



Neuromyelitis optica spectrum disorder in patient with systemic lupus erythematosus – our experience

Bolesti spektra optičkog neuromijelitisa kod bolesnice sa sistemskim eritemskim lupusom – naše iskustvo

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Abstract

Introduction. Neuromyelitis optica spectrum disorder (NMOSD) is a rare demyelinating immune-mediated central nervous system disease. It is extremely rare to occur in patients with systemic lupus erythematosus (SLE), and it represents a diagnostic and therapeutic challenge. **Case report.** A 38-year-old Caucasian woman with medical history of SLE and new onset of flaccid paraparesis, fecal and urinary incontinence, persistent nausea and vomiting was admitted to our hospital. Based on the clinical presentation, magnetic resonance imaging findings and positive aquaporin 4 (AQP4) antibodies, a NMOSD with coexisting SLE were diagnosed. Pulse-doses of cyclophosphamide and glucocorticoids were efficient in patient treatment. **Conclusion.** In a patient with SLE and symptoms of longitudinal extensive transverse myelitis and/or optic neuritis and area postrema syndrome, assessment of AQP4 antibodies is necessary for diagnosing NMOSD. Accurate diagnosis, and timely and long-term administration of immunosuppressive therapy are crucial for favorable outcome of these two coexisting diseases.

Key words:

lupus erythematosus, systemic; neuromyelitis optica; diagnosis; aquaporin-4; antibodies; drug therapy; treatment outcome.

Apstrakt

Uvod. Bolesti iz spektra optičkog neuromijelitisa (BSON) su retka imunska - posredovana demijelinizaciona oboljenja centralnog nervnog sistema. Kako se veoma retko javljaju kod bolesnika sa sistemskim eritemskim lupusom, predstavljaju veliki dijagnostički i terapijski izazov. **Prikaz bolesnika.** Bolesnica, stara 38-godina, sa sistemskim eritemskim lupusom i novonastalom flakcidnom paraparezom, inkontinencijom urinarnog i analnog sfinktera, prolongiranom mučninom i povraćanjem, primljena je u našu kliniku. Na osnovu kliničke prezentacije, nalaza nuklearne magnetne rezonance i pozitivnih antitela prema akvaporinu 4 (AQP4) dijagnostikovana je BSON udružena sa sistemskim eritemskim lupusom. Terapija pulsnom dozama ciklofosfamida i glikokortikoida je bila efikasna. **Zaključak.** Kod bolesnika sa sistemskim eritemskim lupusom i simptomima longitudinalnog ekstenzivnog tranverzalnog mijelitisa i/ili optičkog neuritisa i sindroma *area postrema*, neophodno je odrediti AQP4 antitela radi postavljanja dijagnoze BSON. Tačna dijagnoza, pravovremena i dugotrajna primena imunosupresivne terapije je od presudnog značaja za povoljan ishod udruženosti ove dve bolesti.

Ključne reči:

lupus, eritematozni, sistemski; neuromijelitisa optika; dijagnoza; akvaporin-4; antitela; lečenje lekovima; lečenje, ishod.

Introduction

Neuromyelitis optica (NMO) was described at the end of 19th century by Eugene Devic, and until recently it has been commonly called the Devic's syndrome ¹. Traditionally

it was defined as a monophasic demyelinating disease of central nervous system (CNS) consisting of optic neuritis (ON) and transverse myelitis (TM). It has changed relatively recently, first with the discovery of a highly specific serum aquaporin-4 (AQP4) immunoglobulin G antibody ², then,

with an understanding that affection of central nervous system (CNS) in this disease may be more restricted, or more extensive than previously thought. In turn, this led to understanding that all demyelinating diseases with positive AQP4 antibodies and variable affection of CNS should be labeled as NMO spectrum disorders (NMOSD)³. Current diagnostic criteria also recognise monophasic and relapsing NMOSD, as well as AQP4 antibody positive and AQP4 antibody negative NMOSD, both having characteristic magnetic resonance imaging (MRI) findings in one of six regions of CNS (optic nerve, spinal cord, area postrema, brainstem, diencephalon and cerebellum)⁴.

It is not so uncommon that a patient with NMOSD develops another autoimmune disorder, such as systemic lupus erythematosus (SLE), Sjögren's syndrome, autoimmune thyroiditis, or myasthenia gravis⁵. On the other side, it is estimated that the probability of a patient with SLE developing NMO is extremely low – approximately 1 : 5.000.000⁶. Neurological manifestations similar to NMO and due to CNS demyelination can occur as a part of clinical picture of SLE. It is therefore important to distinguish if the neurological manifestations are caused by autoimmune disease, or, they are just a part of coexisting NMOSD.

Case report

A 38-year-old Caucasian woman with a medical history of SLE was transferred to our hospital due to longitudinally extensive transverse myelitis (LETM) and for further diagnostics and treatment.

