Pediatric Neurology 53 (2015) 456–458

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Pediatric Opsoclonus-Myoclonus-Ataxia Syndrome Associated With Anti-*N*-methyl-D-aspartate Receptor Encephalitis

Brittany Player DO, MS [a,*], Matthew Harmelink MD [b], Brett Bordini MD [a], Michael Weisgerber MD, MS [a], Michael Girolami MD [c], Michael Croix BS, MD candidate [d]

[a] *Pediatric Hospital Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[b] *Pediatric Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[c] *Medical Education Office, Medical College of Wisconsin, Milwaukee, Wisconsin*
[d] *Medical College of Wisconsin, Milwaukee, Wisconsin*

ABSTRACT

BACKGROUND: The full clinical spectrum of anti-*N*-methyl-D-aspartate receptor encephalitis is unknown in the pediatric population. **PATIENT:** We describe a previously healthy 4-year-old girl presenting with opsoclonus-myoclonus together with ataxia who had NR1-specific, anti-*N*-methyl-D-aspartate receptor antibodies in the cerebral spinal fluid. **CONCLUSION:** The presence of NR1-specific, anti-*N*-methyl-D-aspartate receptor antibodies in the setting of opsoclonus-myoclonus and ataxia syndrome may represent an expansion of the clinical presentations of anti-*N*-methyl-D-aspartate receptor encephalitis.

Keywords: pediatric, myoclonus, encephalitis, ataxia, paraneoplastic syndrome, anti-NMDA receptor, opsoclonus-myoclonus-ataxia syndrome

Pediatr Neurol 2015; 53: 456-458

Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS) and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis are rare neurological disorders resulting from autoimmunity. Because they are often encountered within the context of an underlying malignancy but are not directly attributable to the effects of the associated neoplasm,[1] both entities are considered paraneoplastic disorders mediated instead by antibody-induced dysfunction of neuronal cell surface and intracellular autoantigens. Molecular targets in OMAS include cerebellar granule cells and Purkinje fibers.[2-4] In anti-NMDAR encephalitis, the NR1 subunit of the NMDA receptor, which is found throughout the brain, though most highly concentrated in the hippocampus, is targeted by antibodies, leading to receptor internalization and a concordant decrease in receptor density and function.[5] OMAS is more common in children, in whom up to half of cases are associated with an underlying neuroblastoma. Conversely, anti-NMDAR encephalitis was initially described as a paraneoplastic process occurring primarily in adult women with ovarian teratomas. However, it is increasingly recognized in children, many of whom have no identifiable associated neoplasm.[6,7] Despite this increased recognition in children, the extent of clinical manifestations in pediatric anti-NMDAR encephalitis has not been fully characterized. OMAS and anti-NMDAR encephalitis have previously been thought to represent two distinct entities. Here we present a 4-year-old girl with OMAS, encephalitis, and the presence of anti-NMDAR antibodies, without associated tumor at the time of diagnosis, suggesting a possible expansion of the manifestations seen with this autoimmune process.

Patient Description

A previously healthy 4-year-old girl presented with a 1-month history of progressive ataxia, abnormal eye and

Article History:
Received March 26, 2015; Accepted in final form July 25, 2015
* Communications should be addressed to: Dr. Player; Suite C560; Children's Corporate Center; PO Box 1997; Milwaukee, WI 53201-1997.
E-mail address: bplayer@mcw.edu

0887-8994/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.07.010

limb movements, and behavioral changes. Four weeks before presentation, she developed extremity tremors that progressed to frequent falls and difficulty holding objects. Additional symptoms included bowel and bladder urgency, insomnia, decreased appetite, and aggression. There were no preceding illnesses or fevers and no vaccinations given in the 4 months before symptom onset. One week before presentation, her parents noted abnormal eye movements, worsening tremors leading to an inability to feed herself, and expressive aphasia, prompting medical evaluation and hospitalization. Physical examination demonstrated neutral gaze nystagmus, severe hypometric intrusions into the smooth pursuits of her eyes, a wide-based ataxic gait, upper extremity intention tremor and dysmetria, truncal and head titubation, and spontaneous digital myoclonus; there was no evidence of catatonia. Vital signs and remaining physical examination were normal. By hospital day 2, her ocular examination progressed to frank opsoclonus.

