Doose Delphi consensus statement by core panel after literature research

For this section 16 article were accessed. All evidence is AAN class 3 or 4

- Doose syndrome (myoclonic astatic epilepsy) is characterized by an onset of epilepsy between 18-60m, with a mean age at presentation of 3 years. (Trivisano et al. 2011; Deng et al. 2011; Eschbach et al. 2018; Oguni et al. 2001; Stephani 2006; Caraballo et al. 2013).
- Development prior to seizure onset is typically normal(Trivisano et al. 2011) (Nickels et al. 2018; Oguni et al. 2001; Oguni et al. 2002; Kaminska et al. 1999; Deng et al. 2011; Eschbach et al. 2018; Caraballo et al. 2013; Stephani 2006) . Mild speech delay prior to seizure onset has been accepted by some authors as meeting inclusion criteria(Kaminska et al. 1999).
- The initial seizure types at onset include generalized tonic clonic, myoclonic, myoclonic atonic, and the majority develop all of these seizure types early in the course of their epilepsy (all refs below).
- Other seizure types which may be seen include atonic seizures and atypical absences in the majority of cases (Trivisano et al. 2011; Deng et al. 2011; Kaminska et al. 1999; Caraballo et al. 2013; Oguni et al. 2001; Kelley and Kossoff 2010), Tonic (nonvibratory and vibratory) seizures develop in significant minority (Kaminska et al. 1999; Caraballo et al. 2013; Eschbach et al. 2018; Deng et al. 2011).
- Non-convulsive status epilepticus is seen in 17-40% (Trivisano et al. 2011; Kaminska et al. 1999), the occurrence specifically of longer duration being association with a poorer prognosis (Kaminska et al. 1999; Caraballo et al. 2013). During this time, there is often an increase in other types of generalized seizures including generalized tonic clonic, atonic and tonic seizures, as well as absence and myoclonic seizures(Trivisano et al. 2011; Kaminska et al. 1999; Caraballo et al. 2013). This period of worsening seizures may begin as early as 1 month after seizure onset, but more typically 3 months or more after onset: (range 2-60 months with a mean of 17.5 months after onset)(Kaminska et al. 1999). Kaminska ett al also describe change in vigilance, loss of contact, increased somnolence, oromotor dysfunction with increased drooling, dysarthria, and increased ataxia have been described during these episodes in addition to worsening of the EEG with abnormal background activities, increased discharges and slow waves.
- Males are more commonly affected and comprise more than two-thirds of cases (Trivisano et al. 2011; Eschbach et al. 2018; Caraballo et al. 2013).
- A history of previous febrile seizures may be present in 8.7-53% of cases (Trivisano et al. 2011; Eschbach et al. 2018; Kaminska et al. 1999; Deng et al. 2011; Caraballo et al. 2013).
- A family history of epilepsy is present in 5.5-44% (Trivisano et al. 2011; Deng et al. 2011; Kaminska et al. 1999; Caraballo et al. 2013).
- Many develop ataxia, hyperkinesis during prior of worsening seizures (Trivisano et al. 2011; Caraballo et al. 2013). This may persist in poor prognosis group.
- **Outcome and prognostic factors:** approximately 2/3 have a favorable prognosis with seizure remission typically within a year of onset in most cases (Trivisano et al. 2011; Deng et al. 2011; Kaminska et al. 1999; Caraballo et al. 2013). If seizure remission occurs, cognitive outcome is often normal, with only 20% of pts having an IQ<70 (Kaminska et al. 1999; Trivisano et al. 2011; Caraballo et al. 2013).
- Approximately 1/3 have poorer outcome with ongoing seizures, often evolving with the occurrence of nocturnal tonic seizures and more frequent NCSE over a longer period of time (>1 month)(Eschbach et al. 2018; Kaminska et al. 1999; Caraballo et al. 2013). While some of these patients may have ultimate remission of seizures, seizures are drug resistant during the stormy

period. Cognitive outcome in the poor prognosis group is concerning, with >80% having an IQ<50, and many developing aggression and hyperkinesis (Kaminska et al. 1999; Caraballo et al. 2013).

- While some of these patients may have ultimate remission of seizures, seizures are drug resistant during stormy period.
- When seizure freedom is achieved it typical occurs within three years of seizure onset but may occur as late as six years after seizure onset(Eschbach et al. 2018).
- Cognitive outcome in the poor prognosis group is concerning, with >80% having and IQ<50, and many having aggression and hyperkinesis (Kaminska et al. 1999; Caraballo et al. 2013).

Poor prognostic factors that have been reported in several studies include:

- Tonic seizures, especially tonic vibratory (Kaminska et al. 1999; Caraballo et al. 2013; Eschbach et al. 2018; Kelley and Kossoff 2010).

