How Do We Diagnose and Treat Epilepsy with Myoclonic-Atonic Seizures (Doose Syndrome)? Results of the Pediatric Epilepsy Research Consortium Survey

1. Introduction

Epilepsy with myoclonic-atonic seizures (EMAS), formerly known as myoclonic-astatic epilepsy (MAE), or Doose syndrome was initially classified by the International League Against Epilepsy (ILAE) as a symptomatic generalized epilepsy in 1989, with the following defining characteristics: normal development prior to seizure onset; no organic or obvious cause of seizures and not consistent with Dravet syndrome, Lennox-Gastaut syndrome (LGS), or benign myoclonic epilepsy; onset of myoclonic-atonic seizures between seven months and six years of age; a 2:1 male: female ratio (except in the first year when it is equal); multiple seizure types, including: myoclonic, atonic, myoclonic-atonic, absence, tonic, clonic, generalized tonic clonic; status epilepticus is common; and EEG is initially normal (or centro-parietal theta) then generalized polyspike and wave epileptiform activity (Berg, et al., 2010; Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Doose, et al., 1970). EMAS likely has a genetic component, with a positive family history of seizures in approximately 1/3 of cases. The heterogeneity of seizure types and EEG findings in families of EMAS probands, however, suggests a more multifactorial inheritance (Tang and Pal, 2012). Reported gene abnormalities associated with EMAS include SCN1B, GABRG2, SLC2A1 (Mullen, et al., 2011; Tang and Pal, 2012), SLC6A1 (Carvill, et al., 2015; Palmer, et al., 2016), STX1B (Vlaskamp, et al. 2016), SYNGAP1 (Mignot, et al., 2016), and a microduplication of 4q21.22-q21.23 (Ottaviani, et al., 2015).

Unlike most epileptic encephalopathies, the prognosis for EMAS is variable, ranging from normal cognition to severe intellectual disability, with favorable outcomes most likely if seizures resolve and the EEG does not show persistent abnormalities (Kelley and Kossoff, 2010; Stephani, 2006). Therefore, quickly identifying EMAS and initiating effective treatment may affect the long term seizure and cognitive outcomes. Currently, seizure remission and normal cognition have been reported in 58-68% and 26-43%, respectively (Doose, et al., 1970; Kaminska, et al., 1999; Kilaru and Bergqvist, 2007; Oguni, et al., 2002).

Unfortunately, EMAS is often difficult to diagnose confidently due to a lack of consensus regarding the clinical definition. EMAS can be especially difficult to differentiate from Lennox Gastaut syndrome (LGS), as both syndromes can be associated with febrile, myoclonic, myoclonic-atonic, generalized tonic-clonic or absence seizures (Kelley and Kossoff, 2010; Stephanu, 2006). Features that may help differentiate the two syndromes include: normal development prior to seizure onset in EMAS; EEG in EMAS may initially be normal, followed by background slowing and generalized 2-5 Hz spike and wave discharges; and background rhythms and sleep architecture are often preserved in EMAS. By contrast, EEG in LGS demonstrates slower spike and wave discharges with slower and more abnormal background activity (Kelley and Kossoff, 2010). EMAS should also be differentiated from Dravet Syndrome (DS), which can also be preceded by normal development and febrile seizures. However, children with Dravet syndrome typically present prior to age one year, often have focal seizures and EEG features, and the myoclonus in Dravet syndrome rarely has an atonic component (Kelley and Kossoff, 2010; Stephanu, 2006).

Further complicating the diagnosis of EMAS, more recent studies have proposed variations of diagnostic criteria. When studying the role of GLUT1 in EMAS, Mullen, et al. (2011) used both “narrow” and “broad” definitions of EMAS. Furthermore, whereas epileptic spasms were previously thought to exclude a diagnosis of EMAS, these have now been reported in children who otherwise fulfil diagnostic criteria for EMAS (Weimer-Kruel, et al., 2017).

