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Results of an International Delphi Consensus in Epilepsy with Myoclonic Atonic Seizures/ Doose syndrome

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Objective: To establish a standard framework for early phenotypic diagnosis, investigations, expected findings from investigations, evolution, effective therapies and prognosis in the syndrome of Epilepsy with myoclonic atonic seizures (EMAS) also known as Doose syndrome.

Methods: A core study group (CSG) interested in EMAS was convened. CSG then identified and nominated 15 experts in the field of EMAS. This expert panel (EP) from English speaking nations with previously documented clinical expertise and publications in EMAS was invited to participate in anonymous questionnaires on the basis of their clinical expertise and a literature review that was provided to them (supplement 1). Three rounds of questionnaires were sent to identify areas of consensus, strength of consensus and areas of contention.

Results: Strong consensus was obtained regarding the clinical phenotype of EMAS. Mandatory seizure types were identified. A new term “stormy phase” (SP) was designated to delineate a characteristic phenotypic evolution in EMAS patients associated with seizure worsening. There was strong consensus regarding the existence and time of onset of the SP. Strong consensus for mandatory investigations to be performed early and later in the clinical course of EMAS, first and second tier treatment and prognostic factors for poor outcome were identified. Areas of lack of consensus included some seizure types that are necessary to diagnose EMAS, interictal findings that prognosticate the course of EMAS, overall duration of SP, time to complete remission, and best approach to treat drug resistant EMAS.

Significance: Expert consensus on core diagnostic criteria of EMAS necessary for natural history studies, phenotype-genotype correlations, and clinical trials including comparative studies was demonstrated here. Areas of disagreements relating especially to prognostic features and treatment options need further research.

Key words: EMAS, Doose, Delphi, Consensus, Stormy phase

Word count: 3272/ 4000

Introduction: 565/600

Epilepsy with myoclonic-atonic seizures (EMAS), previously known as epilepsy with myoclonic astatic seizures, or Doose syndrome, is a syndrome characterized by the presence of myoclonic-atonic seizures in an otherwise normal child who may have a history of febrile and/or afebrile generalized seizures (generalized, myoclonic , atypical absence, and tonic seizures) [1-8] . EMAS is also considered to be an epileptic encephalopathy. Non-convulsive status epilepticus is seen in 17-40% [1, 5], with longer duration correlating with a poorer prognosis [1, 6] .The term "stormy phase" or "stormy course" has been used by some clinicians to describe the periods of clinical and EEG worsening, often culminating in non-convulsive status epilepticus as originally described in a subset of EMAS patients in large clinical series[1, 5, 6]. The 'stormy phase' may be observed as early as 1 month, but more typically 3 months or more after seizure onset (mean 17.5 months, range 2-60) [1, 9]. In addition to increased seizures, children exhibit decreased vigilance and decreased social interaction, somnolence, oromotor dysfunction with increased drooling, dysarthria, and increased ataxia, consistent with an acute epileptic encephalopathy [1, 10]. During this time, the EEG shows diffuse slowing and increased, often near continuous discharges.

While several genes have been implicated in EMAS [11] patients with pathogenic variants represent a relatively small proportion of children. Glucose transporter deficiency should be excluded [12]. CLN2 disease may also present initially with similar symptoms.

There is no defined treatment of choice for EMAS and evidence for existing therapies is based on retrospective case series (AAN class 3,4) [13 14-16]. The ketogenic diet has been reported to be particularly beneficial in many children [13].

Long term prognosis varies. Remission has been reported to occur in two thirds of cases, often without long term developmental consequences. [5 1, 4, 6]. Conversely, the remaining children are often left with ongoing seizures which are drug-resistant, and variable degrees of intellectual disability.

As most children are developmentally normal at onset of EMAS, it is critical to define the most effective therapies. It is currently not known if there are early biomarkers that will identify children who will have a favorable outcome or who will have drug resistant epilepsy. What factors predispose to evolution into the stormy phase or predict a longer stormy phase duration- which in turn is suspected to correlate with poorer development and higher risk of persisting drug-resistant epilepsy – are not known.

The diagnosis of EMAS is clinical, combining seizure semiology and other historical data with EEG features. Yet, there are no widely accepted and well-defined criteria for the diagnosis. Furthermore, clinical and EEG features take time to evolve, which can make early definitive diagnosis challenging. EMAS has overlapping clinical features with other developmental and epileptic encephalopathies, most notably Lennox Gastaut syndrome which commonly leads to diagnosis switching [17].

Our goal was to gather international expert opinion and collective clinical expertise to determine consensus parameters on the clinical presentation, evolution, recommended investigations and treatment of EMAS.

Methods: The concept of this study was initially proposed by CJ who convened a core study group (CSG) consisting of KN, EW, SD, HC and CE, based on mutual interest in the establishment of consensus on EMAS, past collaboration on EMAS projects, and publications. This CSG provided input on the study design and content.

