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Epilepsy with myoclonic absences: a case series highlighting clinical heterogeneity and surgical management

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ABSTRACT

Objective. Epilepsy with myoclonic absences is a rare epilepsy syndrome with distinct features and high rates of drug resistance. Identifying this syndrome may help guide treatment decisions. We highlight clinical heterogeneity in this case series and two cases in which corpus callosotomy was performed.

Methods. Medical records were reviewed between 2017 and 2021 to identify demographics, comorbidities, age at onset, EEG findings, diagnostic evaluations, seizure semiologies, seizure frequency, anti-seizure medications, diet therapy and surgical treatments in patients with myoclonic absences.

Results. Ten patients were identified including twins with myoclonic absence status epilepticus. Forty percent had an atonic component, 20% presented with myoclonic absence status epilepticus and 60% had incomplete control of seizures at last follow-up visit. Two patients with epilepsy with myoclonic absences with atonia underwent corpus callosotomy; one patient was seizure-free eight months after surgery and the other had greater than 50% seizure reduction over a five-month period.

Significance. Phenotypic heterogeneity was evident based on seizure semiologies, comorbidities, seizure frequency and response to anti-seizure medications and non-medication treatments. Of patients with an atonic component, 75% did not achieve seizure freedom with medication alone. Corpus callosotomy was performed in two of these patients with encouraging seizure response thus far, however, the efficacy of this treatment should be further evaluated in a larger study.

Key words: epilepsy with myoclonic absences, clinical heterogeneity, corpus callosotomy, seizure freedom

VIDEO ONLINE

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Epilepsy with myoclonic absences (EMA) is a rare epilepsy syndrome with distinct features compared to childhood absence epilepsy (CAE) [1]. While CAE is a common genetic generalized epilepsy occurring in 10-17% of all school-aged children with epilepsy diagnoses, EMA has an incidence of <1% [2]. In addition, EMA patients may not respond to anti-seizure medications (ASMs) and are more likely to have intellectual impairment compared to those with CAE [3]. Another epilepsy syndrome with some overlapping features with EMA is epilepsy with myoclonic-atonic seizures (formerly called "Doose syndrome" or "epilepsy with myoclonic-atonic seizures"). Epilepsy with myoclonic-atonic seizures is distinct from EMA in that the primary

