

# Rapid Resolution of Enterovirus 71-Associated Opsoclonus Myoclonus Syndrome on Intravenous Immunoglobulin

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## Abstract

Nonparaneoplastic opsoclonus–myoclonus ataxia syndrome is a rare neuroinflammatory condition featured by opsoclonus, myoclonus, ataxia, and cognitive behavioral disturbance. The authors report an observation of enterovirus 71-associated opsoclonus–myoclonus ataxia syndrome evolving toward full recovery on intravenous immunoglobulin (IG) treatment. Based on this case report, enterovirus 71 should be added to the list of infectious agents likely involved in opsoclonus–myoclonus ataxia syndrome, including the emerging subgroup of opsoclonus–myoclonus ataxia syndrome recovering without aggressive or prolonged immunosuppressive intervention. Further studies are mandatory to define the precise role, incidence, treatment, and outcome of enterovirus 71 and other infectious agents in benign forms of opsoclonus–myoclonus ataxia syndrome.

## Keywords

Cerebellitis, Neuroinflammation, Paraneoplastic Syndrome, Glucocorticoids

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Opsoclonus–myoclonus ataxia syndrome is a neuroinflammatory condition featured by opsoclonus, myoclonus, ataxia, and cognitive behavioral disturbance. Opsoclonus–myoclonus ataxia syndrome has been associated with direct infection of the central nervous system or autoimmune mechanisms involving anti-N-methyl-D-aspartate (NMDA) receptor, Hu, and gamma-aminobutyric acid B receptor antibodies, either in a postinfectious or paraneoplastic context, mainly featured in children by neuroblastoma.<sup>1</sup> However, the precise origin, nature, and respective balance between the presumed etiological pathways remain unsettled.

Enterovirus 71 is an increasingly prevalent cause of gastroenteritis, herpangina, and hand-foot-and-mouth disease, often complicated by severe neurological manifestations, such as meningitis, encephalitis, myelitis, Guillain-Barré syndrome, and poliomyelitis-like disease.<sup>2</sup> Enterovirus 71 outbreaks and related neurological complications have been increasingly recognized over the past 10 years, and enterovirus 71 infection eventually emerged as a global public health issue.

To our knowledge, enterovirus 71 has only been reported once in childhood in association with opsoclonus–myoclonus ataxia syndrome.<sup>3</sup> The authors report a new patient with enterovirus 71-

associated opsoclonus–myoclonus ataxia syndrome who evolved toward full recovery on intravenous immunoglobulin (IG).

## Case Report

Informed consent of the family was obtained for the case report according to the Canadian and institutional rules. A 3-year-old girl, with previously normal development, presented to the emergency department with progressive irritability associated with ataxia, myoclonus, and opsoclonus. She had a 6-day history of abdominal pain and cough, associated with vomiting, fatigue, and decreased appetite. Three days before presenting,

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she became irritable, with sleep disturbances. Then, she developed unsteady gait and myoclonic movements throughout her body. The myoclonus joined to the other manifestations precluded weight bearing and walking. There was no history of documented fever, diarrhea, or rash. Her brother had had hand-foot-and-mouth disease a week prior to the onset of her symptoms. There was no family history of autoimmune disease.

At the admission, the patient was vitally stable. She had rapid and conjugate multidirectional eye movements that were irregular and intermittent. Multifocal myoclonus was present, impeding intentional actions. Her irritability was evident to the point where the patient had bitten herself and had to be restrained. She presented diffuse hypotonia, mutism, as well as truncal and gait ataxia.

Cerebrospinal fluid obtained on the day of admission (D1) contained 10 leukocytes/ $\mu$ L (61% lymphocytes), 0 erythrocytes, 27 mg/dL protein, and 3 mmol/L glucose concentrations. Bacterial and viral cultures were negative. A stool sample (D5) culture was positive for enterovirus 71. The cerebrospinal fluid was negative for anti-NMDA antibody and enterovirus polymerase chain reaction (PCR). Cerebrospinal fluid bacterial culture was negative, as were serologies (D1-D5) for cytomegalovirus, Epstein-Barr virus, varicella zoster virus, herpes simplex, *Bartonella henselae*, mycoplasma, Lyme, East Equine encephalitis, Powassan virus, West Nile virus, Jamestown Canyon virus, Snowshoe hare virus, human immunodeficiency virus, and hepatitis C virus.