Identification of the Expert Panel (EP): Each member of the CSG was asked to identify three to five international English-speaking clinicians with recognized expertise on EMAS based on either publications (either 2 or more) or personal knowledge of their clinical activity in the field. This list was collated, and each member of the CSG ranked these nominees. The top fifteen were chosen by consensus and invited to serve on this panel. We limited EP to one expert per hospital/center and no more than 2 expert panelists per country. The EP who accepted our invitation consisted of experts from Europe, North America, South America, Oceania and Asia (supplement2)

Literature Review and Summary: Members of the CSG reviewed the literature up to 2019 to retrieve data on (1) clinical presentation, (2) investigations, (3) comorbidities and (4) treatment in EMAS. Two members of the CSG were assigned to review and summarize the literature regarding each of the 4 topics. The CSG collated these reviews, graded them based on AAN criteria, converted these into a single document with attached references, which was distributed electronically to each of the EP members prior to study onset.

Creation of Questionnaires: A three-round Delphi approach was conducted to generate the recommendations included in these standards. Questionnaires were sent electronically using REDCAP, which was housed at the University of Colorado. Members of the EP were given 3 weeks to respond to each round and all answers were anonymous. A reminder was sent after 2 weeks to EP members who had not yet responded.

The initial iteration was designed by input from all CSG members based on the literature review and broadly classified into sections on clinical presentation- development, prognosis, investigations and treatment- with subsections amongst each of these major sections (supplement 3) Text boxes were included to encourage free text responses from panelists. Responses from Round 1 were collated by CJ and EW. Actual questionnaires sent can be accessed in supplement 3.

Iteration #2 was created and forwarded to panelists to confirm areas of consensus and clarify areas where consensus was not yet reached. This round consisted of statements, based on input from Iteration #1. To confirm consensus, panelists were asked to rank these statements using a five-point Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). For any statement ranked as neutral or less, panelists were asked to provide comments to support their position. Round#3 aimed to further clarify any pending questions on the basis of rounds #1 and 2.

Study facilitators: Drs. CJ and EW collated responses from the EP and devised a series of statements through mutual discussion reflecting responses of all EP members. They determined if consensus had been reached using predetermined criteria for defining consensus and determined when opinions were too diverse to achieve consensus. Delphi rounds 2 and 3 were designed to assess strength of consensus/ clarify points where consensus could or could not be reached.

IRB approval:

This study was considered IRB exempt by the University of Colorado, Anschutz Medical Campus since no human subjects were directly involved.

Analysis:

The following definitions were used for strength of consensus:

a. Strong: more than 75% (11/15) of the EP members agreed or strongly agreed and no more than 3 disagreed.

b. Modest 50-<75% (8-11/15) agreed or strongly agreed and no more than 3 disagreed

c. No consensus: if neither of the above criteria were met.

Questionnaires for all 3 rounds (supplement 3 sections a-c)

Each questionnaire is included as a supplemental Table (Supplemental Table 3 sections a-c). Data was collected electronically using a REDCAP database that was housed at the University of Colorado, Denver.

Data from all three rounds were then summarized into a draft consensus statement indicating areas where consensus was reached as well as areas of contention and sent out to EP members for their final feedback.

Results:

Table 1 summarizes degrees of consensus for each statement.

Clinical presentation:

EMAS presents between 1 and 6 years of age, and the diagnosis is suspected in the majority by 6-12 months after seizure onset. Prior to seizure onset, mild delay is present in a minority, but moderate to severe delays should suggest an alternative diagnosis. Prior history of febrile seizures is noted in less than half the patients while a family history of febrile seizures or epilepsy is also uncommon.

Seizure types:

Myoclonic-atonic seizures are the only mandatory type for diagnosis, and typically begin in the first year. There was no consensus regarding whether myoclonic or atonic seizures were mandatory for diagnosis. Myoclonic seizures are seen early in the epilepsy course in the majority of patients. There was strong consensus that generalized tonic clonic and atypical absence seizures are not mandatory for diagnosis. Generalized tonic clonic seizures are commonly noted within the first year. Tonic seizures are uncommonly seen in the first year after seizure onset but may occur after that time, and do not exclude the diagnosis of EMAS when present.

A stormy phase and non-convulsive status epilepticus are typically seen in up to half of patients and usually occur in the first year.

Development:

Hyperactivity and behavioral problems are eventually seen in up to a quarter of patients with EMAS even in the absence of a stormy phase.

Developmental plateauing is noted in upto half the patients even in the absence of a stormy phase.