SLE was diagnosed a year prior to this, and was based on nonerosive polyarthritis, leukolymphopenia, positive antinuclear antibodies (ANA) and antibodies to double-stranded DNA (anti-dsDNA). Since then, the patient had been treated with prednisolone 10 mg/day and hydroxychloroquine 400 mg/day. After introduction of the therapy the patient was generally well with the exception of periodical polyarthralgia.

Three weeks before admission to our institution, a fever, persistent nausea, vomiting, hiccups, headache, abdominal pain and dry cough occurred. She was admitted to a local hospital and initially treated for gallbladder calculosis and cholecystitis. During the second week in the hospital, she became somnolent, developed a rapidly progressive paraparesis (within 24 hours) and fecal and urinary incontinence. MRI scanning of the cervical and thoracic spine showed hyperintense signal in T2-weighted sequence in C7-T1, T1-T4 and T8-T11 spinal cord segments (Figure 1). MRI scanning of the brain showed hyperintense signal in T2-weighted sequence in dorsal and lateral medulla on the left (Figure 2). Postcontrast signal enhancement in both optical nerves was observed. The NMO was suspected. The patient was treated with pulse doses of methylprednisolone 1 gram daily for 5 days followed by intravenous immunoglobuline (IVIg) 400 mg/kg day for 4 days, while hydroxychloroquine was discontinued. Patient's state was deteriorating despite the treatment, so she was transferred to our hospital.

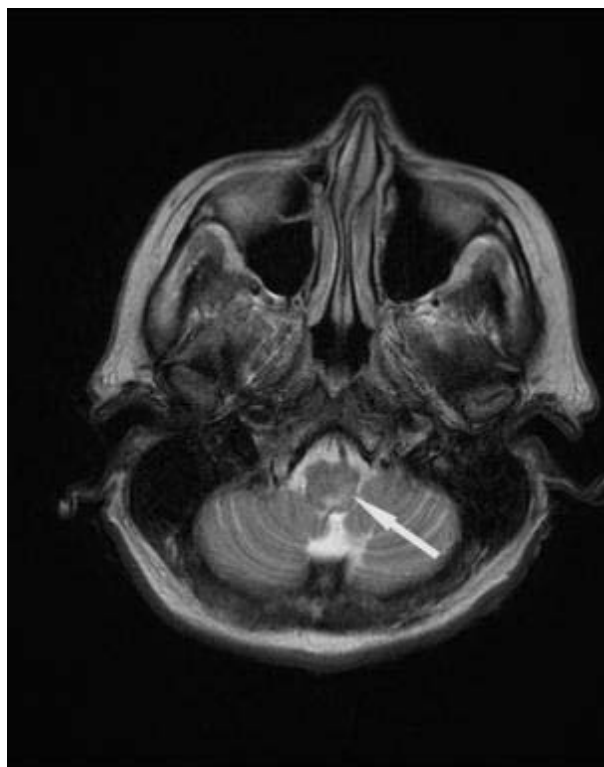


Fig. 1 – T2W magnetic resonance imaging (MRI, sagittal section) of cervical and thoracic spine showing hyperintense signal in C7-T1, T1-T4 and T8-T11 spinal cord segments (arrow).

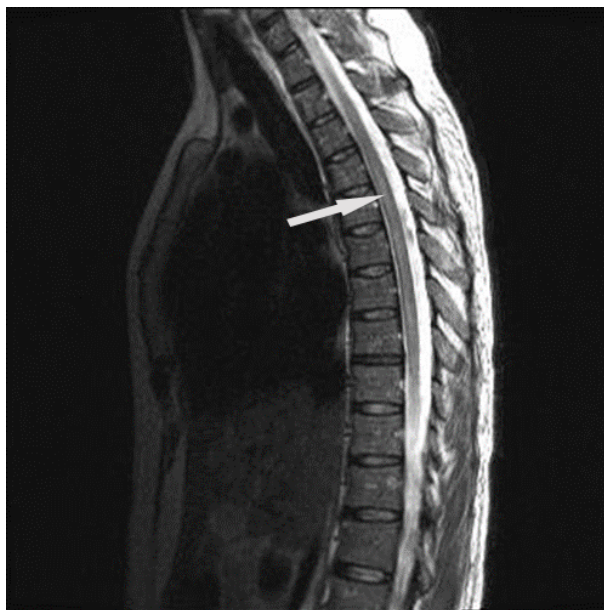


Fig. 2 – T2W magnetic resonance imaging (MRI, axial section) of brain showing hyperintense signal in dorsal and lateral medulla oblongata on the left (arrow).

On admission, she had a low grade fever (37.8°C), mild malar rash and low blood pressure (80/60 mmHg). Basal respirations were auscultatory inaudible. Flaccid paraplegia and spastic paresis of both arms as well as urinary retention and fecal incontinence were the dominant neurological findings upon admission. There was also a discrete right peripheral *n. facialis* weakness, bilateral hand action tremor, mild impa-

irment of light touch, pinprick and vibration sensation in the legs, but without a clear sensory level. Expanded disability severity scale (EDSS) at this point was 8.5.

