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Case report

Severe course of neuromyelitis optica in a female patient with chronic C hepatitis

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ABSTRACT

Neuromyelitis optica (NMO) is a rare, disabling, recurring inflammatory demyelinating disease affecting the spinal cord and optic nerves with predominance in women.

We present the case of a female patient with chronic C hepatitis, who, despite treatment, developed severe symptoms of NMO during pregnancy and postpartum.

1. Introduction

Neuromyelitis optica (NMO), also known as Devic's disease, is a severe, recurring inflammatory demyelinating disease affecting the spinal cord and optic nerves. Studies are underway to understand the etiology of the disease. Current data indicates that a humoral immune response (NMO-IgG) directed against aquaporin-4, a water channel protein located in the membrane of astrocytes, plays a key role in the disease pathogenesis. Moreover, the high prevalence of NMO in women compared to men (9:1) suggests that genetic, epigenetic and hormonal gender-associated factors affect the pathomechanism of the disease [1]. The first symptoms of NMO may be observed in young women and during pregnancy, when sex hormone levels (estrogen and progesterone) increase. It has also been shown that the immunological changes occurring during pregnancy are likely to impact NMO [2]. Therefore, it is important to recognize the relationship between pregnancy and the disease course of NMO, which may facilitate the choice of a therapy safe for both the mother and the child.

The authors present the case of a 37-year old woman with chronic C hepatitis, who, despite treatment, developed symptoms of NMO during pregnancy and postpartum.

2. Case report

A 37-year old woman in the 22nd week of pregnancy was admitted to the Neurology Department with signs of right limb muscle weakness with an onset a day prior to admission. Six

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months earlier, the woman was diagnosed at another neurological care unit for acute bilateral reduction in visual acuity. At the time, the neurological, ophthalmic examinations and optical coherence tomography (OCT) were normal, and the cause of the visual deficits was not identified. Visual evoked potentials were not recorded. A brain MRI revealed a few 6 mm large foci corresponding to vascular or demyelinating lesions. Type IV oligoclonal bands, associated with a chronic infection with the hepatitis C virus, were identified in the serum and cerebrospinal fluid. In addition, the patient was diagnosed with nodular goiter and hypothyroidism. No causes of visual impairment were found. A conversion disorder was considered, and the patient was referred for psychological and psychiatric consultations. An anti-aquaporin 4 antibody test was not performed because NMO was not suspected.

The patient was then admitted to our Neurology Department. The subsequent neurological examination revealed right Horner syndrome, converging eyeballs, horizontal-rotatory nystagmus when looking sideways, bilaterally decreased visual acuity (the patient was able to count her fingers at a distance of 1 m), mild right limb paresis (a score of 4/5 on the Lovett scale except the right foot muscles, which scored 3/5), reduced knee and ankle-jerk reflexes, the presence of the Babinski reflex in the right foot, and a positive Romberg test. Sensory disturbances were not found. The patient was able to walk only with assistance of two people.

Control brain MRI revealed very fine, nonspecific sites of hyperintense tissue signal on T2-weighted and FLAIR sequences indicative of mild perivascular gliosis (Fig. 1). Cervical and thoracic spinal cord MRI revealed an extensive T2-weighted hyperintense lesion approximately 15 cm long, extending from level C2 to Th4. It asymmetrically extended in the spinal cord, mainly occupying the right half of the cord, including the lateral and posterior funiculus as well as the spinal cord gray matter on the right. These lesions were most visible at the C6 level and occupied more than half of the spinal cord. The primary differential diagnosis provided by the radiologist was a demyelinating process in the acute/subacute stage (including