A stormy phase is correlated with developmental regression in up to 50%

Investigations:

A routine EEG and MRI should be performed in all patients at baseline. There was only a modest consensus on the need for a metabolic panel in children presenting with an EMAS picture. Glucose transporter deficiency syndrome (GLUT1DS) should always be considered in the differential diagnosis and excluded by appropriate investigation {lumbar puncture (LP) or genetic testing}, however there was no consensus on whether an LP should be performed if SLC2A1 testing is negative. An epilepsy panel should be considered in all patients while whole exome sequencing should be performed in select cases of drug resistance where an epilepsy panel is negative. There is limited role of chromosomal microarray or karyotype in EMAS except in selected cases due to other clinical concerns.

A routine EEG is also indicated to confirm seizure freedom while a prolonged EEG with video is suggested to elucidate different seizure types, confirm a clinical suspicion of nonconvulsive status epilepticus (NCSE) and also exclude features of LGS where suspected.

Neuropsychological testing should be performed where available at least once in all patients prior to school entry and especially when developmental delay is suspected, should be repeated yearly to monitor progress.

Diagnostic reconsideration: There was no factor identified that singularly would lead to a diagnostic reconsideration. However, there was strong consensus that in the presence of other atypical features; a child either less than 2 years old or greater than 6 years old at onset with prominent tonic/ vibratory tonic seizures and an EEG showing generalized paroxysmal fast activity would be considered for alternate diagnosis.

There was modest consensus that the term Lennox Gastaut Syndrome should not be used to describe drug resistant EMAS. Most experts accepted that tonic seizures did not exclude a diagnosis of EMAS.

Treatment:

Valproic acid and clobazam should be considered as first-line therapy while the ketogenic diet is considered the optimal second line treatment. Clonazepam, and levetiracetam are also considered useful as first line while ethosuximide was strongly recommended as second line therapy.

For the stormy phase, ketogenic diet, valproic acid, benzodiazepines should be strongly considered either singly or in combination and steroids should be considered in some cases.

Cannabinoids, carbamazepine, phenytoin, vigabatrin were not considered useful in EMAS. Lamotrigine, topiramate, zonisamide were considered useful as a later therapy. While perampanel and rufinamide were also considered useful there was no consensus on use of felbamate- however 50% of the respondents mentioned that felbamate was not approved in their country of practice.

Surgical therapies using vagus nerve stimulator (VNS) or corpus callosotomy (for drop attacks) should be offered only after a trial of the ketogenic diet and after drug resistance to several ASMs is established. Corpus callosotomy is favored over VNS for drop attacks.

Prognosis:

Complete seizure remission (no seizures and no antiseizure medications) is seen in at least half of patients. Although it is unclear as to when this remission is likely to occur, if seizures persist beyond five years after the first afebrile seizure, remission is highly unlikely. Although more than half of the patients, who achieve complete remission are developmentally normal, learning disorder without intellectual disability is expected in a quarter of children who remit completely. There was strong consensus that patients who continued to have seizures after 5 years are unlikely to achieve long term remission (off antiseizure medication). Although patients with drug resistant EMAS and ongoing seizures are likely to have mild to moderate developmental delay; overall cognitive prognosis in EMAS patients who are drug resistant is better than drug resistant patients with Lennox Gastaut syndrome (LGS).

Discussion: word count: 1166/1200

Our understanding of EMAS has evolved over time with an initial categorization into the "symptomatic epilepsies" [18] , later; to idiopathic epilepsy syndromes [19]and finally one of the developmental and epileptic encephalopathies (DEE) [20] . Syndromic classification is not perfect in predicting eventual developmental outcomes. EMAS is a DEE with variable prognosis from remission of epilepsy with normal developmental outcome to one of long-term drug resistant seizures, repeated bouts of NCSE and associated developmental regression that can lead to significant residual delays.

We still depend on phenotypic classification of most epilepsy syndromes. The defining criteria of EMAS are variable across centers [8 21] . Similar disagreements about associated seizure types, EEG characteristics, investigations and best treatments were identified in a survey sent to US based neurologists and epileptologists [7] . In drug resistant EMAS patients, in the absence of uniformly followed parameters of syndrome classification, it is difficult to identify or study biomarkers that predict poor outcomes and resultantly introduce effective therapies early in the course. In general, patients that evolve into a stormy phase are likely to do poorly particularly if this phase is repeated or prolonged and responds poorly to treatment.

This Delphi process explored wide ranging aspects of the phenotype, work up and treatment of EMAS with an expert panel of clinician researchers with established track records related to EMAS.

Clinical presentation: As against the traditional diagnosis of EMAS using ILAE criteria [18], there was strong EP consensus that development does not have to be normal prior to seizure onset and that a small percentage of patients with EMAS have mild preceding developmental delay. Additionally, although myoclonic, myoclonic atonic and atonic seizures are described in the ILAE criteria- myoclonic atonic seizures was the only seizure type agreed upon as being mandatory for diagnosis. EP could not reach consensus on the requirement of myoclonic and or atonic seizures in the diagnosis of EMAS.

