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Opsoclonus-Myoclonus Syndrome in Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

Background—Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has been recently reported as autoimmune/paraneoplastic encephalitis, affecting mostly young females.

Objective—To describe opsoclonus-myoclonus syndrome in association with anti-NMDAR antibodies.

Design—Case report.

Setting—Geneva University Hospital.

Patient—A 23-year-old woman with opsoclonus-myoclonus syndrome.

Results—Two weeks after an episode of gastroenteritis, the patient developed symptoms of depression associated with psychomotor slowing, progressive gait instability, and opsoclonus-myoclonus. Cerebrospinal fluid examination showed mild lymphocytic pleocytosis and intrathecal IgG synthesis with oligoclonal bands. The patient's condition worsened rapidly to an akinetic mutism, followed by a period of agitation, delirium, and hallucinations. These gradually subsided; however, a frontal behavior and executive dysfunction persisted 5 months after symptom presentation. No tumor was found. Anti-NMDAR antibodies were found in the cerebrospinal fluid.

Conclusions—Opsoclonus-myoclonus may occur in patients with anti-NMDAR encephalitis. Prompt diagnosis of this disorder is important because after tumor removal and immunomodulatory therapies it has a relatively good prognosis.

Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, initially described in 2007, is characterized by a well-defined set of clinical and immunologic characteristics. According to a recently published series of 100 patients, it affects mostly young females, and in approximately half of them, an ovarian teratoma is found. Typically, after a viral-like

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prodromal event, prominent psychiatric symptoms develop, followed by a decreased level of consciousness (usually in association with abnormal movements and autonomic instability) and finally a gradual recovery phase. Anti-NMDAR antibodies can be detected in serum or cerebrospinal fluid (CSF). Despite the severity of the illness, which might include central hypoventilation necessitating ventilatory support, many cases are self-limited and respond well to tumor removal and/or immunomodulatory therapies. However, some patients may develop a chronic autoimmune disease. ¹

The etiologies of opsoclonus-myoclonus syndrome include paraneoplastic, para-infectious, toxic, and metabolic causes. As far as immunologic mechanisms are concerned, no single antibody marker has been identified.2 Anti-Ri antibodies have been reported in several cases of paraneoplastic opsoclonus-myoclonus, and anti-glutamic acid decarboxylase antibodies have been found in the serum and CSF of 1 patient with idiopathic opsoclonus-myoclonus-ataxia syndrome.³ Two cases of opsoclonus-myoclonus syndrome have been reported with benign ovarian teratoma, but anti-NMDAR antibodies were not found (I.T.Y. Kawachi, MD, PhD, et al, unpublished data, 2009).⁴ Herein we describe a patient who developed opsoclonus-myoclonus syndrome and ataxia along with an otherwise typical presentation of anti-NMDAR encephalitis.

REPORT OF A CASE

A 23-year-old female patient had an uncomplicated episode of gastroenteritis with fever, which resolved spontaneously. Two weeks later, she presented with speech difficulties, hypophonia, anxiety, and tremulous eye and head movement followed by increasing gait instability. She was diagnosed with depression and initially hospitalized in the psychiatric division. Neurological examination revealed severe psychomotor slowing, apathy, hypomimia, bifacial paresis, opsoclonus, myoclonic head and trunk movements, static and kinetic ataxia, as well as a right-sided hemiparesis (video, day 1, available at http://www.archneurol.com). Results of initial CSF examination showed mild lymphocytic pleocytosis (29 leukocytes/ μ L [to convert to $\times 10^9$ L, multiply by 0.001), 4% plasmocytes, normal protein and glucose concentrations, and intrathecal IgG synthesis with oligoclonal bands. Infectious, toxic, and metabolic workup results were negative. Brain magnetic resonance imaging results were normal; electroencephalography showed generalized slowing of activity with left-sided predominance and no epileptiform discharges.

