Encephalomyelitis Associated with Anti-myelin Oligodendrocyte Glycoprotein Antibodies and Adenovirus

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An 11-year-old female presented with encephalomyelitis in the presence of anti-myelin oligodendrocytes glycoprotein (MOG) antibodies (Abs), suspected to be triggered by concurrent respiratory adenovirus infection. The prognosis of such cases depends on prompt treatment; therefore, early diagnosis is crucial.

PATIENT DESCRIPTION

An 11-year-old female was admitted to the pediatric department due to neck pain, general weakness, and 3 days of hypoesthesia of the proximal lower limbs, lower abdomen, and back. Medical history of the patient included subclinical hypothyroidism and appendectomy at the age of 6 years. There was no personal or family history of developmental delay or neurological disease. No recent febrile disease was described.

Positive findings included fever (38°C), tachycardia, bladder distension, hypoesthesia of the lower abdomen and back, and slightly weakened tone of the anal sphincter. A urine catheter was inserted.

Two days after admission, the patient expeditiously developed nuchal rigidity, loss of consciousness, hypothermia, and oxygen desaturation in addition to involuntary tonic-clonic movements of the limbs and deviation of the gaze to the left, which is consistent with focal onset seizure with altered alertness.

After treatment with midazolam and levetiracetam, resulting in cessation of the seizure, she was transferred to the pediatric intensive care unit. Acyclovir, doxycycline, and levetiracetam were administered on a working diagnosis of meningoencephalomyelitis. Head and spine magnetic resonance imaging (MRI) was performed on the same day and demonstrated multiple bilateral asymmetric cortical lesions with T2/FLAIR hyperintensity and associated diffusion restriction. There was no evidence of contrast enhancement, and the ventricles were normal in size. A long segment of abnormal intramedullary signal intensity extending between c3 to t3 was present. Conus medullaris, filum terminale, and cauda equina nerve roots showed normal appearance. Imaging findings were compatible with encephalomyelitis [Figure 1]. Electroencephalogram showed diffuse generalized slow wave background activity compatible with encephalopathy, without epileptiform activity. Opening pressure on lumbar puncture was 26 cmH_2O, cerebrospinal fluid (CSF) contained eight white blood cells, and glucose and protein levels were within normal limits. Anti-MOG Abs in serum were positive (cell-based assay). Oligoclonal bands, anti-aquaporin-4 antibodies, anti-NMDA receptor, anti-AMPAR, anti-CASPR2, and anti-LG1 antibodies in CSF were negative. CSF biofire panel was negative for cytomegalovirus, herpes, enterovirus, varicella zoster, parechovirus, *Escherichia coli* K1, *Haemophilus influenzae*, listeria, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*. CSF was also negative for bacteria and mycobacteria (both cultures and polymerase chain reaction [PCR]). No antibodies against bartonella, brucella, West Nile fever, and Q-fever were detected. PCR of the nasopharyngeal swab was positive for adenovirus. PCR of the nasal and pharyngeal swab was negative for coronavirus disease 2019 (COVID-19).

Pulse methylprednisolone therapy (30 mg/kg/day for 3 days) was initiated after MRI and lumbar puncture were performed. After expedited positive anti-MOG-Ab results were received at the end of the pulse therapy, a 2 gram/kg intravenous immunoglobulins (IVIG) therapy course was initiated, followed by oral corticosteroids. The patient gradually returned to full consciousness and 12 days later motor skills improved, sensory examination was intact, and bladder control was sufficient with no need of a catheter. She was discharged from the hospital with recommendations for ambulatory physical therapy, oral corticosteroids in

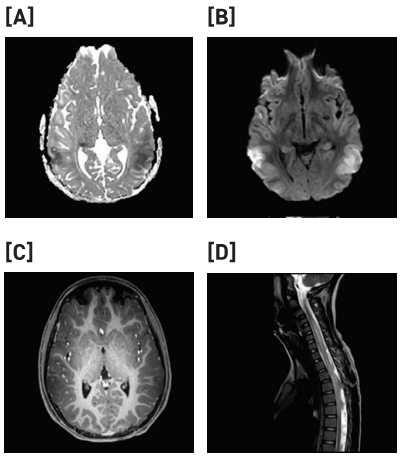
Figure 1. Head and spine MRI of the patient during admission

[A,B] Diffuse-weighted imaging MRI demonstrates bilateral parietal cortical edema

[C] T1-weighted MRI with gadolinium shows no enhancement of the parietal findings

[D] Spinal MRI reveals abnormal continuous sign of the grey matter from C3 to T3.

MRI = magnetic resonance imaging



tapering down dosage, and levetiracetam treatment. Six months after discharge anti-MOG Abs in the serum were negative. On the last follow-up visit at the neurological clinic 12 months later, cognitive, motor, and autonomic functions were fully restored. Based on conversations with the patient and physical examination, no formal cognitive test was performed. Levetiracetam treatment was discontinued following normal electroencephalogram. There was no need for further disease modifying agents.