- Recurrent NCSE – Both greater numbers of NCSE episodes as well as longer duration of predisposition to NCSE (lasting >1 month) (Kelley and Kossoff 2010; Trivisano et al. 2011; Kaminska et al. 1999; Oguni et al. 2002; Caraballo et al. 2013)

- EEG showing very frequent or near continuous irregular generalized spike-wave, slow spike-wave or generalized paroxysmal fast activity(Caraballo et al. 2013; Kaminska et al. 1999; Eschbach et al. 2018)

Potential poor prognostic factors identified in only single reports include:

- Massive myoclonus at presentation(Kaminska et al. 1999)

- Generalized tonic clonic seizures in the first two years (Kelley and Kossoff 2010)

- Family history of epilepsy (Oguni et al. 2002)

- Focal spikes may be correlated with worse prognosis(Inoue et al. 2014), not reproduced by (Eschbach et al. 2018)

Prognosticators may be cumulative with the chances of seizure freedom or normal development being reduced by the presence of multiple poor prognostic factors (Eschbach et al. 2018).

Investigations

- Epilepsy with myoclonic-atonic seizures (EMAS) is felt to be due to genetic etiology with polygenic inheritance and variable penetrance(Doose and Baier 1987).
- In up to 50% of families, there may be a history of febrile seizures. Other epilepsy syndromes, such as genetic epilepsy with febrile seizures plus, are also seen in other family members. However, specific etiologies are challenging to identify.
- Investigations are pursued to exclude or confirm the electroclinical syndrome diagnosis of EMAS, help determine the expected long term outcome of the child, and determine preferred treatments. Recommendations in the literature for preferred investigations for EMAS are variable.
- *Electroencephalogram (EEG)*

Routine EEG is recommended as part of the evaluation for any first seizure in children(Hirtz et al. 2000). However, prolonged video EEG is helpful for syndrome classification and prognosis for EMAS. Surface EMG channels on the neck and deltoid can be helpful to detect the atonic component of the myoclonic seizures (Dragoumi et al. 2016).

EMAS can be challenging to differentiate from other epileptic encephalopathies. When epileptic drop attacks of children with symptomatic epilepsy were compared to those with EMAS, the drop attacks in children with symptomatic epilepsy were more likely to be consistent with epileptic spasms and had EEG correlate of generalized slow sharp and wave complexes or electrodecrement. Those with EMAS were more likely to have myoclonic-atonic seizures with EEG correlate of generalized high amplitude spike or polyspike and wave complex(Itoh et al. 2015). Finally, when a small group of children with EMAS with favorable prognosis were compared to those with poor prognosis, it was noted that all the children with poor prognosis had focal spike discharges. By comparison, the majority of those with good prognosis had only generalized epileptiform discharges (Inoue et al. 2014).

- *Neuroimaging*

Neuroimaging in EMAS is expected to be normal. MRI is recommended for nearly all patients as part of ruling out other epilepsy syndromes and structural etiologies(Nickels et al. 2018).

- *Genetic testing*

Multiple genetic mutations, deletions, and duplications have been reported with EMAS (Palmer et al. 2016; Trivisano et al. 2015; Vlaskamp et al. 2016; Carvill et al. 2015; Helbig et al. 2019; Johannesen et al. 2018; Moller et al. 2017; Granadillo et al. 2014; Coppola et al. 2013; Tang and Pal 2012; Ebach et al. 2005; Larsen et al. 2015; Mullen et al. 2011; Mulhern et al. 2018)(Tang Am J Med Genet A. 2017; Ottaviani Genet Couns 2015; Ebach Neuropediatrics 2005; Sachdev Seizure 2017; Yordanova Neurosci Lett. 2011; Heron Ann Neurol 2007).

However, the diagnostic yield of genetic testing has been low. For example, genetic testing in a cohort of 77 patients yielded a genetic cause in 6 (one from microarray, two from epilepsy panel, three from whole exome sequencing(Angione et al. 2019). However, combining microarray and whole exome sequencing may increase the yield of genetic testing. When the two techniques were combined in 27 patients, disease-causing variants were identified in 41% (Routier et al. 2019).

Genetic testing with microarray was a recommended evaluation, and specific gene testing or whole exome sequencing were possible evaluations, among a poll of physicians who care for children with EMAS (Nickels et al. 2018). Some of the variability in genetic testing yield is likely related to a lack of consensus diagnostic criteria for EMAS. In some cases, patients reported in these references have additional symptoms beyond those routinely seen in EMAS (such as ataxia or movement disorders) that may increase the yield of genetic testing or guide more targeted testing.

