibodies are directed against gangliosides GM1, GM1b, GD1a, GD1b, GT1a, GT1b, GQ1b, which correlates with the acute motor conduction block (4). In patients with neuromyelitis optica, the presence of antibodies against aquaporin 4 (AQP4 Abs) has been proven, but recently the antibodies against myelin oligodendrocyte protein (MOG Abs) have been evidenced as well. Kitley et al. have studied the basic characteristics of patients with NMO and MOG Abs and compared them with the patients with positive AQP4 Abs, drawing the conclusion that those with MOG Abs had more favorable outcomes (5). In the CNS sera of patients with MS, Siravasta et al. have identified specific antibodies against glial potassium channels – KIR 4.1 (6, 7).

However, there have been papers in the available literature describing the cases with associated MS and Guillain-Barre syndrome. In their early reports in 1958, Hasson et al. demonstrated demyelinating changes in the peripheral nerves in MS patients, which was confirmed on autopsy as well (8). Biopsies of the sural nerve in 10 patients with MS demonstrated myelin changes in peri-

peripheral nerves as well (9). Capello *et al.* presented the case of a female patient with relapsing-remitting form of MS and clinical picture of acute severe quadriplegia. A CSF examination, electroneuro-myography, and sural nerve biopsy demonstrated the axonal form of Guillain-Barre syndrome in the same patient. Trapanio *et al.* showed two patients with the diagnosis of MS and peripheral demyelinating polyneuropathy and concluded that these conditions may have a similar underlying pathogenic mechanism in terms of activation of a non-specific inflammatory cascade responsible for demyelination, axonal loss, and disease progression (10, 11).

Lassman *et al.* reported the patients with CNS demyelination and inflammatory demyelination and remyelination of the spinal nerve roots. The lesions of the peripheral nervous system took the form of inflammation, demyelination, and remyelination (12). Mao *et al.* used a web site database containing scientific articles about six presented cases with GBS and acquired demyelination of the CNS. An analysis of clinical and prognostic data was performed. Transverse myelitis was the most common demyelinating syndrome in patients with GBS and demyelination of the CNS. Patients with Miller-Fisher syndrome and acquired demyelination of the CNS were predominantly female, middle-aged, and with prevalent involvement of the subtentorial region. The predictor of poor prognosis was a sensory damage, while visual deficits usually meant more favorable prognosis. Patients with Miller-Fisher syndrome predominantly had the involvement and changes in the brainstem (13).

MS and HIDP are the diseases mediated via T-cell immunity, which is specific to myelin antigens. Peripheral and central myelin have different protein components, but they also have some common ones, such as myelin basic protein (MBP) and myelin-associated glycoprotein (MAG). Therefore, an abnormal autoimmune response to common antigens should be suspected in the pathogenesis of these diseases (14-16). Yoko *et al.* published their nerve conduction study performed on 58 patients diagnosed with MS and 23 with NMO in order to detect peripheral neuropathy. They studied the basic characteristics and differences of peripheral neuropathy as a complication of MS and NMO. The total of 9 patients, 6 with MS and 3 with NMO diagnosis, fulfilled the criteria for HIDP. Nerve conduction examination findings did not differ significantly in the group of MS patients as compared to NMO ones (17). Concomitant demyelination in the central and peripheral nervous systems is a very rare phenomenon. In a small number of cases, HIDP may be accompanied with CNS involvement, with clinical signs of optic nerve disease, hyperreflexia, positive Babinski sign, and MRI abnormalities of the CNS in the form of demyelinating plaques. However, it is still not quite clear whether the combination of these signs represents one and the same disease or it is just a coin-

idence. Some of the recent studies have proven the presence of neurofascin, an autoimmune target antigen (IgG4 antibodies against neurofascin-155) in patients with concomitant signs of damage to the central and peripheral nervous system. It is in fact a new entity, HIDP, characterized by demyelination of the CNS as well. It manifests in the form of a chronic progressive distal sensorimotor, predominantly sensory polyneuropathy with severe tremor and electrophysiologically confirmed demyelination. A good therapeutic response can be achieved by administering corticosteroids or with therapeutic plasma exchange (18-20).

The group of acquired demyelinating neuropathies with possible concomitant damage to the central nervous system as well are anti-MAG neuropathies, in which IgM antibodies against myelin-associated glycoprotein (MAG) – a membrane protein involved in the process of myelination – can be demonstrated in the serum. This type of neuropathy usually occurs around the age of 50. Clinically, it presents as a distal symmetrical sensorimotor, prevalently sensory neuropathy with ataxia and pain. Electrophysiologically, demyelination predominates (very prolonged distal latencies, slow conduction velocities, temporal dispersion, without conduction blocks), while in later stages of the disease a secondary axonal degeneration occurs. Intravenous immunoglobulins (IVIg) and rituximab are the principal therapeutic agents.

