



A Novel Case of Idiopathic mGluR1 Encephalitis in a Pediatric Patient

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Abstract

Metabotropic Glutamate Receptor 1 (mGluR1) encephalitis is a rare encephalitis characterized by ataxia, neuropsychiatric symptoms, dysarthria and cognitive impairment. This disease process has been described in several adult patients and has been associated with paraneoplastic syndrome in Hodgkin's lymphoma and other cancers as well as parainfectious and underlying autoimmune etiologies. However, only two cases of anti-mGluR1 encephalitis in children have been reported in the literature. The underlying etiology of one case was not provided but post-infectious disease has been reported. Here, we report the first case of anti-mGluR1 encephalitis in a child with a presumed "idiopathic" basis.

Keywords

ataxia, autoimmune, cerebellum, encephalitis, neuroimmunology, pediatric

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Introduction

Autoimmune encephalitis¹⁻⁷ is an inflammatory disorder of the brain, characterized by progressive encephalopathy and debilitating neurological symptoms.⁸ Our knowledge of pathogenic autoantibodies implicated in autoimmune encephalitis and the availability of commercial testing continues to expand. Classification of autoimmune encephalitides regarding presumed etiology was proposed in previous medical literature as follows: 1. Neurological manifestations of systemic autoimmune disease, 2. Paraneoplastic disease, 3. Parainfectious disease, or 4. Idiopathic disease. On a pathologic level, antibodies associated with autoimmune encephalitis can be classified as the following: 1. Intracellular paraneoplastic antibodies, 2. Cell surface/synaptic antibodies, or 3. Antibodies of uncertain significance.⁸

Glutamate is one of the primary excitatory neurotransmitters in the central nervous system (CNS). Metabotropic glutamate receptors (mGluRs) are a large family of g-protein coupled receptors that mediate this excitatory neurotransmission within the central and peripheral nervous system.⁴ mGluR1 is specifically located primarily post-synaptically, with a heavy concentration of mGluR1 in the cerebellum and limbic system,⁹ and whose activity plays a role in cerebellar motor development and plasticity.¹⁰ Activation of mGluR1 results in

potentiation of n-methyl-d-aspartate (NMDA) receptor activity.⁴ However, excitotoxicity can eventually lead to neuronal cell death and subsequent neurological symptoms.¹¹

The clinical features of mGluR1 encephalitis seem to consist of a 3-phase response. The first symptoms include prodromal headache, fatigue, nausea, and myalgias. During the second phase of the illness patients develop cerebellar dysarthria, gait and trunk instability, nystagmus, and limb ataxia. Lastly, patients may exhibit neuropsychiatric changes of altered mental status, memory deficits, and mood changes.⁴ While the common clinical presentation includes a cerebellar syndrome, the disease progression and long-term prognosis varies with each patient and can be difficult to predict. Furthermore, as with other autoimmune encephalitides, the underlying etiology (either paraneoplastic, parainfectious, or systemic autoimmune) of mGluR1 encephalitis has yet to be

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consistently shown. Here, we present the first case of idiopathic mGluR1 encephalitis in a child.

Case Report

A previously healthy, fully vaccinated 5-year-old girl presented to our emergency department (ED) with <24-hour history of nausea, vomiting, abdominal pain, fever, and headache. Her initial neurological examination was documented as “normal,” but there was no specific documentation regarding the presence/absence of meningeal irritation or cerebellar signs. Abdominal x-ray showed a large stool burden and urinalysis showed proteinuria and ketonuria. She was discharged home after receiving oral Zofran. Three days later she returned with persistent vomiting, newly altered mental status, and decreased speech. She had woken up, screamed, and was found unresponsive with her eyes open in an upward gaze. This was all in the setting of new onset unsteady gait. On evaluation in the ED, head computed tomography was obtained and normal. The patient was admitted for EEG due to persistently altered mental status. Of note, her family history was notable for both maternal and paternal grandmother with lupus, and mother with type 2 diabetes.

