Does Autoimmunity have a Role in Myoclonic Astatic Epilepsy? A Case Report of Voltage Gated Potassium Channel Mediated Seizures

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Abstract

Background: There is expanding knowledge about the phenotypic variability of patients with voltage gated potassium channel complex (VGKC) antibody mediated neurologic disorders. The phenotypes are diverse and involve disorders of the central and peripheral nervous systems. The central nervous system manifestations described in the literature include limbic encephalitis, status epilepticus, and acute encephalitis.

Patient Description: We report a 4.5 year-old boy who presented with intractable Myoclonic Astatic Epilepsy (MAE) or Doose syndrome and positive VGKC antibodies in serum. Treatment with steroids led to resolution of seizures and electrographic normalization.

Conclusion: This case widens the spectrum of etiologies for MAE to include autoimmunity, in particular VGKC auto-antibodies and CNS inflammation, as a primary or contributing factor. There is an evolving understanding of voltage gated potassium channel complex mediated autoimmunity in children and the role of inflammation and autoimmunity in MAE and other intractable pediatric epilepsy syndromes remains to be fully defined. A high index of suspicion is required for diagnosis and appropriate management of antibody mediated epilepsy syndromes.

Keywords: VGKC antibody; Myoclonic astatic epilepsy; Doose syndrome; Autoimmune epilepsy; Generalized epilepsy

Introduction

Voltage gated potassium channel (VGKC) complexes of the central and peripheral nervous system play an important role in synaptic transmission, conduction and repolarization [1]. Auto antibodies to VGKCs are reported in a range of central and peripheral nervous system disorders in adults and in children [2]. The proposed mechanism of pathogenicity is binding of antibodies to transmembrane VGKCs which impair ion channel function leading to hyperexcitability. In the central nervous system this leads to diffuse dysfunction, clinically manifesting as encephalopathy and seizures. Initial electroencephalogram (EEG) may also be normal with progression to generalized spike or polyspike.
Many cases are refractory to anti-seizure medications (ASM). We present a child with characteristic features of MAE with positive serum VGKC antibodies and excellent clinical and EEG response to immunotherapy.

Case Presentation

A 4.5 year-old right-handed previously healthy and developmentally normal boy presented to our emergency room (ER) following new onset generalized tonic-clonic seizures. Intravenous lorazepam and levetiracetam were administered for recurrent seizures in the ER. He was admitted to the hospital where he had frequent seizures characterized by brief (5-45 second) episodes of staring with activity arrest, eye fluttering and clonic movements of the face. He had no post-ictal confusion. An initial EEG was normal and an MRI brain was unremarkable. Infectious workup, including urine, blood and cerebrospinal fluid (CSF) cultures was negative. Despite initiation of maintenance levetiracetam (30 mg/kg/day) he continued to have daily seizures but interictal mental status was normal. Three days after presentation, a subsequent EEG showed continuous theta slowing with frequent generalized spike and slow wave discharges (Figure 1). After a four-day admission, he was discharged home on levetiracetam (50 mg/kg/day).

The following day, he returned to the ER with recurrent, frequent seizures now with bilateral clonic arm jerks and facial clonic movements, involving the right more than left side. Valproic acid (15 mg/kg/day) was started and maintenance levetiracetam was increased to 60 mg/kg/day. He continued to have repetitive seizures and given the fulminant onset and refractory nature of seizures despite rapidly titrating ASMs a pre-surgical evaluation was performed. EEG demonstrated background slowing and generalized epileptiform discharges. Seizures were clinically characterized by bilateral upper extremity myoclonus, rapid eyelid fluttering, facial twitching and subtle head drop. Ictal EEG showed 1-2 Hz generalized epileptiform
discharges (Figure 2). Ictal SPECT was non-lateralized.