Blood tests showed erythrocyte sedimentation rate (ESR) of 96 mm/h, C-reactive protein (CRP) of 29.63 mg/L (normal range: < 5 mg/L), leukocytes $2.7 \times 10^9/L$ (normal range $4-10 \times 10^9/L$), hemoglobin 74 g/L (normal range: 130–180 g/L). Serology testing showed positive ANA 1 : 160, anti dsDNA 167 (normal range: 0–25) and positive direct Coombs test, polyclonal hypergammaglobulinemia IgG of 18 g/L (normal range: 5–16 g/L), low C3 and C4. Serum AQP4 antibody (indirect immunofluorescence test) was 1 : 2,560 (normal range < 1 : 10). Anticardiolipin antibodies, lupus anticoagulant and anti-Smith antibody were negative.

Cerebrospinal fluid analysis showed elevated level of protein 0.69 g/L (normal range < 0.45 g/L), lowered glucose 1.9 mmol/L (normal range: 2.2–4.6 mmol/L), elevated albumin index 11.23 (normal range < 5.7), without pleocytosis and with normal IgG index. Oligoclonal bands, *Borrelia*, neurotropic viruses and acid-resistant bacillus were negative.

Computed tomography of the chest showed bilateral pleural effusions.

Visual evoked potentials (VEP) showed prolonged P100 latencies of 127 ms on the left and 121 ms on the right eye. The patient did not report any visual loss, nor could any visual disturbance be observed through usual clinical examination.

Based on the presence of longitudinally extensive transverse myelitis (LETM), subclinical ON, area postrema syndrome and positive AQP4 antibodies, NMOSD were diagnosed. SLE erythematosus disease activity index 2,000 (SLEDAI-2K) was at this point 9.

Monthly cyclophosphamide (CF) pulses of 15 mg/kg were introduced, and methylprednisolone 1 mg/kg was continued for 2 weeks, then, gradually reduced. Followed by therapy introduction the neurological symptoms gradually improved and sphincter function completely recovered.

Over the next 6 months the patient received 6 monthly pulse doses of CF and methylprednisolone dose was 10 mg/day. On follow-up after 6 months, she was ambulatory without any assistance on distances greater than 1,000 m. Neurological examination revealed residual spastic paraparesis to a lesser degree, with EDSS of 3.5. SLE activity was low (SLEDAI-2K: 3).

Discussion

In the SLE patient, according to American College of Rheumatology nomenclature, 19 neuropsychiatric syndromes (NPSLE) can be defined⁷. Among the least frequent is myelitis, present in 1–2% of patients⁸. It can present itself as TM consisting of spinal cord lesions of one to two spinal segments

or as LETM extending 3 or more vertebral segments confirmed by T2-weighted MRI⁹.

The relationship between TM and present antiphospholipid (APL) antibodies in SLE is proven. It is considered that APL-induced vasculitis of spinal blood vessels and direct cytotoxic effect to nervous tissue have a role in occurrence of TM in patients with SLE¹⁰.

Since LETM represents a very rare manifestation of SLE, other possible causes should be sought for, including multiple sclerosis, infections, tumors, trauma and nutritional deficiencies. LETM is also one of the main clinical characteristics and a part of the modern diagnostic criteria for NMOSD¹¹. In our patient, repeated assessment of antiphospholipid antibodies was negative, possible infective causes were excluded and McDonald's revised 2010 criteria for multiple sclerosis were not met¹². VEP latencies are often delayed in NMOSD (as it was in this case), but this finding, although illustrative of optical nerve demyelination is not specific for NMOSD, and can be seen in a variety of clinical entities, especially in multiple sclerosis¹³. In our case, there were several more unique clinical characteristics of the NMOSD – constant hiccups, nausea and vomiting. These are manifested in 15.7–62% of patients¹⁴. Area postrema and solitary tract nuclei in dorsomedial medulla are frequently affected areas (as confirmed in the presented case by MRI finding), which can be explained by a rich expression of AQP4 in this area¹⁵.

So far, the interconnection between autoimmune diseases and NMOSD has not been completely clarified. It is considered that there is a genetic predisposition of certain patients for developing several types of autoimmune diseases. It has been demonstrated that only patients with SLE who have ON and/or myelitis have positive AQP4 antibodies, whereas those with other NPSLE do not have¹⁶.

In the NMOSD treatment, pulse-dose corticosteroids, plasmapheresis and IVIGs are recommended in acute phase. This is followed by long-term immunosuppression with rituximab, azathioprine and mycophenolate mofetil as recommended¹⁷. There are no recommendations for the treatment of patients with coexisting SLE and NMOSD. Current knowledge is based on retrospective cases and short series¹⁸.

Conclusion

Antiaquaporin-4 antibody should be sought for in patients with SLE and the first attack of LETM, ON and/or area postrema syndrome. Positive anti aquaporin-4 antibodies in these cases can easily lead to diagnosing a coexisting NMOSD in patient with SLE.

Accurate and timely diagnosis followed by a long-term immunosuppressive therapy are necessary to reduce neurological sequelae and establish adequate control of both diseases.

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