On evaluation, she was afebrile, tachypneic, responsive only to noxious stimulation, produced no spontaneous speech, and had evidence of meningeal irritation. Due to immediate concern for meningoencephalitis, she was started on empiric Acyclovir, Vancomycin and Ceftriaxone pending cerebrospinal fluid (CSF) examination. EEG, MRI, CSF studies, and basic serum studies were ordered. Brain MRI showed T2 hyperintensity in the cerebellar vermis and adjacent cerebellar hemispheres, R>L (Figure 1). EEG showed diffuse slowing of the background, no interictal epileptiform discharges, and no electrographic seizures. Initial CSF studies were inconclusive, and lumbar puncture (LP) was repeated on hospital day 5 (Table 1).

Based on the subacute onset of symptoms, CSF, imaging, serum studies (Tables 2 and 3, Figure 1), and physical examination, she was started on 30 mg/kg/dose daily of IV methylprednisolone for the working diagnosis of autoimmune encephalitis. She had minimal improvement after steroids and continued to have waxing and waning mental status. Due to her lack of

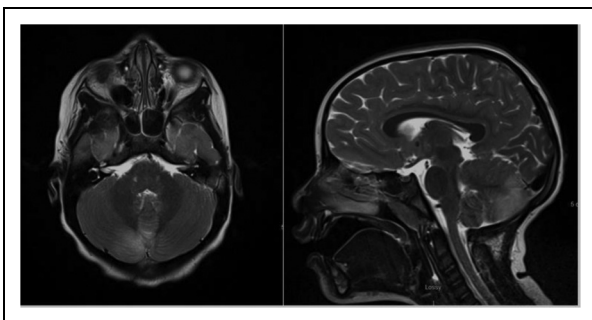


Figure 1. (A) Axial T2 showing hyperintensity in cerebellar vermis and medial cerebellar hemispheres R>L, (B) Sagittal T2 showing hyperintensity in the midline cerebellum/vermis.

Table 1. Results of second lumbar puncture.

Second Lumbar Puncture	
RBC	8 cells/ μ L
WBC	39 cells/ μ L
Neutrophils	3%
Lymphocytes	97%
Glucose	64 mg/dL
Protein	35 mg/dL
Oligoclonal Bands	> 4
Pediatric Encephalopathy Autoimmune Panel	1:64 anti-MGluR1 antibodies

Other Images:

Abdominal Ultrasound: Debris seen within a distended urinary bladder. No evidence of appendicitis or intussusception.

Table 2. Results of serum studies.

Serum Studies	
CRP	2.1 mg/dL
ESR	24 mm/hr
Pro-calcitonin	normal
Blood culture	no growth
Urinalysis & culture	Protein 10 mg/dL Ketone 100 mg/dL Culture: no growth
Amylase	123 Units/L
SARS CoV2 IgG and IgM	negative
ANA	normal
C3	normal
C4	normal
TSH/T4	normal
Serum T and B cell Immunophenotyping	No monoclonal population to suggest malignancy

Abbreviations: CRP, C-reactive protein; ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; TSH, thyroid stimulating hormone.

Table 3. Results of initial lumbar puncture.

Initial Lumbar Puncture	
RBC	370 000 cells/ μ L
WBC	240 cells/ μ L
Neutrophils	83%
Lymphocytes	15%
Glucose	60 mg/dL
Protein	77 mg/dL
Cerebral Pathogen Panel	Negative
Opening pressure	Not obtained
Oligoclonal Bands	Not tested due to traumatic low volume LP
Complications	Unsuccessful bedside LP Completed by IR Low volume spinal fluid (3 mL total obtained)

Abbreviations: RBC, red blood cell; WBC, white blood cell.

significant clinical improvement following five days of high dose IV steroids, she received 1 g/kg daily of IVIg for 2 days. Following treatment with IVIG, she had progressive improvement in gait and speech. She was ultimately discharged to acute inpatient rehabilitation. After discharge, the Pediatric Autoimmune Encephalopathy Panel CSF (repeat CSF sample) resulted positive for anti-MGluR1 antibodies in the CSF, with immuno-fluorescent assay titer of 1:64 and presence of anti-MGluR1 antibodies confirmed by cell-based assay (CBA). Further workup including blood immunophenotyping found no evidence of a monoclonal population to indicate underlying malignancy. At the time of this report, she is 17 months from her initial clinical presentation. Her neurological exam was normal at last clinic visit with no apparent sequelae related to anti-MGluR1 encephalitis.