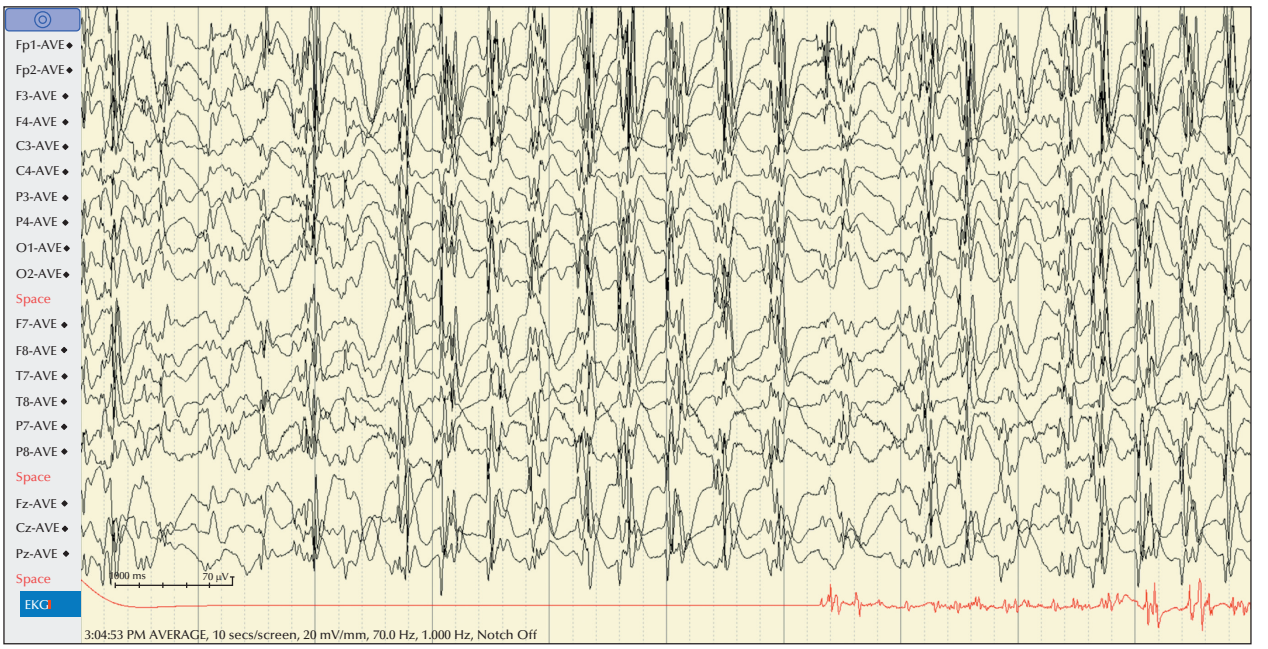
seizure semiologies are myoclonic-atonic and atonic seizures [4]. Other seizure types that may be seen in epilepsy with myoclonic-atonic seizures include myoclonic, absence, tonic, clonic and bilateral tonic-clonic seizures [4]. The electrographic pattern in epilepsy with myoclonic-atonic seizures typically involves higher frequency (2-5-Hz) spike-and-wave and polyspike-and-wave discharges and the atonic component is associated with an aftergoing high-voltage slow wave [4]. Clinically, myoclonic absence (MA) seizures involve rhythmic myoclonic jerking of the bilateral upper extremities, which results in ratcheting movements with sequential rise of the arms in discrete steps and altered awareness [1, 2, 5]. An atonic component may be present, although reportedly uncommon, and is usually described as loss of tone of the upper body or whole body resulting in a slow fall and preceded by ratcheting bilateral upper extremity movements [1, 5]. Electrographically, EMA patients have ictal patterns consisting of rhythmic 3-Hz generalized polyspike-and-wave and spike-and-wave discharges that are time-locked to ratcheting arm movements [1, 2, 5]. Other seizure types may be seen in EMA patients and include bilateral tonic-clonic seizures, absence seizures and atypical absence seizures [1, 6, 7]. In a single case report, focal seizures were also reported with EMA [6].

The most common ASMs, beneficial in the management of EMA, include valproic acid, ethosuximide and lamotrigine, either in combination or alone [1, 2, 5, 7]. Other less effective options include levetiracetam, zonisamide, topiramate and lacosamide. Rufinamide as an adjunct therapy showed benefit in a small case series of three patients with two patients becoming seizure-free and one patient with a greater than 50% reduction in seizure frequency [8]. Non-medication options reported in the literature include vagus nerve stimulation (VNS) or diet therapy, such as the ketogenic diet or modified Atkins diet (MAD) [2]. Brain imaging is usually normal with non-specific findings, such as generalized cortical atrophy, seen in nearly 20% of EMA patients [9]. Like many features of this epilepsy syndrome, the etiology is heterogeneous with prematurity, perinatal parenchymal injury and chromosomal abnormalities reported in more than one third of patients with EMA [8]. Prognosis is variable with some patients achieving seizure resolution while others become refractory with new and evolving seizure semiologies [9]. Developmental delay or learning disorders may depend on the etiology and has been reported in up to 45% of EMA patients at diagnosis, increasing up to 70% over time [2]. The presence of bilateral tonic-clonic seizures is associated with an increased likelihood of developmental delay compared to EMA patients with MA seizures alone [1, 2, 10]. Given the rare incidence of this epilepsy syndrome compared to CAE, we highlight the clinical heterogeneity of EMA patients by presenting a retrospective review of 10 pediatric patients, including twin siblings, and emphasize successful outcomes after corpus callosotomy in EMA patients with an atonic component to their MA seizures.