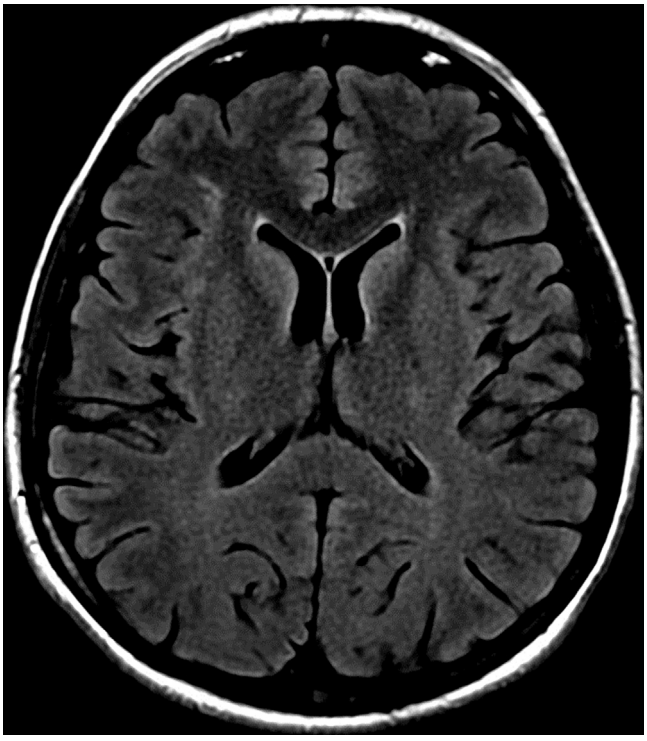

Fig. 1 – An MRI brain scan (FLAIR sequence) showing nonspecific sites of hyperintense tissue signal indicative of mild perivascular gliosis.

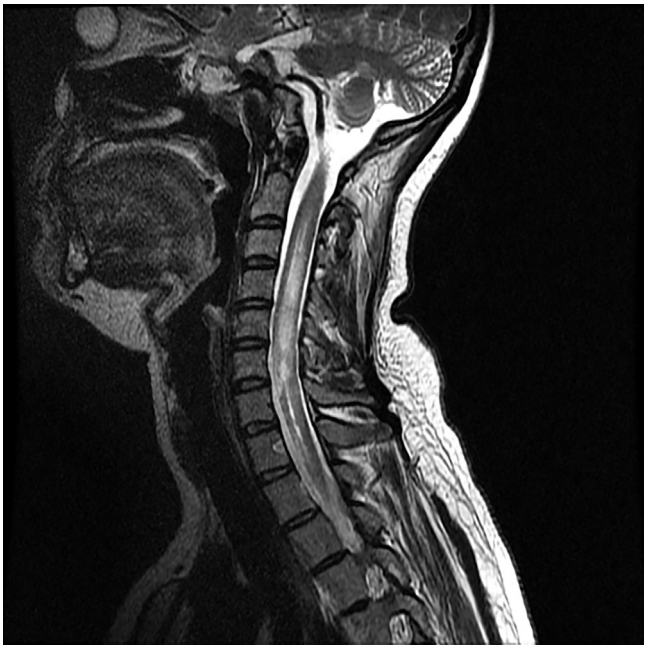

Fig. 2 – Cervical and thoracic spinal cord MRI revealed an extensive T2-weighted hyperintense lesion from level C2 to Th4.

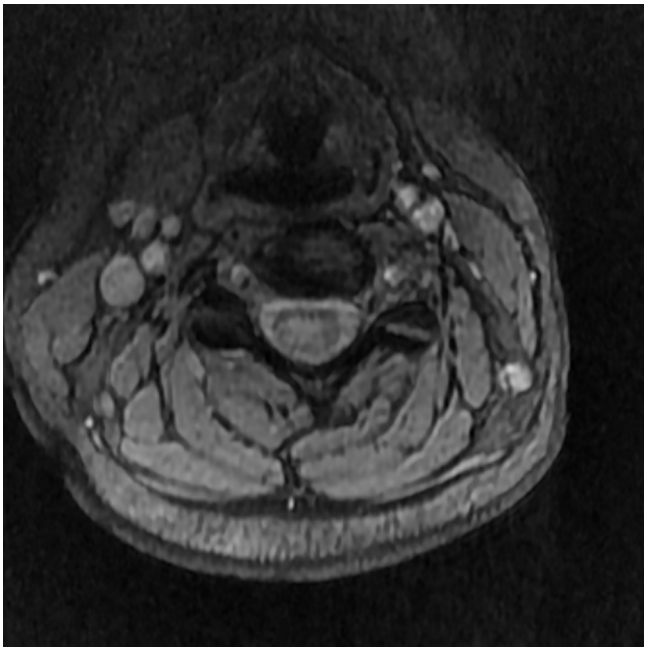

Fig. 3 – Cervical spinal cord MRI at the C6 level revealed occupied more than half of the spinal cord.

