Opsoclonus myoclonus ataxia may differentiate postinfectious autoimmune encephalitis from infectious encephalitis

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Dear Editor,

We report a patient who could be diagnosed as autoimmune postinfectious encephalitis due to occurrence of opsoclonus myoclonus ataxia syndrome (OMS) while initially treated under the impression of herpes simplex virus (HSV) encephalitis.

A 19-year-old male presented with 4 days of fever, headache, and nausea. Upon clinical examination, meningeal irritation sign was positive without focal neurological deficits. Cerebrospinal fluid (CSF) study showed elevated opening pressure, white blood cell count of 130 (lymphocyte 86%), elevated protein of 154 mg/dL, and glucose of 50 mg/dL. Brain magnetic resonance imaging (MRI) showed T2 hyperintensities and swelling of bilateral medial temporal lobes (Fig. 1A). Serologic test for HSV IgM was equivocal, while Mycoplasma pneumoniae IgM was positive (titer 2.6 [0.0–0.8]). CSF HSV PCR was negative (Table 1). Under the impression of HSV meningoencephalitis, IV acyclovir and oral doxycycline was started. On HOD2 patient developed diplopia, downbeat, and torsional nystagmus. Over the next few days, the patient was neurologically stable, but fever did not subside. The patient deteriorated on HOD 6 with fluctuating right ptosis and esotropia. Intermittent bouts of uncontrolled multivectorial rapid eye movements which could be classified as opsoclonus occurred (Fig. 2, Video) with truncal ataxia and limb dysmetria. The frequency of opsoclonus was 6–8 Hz, with an amplitude of 5–10 degrees, and was provoked by initiation of saccades. The patient also complained of confusion and vivid dreams. Under the syndromatic diagnosis of OMS, postinfectious etiology was suspected, and IV steroid therapy was started. The results of paraneoplastic antibodies and autoimmune synaptic antibodies were negative. There was partial response to steroids, but the patient complained of urinary retention. Brain MRI on HOD12 revealed patchy T2 high signal intensities in cerebellar dentate nucleus, bilateral thalamus, and basal ganglia (Fig. 1A). Spinal MRI revealed signal changes in T1–4 and T4–T12 levels (Fig. 1B). The patient further underwent 5 cycles of plasma exchange with excellent clinical response. Serologic exam at HOD17 showed negative conversion of HSV IgM and positive HSV IgG. Mycoplasma pneumoniae IgM also showed negative conversion, with positive Mycoplasma pneumoniae IgG (> 100AU/mL [0.0–11.9]). The patient was able to be discharged home at HOD24 and has not shown recurrence for over 6 months.

The causes of OMS in adults include paraneoplastic, parainfectious, toxic-metabolic, and idiopathic etiologies, while the pathophysiology is thought to be immunological [7]. Reported parainfectious cases are associated with HIV, Mycoplasma pneumoniae, and Salmonella, among others [7]. On the contrary, neuro-ophthalmologic presentation in HSV encephalitis, other than cranial nerve signs, due to increased intracranial pressure, is rare [2, 8]. Based on such factors, the development of OMS led us to suspect an underlying autoimmune mechanism.

The preceding infection may have been HSV meningoencephalitis, or Mycoplasma pneumoniae infection. Reported clinical picture of post HSV autoimmune encephalitis is somewhat different from this patient [1], with longer days from initial encephalitis to relapsing autoimmune encephalitis, and neuropsychiatric presentations. Typical enhancing frontotemporal T2 hyperintensities and positive NMDA receptor antibodies were also not seen in this patient.

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Neurological manifestations of *Mycoplasma* infections occur through three major mechanisms, direct neuronal damage, vascular occlusion type pathology, and indirect autoimmunity [5]. Immune pathogenesis is usually suggested in cases of OMS associated with *Mycoplasma pneumoniae* [3, 4, 6].

Characteristic bilateral MRI lesions are reported, involving the pons, thalamus, basal ganglia, brainstem, or splenium, and there is evidence that both vascular occlusive pathology and indirect autoimmune mechanisms are responsible [5]. While we can not reach a conclusion to the underlying infectious pathogen, this case highlights that prompt recognition