In addition, there is also no clear consensus for recommended treatments of EMAS. EMAS has consistently been reported as refractory to treatment and a 2007 study reported patients being exposed to five anti-seizure treatments (AST), on average (Kilaru and Bergqvist, 2007; Oguni, et al., 2002). However, valproic acid, lamotrigine, ethosuximide, topiramate and levetiracetam have been reported to show efficacy (Kelley and Kossoff, 2010; Kilaru and Bergqvist, 2007; Stephani, 2006). The ketogenic diet (KD) has been associated with seizure freedom in 18-58% and >50% seizure reduction in 35-55% (Kilaru and Bergqvist, 2007; Oguni, et al., 2002; Pillau, et al., 2016). A more recent study from 2017 reported that 25/30 patients achieved >50% seizure reduction on a Modified Atkins Diet (MAD) after an average of six ASTs (Caraballo, et al., 2006).

Epileptic encephalopathies are typically associated with poor cognitive outcomes and continued refractory seizures. However, the prognosis for EMAS is variable and appropriate syndrome diagnosis and initiation of effective treatment may affect the long term outcome of EMAS. However, currently there is a lack of consensus regarding diagnostic criteria or treatment. Therefore, the objective of this study was to obtain and assess opinions on diagnostic criteria, as well as recommended investigations and therapeutic options, from a large group of physicians who care for children with EMAS.

1. Methods:

The Epilepsy with Myoclonic-Atonic seizures (EMAS) focus group of the Pediatric Epilepsy Research Consortium (PERC) was established to collaborate multicenter research on EMAS, and is comprised of eight US-based pediatric epilepsy specialists practicing in six pediatric epilepsy centers and one research assistant. As a precursor to designing prospective studies, this group created a survey to assess the opinions of pediatric neurologists who care for children with EMAS regarding diagnosis and treatment of this condition. A telephone conference was held to establish the content of the survey. A draft was created and sent back to all members for editing. The final survey was approved by all group members.

Requests to complete the survey were sent to members of PERC, the American Epilepsy Society (AES), and the Child Neurology Society (CNS) via email, with a link to the survey embedded in the email. Members were asked to complete the survey if they were physicians who cared for children with EMAS and were given 30 days to complete the survey. The physicians could reside outside the United States, as long as they were members of AES or CNS. Those who were members of multiple sections could complete the survey only once.

* 1. Survey

The on-line survey consisted of nine questions (Appendix). Two questions provided information regarding type and location of the physician’s practice. Questions three to five used a Likert scale to assess the physician’s opinion regarding the importance of specific diagnostic and exclusion clinical criteria (five point Likert scale) and investigations (four point Likert scale) for diagnosing EMAS. While no specific diagnostic criteria for EMAS exist, the International League Against Epilepsy (ILAE) description of EMAS was used to create the list of diagnostic and exclusion criteria. The respondents were also given a free text option to add additional investigations they would request when evaluating a child with potential EMAS (questions six and seven).

Question eight listed all potential therapies for epilepsy - including medications, diet, surgery, and supplements. Physicians were asked to rank when or if they would recommend each treatment for EMAS based on a six point Likert scale, ranging from *first line therapy* to *would not use*. At the end of the survey, physicians were invited to add any additional comments, questions, or concerns (question nine).

* 1. Data analysis

Due to the small number of responses, the results were grouped according to the following:

* **Diagnostic criteria** (five point Likert scale): little importance (one/two), moderate importance (three), very important/essential (four/five)
* **Exclusion criteria** (five point Likert scale): little importance (one/two), moderate importance (three), very important/excludes (four/five)
* **Investigations** (four point Likert scale): Always/almost always request test (one/two), would request test only if atypical features present (three), never/almost never request test (four)
* **Treatment** (fix point Likert scale): preferred treatment (first or second therapy) (one), beneficial if first and second therapy fails (two/three), indeterminate benefit (four), would not use this/ contraindicated in EMAS (five)

Inclusion and exclusion criteria were *critical* criteria if >= 80% said they were very important or essential/exclusionary, *strong* criteria if >=80% said they were of moderate importance, very important, or essential/exclusionary, and *modest* criteria if 50-79% said they were of moderate importance, very important, or essential/exclusionary.

