ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS WITH POSITIVE SERUM ANTITHYROID ANTIBODIES, IGM ANTIBODIES AGAINST *MYCOPLASMA PNEUMONIAE* AND HUMAN HERPESVIRUS 7 PCR IN THE CSF

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Abstract: We report the case of a boy with an encephalopathy associated with extrapyramidal and psychiatric symptoms and anti-N-methyl-D-aspartate receptor antibodies. He had positive serum antithyroid antibodies, IgM antibodies against *Mycoplasma pneumoniae* and human herpesvirus 7 polymerase chain reaction in the cerebrospinal fluid. He was successfully treated with rituximab, after steroids, intravenous immunoglobulin and plasma exchange. The pathophysiology of this disorder may be post-infectious and autoimmune.

Key Words: encephalitis, N-methyl-D-aspartate receptor, *Mycoplasma pneumoniae*, HHV-7, rituximab

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis first characterized by Dalmau et al[1] in 2007. The disorder affects predominantly children and young adult women.[2] It is associated with a tumor in 42% of the patients, but the precise pathological background remains elusive.[2]

Clinical features are psychiatric symptoms, disturbance of consciousness, generalized seizures, abnormal involuntary movements, autonomic dysfunction and central hypoventilation.[2,3] The diagnosis is based on the clinical course and, in addition, on the demonstration of anti-NMDAR antibodies in the serum and cerebrospinal fluid (CSF).

In patients with a tumor, predominantly an ovarian teratoma, the condition is treated by tumor removal, whereas first-line immunotherapy [corticosteroids plus intravenous immunoglobulin (IVIg) or plasma exchange] has been proposed in previous reports.[2] When no response is seen second-line immunotherapy (rituximab and/or cyclophosphamide) should be considered.[4–6]

The pathogenesis of anti-NMDAR encephalitis is unclear. Although recent studies showed that a few patients with non-tumor-associated anti-NMDAR encephalitis have elevated antithyroid peroxidase (anti-TPO) antibodies,[5–7] the combined occurrence of anti-NMDAR and anti-TPO antibodies was not followed up in detail in the literature.

Neurologic disease associated with *Mycoplasma pneumonia* and Human herpesvirus 7 (HHV-7) infections have been described rarely contrasting with the occurrence of nearly universal primary infection in early childhood.[8]

We report an anti-NMDAR encephalitis in a 9-year-old boy, not associated with malignancy, with positive serum antithyroid antibodies, IgM antibodies against *Mycoplasma pneumoniae* and HHV-7 polymerase chain reaction (PCR) in the CSF that showed significant improvement after administration of rituximab.

CASE PRESENTATION

A 9-year-old boy initially had upper respiratory symptoms and low-grade fever. One week later, he progressively developed limb muscle weakness, fatigue, waddling gait, refusal to walk, changes of mood and self-injurious behavior. He was seen at a local hospital with a severe headache and vomiting. CT-scan was normal and the symptoms improved. Two weeks later, he manifested incoherent delirious and obsessive thoughts, slurred speech and a mild motor incoordination. He was fully awake, with periods of agitation. Neurologic examination did not indicate any other abnormalities. Extensive investigations for metabolic, infectious, toxic, autoimmune and central nervous system disorders were performed. CSF cyto and biochemical analyses were normal. Brain magnetic resonance imaging fluid-attenuated inversion recovery showed bilateral medial temporal lobe hyperintensities, predominantly involving the left hippocampus. Electroencephalogram demonstrated right-sided, fronto-temporal slowing without epileptiform discharges. Considering encephalitis, he was treated with acyclovir, ceftriaxone and ciprofloxacin.

Further CSF analysis showed elevated IgG and IgM indexes, oligoclonal bands and a pattern of increased permeability of the blood-brain barrier. CSF culture was negative for bacteria. PCR-based analysis of CSF and enzyme-linked immunosorbent assays antibody titers in serum and CSF samples were suggestive of *Mycoplasma* infection with positive IgM in serum (negative antibodies and PCR in CSF); it also revealed a positive PCR for HHV-7 (in 2 consecutive samples). He completed a 21 day course of ceftriaxone and ciprofloxacin. After acyclovir, he completed a 10 day course of foscarnet. HHV-7 CSF PCR became negative after this treatment.

Serum anti-thyroglobulin (TG-138 U/mL, normal range 0~60 U/mL) and anti-TPO (>1300 U/mL, normal range 0–60 U/mL) antibodies were markedly elevated, with normal thyroid stimulating hormone and mildly diminished free T3 (2.1 pg/mL).

During the first week after admission, the patient's condition deteriorated progressively: psychiatric symptoms worsened (severe agitation, auditory hallucinations, delusions, crying out and perseveration), he developed a sleep disorder (hypersomnia and insomnia) and speech production diminished to a state of mutism. Intense orofacial dyskinesia, sometimes associated with lip-biting and choreic movements in the left upper limb supervened. He also had autonomic dysfunction (constipation, mild tachycardia, hypertension, apnea and hyperventilation). Electroencephalogram on day 2 revealed a background of generalized slow and disorganized activity, but also intermittent low voltage beta that was phase locked to underlying delta activity. Risperidone and imipramine were added to treatment at this time. Because the patient's condition did not improve, he was subsequently treated with methylprednisolone (30 mg/kg/d for 3 days/2 cycles), IVIg (1 g/kg/d for 2 days) and plasma exchange (5 times/2 cycles and 3 weekly sessions), with minor improvement.