An electroencephalography (EEG; D2) revealed a moderate diffuse disturbance of cerebral activity in the form of a slow background for age. The myoclonic jerks were not associated with any EEG abnormality. A 3-T brain magnetic resonance imaging without contrast (D2) was normal. Chest X-ray (D1) and abdominal ultrasound (D1) were also normal. A coronal T2 fat-saturated magnetic resonance imaging of the chest obtained at the same time as the brain magnetic resonance imaging (D2) showed no evidence of any neck or mediastinal mass. Urine homovanillic acid and vanillylmandelic acid (D1) were normal.

The patient was started on clobazam 0.3 mg/kg/d (D1), then 0.7 mg/kg/d (D2). She was also started on intravenous IG 400 mg/kg/d (D1) for 5 days with concomitant stabilization and rapid improvement in neurobehavioral manifestations. She was discharged on D7.

On follow-up, she had no abnormal movements at the first follow-up visit (D24). Her speech abilities fully recovered. She was still mildly ataxic. She was given another course of intravenous IG: 600 mg/kg/d for 3 days started on D24. Clobazam was stopped on D39 without any recurrence of symptoms. On follow-up at D41, she had completely returned to normal. One year later, the patient remained symptom-free with a normal development.

## Discussion

The authors report the case of a 3-year-old girl with opsoclonus-myoclonus ataxia syndrome associated with enterovirus 71 infection who rapidly and fully recovered on intravenous

IG treatment. This observation is in line with some others reporting self-limited or intravenous IG-responding opsoclonus-myoclonus ataxia syndrome in infectious contexts, such as enterovirus, rotavirus, adenovirus, or mycoplasma pneumonia infections.<sup>4,5</sup> Most of these parainfectious cases of opsoclonus-myoclonus ataxia syndrome seem to be due to postinfectious immune mechanisms rather than a direct infection, as it is in our patient presenting a positive enterovirus 71 stool culture but negative cerebrospinal fluid culture and enterovirus PCR. Opsoclonus-myoclonus ataxia syndrome is considered as a rare manifestation of enterovirus 71 across all age groups, even though brain stem symptoms are identified as the most common form of encephalitis caused by this agent.<sup>6,7</sup> As far as the authors know, opsoclonus-myoclonus ataxia syndrome has been reported once in the pediatric literature to be associated with an enterovirus 71 infection, in a 1-year-old girl having favorable outcome.<sup>3</sup> There are limited evidence about the incidence of benign forms of opsoclonus-myoclonus ataxia syndrome. However, a prospective United Kingdom study reported 2 (10.5%) of 19 consecutive cases of opsoclonus-myoclonus ataxia syndrome with spontaneous resolution of the symptoms and drew attention to the fact that opsoclonus-myoclonus ataxia syndrome with such presentations might be missed and their frequency underestimated.<sup>5</sup>

High-dose corticosteroids and adrenocorticotrophic hormone may control the manifestations of opsoclonus-myoclonus ataxia syndrome. However, symptoms will commonly relapse, as doses are tapered. Moreover, there is concern regarding the complications of long-term steroid treatment.<sup>8</sup> Rituximab and cyclophosphamide have also been suggested as treatment, with the early introduction of rituximab therapy showing improvement in relapse reduction and developmental outcome in some patients. However, there has not been a trial comparing these treatment protocols in opsoclonus-myoclonus ataxia syndrome. Some preclinical and clinical observations raised concerns about adverse—and even possibly lethal—effects of glucocorticoids administered in enterovirus—including enterovirus 71—infection, especially if used during the first few days of infection.<sup>9-11</sup> Such observations suggest, as advised by other authors,<sup>9-11</sup> to limit the treatment to symptomatic measures and/or intravenous IG during the initial phase (first 2-3 weeks) of parainfectious opsoclonus-myoclonus ataxia syndrome and to refrain from using any other rapid immunosuppressive interventions.<sup>11</sup>

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## Author Contributions

SG contributed to conception and design, contributed to acquisition, analysis, and interpretation, critically revised the manuscript, and gave final approval. GL contributed to conception and design, contributed to acquisition, drafted the manuscript, critically revised the manuscript, and gave final approval. SA contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted

the manuscript, critically revised the manuscript, and gave final approval. SG, GL, and SA agree to be accountable for all aspects of work ensuring integrity and accuracy.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Ethical Approval

This work has been performed in full compliance with the ethical rules of our institution.

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