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How do we diagnose and treat epilepsy with myoclonic-atonic seizures (Doose syndrome)? Results of the Pediatric Epilepsy Research Consortium survey

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ABSTRACT

Objective: To obtain and assess opinions on EMAS diagnostic criteria, recommended investigations, and therapeutic options, from a large group of physicians who care for children with EMAS.

Methods: The EMAS focus group of PERC created a survey to assess the opinions of pediatric neurologists who care for children with EMAS regarding diagnosis and treatment of this condition, which was sent to members of PERC, AES, and CNS. A Likert scale was used to assess the respondents' opinions on the importance of diagnostic and exclusion criteria (five point scale), investigations (four point scale), and treatment (six point scale) of EMAS. Inclusion/exclusion criteria were then classified as critical, strong, or modest. Investigations were classified as essential, recommended, or possible. Therapies were classified as first line, beneficial, indeterminate benefit, or contraindicated.

Results: Survey results from the 76 participants determined the following:

EMAS inclusion criteria: history suggestive of MAS (critical), recorded or home video suggestive of MAS, generalized discharges on inter-ictal EEG, normal neuroimaging, normal development prior to seizure onset (strong).

EMAS exclusionary criteria: epileptic spasms, abnormal neuroimaging, focal abnormal exam, seizure onset < six months or > six years (strong).

Recommended investigations: EEG and MRI (essential), amino acids, organic acids, fatty acid/acylcarnitine profile, microarray, genetic panel, lactate/pyruvate, CSF and serum glucose/lactate (strong).

Recommended treatments: Valproic acid (first line), topiramate, zonisamide, levetiracetam, benzodiazepines, and dietary therapies (beneficial).

Significance: To date, no similar surveys have been published, even though early syndrome identification and initiation of effective treatment have been associated with improved outcome in EMAS. Medications that exacerbate seizures in EMAS have also been identified. This survey identified critical and preferred diagnostic electro clinical features, investigations, and treatments for EMAS. It will guide future research and is a crucial first step in defining specific diagnostic criteria, recommended evaluation, and most effective therapies for EMAS.

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:

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normal development prior to seizure onset; no cause of seizures; onset of myoclonic-atonic seizures between seven months and six years of age; a 2:1 male: female ratio; multiple generalized seizure types; 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 multifactorial inheritance, with a positive family history of seizures of variable types in approximately 1/3 of cases (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), STX1 B (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 other epileptic encephalopathies, including Lennox Gastaut syndrome (LGS) and Dravet Syndrome (DS), which can be associated with febrile, myoclonic, myoclonic-atonic, generalized tonic-clonic or absence seizures (Kelley and Kossoff, 2010; Stephani, 2006). There are also variations in diagnostic criteria (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 antiseizure 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 in several reviews and studies (Kelley and Kossoff, 2010; Kilaru and Bergqvist, 2007; Stephani, 2006). Other recommended treatments to consider include clobazam, rufinamide, and felbamate (McTague and Cross, 2013). 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; Pittau et al., 2016). A recent study reported that 25/30 patients achieved > 50% seizure reduction on a Modified Atkins Diet (MAD) after an average of six ASTs (Weimer-Kruel et al., 2017).

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 neurologists who care for children with EMAS.

2. Methods

The Epilepsy with Myoclonic-Atonic seizures (EMAS) focus group of the Pediatric Epilepsy Research Consortium (PERC) was established to foster collaboration and stimulate multicenter research on EMAS, and is comprised of eight US-based pediatric epilepsy specialists practicing in six pediatric epilepsy centers and one research assistant. PERC members are pediatric epileptologists in multiple centers across the US, all of whom have trained in multiple centers, and many of whom are leaders in the pediatric epilepsy field. PERC are also members of the American Epilepsy Society (AES). 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.

2.1. Survey

The on-line survey consisted of nine questions (Appendix A). 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).

2.2. 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** (six 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