The clinical profile was suggestive of anti-NMDAR encephalitis: serum and CSF anti-NMDAR antibodies collected on day 5 (*Molecular Biology Laboratory, Oxford Hospital*), before immunotherapy and plasma exchange had been initiated, were highly positive. Whole-body PET scan revealed no indication of a tumor lesion. We started, on the 51st day in hospital, weekly rituximab, a monoclonal anti-CD20 antibody, 375 mg/m^2/wk, approved by the hospital´s Ethics Committee, for a total of 4 doses. One isolated anaphylaxis episode was associated with the first dose of rituximab; this resolved promptly with adrenaline.

Clinical symptoms, including the disturbance of consciousness, psychiatric symptoms, involuntary movements and autonomic dysfunction markedly improved 1 week after the first administration. In parallel, abnormal findings on electroencephalogram progressively normalized. On day 65, the patient was discharged,

with only mild self-injurious behavior when facing frustrating situations and coprolalia.

Progressive improvement of cognitive and motor neurological functions took place over the next 6 months, returning to school with a good recovery. He was able to return to school and resumed all his previous activities. Testing for anti-TG and anti-NMDAR antibodies was negative 6 months after diagnosis. Serum anti-TPO antibodies titers persisted elevated.

DISCUSSION

Our case had a classic clinical picture of anti-NMDAR encephalitis resulting from the loss of NR1 subunit of NMDA receptors as presented in the current literature, including psychotic behavior, dysfunction of dopaminergic pathways (orofacial dyskinesia) and dysautonomia (cardiac dysrhythmia and central hypoventilation).[2]

M.pneumoniae serology was positive, but CSF antibody tests and PCR were negative, as reported by others. The significance of this finding is unclear given the high prevalence of positive serologies in most series of pediatric encephalitis.[2,3] However, *M. pneumoniae* infection can result in the development of autoantibodies against neuronal membrane and this biological mimetism can be associated with central nervous system immunologic events.[3] Despite the high sensitivity of enzyme-linked immunosorbent assays, relying on a single serological test can be clinically misleading. Moreover, plasmapheresis made it impossible to base the diagnosis of acute infection on seroconversion measured simultaneously in assays for both IgM and IgG, as recommended.

HHV-7 can produce encephalopathy in children but many cases in which HHV-7 is detected in the CSF have an alternative etiology for their illness, as latent DNA integrated or reactivated virus may not be causally related to disease. In our case, however, CSF PCR became negative after treatment with foscarnet and this may be relevant.[8] HHV-7 has been described in association with influenza-associated encephalopathy, but the authors have not found any reported case stating this evidence.[8] Recent observations suggest that herpesviruses may have a unique role in promoting development of autoimmune antibodies, as patients with herpes simplex 1 encephalitis developed anti-NMDAR encephalitis weeks or months after acute episode.[9]

Anti-NMDAR encephalitis is not always a paraneoplastic disorder; a post-infectious autoimmune process may also be implicated in etiology, reinforcing the possible relevance of *Mycoplasma* and HHV-7.[2]

In patients without a tumor, first-line immunotherapy, using corticosteroids, IVIg, plasma exchange may not be effective, thus second-line immunotherapy (eg, rituximab and/or cyclophosphamide) is usually needed.[3,4] Globally, nearly 75% of the patients make a good recovery after tumor removal and/or immune-modulatory treatments, although the time to full recovery is variable (1–14 months), with a median of 2.5 months.[2] Our patient fully recovered in 6 months.

Importantly, serial NMDAR antibodies levels seem to correlate with clinical severity. Rituximab causes a decrease in B cells, prevents maturation into antibody-secreting cells and suppresses B cell function more selectively and continuously than first-line immunotherapy.[10] In addition, it causes a form of immune system resetting because of the depletion of memory B cells and prevents them from stimulating T lymphocytes. Therefore, rituximab seems effective for treatment of anti-NMDAR encephalitis resistant to first-line immunotherapy.[10] An infusion related reaction, tachycardia and anaphylaxis, was seen in our case but resolved promptly, without further serious adverse effects. The available evidence that rituximab is effective for this type of encephalitis enhances our understanding of the disease. It is unclear whether its early use to control the immune response within the central nervous system would shorten the duration of symptoms. Thus, considering the B cell-selective pharmacological effects and the limited side effects of rituximab, this treatment may be particularly useful in young anti-NMDAR encephalitis patients without tumor lesions.[2,4]

Unlike 2 recently reported patients with anti-NMDAR encephalitis cases with anti-TPO and infectious serology concurrence,[11] our patient had a complete clinical recovery both on discharge and 6 months later. Persistent high titers of serum anti-TPO antibodies not only suggest a propensity to autoimmunity in cases of anti-NMDAR encephalitis, but also support the notion that neuronal and thyroid autoimmunities may be part of a pathogenic spectrum. More detailed clinical analysis is necessary to elucidate the etiology of anti-NMDAR encephalitis.

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ACQUIRED DRUG RESISTANCE DURING INADEQUATE THERAPY IN A YOUNG CHILD WITH TUBERCULOSIS

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Abstract: Drug resistance in children with tuberculosis is usually primary (transmitted); however, resistance acquisition during treatment is possible. We describe a child with tuberculosis who acquired drug resistance while receiving directly observed but inadequate first-line therapy and the programmatic and clinical factors that may have contributed to resistance acquisition.

Key Words: tuberculosis, children, isoniazid monoresistance, acquired antibiotic resistance, multidrug resistance