COMMENT

To the best of our knowledge, this study is the first report of MOG-Abs positive encephalomyelitis in the presence of nasopharyngeal infection with adenovirus. MOG is a glycoprotein localized on the surface of the myelin sheath as well as on the oligodendrocyte cell surface. Anti-MOG-Abs may be present in the peripheral blood circulation but are clinically insignificant unless they penetrate the central nerve system (CNS). The presence of anti-MOG-Abs is associated with a broad clinical spectrum of acquired demyelinating syndromes of the CNS, as well as non-demyelinating autoimmune encephalitis [1]. Accordingly, the clinical manifestation of anti-MOG disease varies with different prognosis. Moreover, there is a growing body of evidence for the involvement of anti-MOG-Abs in the pathogenesis of non-acute disseminated encephalomyelitis (ADEM), similar to our case [2]

Armangue et al. [2] investigated the clinical syndromes associated with MOG-Abs. Among patients with autoimmune encephalomyelitis, MOG-Abs were more common than all anti-neuronal Abs combined. About one-fifth of the study population had encephalomyelitis and presented with altered consciousness, seizures, fever, abnormal behavior, and motor deficits. Extensive bilateral cortical lesions, symmetrical isolated lesions within basal ganglia, single cortical, and subcortical lesions have been shown on MRI.

Persistent MOG-Abs seropositivity is associated with a 70% relapse rate. Different studies show a relapse rate of 17% to 38%. In the Armangue study [2], 85% of patients had full or almost full recovery by the last follow-up. Neurologic sequela was significantly more prevalent among the encephalomyelitis group compared to patients with demyelinating disorders. Prompt diagnosis and treatment initiation might be a significant prognostic factor. Therefore, it is important to test for MOG-Abs in patients with non-demyelinating CNS diseases.

The treatment of anti-MOG-Abs associated disease lacks established prospective data. First-line treatment usually includes corticosteroids and IVIG. In some cases, rituximab or other immunosuppressive treatments such as methotrexate, azathioprine, and mycophenolate mofetil, are used [2].

Adenovirus is a common pathogen in the pediatric population, usually causing a febrile illness with respiratory and gastrointestinal symptoms. CNS manifestations are rare among immunocompetent children. Another large retrospective study showed that 3.3% of patients with adenovirus infection presented with CNS symptoms, mostly children younger than 5 years old [3].

Clinical manifestations of adenovirus-associated CNS disease are variable and may include seizures, altered consciousness, headache, visual hallucinations, lethargy, hemiplegia, and other neurologic deficits. Mortality rate may reach 21% and neurologic sequelae including convulsive disorder, spasticity, paresis, and dystonia have been reported in 9% to 17% of the patients. Interestingly, the virus was detected in the respiratory tract in all cases, but not in the CSF [3]. Thus, it remains unclear whether the neurological presentation associated with adenovirus infection is caused by direct infection of the CNS or rather by immune-mediated response.

The combination of encephalomyelitis with positive anti-MOG-Abs and the presence of adenovirus in the respiratory tract in our patient raised the question of adenovirus being the trigger for the MOG-Abs associated disease. Viral infections play a role in the pathogenesis of autoimmune diseases through various mechanisms, such as molecular mimicry and cross-reactivity. The association between viral respiratory infections and different neurologic manifestations including encephalomyelitis, ADEM, multiple sclerosis, and transverse myelitis have been widely described [4]. Moreover, experimental models have shown a large number of molecular homologs of the extracellular domain of MOG [5]. In our case PCR for adenovirus in CSF was not tested; therefore, we cannot precisely elucidate the association between adenovirus infection and encephalitis. Furthermore, PCR for nasopharyngeal adenovirus may remain positive for 2–3 weeks, so the sequence of events cannot be accurately established. We speculated

that infection with adenovirus may have triggered autoimmune response via molecular mimicry between the pathogen and MOG or by exposing previously covered antigens on the neurons.

CONCLUSIONS

Our patient had clinical and radiological findings compatible with encephalomyelitis mainly involving the grey matter of the brain and the spinal cord. Adenovirus infection may have been the trigger for the MOG-Abs mediated inflammatory response. Early diagnosis and treatment are extremely important in such cases and may have significant prognostic influence.

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The little I know, I owe to my ignorance.
Sacha Guitry (1885–1957), French stage actor, film actor, director, screenwriter, and playwright

Maybe all one can do is hope to end up with the right regrets.
Arthur Miller (1915–2005), playwright and essayist

Capsule

Antiviral after infection through ACE2

Macrophages are critical first responders to infection, but they are also implicated in driving severe inflammation, particularly in SARS-CoV-2 patients. Because relatively few lung-resident macrophages have the SARS-CoV-2 receptor ACE2, **Labzin** and colleagues explored its role in the response of these cells to infection. SARS-CoV-2 infected all cultured macrophages but replicated and induced an antiviral cytokine response only in those engineered to express ACE2. This finding suggests that ACE2-positive and ACE2-negative lung macrophages may contribute to differential responses to infection in patients.

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Eitan Israeli

Capsule

Cysteine carboxyethylation generates neoantigens to induce HLA-restricted autoimmunity

Autoimmune diseases such as ankylosing spondylitis (AS) can be driven by emerging neoantigens that disrupt immune tolerance. **Zai** et al. developed a workflow to profile posttranslational modifications involved in neoantigen formation. Using mass spectrometry, the authors identified a panel of cysteine residues differentially modified by carboxyethylation that required 3-hydroxypropionic acid to generate neoantigens in patients with AS. The lysosomal degradation of integrin αIIb [ITGA2B (CD41)] carboxyethylated at Cys96 (ITGA2B-ceC96) generated carboxyethylated peptides that were presented by HLA-DRB1*04 to stimulate $CD4^+$ T cell responses and induce autoantibody production. Immunization of HLA-DR4 transgenic mice with the ITGA2B-ceC96 peptide promoted colitis and vertebral bone erosion. Thus, metabolite-induced cysteine carboxyethylation can give rise to pathogenic neoantigens that lead to autoreactive $CD4^+$ T cell responses and autoantibody production in autoimmune diseases.

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