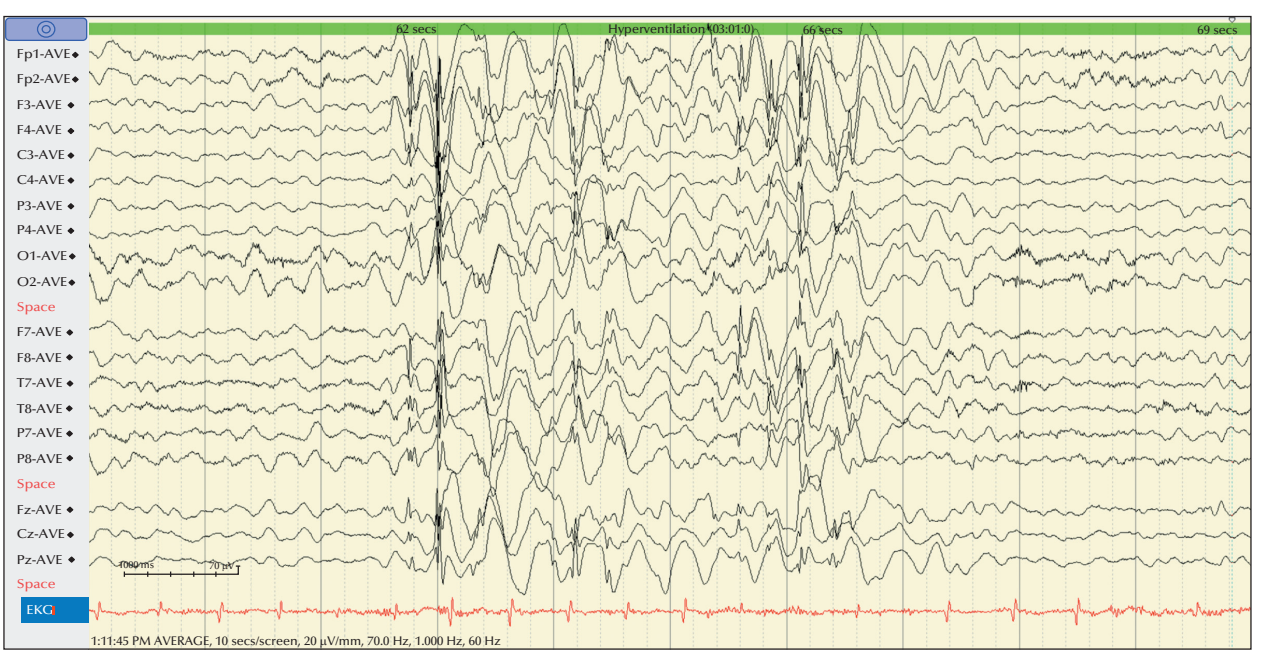
Case series

Institutional Review Board approval (IRB #210770) was obtained at Vanderbilt University Medical Center (VUMC) for this descriptive case series of pediatric patients with EMA. Patients seen at Monroe Carell Jr. Children's Hospital at Vanderbilt (MCJCHV) were identified through Epic's Clarity data warehouse using a free-text search of "absence," "myoclonic" and "myoclonic absence" in video EEG reports in patients less than 22 years old, between November 2017 and April 2021. This search identified eight patients who had MA seizures recorded on EEG. An additional two patients, twin siblings, with the diagnosis of EMA made prior to November 2017, were also included. After identification, medical records were retrospectively reviewed, looking at each patient's demographics, age at onset, EEG reports, other seizure semiologies, ASM history, non-medication treatments, surgical treatments, seizure frequency during follow-up, comorbidities and diagnostic evaluations.

Ten patients were identified with the diagnosis of EMA based on both clinical features and ictal EEG findings consistent with EMA. Age at onset in these patients ranged from six months to nine years old, and half were female (n = 5/10). Only one patient (n = 1/10) had MA seizures and bilateral tonic-clonic seizures. Forty percent (n = 4/10) of our patients had an atonic component associated with their MA seizures (n = 4/10). Twin siblings had initial seizure presentation characterized as MA status epilepticus (*figures 1, 2, video*). More than half of the patients, 60% (n =6/10), had daily MA seizures. Regarding ASM history, a majority of patients were on valproic acid (n = 6/10) and were more likely to be on monotherapy compared to other ASMs (monotherapy with valproic acid, n = 5/6). Of patients whose MA seizures resolved, seizure freedom was achieved with monotherapy in three of the four patients. In this series, no patients were treated with ketogenic diet or VNS. Of the five patients with genetic testing, one patient had tuberous sclerosis complex (TSC), one had a 17p13.3 deletion and one had a likely pathogenic mutation in *SYNGAP1*. Learning disorders or developmental delay was noted in half of our EMA patients (n = 5/10). Two patients underwent corpus callosotomy for treatment of MA seizures with atonia. One patient