An investigation was an *essential* investigation for all patients if >=80% said they would always/ almost always request that test, a *recommended* investigation for majority of patients if >=80% said they would request always/almost always or if there were atypical features (minor or significant) present, and a *possible* investigation if 50-79% said they would request the test always/almost always or if atypical features were present.

Therapies with which >=50% of respondents reported they had no experience were excluded from analysis. Recommended *first line* therapies were those used as preferred treatment by >70% of respondents who had experience with that therapy. *Beneficial* treatments after first line therapies failed were those recommended as choices one-six by >70%. Medications that were unlikely to be beneficial, but were not contraindicated (*indeterminate benefit*) were those used as choice one-six by <70%, but were choice at some time by >70%. Contraindicated treatments were those not used to treat EMAS in >70% of physicians.

1. Results
   1. Participants

There were 76 providers who responded in total: 36 from PERC, 22 from CNS, and three from AES. Of those, 51 were child and adolescent epilepsy subspecialists, 24 child and adolescent neurologists, and one adult neurologist. The majority (61) practice in the United States, four practice in Canada, and two in Europe. The survey questions and possible answers are included in the supporting information (Appendix).

3.2. Survey results

3.2.1. EMAS diagnostic criteria (Figure 1)

The only critical diagnostic criterion was a history suggestive of myoclonic atonic seizures, with 90.8% of respondents saying this was essential or very important. Strong criteria (essential, very/moderate important for >80% of respondents) included: recorded myoclonic atonic seizures, a home video suggestive of myoclonic atonic seizures, generalized spike wave discharges on inter-ictal EEG, normal neuroimaging, and normal development prior to seizure onset. The presence of other generalized seizures was considered modest diagnostic criteria (essential, very/moderate importance for 50-79%). Neither a family history of epilepsy or seizures, nor diffuse theta with centroparietal predominance was important.

3.2.2. EMAS exclusionary criteria (Figure 2)

There were no critical exclusionary criteria. Strong criteria (exclusionary, very/moderate important for >80% of respondents) included: a history of epileptic spasms, abnormal neuroimaging, focal abnormalities on neurologic exam, and seizure onset before six months or after six years. Modest exclusionary criteria (exclusionary, very/moderate important for 50-79% of respondents) included: developmental delay prior to seizure onset, low cerebrospinal glucose, focal or tonic seizures, and focal EEG abnormalities. A history of febrile status epilepticus was not an exclusionary criterion.

3.2.3. EMAS recommended investigations (Figure 3)

Routine and/or prolonged EEG and MRI brain were essential evaluations, requested for nearly all patients by 93.4%, 84.2%, and 90.4% of respondents, respectively. Recommended evaluations (requested for nearly all or if atypical features were present) included: quantitative serum amino acids, urine organic acids, fatty acid oxidation/acylcarnitine profile, microarray, genetic panel, lactate and pyruvate, and CSF and serum glucose and lactate. Specific gene testing, whole exome sequencing, electrolytes and additional metabolic testing were possible evaluations (requested for all or if atypical features were present by 50-79% of respondents).

3.2.4. EMAS recommended treatments (Figure 4)

Deep brain stimulation, ezogabine, and sulthiame were excluded from analysis due to lack of experience with these therapies. The only recommended first line therapy was valproic acid, being recommended as a preferred medication by 71.6%. Beneficial treatments (choice one-six by >70% of respondents) included: topiramate, zonisamide, levetiracetam, benzodiazepines, and the dietary therapies (ketogenic diet, Modified Atkins Diet, low glycemic index diet). Possible (indeterminate) treatments included: acetazolamide, ethosuximide, felbamate, lamotrigine, rufinamide, and VNS. Contraindicated therapies included carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, and tiagabine. The remainder were neither recommended nor contraindicated.

1. Discussion

This is a large survey of physicians who specialize in treating children with epilepsy across multiple epilepsy centers. To date, no similar surveys have been published to help identify preferred diagnostic and treatment practices for EMAS, even though early syndrome identification and initiation of effective treatment have been associated with improved outcome (Kelley and Kossoff, 2010; Stephani, 2006). Furthermore, medications that exacerbate seizures in EMAS have also been identified (McTague and Cross, 2013). A retrospective review of treatment of EMAS in a large pediatric institution revealed the first two medications typically used were oxcarbazepine and carbamazepine, both of which have been associated with worsening of seizures in EMAS. This was attributed to lack of ability to identify EMAS early (Kilaru and Bergqvist, 2007).

