Autoimmune Neurological Disorder with Anti-Ma2/Ta Antibodies in a Pediatric Patient

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For editorial see page 649

The dynamic development of immunology in recent decades has led to the discovery of a group of disorders that develop secondary to the formation of autoantibodies against intracellular and extracellular antigens. These disorders manifest as inflammatory diseases of the central and peripheral nervous system. The relationship between tumors and symptoms of nervous system damage has been known for about 50 years [1].

Originally, researchers hypothesized an association between cancer products and toxins that damaged the nervous system. Later, an immune-mediated mechanism was suggested as the etiology of nervous system injury.

A group of autoantibodies was distinguished as anti-onconeural. Of these, antibodies against intracellular antigens (anti-Hu, anti-Yo, anti-Ri, anti-Ma2) and anti-amphiphysin antibodies are the most common [1]. Since 2005, many antigens related to neuronal cell-surface structures have been described and their relation to tumor presence has been observed.

Researchers have also confirmed that an infection can often precede the wide range of clinical symptoms present in autoimmune encephalitis [2]. With recent advances, the relationship between the expression of specific antibodies and their triggering factors is better understood and molecular mimicry is considered to be the basis for this association [2]. Nevertheless, it is impossible to predict the clinical course of disease based solely on the presence of specific antibodies. The clinical presentation of the patient described in this case communication demonstrates the complexity of these issues.

PATIENT DESCRIPTION

A four year old girl presented to the hospital in July 2013 with a 2 day history of involuntary movements. Neither she nor her family had significant history of neurological disease. Symptoms included postural tremors, myoclonus of the upper and lower limbs, gentle choreic movements (especially of the upper limbs), and balance disturbances.

The girl had been diagnosed with a pyretic infection, which was treated symptomatically a few weeks before admission. After admission, she was hypotonic, irritable, and emotionally unstable. The involuntary movements increased in activity. She demonstrated a high level of cognitive development and an Intelligence Quotient of 141 on psychological.

Based on the clinical picture and diagnostic tests [Table 1], *opsoclonus-myoclonus*-ataxia (OMA) was suspected as an initial diagnosis, and treatment with tetracosactide, a synthetic adrenocorticotropic hormone (ACTH)-analogue, was initiated (0.5 mg/day for 1 week). After a few weeks, symptoms almost completely disappeared, although a weak postural tremor was noticed occasionally. Improvement in the girl's condition lasted for a few months.

The first relapse of symptoms occurred in November 2013. This relapse, and all other relapses, were characterized by major behavioral changes, namely aggression, irritability, and emotional instability. She was treated with tetracosactide and intravenous immunoglobulins (IV-Ig) as a 2 g/kg total dose, which successfully diminished the symptoms. After that, the girl received four courses of IV-Ig (1 g/kg per course) and 0.5 mg dose intramuscular (IM) tetracosactide. The last course of IV-Ig was administered in September 2014.

A second relapse occurred in February 2015. In addition to the aforementioned behavioral changes, this relapse was characterized by impaired walking and penmanship, tremor, and myoclonus. She was treated with IV-Ig (2 g/kg) and tetracosactide (0.5 mg IM) with clinical improvement. Deterioration of behavior and a slight tremor appeared in the second half of 2016. She was treated with IV-Ig (2 g/kg) and intravenous methylprednisolone (6 × 500 mg) with clinical improvement. There were no signs of cognitive development regression during a psychological examination.

