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Anti-MOG associated myelitis

There is now increasing evidence that demyelinating disease with anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies is an independent nosological unit. The paper describes a clinical case of anti-MOG associated myelitis at the CI-TX level. Differential diagnosis was made between multiple sclerosis, Devic's myelitis optica, and idiopathic transverse myelitis. The clinical, morphopathological, and diagnostic features of anti-MOG associated myelitis are discussed. There are new diagnostic criteria for neuromyelitis optica spectrum diseases (NMOSD), as well as red flags, in the absence of which the diagnosis of NMOSD can be established as a diagnosis of exclusion.

Key words: *anti-MOG associated myelitis; anti-MOG antibodies; anti-aquaporin-4 antibodies; transverse myelitis; multiple sclerosis; Devic's myelitis optica; neuromyelitis optica spectrum diseases.*
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The term «neuromyelitis optica spectrum disorders» (NMOSD) was coined in 2007 to refer to demyelinating diseases of the central nervous system (CNS) with dominating lesions of the optic nerves and/or the spinal cord and detection of aquaporin-4 (AQP-4)-antibodies, highly specific autoantibodies to water channel protein [1], in the blood serum.

The clinical picture of NMOSD may resemble that of multiple sclerosis (MS), but there are differences in the course and prognosis of the diseases, and they have their own management characteristics as well.

The first clinical case of simultaneous acute lesion of the spinal cord and the optic nerve was reported by T. Albutto in 1870. An attempt to specify optic myelitis as a separate medical entity was made by E. Devic and F. Gaultin in 1894 [2]. However, NMOSD had been considered as one of the malignant forms of MS until 2004, when V. Lennon et al. detected AQP-4 antibodies (NMO-IgG, AQP-4) that are specific for optic neuromyelitis [3]. AQP-4 can be found in any part of the CNS but is mostly present in the optic nerves and the spinal cord; that explains the direct influence of AQP-4 on the clinical presentation of optic neuromyelitis. Absolute specificity and correlation with the disease activity, a higher recurrence rate, and a more severe disease course comparing with the one in seronegative patients, prove that AQP-4 antibodies are involved in the pathogenesis of NMOSD [3].

In case AQP-4 antibodies are not present, anti-MOG antibodies [3] (antibodies to Myelin Oligodendrocyte Glycoprotein, the component of myelin, which is synthetized by oligodendrocytes in the CNS) can be found in some patients with the clinical picture of optic neuromyelitis. According to a group of scientists, anti-MOG antibodies are detected in 21% of patients that are seronegative for AQP-4 [4]. Anti-MOG antibodies were not found in all patients with seropositivity for AQP-4 and patients with MS [5]. Higher prevalence in male patients, monophasic disease course, with the optic nerves being more affected than the spinal cord, a more caudal location of lesions and better recovery rates are typical of anti-MOG optic neuromyelitis [6]. In children the disease is mostly present as a form of acute disseminated encephalomyelitis [7], while bilateral optic neuritis is more common in adults [7]. Though the role of AQP-4 antibodies in the pathophysiology of NMOSD has been confirmed in many clinical and experimental studies, the underlying mechanisms of various demyelinating phenotypes of anti-MOG diseases are yet to be discovered. Only a few cases of anti-MOG diseases have been reported in Russian literature [8].

Hereby we provide the description of a patient with anti-MOG associated myelitis that we observed in A.Ya. Kozhevnikov Clinic of Nervous Diseases of University Clinic №3, I.M. Sechenov First Moscow State medical university (Sechenov University), Moscow.

Patient M.*, 26 y.o., presented to the Clinic of Nervous Diseases with bilateral hypersensitivity in the legs and axillary regions, urinary incontinence, and hyperhidrosis.*

The patient considers himself sick since 09.06, when, after an episode of respiratory infection with low-grade fever, he noticed a shooting pain in the cervical spine for the first time and bilateral skin discomfort from touch in the upper limbs and shins that spread to the thigh area over the next 24 hours. A day later, the patient developed urinary incontinence and consulted a urologist and a general practitioner; the specialists did not find any objective urological or general pathology explaining the symptoms. MRI of the brain and spinal cord, recommended after a neurological consultation, was performed on 16.06. The brain MRI showed no abnormalities, while diffuse confluent poorly demarcated lesions, up to 1.7x0.5 in size, with no volume effect, were found at the level of C-spine, and dystrophic changes of the spine were detected during the spinal cord MRI.