Diagnostic criteria for EMAS- including necessary/exclusionary seizure types, age of onset, EEG patterns, and etiology- has varied throughout the literature, making identification of this syndrome challenging (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Kelley and Kossoff, 2010; Larsen, et al., 2015; Mullen, et al., 2011; Tang and Pal, 2012). However, the only critical diagnostic criterion identified in this survey was a history of myoclonic atonic seizures. This is consistent with previous studies of children with EMAS that documented variable seizure types, but children all had myoclonic atonic seizures (Caraballo, et al., 2013; Trivisano, et al, 2011). The presence of myoclonic atonic seizures, rather than epileptic spasms or atonic seizures, can also help differentiate EMAS from other epileptic encephalopathies (Itoh, et al., 2015). Supportive information included recorded myoclonic atonic seizures, normal neuroimaging, and normal development prior to seizure onset.

Previously reported associated EEG findings have included normal EEG at the time of seizure onset, followed by non-specific centroparietal slowing, generalized slowing, and emergence of generalized slow spike and wave and atypical spike and wave discharges. Continuous irregular activity that may resemble hypsarrhythmia has also been reported (Kelley and Kossoff, 2010; Tang and Pal, 2012). EEG demonstrating generalized spike and wave discharges was also felt to be a strong supportive criterion in this survey. By contrast, background centro-parietal theta slowing was not important. This is likely related to the expected variability in EEGs in children with EMAS (Kelley and Kossoff, 2010). Furthermore, although a family history of seizures has been reported in up to 1/3 of cases (Tang and Pal, 2012), presence or absence of a family history was not viewed as important.

Due to the similarities of EMAS with other epileptic encephalopathies, such as Dravet syndrome and LGS, identifying criteria to exclude these syndromes is important. It is also recommended that glucose transporter deficiency syndrome (GLUT1) be excluded as this represents a unique syndrome from EMAS (Larsen, et al., 2015). In this survey, no critical exclusionary criteria were identified. However, a history of epileptic spasms as well as focal features on exam or neuroimaging, were strong exclusionary criteria. These findings would be more consistent with LGS or other epileptic encephalopathies. Focal or tonic seizures and developmental delay prior to seizure onset could also be suggestive of LGS, but are less specific and were viewed as only modest exclusionary criteria. Although it has previously been recommended to exclude GLUT1, low CSF glucose was only a modest exclusionary criterion. A history of febrile status epilepticus would be most consistent with Dravet syndrome, but febrile seizures can precede EMAS (Caraballo, et al., 2013). Therefore, this history was not an exclusionary criterion.

Investigations for underlying etiology in children with epileptic encephalopathies are often extensive and include neuroimaging, genetic, and metabolic evaluations. Identification of an underlying etiology can help identify potential more effective therapeutic options than medications alone. Furthermore, an identifiable metabolic cause for seizures in children with a history of myoclonic-atonic seizures is helpful in excluding EMAS. However, extensive testing is costly. A previous study of the most cost effective evaluation for a different epileptic encephalopathy, West syndrome, demonstrated that EEG, neuroimaging, and epilepsy gene panel were the most preferred (Wirrell, et al., 2015). Similarly, EEG, and MRI brain were recommended for all patients in this survey. Epilepsy gene panel was also recommended. Although metabolic testing was low yield in the West syndrome group, and low CSF glucose was only a modest exclusionary criterion, CSF and serum glucose and lactate were recommended for the majority of patients. Additional metabolic and genetic testing was also recommended for the majority of patients.