Combined demyelination in the CNS and PNS expands the range of demyelinating diseases, and may be suspected in patients with GBS who develop the symptoms of encephalopathy. In GBS and ADEM, the autoantibodies detected in CNS demyelination have not been observed. Future research should focus on autoantibodies directly targeting the myelin epitopes in the Schwann cells of the peripheral nervous system and oligodendrocytes of the central nervous system (21).

### Case report

A 42-year-old female patient was hospitalized at the Clinic of Neurology, Clinical Center Niš, in December 2012, complaining of weakness and numbness in her arms and legs.

A detailed patient history revealed that the reported symptoms had appeared acutely a week before the admission, in the form of foot numbness and with gradual expansion upwards to the knee level. Further on, she had felt numbness and pain in her upper limbs and instability while walking. Prior to the onset of all these symptoms, the patient had had a cold.

Our neurological examination revealed the following in the upper limbs (GE): global weakness, prevalent of distal segments at the grade level 4; stretch reflexes (MTRs) were generally low, but readier in the right arm and right leg, with a conspicuous dorsal flexion of the big toe to the right. In the lower limbs (DE), weakness of the proximal and distal segments was at the grade

level 3. There was an ataxic, wide-based gait present. Vibration sensitivity shortened to the ankle level – grade 2; to the level of spina iliaca anterior superior – grade 4. Cranial nerve findings were in order. Cerebellar tests on the right were positive. The neck was free, meningeal signs were negative.

On the basis of the patient's medical history and neurological findings, the working diagnosis of AIDP was proposed, but because of the acute onset and signs of damage to the pyramidal system, the differential diagnosis of MS was taken into consideration as well, and further patient management was conducted accordingly.

Laboratory analysis: Glucose, Urea, Crea, AST, ALT, GGT, LDH, HBDH, CK, CK-MB, Na, K, Ca, Mg, ESR, CRP, CBC and Le formula were within normal ranges.

Serum protein electrophoresis with immunofixation: the finding was in order.

Immunological analysis: C3, C4, ANA, ANCA, antiDSDNA – the findings were in order.

Virological analysis: CMV, EBV, Hb, HCV, HIV were normal.

Lumbar puncture: cytochemical CSF examination: clear fluid was obtained, with albuminocytologic dissociation (1,47 g/l protein); oligoclonal strips were negative.

Electromyography (EMG): In the examined GE and DE muscles in relaxation, spontaneous activity was not observed. In moderate and maximum voluntary contractions, a neurogenic curve of milder severity was recorded, with motor unit potentials of variable amplitude (normal and/or higher), normal and/or prolonged, and with moderately polyphasic form. Electromyoneurographic (ENG) test findings: n. medianus, n. ulnaris, n. tibialis, n. peroneus, and n. suralis were the tested nerves; M potentials were of low amplitudes, extended life, very prolonged distal latencies, some of them with temporal dispersion as well. F responses of both n. peroneus were of slightly prolonged duration, and other nerves were within normal limits. Sensory neurograms were of lower amplitudes and prolonged latencies. Motor and sensory conduction velocities were slower. Overall, these findings were suggestive of primary demyelinating polyneuropathy.

Somatosensory evoked potentials of the median and tibial nerve were as follows: stimulation of both n. medianus produced normal cortical responses; stimulation of right n. tibialis produced a cortical response of borderline latency, and stimulation of left n. tibialis produced a cortical response of prolonged latency, with lower amplitude compared to the contralateral nerve.

Nuclear magnetic resonance (NMR) of the brain demonstrated demyelinating lesions of the supratentorial white matter.

NMR of the cervical spine showed a „bulging“ discus C6-C7 C6-C7 without adverse effects to the neural structures.

Based on the patient history data about the onset and course of the disease, neurological and

other diagnostic tests, the clinical picture of a demyelinating disease of the peripheral and central nervous systems was clearly present, and therapeutic plasma exchange was administered for five times.

After the administered therapy, an improvement was observed in the form of improved muscle strength, while the sensation of numbness in the hands and light instability walking were still present.

Neurological findings were as follows: mildly ataxic gait; MTR generalized, low; right „silent sole“; reduced vibration sensibility to the ankle level only.

The patient was discharged with the diagnosis of cephalopolyradiculoneuritis.

A month after discharge, at the following control visit, the patient felt significantly better in terms of muscle strength, but her sensory complaints still persisted. A control ENG was also done again, with slightly better results than the previous one.

A year later, the patient had no complaints, neurological findings were in order, but the ENG changes were still evident in the form of borderline motor and sensory conduction velocities, borderline distal latencies and normal to slightly lower M potentials of peripheral nerves. Six months after that, her ENMG findings were within normal, physiological ranges.