Systematic control of liver tests showed

Table 1. Summary of the patient's imaging, EEG, and laboratory test results

Test	Result	Comment
Magnetic resonance imaging of the brain	Normal	Performed twice at 1 month intervals during the first episode Performed several times during relapses. Last imaging performed in 2018
Electroencephalography	Normal (2013) Normal (2014)	
Lumbar puncture Cerebrospinal fluid exam	Pleocytosis: normal Intra-fluid synthesis: normal, no intra-CNS Ig synthesis, no blood-brain barrier damage Oligoclonal bands (-) in 2013 and 2015, (+) in Sep. 2016	
CBC, urea, electrolytes, CRP, ESR, VitD3, T3, T4, urinalysis, anti-EBV IgG, anti-CMV IgM and IgG.	Normal	
Immunological diagnostics		
ANA-Ab	Present in titer 1:640 (first relapse) Present in titer 1:320-1:160 (remission)	Method: mosaics biochip (hep-20-10 cells), indirect immunofluorescence confirmed by line blot with recombinant antigens
Anti-dsDNA Ab	Strongly positive in 2013 Negative in consequent tests	
Anti-PM/Scl Ab	Borderline (2013) Negative in consequent tests	
Anti-nucleosome, Sm, Po, histone, U1snRNP, Ro60, Ro52, La, Scl70	Negative	
ANCA Ab	Negative	
Rheumatoid factor	Negative	
ASO level	311.0 IU/ml (N < 200)	
Antineuronal Ab against cell-surface antigens in plasma (NMDA, AMPA1, AMPA2, CASPR2, LGI1, GABARB1/B2, GAD 65)	Negative	Method: indirect immunofluorescence. Tests were repeated several times
Ab against thyroid peroxidase, thyroid globulin	Negative	Method: indirect immunofluorescence. Tests were repeated several times
Intracellular onconeural antibodies in serum	Confirms the presence of anti-Ma2/Ta Ab.	Result was repeated and confirmed. Other onconeural antibodies were not found. Method: Western blot
Tumor screening		
Total-body scintigraphy with MIBG	Normal (2013, 2016)	Method: MIBG tracer. Performed twice (2013, 2016)
Non-specific enolase, α-fetoprotein	Normal	
24 hour urine collection for presence of catecholamines VMA and HVA	Normal (2016)	
MRI imaging of the neck, chest, abdomen	Normal (2016)	

ANA = antinuclear antibodies, ANCA = anti-neutrophil cytoplasmic antibodies, ASO = antistreptolysin O, CBC = complete blood count, CMV = cytomegalovirus, CRP = C-reactive protein, EBV = Epstein–Barr virus, EEG = electroencephalography, ESR = erythrocyte sedimentation rate, HVA = homovanillic acid, Ig = immunoglobulin, MIBG metaiodobenzylguanidine, = MRI = magnetic resonance imaging, VMA = vanillylmandelic acid

increased transaminase levels in 2016. Diagnostics directed at liver diseases were then performed. Based on a liver biopsy, hepatitis, most likely of autoimmune origin, was confirmed. She was initially treated with prednisone, then deflazacort, and later with additional azathioprine in a 100 mg dose.

All reported relapses were consistently diagnosed after infection or following strenuous physical activity. The longest time between relapses lasted over a year. Results of imaging, electroencephalography (EEG), and laboratory tests are presented in Table 1.

COMMENT

OMA syndrome is a rare neurological disorder that manifests as a combination of opsoclonus (multidirectional, chaotic eye movements), myoclonus (irregular muscle spasms of the head, trunk, or extremities), and uncoordinated movement (ataxia) [3].

Our patient's first symptoms were myoclonus, chorea, and ataxia, which appeared shortly after a pyretic infection. Opsoclonus was not observed. Opsoclonus is not always noticed in OMA. It or can be very discrete [3]. There are no biochemi-

cal markers that confirm the diagnosis of OMA. Diagnosis is based on the clinical picture and on additional exams that exclude inflammatory and metabolic disorders.

OMA syndrome was accompanied by anti-Ma2/Ta antibodies in our patient. Only a few reports in the literature present children with a neurological condition and anti-Ma2/Ta antibodies. Hu et al. [4] described a child with a history of neuroblastoma, opsoclonus-myoclonus in infancy, and anti-Ma2 and anti-CV2/CRMP5 onconeural antibodies. This patient presented with pharmacotherapy-resistant epilepsy with continuous spikes and waves during slow sleep. Changes in the EEG record were discovered after treatment with methylprednisolone [4].