Discussion

In a recent case series, the median age of diagnosis of mGluR1 encephalitis was 55 years old, and ~41% of patients presented with prodromal symptoms of nausea, fatigue, weight loss, headache, or flu-like symptoms.⁴ 97% of patients presented with a cerebellar syndrome characterized by ataxia, dysarthria, head or trunk tremor or titubation.⁴ Similar to other encephalitides, therapy consists of high dose IV methylprednisolone, plasmapheresis or IVIG, or some combination of all 3 agents. However, in some cases, patients required second line immunotherapy.⁴

The underlying etiology of mGluR1 encephalitis remains unclear. There have been case reports of paraneoplastic associations including Hodgkin Lymphoma, prostatic adenocarcinoma, cutaneous T-cell lymphoma, acute lymphoblastic leukemia, and Mantle Cell non-Hodgkin lymphoma.^{1,2,4} In the case series published to date, 1 of 18 patients,¹ 3 of 12 patients,⁴ and 5 of 11 patients² had an underlying systemic autoimmune condition. Only 1 of 18 patients¹ had a recent infection, but the one pediatric case in this series⁴ did occur following a streptococcal pharyngitis. Lastly, patients may develop idiopathic mGluR1 encephalitis, with no evident paraneoplastic, infectious, or systemic autoimmune diagnosis. When no identifiable etiology can be identified, one may classify these cases as idiopathic. In the past, the term “idiopathic” denoted disease without an identifiable cause but a genetic basis was presumed. The term “idiopathic” has been abandoned in other neurological disease, eg, epilepsy, in favor of more descriptive terms. However, given the relative paucity of literature regarding descriptive terminology that indicates the presumed etiology of autoimmune encephalitis, use of the term “idiopathic” may be reasonable pending new developments in this area.

While there is minimal data in the pediatric population thus far, conclusions regarding the variability in pediatric versus adult onset mGluR1 encephalitis can be drawn. First, children with mGluR1 encephalitis seem to have a more acute onset when compared to the adult population.⁷ Secondly, at least one prior pediatric case was characterized by orofacial and

appendicular choreoathetosis,⁴ and our patient exhibited head titubation which ultimately resolved. Therefore, pediatric cases may be further characterized by new onset movement disorder. Thirdly, our patient had a strong family history of autoimmune conditions including Lupus on both maternal and paternal sides of the family, and the other reported pediatric case had a family history of Multiple Sclerosis.⁷ Therefore, it could be beneficial to know if patients with strong predispositions to autoimmune conditions are more likely to have idiopathic mGluR1 encephalitis as opposed to post-infectious or paraneoplastic presentations. Furthermore, in the pediatric population of idiopathic mGluR1 encephalitis, one could consider annual or biennial screening for both malignancy and underlying autoimmune conditions. Lastly, mGluR1 encephalitis should be considered in pediatric patients with acute onset cerebellar symptoms.^{1,3-7,11}

Conclusion

Our patient is the third reported case of anti-MGluR1 antibody associated encephalitis in a child to our knowledge.⁷ This case was novel in that it was only the third reported case in the literature, and no associated systemic autoimmune disease, paraneoplastic etiology, or recent infection was identified. We propose that pediatric patients who present with prodromal symptoms followed by the acute onset of cerebellar symptoms or undergo diagnostic workup and evaluation of autoimmune encephalitis. mGluR1 encephalitis should be considered in patients with acute onset cerebellar ataxia/symptoms. Cerebellar ataxia in children often improves with time, but if attributed to mGluR1 encephalitis aggressive treatment may be warranted. Furthermore, as with other autoimmune encephalitides, these individuals should undergo tumor screening, autoimmune and infectious workup. While more often adult onset autoimmune encephalitis is associated with malignancy/paraneoplastic etiology, this should still be part of the diagnostic workup in children. If these studies all remain negative, the etiology is presumably idiopathic.