■ **Figure 1.** Myoclonic absence status epilepticus showing near-continuous, rhythmic 2.5-3-Hz high-voltage, generalized spike-and-wave discharges associated with rapid, irregular jerking of bilateral upper extremities, and eyelid myoclonia (EEG settings: average montage, 10 seconds/screen, sensitivity 20 µV/mm, 70-Hz high-frequency filter, 1 Hz low-frequency filter).



■ **Figure 2.** Myoclonic absence seizure during hyperventilation showing a burst of rhythmic 2.5-3 Hz high-voltage, generalized spike-and-wave discharges associated with behavioral arrest, rapid, irregular jerking of bilateral upper extremities, and eyelid myoclonia that lasted for four seconds during hyperventilation (EEG settings: average montage, 10 seconds/screen, sensitivity 20 µV/mm, 70-Hz high-frequency filter, 1-Hz low-frequency filter).

▼ **Table 1.** Demographic information, age at seizure onset, video EEG reports, other seizure semiologies, ASM history, non-medication treatments, surgical treatments, seizure frequency at the most recent follow-up visit, co-morbidities and other diagnostic evaluations of 10 patients with EMA at MCJCHV.

Current age	Sex	Age at epilepsy onset	Initial EEG findings	Seizure semiology	ASMs	Prior ASMs	Non-ASM therapy	Surgical treatment	Current seizure burden	Co-morbidities	Diagnostic evaluation
6 yo	M	1 yo	Ictal: two 3.5-4-Hz absence seizures (1 with myoclonus) Interictal: frequent 3.5-Hz spike-and-wave discharges	Myoclonic absence seizures	ETX	VPA – ineffective LEV – ineffective	None	None	None	None	Invitae epilepsy panel with 4 VUS (*CACNA1H*, *GABBR2*, *NRXN1*, *PLCB1*)
12 yo	F	3 yo	Ictal: myoclonic absence status epilepticus Interictal: frequent bi-parietal spike-and-wave discharges	Myoclonic absence seizures and absence seizures with eyelid fluttering alone	VPA	ETX – side effects CBD – incomplete control	MAD	None	Daily morning eyelid fluttering	LD ADHD	None
12 yo	F	3 yo	Ictal: myoclonic absence status epilepticus Interictal: frequent 2.5-4-Hz bi-parietal spike-and-wave discharges	Myoclonic absence seizures and absence seizures with eyelid fluttering alone	VPA	ETX – side effects LEV – ineffective CBD – effective	MAD	None	Daily morning eyelid fluttering	LD ADHD	None
13 yo	M	6 mo	Ictal: 4 myoclonic absence seizures at 3-3.5 Hz Interictal: rhythmic delta with embedded generalized sharps	Myoclonic absence seizures	ETX	None	None	None	10-20 seizures/ day	None	None
4 yo	F	2.5 yo	Ictal: ~ 100 myoclonic absence seizures with 1.5-2-Hz spike or polyspike-and-wave discharges	Myoclonic absence seizures with eyelid fluttering, loss of tone, and gasping	VPA	LEV – ineffective TPX – ineffective RFM – ineffective CLB – ineffective Prednisone - ineffective	None	Complete corpus callosotomy 4/2021	None	DD	Invitae Epilepsy Panel with *SYNGAP1* variant

▼ **Table 1.** Demographic information, age at seizure onset, video EEG reports, other seizure semiologies, ASM history, non-medication treatments, surgical treatments, seizure frequency at the most recent follow-up visit, co-morbidities and other diagnostic evaluations of 10 patients with EMA at MCJCHV (*continued*).