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**Fig. 1 The brain and spinal MRI findings.** A On HOD2, swelling and T2 high signal intensity are seen at bilateral medial temporal lobes, raising clinical suspicion of herpes simplex encephalitis. The patient deteriorated on HOD6, but no new brain lesions are seen. Brain MRI performed at HOD12 shows T2 hyperintensities at cerebellar dentate nucleus, bilateral thalamus, and basal ganglia. B T2 hyperintensities in T1-4 and T4-T12 levels are also seen in spinal MRI taken at HOD12. MRI, magnetic resonance imaging; HOD, hospital day
Table 1 Results of serologic and cerebrospinal fluid exams for diagnosis of the encephalitis

|                    | HOD 1                  | HOD 6                  | HOD 8                  | HOD 13                 | HOD 15                 | HOD 17                 |
|--------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Serum tests        |                        |                        |                        |                        |                        |                        |
| CMV IgM            | Negative               |                        |                        |                        |                        |                        |
| HSV IgM            |                        | Eqyivocal              |                        |                        |                        |                        |
| HSV IgG            |                        |                        | Positive               |                        |                        |                        |
| VZV IgM            |                        |                        | Negative               |                        |                        |                        |
| M. pneumonia IgM   | Positive 2.6 (0.0–0.8) |                        |                        |                        |                        |                        |
| M. pneumoniae IgG  |                        |                        |                        | Negative               | Positive > 100 AU/mL (0.0–11.9) |
| Anti-HIV I/II      | Negative               |                        |                        |                        |                        |                        |
| VDRL               | Negative               |                        |                        |                        |                        |                        |
| Paraneoplastic antibody* |                    | Negative               |                        |                        |                        |                        |
| Autoimmune synaptic encephalitis Ab † |                |                        |                        |                        |                        |                        |
| GAD II Ab          | Negative               |                        |                        |                        |                        |                        |
| Aquaporin 4 IgG    | Negative               |                        |                        |                        |                        |                        |
| GD1b Ab, IgM       | Negative               |                        |                        |                        |                        |                        |
| GQ1b Ab            | Negative               |                        |                        |                        |                        |                        |
| MOG Ab             | Negative               |                        |                        |                        |                        |                        |
| Cerebrospinal fluid|                        |                        |                        |                        |                        |                        |
| HSV type I PCR     | Negative               | Negative               | Negative               | Negative               | Negative               | Negative               |
| HSV type II PCR    | Negative               | Negative               | Negative               | Negative               | Negative               | Negative               |
| HSV RT PCR         | Negative               | Negative               | Negative               | Negative               | Negative               | Negative               |
| VZV PCR            | Negative               | Negative               | Negative               | Negative               | Negative               | Negative               |
| Enterovirus RT PCR | Negative               |                        |                        |                        |                        |                        |
| EBV PCR            |                        |                        |                        | Negative               | Negative               | Negative               |
| HHV 6 PSR          |                        |                        |                        | Negative               | Negative               | Negative               |
| Polyoma Virus PCR  |                        |                        |                        | Negative               | Negative               | Negative               |
| M. pneumoniae PCR  |                        |                        |                        | Negative               | Negative               | Negative               |
| JBE virus RT PCR   |                        |                        |                        | Negative               | Negative               | Negative               |
| CMB RT PCR         |                        |                        |                        | Negative               | Negative               | Negative               |
| TB PCR hybridization |                      | Negative               |                        |                        |                        |                        |
| VDRL               |                        |                        |                        |                        |                        | Negative               |

*Paraneoplastic antibody testing was performed for anti-Hu autoantibody, anti-Ri autoantibody, anti-Yo autoantibody, anti-amphiphysin autoantibody, anti-CV2 autoantibody, anti-PNMA (Ma/2Ta) autoantibody, anti-recoverin autoantibody, anti-SOX1 autoantibody, and anti-titin (MGT-30) autoantibody

†Autoimmune synaptic encephalitis antibody was performed for anti-NMDA receptor antibody, anti-LGI1 antibody, anti-CASPR2 antibody, anti-AMPA receptor antibody, anti-DPPX antibody, and anti-GABA-B receptor antibody

CMV cytomegalovirus, HSV herpes simplex virus, HIV human immunodeficiency virus, VDRL Venereal Disease Research Laboratory, GAD glutamic acid decarboxylase, MOG myelin oligodendrocyte glycoprotein, VZV Varicella zoster virus, PCR polymerase chain reaction, RT PCR real-time polymerase chain reaction, EBV Epstein-Barr virus, HHV human herpes virus, JBE Japanese B encephalitis, TB Mycobacterium tuberculosis
of OMS and immunomodulatory treatment can bring excellent outcomes.

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Declarations

Informed consent Not applicable.

Ethical approval This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of Institutional Review Board of Ajou University Hospital.

Conflict of interest The authors declare no competing interests.

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![Figure 2: VNG findings showing opsoclinus. VNG (SLVNG, SLMED, Seoul, South Korea) shows intermittent bouts of fast involuntary spindle shaped multivectorial saccadic oscillations without intersaccadic interval. VNG, video nystagmography](image-url)