The patient's condition worsened rapidly with development of tetraparesis and a pseudobulbar paresis. A second electroencephalography showed more marked diffuse slowing (Figure, A). A pulmonary embolism was discovered on chest computed tomography and a persistent sinus tachycardia, probably due to dysautonomia, required treatment with β -blockers. The patient was initially treated for probable viral or autoimmune encephalitis with acyclovir and a high dose of intravenous methylprednisolone. Her condition continued to worsen to almost an akinetic mutism; she became incontinent and needed tube feeding, but she had no respiratory difficulties (video, day 8). Plasma exchange was started, but the second session was complicated by a systemic hypotension, and it was decided to switch to intravenous immunoglobulins. A slow improvement was observed in the first days she was treated with intravenous immunoglobulins. She started moving and speaking, albeit with dysarthria, stammer, and palilalia, and her opsoclonus diminished. The next 10 days were characterized by a delusional state associated with agitation, hyperventilation, akathisia, obsessions, and hallucinations. These symptoms subsided, leaving a severe frontal dysfunction characterized by disinhibition, familiarity, logorrhea, emotional lability, and executive deficit. The patient's speech, opsoclonus, and ataxia continued to improve. She was able to sit up by the end of the third week, and by the fifth week she was able to walk with support.

Results of repeated magnetic resonance imaging 1 month after the initial study were normal. Immunologic workup revealed the presence of antibodies to NR1/NR2 heteromers of NMDAR, confirming the diagnosis of anti-NMDAR encephalitis. Using immunocytochemistry on HEK293 cells transfected with NR1 and NR2 subunits of NMDAR and equally diluted (1:10) CSF and serum obtained at symptom presentation, antibodies were only identified in the CSF. Cerebrospinal fluid antibody titer by enzyme-linked immunosorbent assay was 2890 relative fluorescence units (normal reference value <200). Despite an extensive oncologic workup, including abdominal computed tomography and magnetic resonance imaging, pelvic ultrasonography and whole-body positron-emission tomography, there was no evidence of tumor. The patient was also negative for tumor markers and other antineuronal antibodies.

Although the patient showed a remarkable improvement, the cognitive and behavioral abnormalities and ataxia persisted and she was treated with a second course of immunoglobulins 6 weeks after symptom presentation. The opsoclonus remained discrete and a continuous improvement of the cerebellar symptoms as well as of the frontal behavior was observed. On the seventh week, she was able to use a computer and walk without assistance. Speech, gait, and behavior continued to improve gradually during the following weeks. Results of electroencephalography and the routine CSF examination became normal (Figure, B). She received 2 more courses of immunoglobulins on the 10th and 14th week, after which she returned home. At the last follow-up 5 months after symptom presentation, most symptoms had resolved, but she had persistent frontal behavioral abnormalities.

COMMENT

Our patient's clinical features are similar to those reported in association with anti-NMDAR encephalitis. In addition, she developed opsoclonus-myoclonus syndrome and cerebellar symptoms, which have not been previously reported in this disorder. Interestingly, using rat brain and cerebellum immunohistochemistry, our patient's CSF and serum did not show any additional reactivity to that observed with anti–NR1/NR2 antibodies (mainly involving neuropil of hippocampus, and to a lesser degree other areas of brain and granular layer of cerebellum; data not shown), suggesting that the opsoclonus was related to dysfunction of the NMDARs and/or to the presence of a yet uncharacterized additional antibody.

In a series of 21 patients with opsoclonus-myoclonus syndrome, potential target autoantigens localized to the postsynaptic density.² The postsynaptic density is a complex of proteins associated with the glutamate NMDAR. This observation suggests that NMDAR dysfunction might be involved, at least in these cases, in the generation of opsoclonus.

Opsoclonus-myoclonus syndrome is often associated with infection or cancer. Despite extensive investigations, including whole-body positron-emission tomography, we did not find any evidence of tumor in our patient. She responded well to immunotherapy and has had a good clinical outcome. From the available literature, it is understood, however, that relapses can occur, especially if a tumor is not removed or detected. It should be noted that in 40% of patients in the Dalmau et al case series, ¹ oncologic assessment did not reveal the presence of any tumor. In 6 patients, the tumor was diagnosed (56 months to 3 years) after recovery from the encephalitis.

The strategies for long-term management of NMDAR encephalitis are limited. Because our patient had an excellent response to intravenous immunoglobulin therapy, we did not opt for a more aggressive immunosuppression. In the case series of Dalmau et al, after discharge, 85% of patients who were left with mild deficits or eventually attained full recovery had signs of frontal lobe dysfunction, including poor attention, impulsivity, and behavioral disinhibition.