Life history: the patient is a research scientist, unmarried and has no children. Medical history: the patient had some paediatric infections, but no chronic diseases, no surgeries, no allergies were

reported; no neurological diseases were present in the family history. The patient denies smoking and substance abuse.

On examination no changes in his physical status are found, blood pressure is 120/80, pulse is 72, of normal strength.

Neurological status: The patient is alert, attentive, and oriented. Meningeal signs are not present. The cranial nerves are intact. Strength is sufficient in all muscle groups (5 points). Muscular tone in the limbs is normal, with no hypotrophy detected. Babinski sign is positive on both sides. There are no pathological carpal reflexes. The following sensation disorders are detected: dysesthesia, cold and tactile allodynia, cold anesthesia of conduction type starting with TIV level. Vibratory sense is decreased in the big toes (6/10 points). Rapid alternating movements and gait are intact. Romberg sign is absent. The patient has urinary urgency. Expanded Disability Status Scale (EDSS) score is 3.5.

CBC, clinical urine test, biochemical blood assay, and coagulation test are normal; HIV, Hepatitis B and C, syphilis tests are negative.

Chest X-ray and ECG are normal.

Contrast MRI of the cervical and thoracic spine and the brain: there are changes in the spinal cord at the level of C_I-T_X, which are more likely to be inflammatory in origin (Fig. 1, a, b); contrast uptake was detected at the level of C_{II} (Fig. 2). No pathological contrast uptake was revealed in the brain (Fig. 3).

Ophthalmological consultation: Visual acuity is 1.0 in both eyes. Ocular motility is normal. There is no nystagmus. The cornea is clear. The anterior chamber is of medium depth, the aqueous humor is transparent. Texture of the iris is normal. The pupil examination reveals round pupils, equally reactive to light and accommodation. The lenses are transparent on both sides. The fundus of the eye: the optic disk is of pale pink color with well-defined borders; course and size of the vessels are normal.

Cerebrospinal Fluid Analysis: the CSF is colorless and clear; proteins – 0.65‰, glucose – 47 mg%, cytosis – 74 cells per 1 mm^3 (223/3), lymphocytes – 66%, neutrophils – 34%. Reinvestigation of CSF 7 days later: the CSF is colorless and clear; proteins – 0.19‰, glucose – 56 mg%, cytosis – 42 cells per 1 mm^3 (106/3), lymphocytes – 90%, neutrophils – 8%, macrophages – 2%.

Testing blood and CSF for oligoclonal bands revealed type 1 synthesis, which is not characteristic of MS. AQP-4 serum test was negative, which is not typical of Devic's disease.

To exclude connective tissue diseases we performed the following immunological tests of the blood serum: cANCA test (proteinase 3 antibodies), pANCA test (myeloperoxidase 3 antibodies), anti-double-stranded DNA test, antinuclear factor test; the results did not reveal any connective tissue pathology.

To exclude infectious diseases we performed the following tests: detection of Borrelia burgdorferi antibodies in the blood serum (negative), enzyme immunoassay for detection of Mycobacterium tuberculosis antibodies in CSF (negative), polymerase chain reaction assay of CSF for detection of Epstein-Barr virus, cytomegalovirus, herpes virus type IV, herpes simplex virus type I and II, Neisseria meningitidis, Streptococcus pneumonia_, Haemophilus influenzae B, Cryptococcus neoformans, fungi of the genus C. albicans, C. glabrata, C. krussei, C. parapsilosis, C. tropicalis, Borrelia spp., Brucella spp., Listeria monocytogenes, Toxoplasma gondii (all negative).

Considering the acute course of the disease in a young patient after an acute respiratory infection, the clinical symptoms typical of the spinal cord involvement at the level of C_I-T_X, focal demyelinating lesions in spinal cord at the mentioned level found on MRI scans, the absence of oligoclonal bands in the blood serum and CSF, and the absence of AQP-4 antibodies, we diagnosed neuromyelitis optica spectrum disorder and acute transverse myelitis at the level of C_I-T_X. The patient was administered pulse therapy with intravenous injection of methylprednisolone 1000 mg daily for 5 days. Rapid significant improvement was noticed: vegetative symptoms regressed up to the almost complete functional recovery of pelvic organs and sensitivity, except for the decrease of cold sensitivity in feet. EDSS score was 1.5 points.

The second cervical and thoracic spine MRI performed in November 2018 revealed no changes. (Fig. 4, a, b).