Devic's disease) (Figs. 2 and 3). The ophthalmic examination revealed bilateral temporal optic atrophy and atrophy of the macula lutea. Scotopic and photopic electroretinography (ERG) response was at the lower limit of the normal range. The latencies of the visual evoked response (VEP) were increased bilaterally. Neurography revealed bilateral lumbosacral radiculopathy at the L4/L5 level with axonal injury of the left peroneal nerve. Laboratory tests showed a moderate and transient electrolyte imbalance, hypoalbuminemia, normocytic anemia, a positive anti-HCV antibody titer, HCV-RNA level was 1,260,000 IU/ml, a progressive decline in the platelet count (thrombocytopenia in pregnancy) as well as a positive anti-aquaporin 4 antibody titer with indirect immunofluorescence technique (IFF). Analysis of cerebrospinal fluid was within normal limits. Consultations with a general internal medicine specialist, an infectious disease specialist, and gynecologist were carried out and abnormalities of the fetus or pregnancy were ruled out.

The patient was diagnosed with NMO. Plasmapheresis was introduced and five cycles of plasma exchange were performed, which resulted in improved muscle strength of the right limbs, improved gait and visual acuity (the patient was able to count her fingers at a distance of two meters). Control laboratory tests indicated an increased platelet count. The patient was discharged.

Three months after the plasmapheresis (34th week of gestation) the patient required hospitalization due to a relapse. The clinical examination revealed a bilateral reduction in visual acuity (the patient counted her fingers at a distance of only 1 m), paresis of all four extremities (a score of 4/5 on the Lovett scale in the upper extremities with flexion contracture of the right hand digits, a score of 3/5 in the lower left extremity, a score of 2/5 in the lower right extremity and a score of 3/5 in the lower left extremity), brisk deep reflexes in the upper right extremity, decreased knee and ankle-jerk reflexes and the presence of the Babinski reflex bilaterally. In addition, the patient had a sacral pressure sore. Periodic limb contractions were also present. Five consecutive cycles of plasma exchange were performed. A slight improvement of the muscle strength in the right limb (3/5) and exacerbation of the left limb paresis (2/5) were observed.

The woman gave birth to a healthy daughter by cesarean delivery in the 40th week of gestation (Apgar score of 10). Lower limb venous thrombosis was present during the postpartum period. Intravenous infusions of immunoglobulins (140 g in total) and symptomatic treatment were administered, which gave slight functional improvement in the lower limbs. During pregnancy deep venous thrombosis prophylaxis was used (a low-molecular-weight heparin). Chronic immunosuppression was excluded due to the presence of the sacral pressure sore and vascular thrombosis. A deferred administration of Rituximab was planned. However, the patient did not return to the neurological care unit following rehabilitation treatment in the Rehabilitation Ward.

3. Discussion

Neuromyelitis optica is a rare disorder characterized by acute or subacute optic neuritis and subacute cervical or cervicothoracic spinal cord injury. The onset of neurological symptoms and the time interval between them may differ between patients. In the described case, the first symptom of NMO was loss of visual acuity, which developed prior to pregnancy. The disease progressed six months later in the 22nd week of gestation, causing mild right hemiparesis, a minor eye movement disorder and slight ataxia. One of the main diagnostic criteria in Devic's disease is the presence of transverse myelitis, causing para- or tetraparesis [3]. In the described patient, the disease was diagnosed late due to the time interval between symptoms of optic nerve damage and spinal cord injury. Cervical MRI and the detection of antibodies against aquaporin 4 gave conclusive results, indicative of NMO.

IgG AQP4 autoantibodies, which bind to the aquaporin 4 receptor localized on the end-feet of astrocytes, play a key role in the pathogenesis of NMO. Their binding activates the complement system, leading to the deposition of the membrane attack complex in a process known as complement-dependent cytotoxicity (CDC) [6]. During pregnancy, a number of homeostatic changes, including immunologic changes that promote the Th2 humoral response take place [4], which are most likely associated with an increase in the concentration of female sex hormones [5]. Increased estrogen levels exert a multidirectional effect on the immune system. They may contribute to an increase in the expression of cytidine deaminase, which is responsible for the production of immunoglobulins [7]. They may also influence the changes in the glycosylation of antibodies [8] modifying their complement and immunoglobulin Fc receptor binding ability [9]. These mechanisms explain why diseases with a predominantly Th-2 type cytokine profile are exacerbated during pregnancy. An increase in the annualized relapse-rate of NMO was found in the third trimester of pregnancy and in the first trimester postpartum [10]. In the presented patient, there was a relapse of Devic's disease which began prior to gestation, in the 22nd and 34th week of pregnancy.