- *Metabolic*

More than 50% of children with EMAS respond to the ketogenic diet, with approximately 1/3 having a >75% reduction in seizures(Caraballo et al. 2006; Kelley and Kossoff 2010). Therefore, glucose transporter (GLUT1), associated with mutation in SLC2A1, has been considered as a cause of EMAS. In a

study of 84 patients with clinically diagnosed EMAS, 4 (5%) were found to have SLC2A1 mutations(Mullen et al. 2011). When 93 patients with generalized epilepsies of variable epilepsy syndrome were tested, SLC2A1 variants were found in 2. One of these had myoclonic-atonic seizures. From this study, it was recommended that testing for GLUT1 be performed in patients with generalized epilepsy with poorly controlled seizures and if there is developmental delay and/or a movement disorder(Lebon et al. 2015). The majority of children with EMAS would fulfill these criteria. There is little evidence to support additional metabolic testing.

- *Autoimmune/autoinflammatory*

Voltage gated potassium channel complex (VGKC) antibodies have been reported in a child with EMAS and the seizures were responsive to steroids(Sirsi et al. 2016). There is an additional case report of a child with acute cerebellitis who developed myoclonic atonic seizures in the setting of truncal ataxia relapse. Antibodies against glutamate receptors N2B and D2 were identified(Matsuura et al. 2017). Therefore, there is a possibility of autoimmune etiology. However, these reports are rare. Furthermore, VGKC-complex antibodies have previously been identified as a nonspecific biomarker of encephalopathy (Hacohen Neurology 2015). Therefore, the importance of autoimmune evaluation remains questionable.

Treatment

- **Pharmacological treatment:**

Myoclonic and myoclonic atonic seizures (initial treatments):

There are no class 1 guidelines for medical management for seizures. However, AAN class 3 evidence suggests use of valproic acid, ethosuximide, lamotrigine, benzodiazepines for myoclonic and myoclonic atonic seizures. (Oguni et al. 2002; Kilaru and Bergqvist 2007; Jeavons, Clark, and Maheshwari 1977; Covanis, Gupta, and Jeavons 1982; Doege et al. 2013).

Myoclonic status and 'stormy phase':

There are small case series suggesting use of corticosteroids(Bast et al. 2014) or ketogenic diet either early in the course or during phase of repeated seizures- also sometimes referred to as "stormy phase" (Oguni et al. 2002; Stenger et al. 2017; Wiemer-Kruel et al. 2017; Caraballo et al. 2006). There are rare case reports using oral ketamine(Mewasingh et al. 2003) or IV lidocaine (Kanemura et al. 1996) during stormy phase .

Medications used as second line are not primarily tested in EMAS but are often a part of a larger study of intractable epilepsies. Often second line therapy includes topiramate (Mikaeloff et al. 2003; Jayawant and Libretto 2003),levetiracetam(Chhun et al. 2011) rufinamide (von Stulpnagel et al. 2012), cannabidiol (Devinsky et al. 2018).

Little is known about which medications are contraindicated but carbamazepine (Lerman 1986), vigabatrin(Guerrini and Aicardi 2003) and levetiracetam(Kroll-Seger et al. 2006) have been reported to worsen seizures.

- **Role of non-pharmacological treatment options**:

Several studies (open studies, uncontrolled) support efficacy of the ketogenic diet , especially in the early phase following initial presentation responder rates with at least 50% seizure reduction up to 80% reported (Stenger et al. 2017; Wiemer-Kruel et al. 2017; Caraballo et al. 2006).

Role and timing to consider therapies like vagus nerve stimulation are either unknown in terms of specific indications for EMAS(Cersosimo et al. 2011) or if at all response is reported, it is late in the course.

It has been considered for small number of patients, belonging to the subgroup with ongoing refractory seizures later in the course. Response is variable and often not specified in relation to targeted seizure types(Caraballo and Dalla Bernardina 2013)

There is a single case report describing successful corpus callosotomy in EMAS (Kanai et al. 2017). A patient undergoing corpus callosotomy with poor response prior to VNS implantation has also been reported in one larger series of 69 patients (Caraballo et al. 2013)

Comorbidities: Some of this is cross covered in clinical characteristics

For this section 10 articles were available and searched. Of these 4 were AAN class 3 and the rest were class 4. All except one reported normal development at outset most by defining EMAS as a condition that includes patients with normal development before onset of seizures. Majority of patients have developmental deterioration during the stormy phase/ phase of repeated seizures. At final follow up 43-66.7% patients had normal development(Trivisano et al. 2011; Oguni et al. 2002; Kilaru and Bergqvist 2007). Although not specifically mentioned it is inferred from the above studies that development correlated with eventual seizure outcome. Trivisano et al found that there was no correlation with eventual developmental outcome but there was a non significant tendency to have lower IQ in patients with epileptic encephalopathy (p=0.07).

No clear incidences exist about proportion/ rate of patients with ADHD or sleep disorders or behavior problems. Instruments used to look for comorbidities were not standardized but some of the instruments used include IQ tests, word repetition tasks, CBCL, Weschler performance scales, Leiter international scale revised.

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