Some important conclusions were reached regarding the presence of tonic seizures: Tonic seizures do not exclude a diagnosis of EMAS but can be seen in a minority of patients even within the first year of diagnosis. This highlights a very interesting point for future research since tonic seizures were also identified as a strong prognostic factor for poor outcome.

While some practitioners have used the term stormy phase to characterize an epoch of very high seizure burden occurring during the evolution of EMAS (where multiple seizure types become evident) and this could be the first indication for drug resistance in some children, this term has only rarely been described in prior EMAS literature. Given the perceived negative impact of this stormy phase on outcome and consensus for its treatment, it will be crucial to use this terminology in future studies.

Genetic testing: Although there was a strong consensus that genetic testing should be performed, there was variability in choice and sequence of which test should be performed based on availability and geographic location of EP. Overall, this is supported by the existing literature that demonstrates a reasonable yield for next generation sequencing testing through panels or whole exome [11, 22]

Diagnosis switching in EMAS: In their comments, some members of the EP felt very strongly that children with EMAS and drug resistant seizures be diagnosed with "drug resistant EMAS" as opposed to "LGS". Some also felt that the two disorders are clinically and etiologically distinct enough and that it would be beneficial to characterize drug resistant EMAS separately in order to design future trials for treatment. This consensus and concept that drug resistant EMAS is different from LGS is important given the literature that suggests that many patients are re-labelled as LGS[17]

Treatment: Cannabinoids (artisanal or Epidiolex) were not preferred treatment option in EMAS, again drawing a distinction between EMAS and LGS where there is specific evidence of efficacy of cannabidiol[23]. Many of the panelists did not have access to Felbamate in their country. Some members of the expert panel felt strongly that lamotrigine should always be paired with valproic acid as first line therapy. There was a strong consensus against surgical treatment (VNS or CC) early in the course unless 4-5 ASM including ketogenic diet were first tried. This Delphi process establishes expert practice and should serve as the basis for a future comparative effectiveness trial.

Areas of lack of consensus: EP did not agree on how frequently certain seizure types were seen in EMAS. This was particularly true for generalized tonic clonic seizures and is further evidence for the need to have prospective studies using uniform diagnostic criteria that will allow rigorous phenotyping of EMAS. The lack of consensus on the impact of factors like the number or duration of NCSE episodes or certain EEG features like slow spike wave, focal spikes or response to ketogenic diet -in the diagnostic reconsideration or prognostication of EMAS also underscores the need to study treatment resistant EMAS as a separate entity. We feel that the lack of consensus for certain investigations such as lumbar puncture to rule out GLUT1DS or video EEG monitoring to confirm seizure freedom in EMAS reflected the availability and experience of the EP in balancing cost benefit ratio of such investigations as determined by their site of practice. Similarly, a lack of consensus in the use of felbamate which is otherwise widely used for drug resistant epilepsy [24] reflected regulations in different geographic regions of the world.

Limitations and strengths of our study:

Our study utilized a modified Delphi process and thus we relied on expert opinion rather than specific patient data. Although implementation of evidence-based medicine is optimal to diagnose and manage patients, many times such information is lacking, and expert opinions are all that is available. Consensus statements generated by using Delphi or the nominal group method are well established and recognized methods of obtaining consensus where no standards of care exist [25]. The Delphi procedure has been standardized over the years, applied in a systematic manner and can effect change in medical care as

evidenced in other rare and devastating epileptic encephalopathies such as West syndrome and Dravet syndrome [26] [27]. While our expert panel consisted of only 15 members, these panelists represented diverse regions of the world and had extensive clinical expertise, in the diagnosis and management of EMAS. Although geographic limitations in investigations and treatment could affect consensus, we find it remarkable that we were able to achieve consensus in many areas. We believe this work will allow earlier and more accurate diagnosis, and earlier initiation of more effective therapies

Conclusions:

This Delphi process establishes a foundation of terminology and criteria that are critical to future systematic research in EMAS. By implementing consensus diagnostic criteria and terminology in future clinical trials, comparative effectiveness studies, natural history and genotype- phenotype correlation studies; we can accelerate our understanding of EMAS and the optimal treatment options.

Author statement and Acknowledgements:

Authors affirm that that the work described is consistent with the Journal's guidelines for ethical publication. 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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JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her work is supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital & University College London.

Key Points:

- International experts weighted in on this Delphi consensus in EMAS.
- Consensus was reached on several key clinical features, diagnosis and treatment in EMAS.
- The term stormy phase should be used to indicate clinical worsening during course of EMAS.
- Steroids should be considered early in treatment of stormy phase.
- Drug resistant EMAS should be studied systematically and not relabeled as LGS.

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