Mrabet and colleagues [5] described a 2 year old girl with anti-Ma2-associated encephalitis accompanied by changes in the left temporoparietal region of the brain seen on magnetic resonance imaging. This patient also presented with convulsions and refractory epilepsy. There was no underlying tumor. Conversely, EEG records in our patient were normal and no epileptic seizures were observed.

The first symptoms observed in our patient were myoclonus, ataxia, gentle choreic movements, and social behavioral deterioration. Each relapse of the disease was associated with similar symptoms, but varied in intensity. The mood and behavior changes, and some discrete neurological deficits, were always observed.

The presence of antinuclear antibodies (ANA), along with antibodies against dsDNA and PM/Scl antigens in our patient can be explained by immune system activation during an infection episode (most likely viral). In some children, OMA is attributable to infections (e.g., Epstein–Barr virus [EBV], *Mycoplasma pneumoniae*, and mumps) [3]. In the course of viral infections, especially EBV and cytomegalovirus, polyclonal activation of B-lymphocytes occurs. Therefore, hypergammaglobulinemia can appear in peripheral blood. Thus, the presence of these antibodies and autoantibodies can be an unspecific phenomenon. In our patient, autoantibodies were positive for a long time period; however, anti-dsDNA and anti-PM/Scl antibodies gradually disappeared. The clinical picture and results of the ancillary tests did not fulfill the diagnostic criteria for systemic lupus erythematosus.

Since the treatment of choice in OMA is still steroid therapy, we prescribed ACTH as a first-line drug [3]. In the literature, the recommended time span of ACTH use is 7–9 months. As supportive therapy, it is recommended to use IV-Ig or immunosupression [3]. In case of relapse, ACTH therapy is recommended in the same dose. In our patient, IV-Ig was added to the ACTH therapy and she achieved full remission that lasted more than 1 year [3]. Due to a subsequent relapse, we decided to replace ACTH therapy with methylprednisolone IV infusions together with IV-Ig therapy. The patient tolerated all therapies well; however, her body weight increased, most likely due to steroid therapy. Consequently, hepatitis and corticosteroid dependence symptoms appeared. Thus, it was decided to add azathioprine to the therapeutic regiment.

OMA is commonly associated with paraneoplastic processes, particularly with neuroblastoma, which is concomitantly present in at least 50% of OMA patients [3]. Various types of autoantibodies have been found in neuroblastoma; however, no specific antibody has been confirmed as pathognomonic for this tumor [3]. Anti-Hu antibodies are expressed in a significant percentage of patients with neuroblastoma [3].

As the presence of autoantibodies may precede the development of neoplastic diseases, Ma2/Ta can be considered as early cancer markers [1]. Due to this suspicion, careful diagnostic assessment directed at tumor presence, especially neuroblastoma, was performed in our patient. Since a risk of cancerous disease is still present, systematic patient control is necessary. If a tumor is found, early oncological therapy is essential for enabling recovery from autoimmune central nervous system disorders.

CONCLUSIONS

This case report demonstrates the diagnostic and therapeutic complexity of autoimmune encephalopathy in children. Currently, a variety of tests detecting neuronal autoantibodies are increasingly available. This finding can facilitate patient management; however, the presence of a certain antibody does not always predict the disease outcome. To the best of our knowledge, the occurrence of anti-Ma2/Ta antibodies in a child with neurological symptoms, neither related to tumor presence nor to epilepsy, is extremely rare. Therefore, diagnosis and treatment of these disorders relies largely on clinical experience related to the previously reported cases.

It can be presumed that tests detecting antineuronal antibodies are rarely carried out in children. Such testing is warranted to discern alternative etiologies of drug-resistant epilepsy in the pediatric population. The natural course of disease in our patient points to the uncertainty of prognosis of autoimmune encephalitis and to the need for careful observation and systematic patient control, including tumor screening.

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