In December 2018 the patient was tested for anti-MOG antibodies with the help of EIA in the Scientific Centre of Neurology; high level of antibodies was detected (41.0 pg/ml; the normal rate is 0–15.0 pg/ml).

Due to the complaints of persisting mild disorders, such as frequent urination, decrease of cold sensitivity in feet, occasional stool retentions, ejaculation problems, and anorgasmia, the patient was admitted to the Clinic of Nervous Diseases in January 2019.

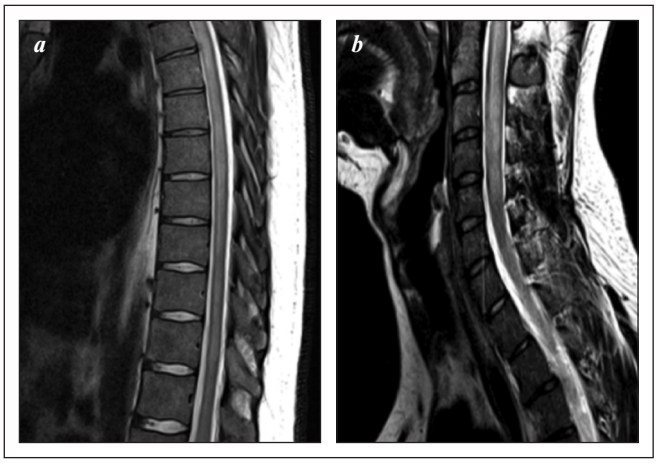

Fig. 1. *Spinal cord MRI, T2 weighted image (a, b): inflammatory changes at the level of C_I-T_X*

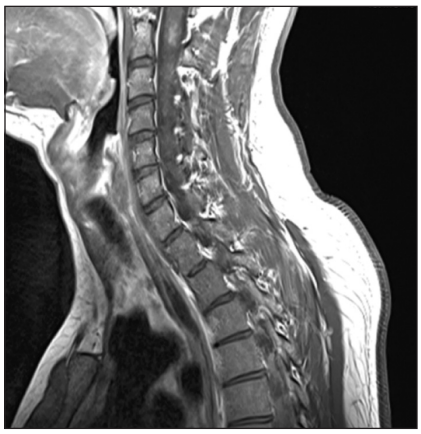

Fig. 2. *Spinal cord MRI, T1 weighted image: contrast uptake was detected at the level of C_{II}*

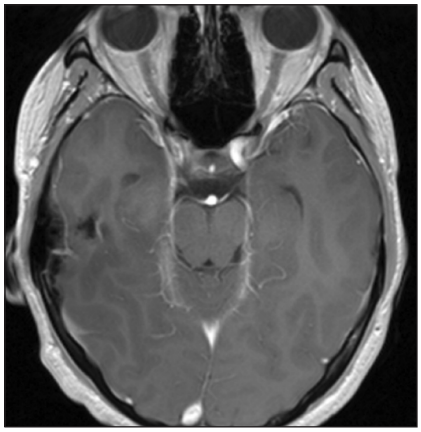

Fig. 3. *Brain MRI, T2 weighted image: no signs of focal lesions*

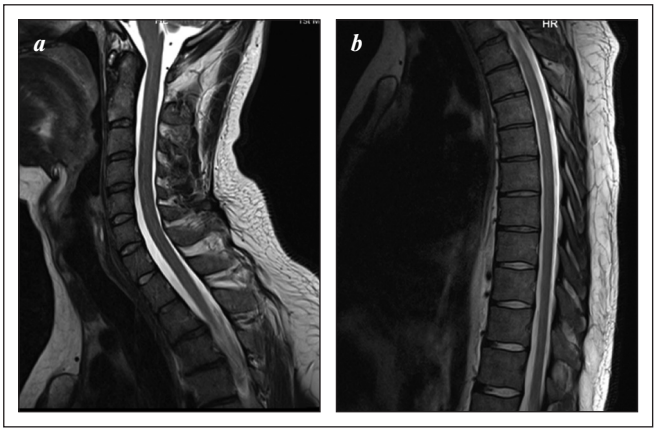

Fig. 4. *Cervical and thoracic spine MRI, T2 weighted image(a, b): no signs of focal lesions*

Cold allodynia in the shins and feet and decreased vibration sensitivity in the feet up to 6 point were detected on the neurological examination. Frequent urination and stool retentions were present. EDSS score was 1.5 points.

Considering all the findings, we diagnosed anti-MOG associated myelitis at the level of C_I-T_X. Clinical improvement was noticed during the pulse therapy with intravenous injection of methylprednisolone 1000 mg daily for 3 days: the sensitivity in the legs increased, pelvic organ dysfunction ameliorated. EDSS score was 1 point.