Brain magnetic resonance imaging (MRI), electroencephalograph, complete blood count, and comprehensive metabolic panel were normal. Urine drug investigation, blood lead level, and heavy metal screen were negative. Spinal MRI, metaiodobenzylguanidine scan, and 24-hour urine vanillylmandelic and homovanillic acid collection for neuroblastoma evaluation were negative. Lumbar puncture demonstrated no pleocytosis, normal glucose, normal protein, unremarkable cerebral spinal fluid (CSF) cytology, and negative bacterial culture. Oligoclonal bands were present in the CSF and distinct from the serum suggesting intrathecal immunoglobulin synthesis. CSF and serum paraneoplastic panels were sent to the Mayo Clinic Medical Laboratories for testing performed by indirect immunofluorescence assay with reflex confirmatory testing.[8] The CSF sample contained NR1-specific anti-NMDAR antibodies, whereas the corresponding serum sample was negative.

Pending this investigation, she was empirically treated with 2 g/kg of intravenous immunoglobulin (IVIG) administered over 7 days for presumed OMAS. Therapy was initially complicated by progressive mood lability and fevers. Her fevers persisted despite halting the IVIG infusion. Investigation into the fever etiology that included blood culture, urinalysis, and urine culture revealed an *Escherichia coli* urinary tract infection, which was treated. Her mood lability and sleep disturbance were treated with clonidine as needed and she tolerated the remainder of the IVIG infusion well. With completion of IVIG, she had noticeable improvement in her ophthalmic, motor, and behavioral symptoms before discharge.

Given the associations between malignancy and both OMAS and anti-NMDAR encephalitis, she has been followed regularly for tumor surveillance for ovarian teratomas, including alpha fetoprotein levels and pelvic ultrasound every 3-4 months for 1 year. At her initial outpatient follow-up, she continued to demonstrate unsteady gait, opsoclonus, tremors, and mood lability. She was prescribed a 5-week course of oral steroids and monthly IVIG infusions for persistent symptoms. Neuropsychological testing was performed and, although limited because of behavioral dysregulation, low frustration tolerance, and varying cooperation, was generally consistent with her estimated preillness functioning. As can be associated with anti-NMDAR encephalitis, she did demonstrate variable working memory and impulsivity, though not significantly discrepant from her performances in other areas.

Seven months after her initial presentation, she continues to receive monthly IVIG infusions and has experienced a near-complete resolution of her ophthalmic and motor symptoms. She continues to have behavioral outbursts while at home, but has successfully returned to school.

Discussion

This is the first description of anti-NMDAR encephalitis associated with OMAS in a pediatric patient. The two previously reported cases described female patients in their twenties. In both cases, there was a preceding acute illness with subsequent behavioral changes and gait instability. Both patients progressed to severe encephalopathy, one worsening to near akinetic mutism and the other requiring cardiopulmonary resuscitation and mechanical ventilation.[9,10] Although our patient did present with behavioral changes and ataxia, there was no preceding identifiable acute illness nor was there progression to such significant encephalopathy.

Neurological dysfunction in anti-NMDAR encephalitis is due to antibody-induced NMDA receptor internalization and a resultant decrease in NMDAR-mediated glutamate signaling. The effects are specific to the NMDA receptor and are both dose-dependent and reversible.[5] NMDARs are widely distributed throughout the central nervous system though are most highly concentrated in the hippocampus, and symptoms in anti-NMDAR encephalitis are likely attributable to disruption of glutamatergic transmission in the hippocampus and corticolimbic networks. Patients typically present with psychiatric symptoms, although in young children these symptoms may be interpreted as temper tantrums or irritability.[11] These behavioral changes are generally followed by altered movements and speech, sleep disturbance, and seizure activity. Approximately one-third of patients will have abnormal MRI findings and a similar percentage of patients have electroencephalograph abnormalities.[12]

The pathophysiology of OMAS is not well-characterized. Autoantibodies against neurons and Purkinje cells have been detected and, more recently, immunoglobulin G autoantibodies and B-cell activation have been characterized in pediatric patients with opsoclonus-myoclonus.[1,13] The most common presenting symptoms of OMAS are high-amplitude, multidirectional eye movements (opsoclonus), focal or diffuse myoclonus, emotional lability, and ataxia.

The distinctions in pathophysiology between these two processes highlights the unique nature of this patient's presentation, which began with ataxia and behavioral changes and was followed by myoclonus, sleep disturbance, and opsoclonus, all of which are associated with normal MRI and electroencephalograph findings. Individuals with either anti-NMDAR encephalitis or OMAS may exhibit behavioral disturbances, neurocognitive decline, and sleep abnormalities. However, in OMAS, movement disorder–related symptoms tend to predominate neurocognitive decline and behavioral symptoms, whereas this patient's

movement disorder–related symptoms were less severely disabling. Were it not for the presence of opsoclonus placing her in the clinical spectrum of OMAS, she may more closely fit the anti-NMDAR encephalitis spectrum, suggesting a possible crossover phenomenon between the two processes. Although it is possible that the anti-NMDAR antibody led to the entirety of her symptoms, it is also possible that the opsoclonus, myoclonus, and ataxia are manifestations of a yet-uncharacterized additional antibody. The presence of NR1-specific anti-NMDAR antibodies in the setting of her symptoms suggests a causative role in the pathogenesis of her presentation. Given that she improved with treatment, anti-NMDAR antibody testing was not repeated, nor was testing for additional autoantibodies performed beyond those included in the initial paraneoplastic panel, potentially limiting the ability to attribute the full clinical spectrum of her presentation to the presence of anti-NMDAR antibodies.