Declaration of Conflicting Interests

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Ethics Approval

Ethical approval to report this case was obtained from the following:


University of Louisville 21.1051 / IRB # 738044

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Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

References

- Christ M, Müller T, Bien C, Hagen T, Naumann M, Bayas A. Autoimmune encephalitis associated with antibodies against the metabotropic glutamate receptor type 1: case report and review of the literature. *Ther Adv Neurol Disord*. 2019;12:175628641984741. <https://doi.org/10.1177/1756286419847418>
- Lopez-Chiriboga AS, Komorowski L, Kümpfel T, et al. Metabotropic glutamate receptor type 1 autoimmunity. *Neurology*. 2016;86(11):1009-1013. <https://doi.org/10.1212/wnl.0000000000002476>
- Marignier R, Chenevier F, Rogemond V, et al. Metabotropic glutamate receptor type 1 autoantibody-associated cerebellitis. *Arch Neurol*. 2010;67(5). <https://doi.org/10.1001/archneurol.2010.51>
- Spatola M, Petit Pedrol M, Maudes E, et al. Clinical features, prognostic factors, and antibody effects in anti-mGluR1 encephalitis. *Neurology*. 2020;95(22):e3012-e3025. <https://doi.org/10.1212/wnl.00000000000010854>
- Iorio R, Damato V, Mirabella M, et al. Cerebellar degeneration associated with mGluR1 autoantibodies as a paraneoplastic manifestation of prostate adenocarcinoma. *J Neuroimmunol*. 2013;263(1-2):155-158. <https://doi.org/10.1016/j.jneuroim.2013.07.015>
- Smitt PS, Kinoshita A, De Leeuw B, et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. *N Engl J Med*. 2000;342(1):21-27. <https://doi.org/10.1056/nejm20001063420104>
- Bien CG, Braig S, Bien CI. Antibodies against metabotropic glutamate receptor type 1 in a toddler with acute cerebellitis. *J Neuroimmunol*. 2020;348:577366. doi:10.1016/j.jneuroim.2020.577366
- Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391-404. doi:10.1016/S1474-4422(15)00401-9
- Kano M, Watanabe T. Type-1 metabotropic glutamate receptor signaling in cerebellar Purkinje cells in health and disease. *Fl1000Res*. 2017;6:416. Published 2017 Apr 4. doi:10.12688/fl1000research.10485.1.
- Kano M, Hashimoto K, Tabata T. Type-1 metabotropic glutamate receptor in cerebellar Purkinje cells: a key molecule responsible for long-term depression, endocannabinoid signalling and synapse elimination. *Philos Trans R Soc, B*. 2008;363(1500):2173-2186. <https://doi.org/10.1098/rstb.2008.2270>
- Levite M. Glutamate receptor antibodies in neurological diseases: anti-AMPA-GluR3 antibodies, anti-NMDA-NR1 antibodies, anti-NMDA-NR2A/B antibodies, anti-mGluR1 antibodies or anti-mGluR5 antibodies are present in subpopulations of patients with either: epilepsy, encephalitis, cerebellar ataxia, systemic lupus erythematosus (SLE) and neuropsychiatric SLE, Sjogren's syndrome, schizophrenia, mania or stroke. These autoimmune anti-glutamate receptor antibodies can bind neurons in few brain regions, activate glutamate receptors, decrease glutamate receptor's expression, impair glutamate-induced signaling and function, activate blood brain barrier endothelial cells, kill neurons, damage the brain, induce behavioral/psychiatric/cognitive abnormalities and ataxia in animal models, and can be removed or silenced in some patients by immunotherapy. *J Neural Transm (Vienna)*. 2014;121(8):1029-1075. doi:10.1007/s00702-014-1193-3