Further diagnostic workup included metabolic, genetic and autoimmune studies. Workup included CSF amino acids, CSF paraneoplastic panel, thyroid functions, liver and muscle enzymes, serum amino acids, urine organic acids, acylcarnitine profile, biotinidase, lactate, pyruvate, karyotype, chromosomal microarray and serum paraneoplastic panel. A repeat MRI with MR spectroscopy was also obtained and was unremarkable. There was no evidence of central nervous system inflammation (CSF glucose 60 mg/dL, CSF protein 17 mg/dL, acellular CSF, CSF oligoclonal bands and neopterin were not obtained). At the time of discharge, it was noted that he had subtle dysmetria and an ataxic gait which was attributed to medication effect.

One month after discharge he remained seizure free on levetiracetam (60 mg/kg/day) and valproic acid (15 mg/kg/day). Tic-like behaviors with sudden vocalization and facial twitches were noted. His mental status and development remained normal for age. He continued to have subtle dysmetria. His karyotype returned abnormal showing a polymorphic centromeric variant on chromosome 4 (p12q12) of unclear significance. Serum paraneoplastic panel was abnormal with positive VGKC antibodies (891 pmol/L; positive > 650 pmol/L). Western blot analysis for LGI1 and Caspr2 antibodies were negative. CSF paraneoplastic panel was normal.

Given the unusual presentation without evidence of encephalopathy and apparent seizure resolution, serum paraneoplastic panel and EEG were repeated. CT imaging of the chest, abdomen and pelvis was completed with no evidence of neoplasm. The follow up video-EEG continued to demonstrate background slowing along with generalized epileptiform abnormalities. In addition, the patient was noted to have electroclinical seizures characterized by eye fluttering and head drop with associated 5-10 second runs of generalized 1-2 Hz spike and slow wave discharges. These events were unnoticed by the family.

Repeat serum paraneoplastic panel continued to show positive VGKC antibodies (884 pmol/L), and western blot for LGI1 and Caspr2 remained negative. He was admitted for immunotherapy and given a five-day course of intravenous methylprednisolone (30 mg/kg/dose). A follow up 24-hour video-EEG after 5 days of methyl prednisolone demonstrated no further seizures. In addition, improvement in the EEG was noted with near normalization of the background and only two brief runs of generalized epileptiform discharges during a 24 hour EEG (Figure 3). He was discharged home on the same ASMs with instructions to complete an oral prednisolone taper over two months, starting at 1.2 mg/kg/day. Approximately three weeks after completing steroid taper the family called to report a break through seizure. However, this seizure was in the setting of missed medications and with resumption of scheduled levetiracetam and valproic acid he became seizure free again.

At 1 year follow up he remained seizure free. A repeat routine EEG and a subsequent 4-hour EEG were normal. The previously noted dysmetria and ataxia were no longer present and his parents reported resolution of his tic like behaviors. Repeat VGKC antibodies remained elevated and essentially unchanged at 762 pmol/L. The patient was tapered off of valproic acid and levetiracetam and at 17 month follow up he remained seizure free off all ASMs.

**Discussion**

There is increasing recognition of antibody mediated epilepsies, specifically VGKC complex mediated autoimmune epilepsy. The antibodies bind to proteins that are a part of the VGKC complex such as leucine rich glioma-inactivated 1 protein (LGI1), contactin associated protein 2 (Caspr2) or yet unidentified VGKC complex proteins [1]. It is the most common of neuronal auto-antibodies identified in adults evaluated for paraneoplastic autoimmunity in some centers [1]. However, the incidence, and spectrum of VGKC autoimmunity in children is yet to be established. The variable clinical presentations may reflect different antigenic targets, age, co-morbidities and other factors that are yet to be determined [1].

Our patient’s clinical presentation is consistent with that of MAE, or Doose syndrome. His normal development, constellation of seizure types, and EEG findings support this diagnosis [9]. Children with...
MAE can have very small myoclonic movements that result in subtle twitches and vocalizations. One might postulate that our patient’s reported tic-like behaviors were in fact subtle myoclonic seizures. Although MAE is a unique well-defined electro-clinical syndrome, the underlying etiology is presumed to be genetic. Genetic mutations including SCN1A, SCN1B, and GABRG2 have been identified in a small number of families but single gene causes are rare. In our patient, additional genetic testing (e.g. whole exome sequencing or an epilepsy genetic panel) was not pursued as he had clinically improved following steroid therapy and it was not felt to be cost-effective. MAE has also been reported in structural epileptogenic conditions such as Sturge-Weber syndrome and metabolic disorders such as cerebral folate deficiency and the glucose transporter disorder, GLUT1 encephalopathy [12]. To our knowledge, there are no cases of VGKC antibody mediated epilepsy presenting as a MAE, and we postulate that this may be a diagnostic possibility with significant therapeutic implications.