Neuroblastoma is present in approximately half of patients with OMAS.[1,14] Anti-NMDAR encephalitis is more typically associated with ovarian teratomas, present in less than 10% of girls age 14 years or younger with anti-NMDAR encephalitis, or, rarely, testicular tumors in boys.[1,11,12] Although the presence of a neoplasm is not required for either diagnosis, the relationship with malignancy necessitates close tumor surveillance.

Treatment of anti-NMDAR encephalitis includes removal of any associated tumor as well as immunotherapy with IVIG, corticosteroids, and/or plasma exchange. Rituximab or cyclophosphamide for refractory cases has shown varied success.[6] OMAS has been historically treated with ACTH and steroids, though IVIG has shown short-term effectiveness. More recently, rituximab in combination with steroids, IVIG, and/or cyclophosphamide has shown promise,[14] with multimodal therapy demonstrating additional efficacy.[15] Additionally, given the accumulation of B cells in the spinal fluid of OMAS children, there may be a role for rituximab over other immune suppressants in multimodal therapy.[15] Our patient improved with regularly scheduled infusions of IVIG without the need for further immunomodulating therapies.

Conclusion

This 4-year-old girl developed OMAS and encephalitis in association with NR1-specific anti-NMDAR antibodies. She may represent an expansion of the traditional clinical spectrum associated with anti-NMDAR encephalitis to include OMAS as an associated finding, warranting further consideration and investigation.

References

1. Wells E, Dalmau J. Paraneoplastic Neurologic Disorders in Children. *Curr Neurol Neurosci Rep*. 2011;11:187-194.
2. Blaes F, Fühlhuber V, Korfei M, et al. Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. *Ann Neurol*. 2005;58:313-317.
3. Bataller L, Rosenfeld MR, Graus F, Vilchez JJ, Cheung NK, Dalmau J. Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Ann Neurol*. 2003;53:347-353.
4. Jen JC, Lopez I, Baloh RW. Opsoclonus: clinical and immunological features. *J Neurol Sci*. 2012;320:61-65.
5. Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti–N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;76:108-119.
6. Florance N, Davis R, Lam C, Szperka C, et al. Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis in Children and Adolescents. *Ann Neurol*. 2009;66:11-18.
7. Raha S, Gadgil P, Sankhla C, Undani V. Nonparaneoplastic Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis: A Case Series of Four Children. *Pediatr Neurol*. 2012;46:246-249.
8. Mayo Clinic Mayo Clinical Laboratories. Available at: http://www.mayomedicallaboratories.com/test-catalog/Overview/61509. Accessed July 2, 2015.
9. Kurian M, Lalive P, Dalmau J, Horvath J. Opsoclonus-Myoclonus Syndrome in Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis. *Arch Neurol*. 2012;67:118-121.
10. Smith J, Dhamija R, Mosely B, et al. *N*-methyl-D-Aspartate Receptor Autoimmune Encephalitis Presenting with Opsoclonus-Myoclonus: Treatment Response to Plasmapheresis. *Arch Neurol*. 2011;68:1069-1072.
11. Florance-Ryan N, Dalmau J. Update on anti-*N*-methyl-D-aspartate receptor encephalitis in children and adolescents. *Curr Opin Pediatr*. 2010;22:739-744.
12. Linnoila J, Rosenfeld M, Dalmau J. Neuronal Surface Antibody-Mediated Autoimmune Encephalitis. *Semin Neurol*. 2014;34:458-466.
13. Raffaghello L, Conte M, De Grandis E, Pistoia V. Immunological mechanisms in opsoclonus-myoclonus associated neuroblastoma. *Europ J Paediatr Neurol*. 2009;13:219-223.
14. Hero B, Schleiermacher G. Update on Pediatric Opsoclonus Myoclonus Syndrome. *Neuropediatrics*. 2013;44:324-329.
15. Tate E, Pranzatelli M, Verhulst S, et al. Active Comparator-Controlled, Rater-Blinded Study of Corticotropin-Based Immunotherapies for Opsoclonus-Myoclonus Syndrome. *J Child Neurol*. 2012;27:875-884.