Current age	Sex	Age at epilepsy onset	Initial EEG findings	Seizure semiology	ASMs	Prior ASMs	Non-ASM therapy	Surgical treatment	Current seizure burden	Co-morbidities	Diagnostic evaluation
6 yo	F	4 yo	Ictal: 27 myoclonic absence seizures with 3-4-Hz spike-and-wave discharges Interictal: frequent spike or polyspike-and-wave discharges	Myoclonic absence seizures with loss of tone and falls	LCM LEV Epidiolex	ZNS – ineffective CLB – sedation VPA – hemorrhagic pancreatitis	None	Anterior 2/3 corpus callosotomy 6/2021	5-10 seizures/day (previously 30 seizures per day)	DD Prematurity Hypotonic CP ADHD	17p.13.3 2Mb deletion
11 yo	M	9 yo	Ictal: one myoclonic absence seizure Interictal: frequent 3-Hz spike or polyspike-and-wave discharges	Myoclonic absence seizures	VPA	None	None	None	None	None	None
7 yo	F	3 yo	Ictal: myoclonic absence seizures with 3-3.5-Hz polyspike-and-wave discharges; previously eyelid myoclonia and some associated with falls	Myoclonic absence seizures with behavioral arrest, myoclonic jerks of upper body and eyelid fluttering; occasional falls	VPA	LEV – ineffective vs non-compliance	None	None	10 seizures/day	LD	Normal CMA
19 yo	M	7 yo	Ictal: eye widening followed by myoclonus seen with associated high-voltage sharply, contoured alpha activity prior to polyspike and wave discharges	GTC seizures, absence seizures with eyelid fluttering and myoclonus	LEV	None	None	None	None	Hereditary lymphedema type 1	None
4 yo	M	2 yo	Interictal: 3-Hz spike-and-wave discharges, 3-5-Hz polyspike-and-wave discharges	Myoclonic absence seizures, component of falling	VPA Everolimus CLB Epidiolex	LEV – incomplete control	None	None	3-8 seizures/day	TSC	Normal CMA and karyotype

ETX: ethosuximide; VPA: valproic acid; LEV: levetiracetam; CBD: cannabidiol; TPX: topiramate; RFM: rufinamide; CLB: clobazam; ZNS: zonisamide; LCM: lacosamide; MAD: modified Atkins diet; LD: learning disorder; ADHD: attention deficit and hyperactivity disorder; DD: developmental delay; CMA: chromosomal microarray.

had previously failed five ASMs and underwent complete corpus callosotomy with resolution of seizures eight months post-surgery. The other patient had previously failed three ASMs and underwent an anterior two-thirds corpus callosotomy with greater than 50% seizure reduction five months post-surgery. Prior seizure burden for this second patient was 30 MA seizures per day with an average of 10 seizures per day, however, post-surgery, the seizures were shorter in duration and rarely involved an atonic component. Neither patient had surgical complications nor new neurological deficits following surgery (*table 1*).

Discussion

In our cohort of 10 pediatric patients with EMA at VUMC, phenotypic heterogeneity was evident regarding age at onset, seizure semiologies, seizure frequency, comorbidities, diagnostic evaluation and response to ASMs and non-medication treatments. Identifying this phenotypically heterogeneous epilepsy syndrome is important in guiding treatment decisions and prognosis. Novel findings in our cohort include identical twin siblings with MA seizures as well occurrence of MA status epilepticus at onset, a high percentage of patients with an atonic component of their MA seizures, and two patients with an atonic component of their MA seizures who underwent corpus callosotomy with improved seizure outcomes. One review article noted an EMA patient with developmental delay and a *de novo SYNGAP1* mutation, which is of interest as a patient included in our cohort also had a *SYNGAP1* variant [9].