This case suggests that in children with MAE who have seizures intractable to ASMs, paraneoplastic antibody testing may change management and prognosis. Earlier case series of children have reported encephalopathy as a prominent feature of VGKC antibody autoimmunity and encephalitis with focal seizures [1,2]. Our patient had no associated mental status change or psychiatric disturbance and had generalized seizures possibly expanding the range of CNS presentations of VGKC mediated disease. The noted subtle ataxia also seems relevant as this improved following steroid treatment.

Although our patient’s serum yielded a positive result, there were no VGKC antibodies present in his CSF. The explanation for this is unclear but this may be due to limitations in testing methodologies. A previous study of VGKC autoimmunity has reported reduced levels (<1% to 10% of serum values) of VGKC antibodies in the CSF [13]. It has been hypothesized that the neuronal surface antibody in the CSF may already be bound to the target antigen and therefore not detectable in CSF [14]. Although elevated, the relatively low serum antibody titers seen in our patient could be an epiphenomenon. However, the dramatic clinical and electrographic response to IV methylprednisolone followed by a regimen of oral prednisolone is an argument for an autoimmune or inflammatory etiology even though a true cause-effect relationship is not possible with this single case. Steroid therapy has been reported as a treatment option in MAE and some studies have reported seizure reduction but sustained seizure freedom is rare in intractable MAE patients treated with steroids [9,15]. A limitation of these studies was that they included multiple different intractable pediatric epilepsy syndromes and they were not specific to MAE. Anti-convulsive and anti-inflammatory effects of oral prednisolone and IV methylprednisolone are hypothesized as mechanisms of action but the anti-epileptic mechanism of steroids is not known [16].

Our case report raises the following questions. Is there a subset of MAE patients where auto-immunity or CNS inflammation plays an important role in epileptogenesis? Will identification of this subset help guide the decision to treat with steroids? In our patient steroid treatment allowed for reduction in AEDs from polytherapy to complete withdrawal of all AEDs within one year after steroid initiation.

With expanding understanding of VGKC antibodies, there is also evidence to support that these antibodies may be a nonspecific marker of CNS inflammation. In a recent publication, Dr. Sonderen and colleagues reported that only patients with VGKC-positive antibodies along with LGI1 and/or Caspr2 positivity are clinically relevant [17]. However, this was a small sample that only included 3 children. Further studies on the role of VGKC antibodies in children with CNS disease are needed. In addition, larger systematic studies investigating the role of autoimmunity and inflammation in MAE syndrome, the characteristics of the MAE patient who will benefit from steroid therapy and subsequently the optimal treatment regimen with intravenous and oral steroids is needed.

**Conclusion**

This case highlights that VGKC complex antibodies can be associated with a diverse range of symptoms including new onset MAE that is intractable to ASMs. Causality of MAE by VGKC antibodies needs further investigation and cautious interpretation. Additional corroborating evidence of central nervous system involvement such as CSF pleocytosis, elevated protein, elevated neopterin, and presence of oligoclonal bands is helpful, but may be absent. There is a need for larger case series and multi-center trials investigating the etiology of unknown, presumed genetic, intractable childhood epilepsy syndromes. Recognition of autoimmune etiologies may in turn lead to appropriate and effective treatments and better prognosis for these children. Early identification could avoid continued trials of ASMs and exposure to their side effects. Prompt treatment with steroids or immune modulatory agents may lead to resolution of seizures and other manifestations. VGKC antibody testing may be considered in children who present with explosive onset of MAE that are refractory to first line ASMs even in the absence of clinical features of encephalitis or encephalopathy.

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