At the beginning of 2020 the condition of the patient is stable, focal neurological symptoms do not progress. There is mild pelvic organ dysfunction (frequent urination). EDSS score is 1 point.

Discussion

In the present clinical case we could see longitudinal extensive transverse myelitis: there were lesions in the lateral funiculi and lateral horns of the spinal cord at the level of C_I-T_X, clinically seen as entire or partial involvement of the spinal cord cross section. Spinal cord MRI with contrast enhancement did not confirm compressive myelopathy. Focal demyelinating lesion with contrast uptake on MRI scans and lymphocytic pleocytosis that was found during CSF analysis indicate the inflammatory origin of the disease. Infectious and systemic diseases were excluded after laboratory tests. The CSF and blood serum analyses revealed type 1 synthesis of oligoclonal bands, which helped us exclude MS. Besides, the extension of the spinal cord lesions for more than 3 vertebral segments is not typical of MS. Devic's disease was not confirmed as AQP-4 serum test was negative. After the positive test for anti-MOG antibodies, the diagnosis of anti-MOG associated myelitis was made.

In 2015 the International Panel for NMO Diagnosis (IPND), which consisted of 18 experts from 9 countries, reached a consensus and approved new clinical, laboratory, and radiological diagnostic criteria (Table 1). [9]. The term 'neuromyelitis optica spectrum disorder' is recommended to denote all patholo-

Table 1. *Diagnostic criteria of NMOSD*

Diagnostic criteria of NMOSD with AQP4-IgG antibodies
1. At least one core clinical characteristic
2. A positive test for AQP4-IgG using the best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses
The diagnostic criteria for NMOSD with negative or unknown AQP4-IgG antibody status
1. At least two core clinical characteristics occurring as a result of one or more clinical exacerbations and meeting all of the following requirements: a) at least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis, or area postrema syndrome; b) dissemination in space (two or more different core clinical characteristics); c) fulfillment of additional MRI requirements as applicable (see below)
2. Negative tests for AQP4-IgG (NMO-IgG) using best available detection method, or, alternatively, testing unavailable
3. Exclusion of alternative diagnoses
Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesion
The additional MRI requirements for NMOSD in patients with negative or unknown AQP4-IgG antibody status
1. Acute optic neuritis: a) brain MRI must show normal findings or non-specific white matter lesions or b) optic nerve MRI with T2-hyperintense lesions or T1-weighted gadolinium enhancing lesion extending over >1/2 optic nerve length or involving the optic chiasm
2. Acute myelitis: spinal cord MRI must show intramedullary lesions extending over ⩾3 contiguous segments (LETM) or ⩾3 contiguous segments of focal spinal cord atrophy in patients having a history of acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periepidermal brainstem lesions

gies of this spectrum, since the pathogenesis, clinical characteristics and treatment approaches of NMOSD do not significantly differ from those of Devic's disease and its partial forms (myelitis with no signs of involvement of the optic nerves and isolated lesions of the optic nerves). Moreover, the diagnosis of NMOSD may be established in patients with negative or unknown AQP4-antibody status, especially if urgent therapy is required [10]. Thus, the presence of AQP4-antibodies has lost its independent diagnostic value [7, 11].

The authors of the criteria claim that none of the clinical, serological or radiological findings is pathognomonic; however, none of the findings excludes this diagnosis. The authors emphasize «the red flags»: if they are not present, NMOSD may be determined as the diagnosis of exclusion (Table 2).

In the presented clinical case acute myelitis corresponds to the criteria of acute longitudinally extensive transverse myelitis (LETM) [12]: 1) spinal cord MRI revealed intramedullary lesion with the length of C_1-T_X; 2) alternative diagnoses were excluded. The following red flags [13], which could prove the diagnosis of MS, were excluded in this patient: 1) progression of the symptoms; 2) presence of CSF oligoclonal bands; 3) T2-weighted MRI imaging features, including Dawson fingers; 4) lesions of moderate extension in T2-weighted MRI scans. Moreover, no acute or chronic infection, connective tissue diseases, or ischemic spinal cord lesions were found.

Compared with MS patients, the following clinical presentation characteristics can be noticed in patients with anti-MOG diseases: milder symptoms, better recovery, relatively rare remittent disease course (29% in anti-MOG diseases and 90% in MS), no female predominance, younger age of disease onset, frequent simultaneous development of acute neuritis and myelitis, the absence of medulla involvement (area postrema lesions), more caudal extension of myelitis, more cerebral lesions [14, 15]. Different pathogenetic mechanisms of disease development in patients with anti-MOG and AQP-4 antibodies are suggested in several articles [16].