Early control of seizures in EMAS may be associated with improved long term outcome (Kelley and Kossoff, 2010; Stephani, 2006). Unfortunately, the majority of children experience seizures that are refractory to medications. Identifying effective and contraindicated therapies for EMAS is essential for maximizing outcome. In this survey, only valproic acid was felt to be the preferred first line treatment- recommended as the preferred medication by 71.6% or respondents. This is consistent with previous reports of valproic acid being the first or preferred anti-seizure medication used in EMAS or other generalized epileptic encephalopathies (Caraballo, et al., 2013; Kilaru and Bergqvist, 2007; McTague and Cross, 2013; Trivisano, et al., 2011). Additional potentially helpful therapies included dietary therapies (ketogenic, modified Atkins, and low glycemic index diets), benzodiazepines, ethosuximide, lamotrigine, levetiracetam, topiramate, and zonisamide. There were also clear contraindicated medications identified, with carbamazepine and oxcarbazepine being identified as a medication not used by >90% of respondents.

1. Conclusions

In summary, this large survey of physicians identified critical and preferred diagnostic electro clinical features, investigations, and treatments for EMAS. However, even among specialists there is continued disagreement in expected associated seizure types and EEG characteristics, as well as best practices for identification of underlying etiology and best treatments for EMAS. Although this is a survey of expert opinion, rather than consensus for definitive treatment guideline, this survey identifies the areas of consensus and controversy to focus future research. Furthermore, the information on preferred treatment from the large number of participants of wide geographical distribution make this a crucial first step in defining specific diagnostic criteria, recommended evaluation, and most effective therapies for EMAS. Additional prospective studies are needed to determine the relative importance of these diagnostic features, as well as identify the most effective treatments for this epileptic encephalopathy.

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Conflicts of interest disclosures

Author KN has served as a paid consultant for Zogenix. Author RT has served as a paid consultant for Ovid Pharmaceuticals. Author EW has served as a paid consultant for Biomarin and Sunovion Pharma. Author EHK has served as a paid consultant for Atkins Nutritionals, Inc., Nutricia, Inc., and NeuroPace; is a member of the DSMB for GW, and has received grants from Nutricia and Vitaflo. The remaining authors have no conflicts of interest.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure legends

Figure 1: Importance of diagnostic criteria for diagnosing EMAS. MAS- myoclonic atonic seizures.

History suggestive of MAS was critical criterion. Recorded MAS, parent/home video suggestive of MAS, generalized spike wave discharges on inter-ictal EEG, normal neuroimaging, and normal development prior to seizure onset were strong criteria. The presence of other generalized seizures was a moderate criterion. Neither a family history of seizures or epilepsy, nor diffuse theta with centroparietal predominance were important.

Figure 2: Importance of exclusionary criteria for diagnosing EMAS.

There were no critical exclusionary criteria. Epileptic spasms, abnormal neuroimaging, focal abnormal neurologic exam, and onset prior to age 6 months or after age 6 years were strong exclusionary criteria. Developmental delay prior to seizure onset, low CSF glucose, focal seizures, tonic seizures, and presence of focal abnormalities on EEG were moderate exclusionary criteria. A prior history of febrile status epilepticus was not exclusionary.

Figure 3: Importance of recommended investigations.

Routine and/or prolonged EEG and MRI brain were essential evaluations, recommended by >80% of respondents for all patients. Serum quantitative amino acids, urine organic acids, fatty acid oxidation/acylcarnitine profiles, microarray, genetic panel, lactate/pyruvic acid, and CSF/serum glucose and lactate were recommended for all patients or those with atypical features by >80% of respondents. Specific genetic testing, whole exome sequencing, electrolytes, and additional metabolic testing were recommended for all patients or those with atypical features by 50-79% of respondents.

Figure 4: EMAS recommended treatments

Valproic acid was the only essential therapy (first or second treatment recommended by >70% of respondents). Topiramate, zonisamide, levetiracetam, benzodiazepines, and dietary therapies were beneficial therapies (recommended as first 6 possible therapies by >70%). Acetazolamide, ethosuximide, felbamate, lamotrigine, rufinamide, and vagus nerve stimulator were of indeterminate benefit (recommended as therapy at some point, but not first 6 by 70%). Tiagabine, phenytoin, oxcarbazepine, eslicarbazepine, and carbamazepine contraindicated.