Studies have found that there is a bidirectional relationship between NMO and pregnancy. Nour et al. [14] reported an increased incidence of miscarriages mainly in early gestation despite no significant association between the miscarriages and the IgG-AQP4 titers. In addition, the incidence of preeclampsia was significantly higher in patients with NMO than in the general population (11.5% vs 3.2%, respectively) [14]. No such complications were observed in the described patient, and she gave birth to a healthy daughter.

Clinical data suggest there is a relationship between immune-mediated nervous system demyelinating processes and active hepatitis C. It has been shown that HCV contributes to immune system dysregulation and stimulates B lymphocytes to produce antinuclear antibodies (ANA), anti GM1, anti-sulfatide and anti-neutrophil cytoplasmic antibodies (ANCA) [15]. The extrahepatic effects of HCV have been reported to include demyelination of the peripheral nervous system (multifocal multiple mononeuropathy, crioglobulin-associated polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy) and central nervous system. Kitadaet al. [16] presented a case of a patient with HCV and AQP4 antibodies who had central and peripheral nervous system demyelination. The condition of the patient improved following sequential treatment with large doses of corticosteroids and plasma replacement. Control studies also revealed a

decrease in the Ig-AQP4 antibody titer. Mariotto et al. [15] presented a case of a 75-year-old man with chronic C hepatitis who was diagnosed with Devic's disease based on the clinical findings and additional tests (including positive Ig-AQP4 antibody titers). These cases suggest that a HCV infection may activate the B-lymphocyte production of antibodies against AQP4 and contribute to Devic's disease.

According to the literature, the main therapy for NMO in pregnancy is immunosuppression in the form of pulses of methylprednisolone. Other drugs are administered less frequently [11,17]. Due to the initial mild neurologic symptoms as well as adverse fetal effects of corticosteroid therapy, together with an infectious diseases specialist and nephrologist, we chose to administer plasmapheresis. Studies indicate that plasmapheresis is a safe form of therapy in pregnant women and may be administered in corticosteroid-resistant relapses of NMO [11]. We obtained significant improvement of gait, muscle strength in the right limbs and a slight improvement of visual acuity. Intravenous administration of immunoglobulins during the second disease relapse gave slight clinical improvement reducing limb paresis. Taking into consideration the disease relapse in the third trimester of pregnancy and an increased risk of further exacerbation in the postpartum period, it is advisable to administer pulses of methylprednisolone followed by an oral steroid and azathioprine therapy with simultaneous ending of lactation [13]. However, due to the lower limb thrombosis following the cesarean section and the presence of a sacral pressure sore, we did not opt to introduce long-term immunosuppressive therapy. Rituximab, which has been reported to be effective and routinely used to treat NMO, was planned for use in the patient [18,19]. Rituximab is a monoclonal antibody against the CD20 antigen found on the surface of B lymphocytes. This drug has been found to decrease the incidence of disease relapse and rarely gives serious clinical complications. Ringelstein et al. [12] described a patient with NMO with antibodies against AQP4 who became pregnant seven months after the administration of Rituximab. The patient did not experience disease relapse during pregnancy, and Rituximab was administered two days after delivery in order to maintain stable neurological results.

4. Conclusion

We present the case of a 37-year old woman diagnosed with NMO with two disease relapses, causing serious disability. Coexisting pregnancy and severe complications of the primary disease (an extensive sacral pressure sore, lower extremity venous thrombosis) did not permit the introduction of proven and effective corticosteroid therapy. The patient was treated with plasmapheresis and intravenous immunoglobulin infusions. The severe course of the disease was most likely caused by an imbalance in hormones caused by the pregnancy and the active HCV infection. Together, these factors contributed to the dominance of humoral immunity, which is fundamental in the pathogenesis of NMO.

Conflict of interest

None declared.

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