Our patient still had features of frontal lobe dysfunction 5 months after symptom presentation. In 1 case of reversible anti-NMDAR encephalitis, serum antibodies were not detected at the 1-year follow-up, though the tumor was not removed. Interpretation of these anecdotal cases should be cautious because relapses may occur several years after initial presentation. In the series of 100 patients (mostly adults) described by Dalmau et al, 15 had 1 to 3 relapses of encephalitis. A more recent series indicated a 25% rate of relapses and slower improvement, particularly in patients without a tumor. On the other hand, disappearance of autoantibodies may indicate a remission. Besides clinical follow-up, repeated antibody measurements in serum and CSF might be helpful in early detection of a relapse.

Recent reports indicate that patients with ovarian teratoma and isolated or classic opsoclonus-myoclonus syndrome do not develop NMDAR antibodies (I.T.Y. Kawachi, MD, PhD, et al, unpublished data, 2009). Our study shows that opsoclonus-myoclonus may overlap with the syndrome described in anti-NMDAR encephalitis in which case patients do have NMDAR antibodies.

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References

- Dalmau J, Gleichman AJ, Hughes EG, et al. Anti NMDA-receptor encephalitis: case series and analysis
 of the effects of antibodies. Lancet Neurol 2008;7(12):1091–1098. [PubMed: 18851928]
- 2. Bataller L, Rosenfeld MR, Graus F, Vilchez JJ, Cheung NK, Dalmau J. Autoantigen diversity in the opsoclonus-myoclonus syndrome. Ann Neurol 2003;53(3):347–353. [PubMed: 12601702]
- 3. Markakis I, Alexiou E, Xifaras M, Gekas G, Rombos A. Opsoclonus-myoclonus-ataxia syndrome with autoantibodies to glutamic acid decarboxylase. Clin Neurol Neurosurg 2008;110(6):619–621. [PubMed: 18433986]
- Fitzpatrick AS, Gray OM, McConville J, McDonnell GV. Opsoclonus myoclonus syndrome associated with benign ovarian teratoma. Neurology 2008;70(15):1292–1293. [PubMed: 18391162]
- 5. Shindo A, Kagawa K, Ii Y, Sasaki R, Kokubo Y, Kuzuhara S. Anti-N-methyl-D-aspartate receptor-related grave but reversible encephalitis with ovarian teratoma in 2 Japanese women presenting with excellent recovery without tumor resection. Eur Neurol 2009;61(1):50–51. [PubMed: 19033688]
- 6. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66(1):11–18. [PubMed: 19670433]

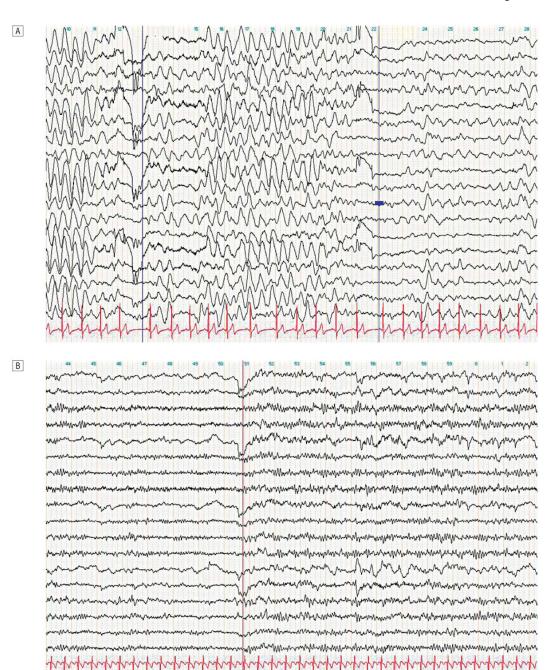


Figure.

Electroencephalography of a 23-year-old woman with opsoclonus-myoclonus syndrome. A, Recording on day 10 shows bursts of diffuse delta activity on a background of theta rhythm. The first marker indicates eye closure; the second marker, eye opening. B, Recording on day 60 shows a normal alpha activity with ocular artifacts in the frontopolar leads; the electrocardiogram shows tachycardia (100 beats/min). The marker indicates eye closure.