## Discussion

Concurrent demyelination in the central and peripheral nervous system is a very rare phenomenon.

In our patient, the signs of damage to both peripheral and central nervous system predominated in the neurological findings, which was subsequently confirmed using electroneuromyography and magnetic resonance imaging of the brain. Since oligoclonal bands were not identified in the CSF at the time, multiple sclerosis was excluded as a possible diagnosis. On the other hand, the onset of symptoms was abrupt, which is usually encountered in AIDP and acute disseminated encephalomyelitis (ADEM).

In the course of further follow-up of our female patient, a year after discharge from the hospital, electroneuromyography was repeated and still showed electrophysiological changes in the peripheral nervous system, although of milder nature, in terms of borderline conduction velocities and distal latencies, and normal to slightly lower amplitudes of M potentials of peripheral nerves, more conspicuous in the lower limbs. Older changes persisted on magnetic resonance imaging, while there were no new active lesions. Six months after that, ENMG findings were in order.

Based on our protracted monitoring and careful consideration of this female patient, the decision was made that her disease was in fact a rare form of acute inflammatory demyelinating

polyneuropathy combined with CNS demyelination.

### Conclusion

In addition to ENMG, in patients whose clinical picture is characterized by peripheral nervous system damage (indicative of polyneuropathy) together with signs of damage to the central nervous system, it is necessary to perform MRI of the endocranium in order to detect possible demyelinating lesions. These are very uncommon clinical entities. In patients in whom the diagnosis of acute disseminated encephalomyelitis is proposed, further monitoring of clinical, electrophysiological, radiological and biochemical

parameters is required in order to establish the final diagnosis. Further differential diagnostic considerations are necessary in terms of identification of AIDP, HADP and other acquired demyelinating polyneuropathies known to occur simultaneously with CNS demyelination. A properly established diagnosis is of utmost importance concerning the appropriate therapy, since therapeutic protocols differ in the above demyelinating disease groups. An early and timely diagnosis is required for both prevention and timely introduction of adequate therapy, aiming to prevent secondary axonal injury as well as permanent and severe neurological deficiencies and disability of the affected patients.

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**Prikaz slučaja****UDC: 616.8-009-097**  
**doi:10.5633/amm.2017.0106****DEMIJELINIZACIJA CENTRALNOG I PERIFERNOG  
NERVNOG SISTEMA- PRIKAZ SLUČAJA***Vanja Đurić, Gordana Đorđević, Jelena Stamenović*

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Inflamatorna demijelinizirajuća oboljenja kao što su multipla skleroza (MS), neuromijelitis optika (NMO), akutni diseminovani encefalomijelitis (ADEM), akutna inflamatorna demijelinizirajuća poliradikuloneuropatija (AIDP) i hronična inflamatorna demijelinizirajuća polineuropatija (HIDP) su autoimuna oboljenja koja oštećuju centralni ili periferni nervni sistem. Retko demijelinizacija može oštetiti centralni i periferni nervni sistem istovremeno. Periferni i centralni mijelin imaju različite proteinske komponente, ali imaju i neke zajedničke, kao što su mijelin bazni protein (MBP), mijelin udruženi glikoprotein (MAG) i neurofascin. Dakle, abnormalni autoimuni odgovor protiv zajedničkih antigena suspektan su u patogenezi oboljenja sa istovremenom demijelinizacijom centralnog i perifernog nervnog sistema (1, 2, 3).

U radu je prikazan slučaj bolesnice kod koje su u neurološkom nalazu istovremeno dominirali znaci oštećenja perifernog i centralnog nervnog sistema, što je potvrđeno pomoću elektroneuromiografije i magnetne rezonance mozga. Diferencijalno-dijagnostički razmatrana je mogućnost AIDP, HIDP i drugih stečenih demijelinizirajućih polineuropatija koje se mogu javiti istovremeno sa demijelinizacijom u centralnom nervnom sistemu, i predstavljaju jako retke entitete.

Kod naše bolesnice postavljena je definitivna dijagnoza retke forme akutne inflamatorne demijelinizirajuće polineuropatije sa demijelinizacijom centralnog nervnog sistema. Postavljanje definitivne dijagnoze je jako bitno, jer se terapijski protokoli razlikuju kod navedenih demijelinizirajućih bolesti.

Dalja istraživanja treba fokusirati na autoantitela, direktno usmerena na zajedničke mijelinske epitope u Švanovim ćelijama perifernog nervnog sistema i oligodendrocite centralnog nervnog sistema (21). Acta Medica Medianae 2015;54(4):39-43.

***Ključne reči:*** demijelinizacija, centralni, periferni, nervni, sistem