In our series, 40% of patients had an atonic component to their MA seizures, all of whom had medically refractory epilepsy and learning disorders or developmental delay. Two of these patients underwent corpus callosotomy. Corpus callosotomy was a proposed surgical treatment option in these two patients given the known benefit of corpus callosotomy in patients with refractory atonic seizures. In reviewing the EMA literature, corpus callosotomy, as a treatment option for EMA, has not been described to date. One patient underwent complete corpus callosotomy with resolution of seizures eight months post-surgery, while the other patient underwent an anterior two-thirds corpus callosotomy with greater than 50% seizure reduction five months post-surgery. Neither patient had surgical complications nor new neurological deficits following surgery. Given these two patients' encouraging seizure response thus far, we propose corpus callosotomy may be a treatment option to consider in patients with EMA who have an atonic component and are refractory to ASMs. While these initial results are promising, larger longitudinal studies are needed to better evaluate the efficacy of corpus callosotomy in EMA patients. ■

Key points

- In our 10 patients with epilepsy with myoclonic absences (EMA), phenotypic heterogeneity was seen regarding age at onset, seizure semiology, seizure frequency, comorbidities, diagnostic evaluation, and response to ASMs and non-medication treatments.
- Novel findings in our cohort include:
- Twin siblings with myoclonic absence status epilepticus at onset.
- A high percentage of patients with EMA involving an atonic component.
- Two patients with EMA and an atonic component underwent corpus callosotomy.

Supplementary material.
Supplementary summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have disclosures or conflicts of interest.

References

1. Bureau M, Tassinari CA. Epilepsy with myoclonic absences. *Brain Dev* 2005; 27(3): 178-84.

2. Covanis A. Epilepsy with myoclonic absences. In : Panayiotopoulos CP, ed. *Atlas of epilepsies*. London: Springer, p. 1025-8.

3. Manonmani V, Wallace SJ. Epilepsy with myoclonic absences. *Arch Dise Child* 1994; 70: 288-90.

4. Kelley S, Kossoff E. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. *Dev Med Child Neurol* 2010; 52: 988-93.

5. Zanzmera P, Menon R, Karkare K, Soni H, Jagtap S, Radhakrishnan A. Epilepsy with myoclonic absences: electroclinical characteristics in a distinctive pediatric epilepsy phenotype. *Epilepsy Behav* 2016; 64: 242-7.

6. Cetin O, Abanoz Y, Kivrak E, Yalcinkaya C, Demirbilek V. A rare finding in epilepsy with myoclonic absences: focal seizure. *Childs Nerv Syst* 2016; 32: 2053-5.

7. Genton P, Bureau M. Epilepsy with myoclonic absences. *CNS Drugs* 2006; 20(11): 911-6.

8. Häusler M, Kluger G, Nikanorova M. Epilepsy with myoclonic absences – favourable response to add-on rufinamide treatment in 3 cases. *Neuropediatrics* 2011; 42: 28-9.

9. De la Jara J, Vasquez-Hernandez C, Ramirez-Rojo E, Moya-Vilches J. Uncommon epileptic syndromes in children: a review. *Seizure* 2021; 90: 17-27.

10. Iyer RS. Proximal upper limp jerking: important clinical sign to diagnose epilepsy with myoclonic absences. *Pediatr Neurol* 2017; 71: 88-9.

Legend for video sequence

This video shows an eight-year-old female who presented to the pediatric neurology clinic in myoclonic absence status epilepticus, recorded on an outpatient video-EEG. At the beginning of her EEG recording, there was high voltage, near-continuous, rhythmic 2.5-3-Hz generalized spike-and-polyspike wave discharges associated with rapid, irregular eyelid blinking and near-continuous, rapid, irregular, synchronous and asynchronous jerks of the torso and bilateral upper extremities ("ratcheting" movements). The patient was able to answer questions during these ictal discharges, albeit with slow and stuttering speech (not seen here). Notably, her identical twin sister had myoclonic absence status epilepticus noted shortly after this EEG.

Key words for video research on www.epilepticdisorders.com

Phenomenology: rapid, irregular eyelid blinking and/or rapid, irregular jerks of the torso and bilateral upper extremities ("ratcheting" movements) with loss of awareness
Localization: generalized
Syndrome: epilepsy with myoclonic absences
Aetiology: genetic

TEST YOURSELF

(1) Other than pathognomonic myoclonic absence seizures, what other seizure types and comorbidities are seen in EMA?

(2) How can early recognition and diagnosis of EMA guide providers?

(3) Pending further validation, what surgical option may be promising for patients with refractory EMA and a strong atonic component?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.