In this clinical case serum AQP-4 antibody test was negative. Monophasic course of disease is more typical of seronegative patients, while the remittent type is more often found in patients positive for AQP-4 antibodies [15].

The presented patient has been observed in the Clinic of Nervous Diseases for less than a year; so we can neither exclude possible disease recurrence, nor determine the type of the course yet. According to the criteria published in 2015, the course of disease when the interval between attacks is shorter than 4 weeks is considered remittent; if there has been no recurrence for 5 or more years, it is considered monophasic and in this case patients may develop residual neurological disorders. Moreover, unlike MS, NMOSDs are not characterized by progressive disease course [9].

Table 2. *Red flags: Findings not typical of NMOSD*

Red flags (clinical/laboratory)
1. Clinical features and laboratory findings
– progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
– atypical time to attack nadir: less than 4 hours (consider cord ischemia/infarction); continual worsening for more than 4 weeks from attack onset (consider sarcoidosis or neoplasm)
– partial transverse myelitis, especially when not associated with LETM MRI lesion (consider MS)
– presence of CSF oligoclonal bands (oligoclonal bands occur in <20% of cases of NMO vs >80% of MS)
2. Comorbidities associated with neurologic syndromes that mimic NMOSD:
– sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g, mediastinal adenopathy, fever and night sweats, elevated serum angiotensin converting enzyme or interleukin-2 receptor levels)
– cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5 associated optic neuropathy and myelopathy or anti-Ma-associated diencephalic syndrome)
– chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)
Red flags (conventional neuroimaging)
1. Brain
a. Imaging features (T2-weighted MRI) suggestive of MS (MS-typical):
– Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers)
– Lesions adjacent to lateral ventricle in the inferior temporal lobe
– Juxtacortical lesions involving subcortical U-fibers
– Cortical lesions
b. Imaging characteristics suggestive of diseases other than MS and NMOSD
– Lesions with persistent (>3 mo) gadolinium enhancement
2. Spinal cord, characteristics more suggestive of MS than NMOSD:
– Lesions <3 complete vertebral segments on sagittal T2-weighted sequences
– Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences
– Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with long-standing or progressive MS)

Note: CRMP-5 – collapsin response mediator protein-5

Pulse therapy with intravenous injection of methylprednisolone 1000 mg daily for 3–7 days followed by oral prednisolone with slow dose decline is the frontline therapy of anti-MOG diseases. It is the most effective method of NMOSD exacerbation treatment. However, it is important to take into account that the effectiveness of this therapy may decrease over time [15]. Plasmapheresis and intravenous injection of human immunoglobulin can be considered as additional or alternative ways.

Administration of rituximab, monoclonal antibody against the protein CD20 of B-lymphocytes, in dosage of 375 mg/m^2 weekly for 4 weeks or as another regimen is discussed as a way of preventing NMOSD exacerbations [17]. Ofatumumab [17] or tocilizumab [18] can be used as second line therapy. There is some evidence about the efficacy of eculizumab [19] and inebilizumab [20]. However, it should be remembered that the agents that change the course of MS, including beta interferon [18] and some medications of monoclonal antibodies, such as fingolimod [21], natalizumab [22], and alemtuzumab [23], are not effective in patients with NMOSD and can even worsen the course of the disease.

The presence of longitudinally extensive transverse myelitis along with high titer of anti-MOG antibodies in patients with no oligoclonal bands in CSF and no AQP-4 antibodies in the blood

serum allows us to make the diagnosis of anti-MOG associated myelitis, where the absence of optic nerve lesions and focal demyelination in the brain are typically not found. Possible false-positive and false-negative test results during anti-MOG diagnostics using EIA should be taken into account. Indirect immunofluorescence assay using transfected cells is regarded as a more precise method of anti-MOG antibodies detection nowadays. The specificity and sensitivity of this method were estimated in 167 patients with NMOSD: the sensitivity was 95.0%; the specificity was 84.1% [24]. The introduction of methods based on cell culture techniques in our country is an important step in optimization of anti-MOG disease diagnostics.

Thus, understanding different pathogenetic mechanisms, clinical course, and diagnostic methods of NMOSD directly affects the treatment approach and can improve the quality of life and decrease disability rate in patients.

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Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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