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Epilepsy With Myoclonic Atonic Seizures: Why Is the Yield of Genetic Testing for a "Presumed Genetic" Epilepsy Low?

Phenotypic and Genetic Spectrum of Epilepsy With Myoclonic Atonic Seizures

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Objective: We aimed to describe the extent of neurodevelopmental impairments and identify the genetic etiologies in a large cohort of patients with epilepsy with myoclonic atonic seizures (MAEs). Methods: We deeply phenotyped patients with MAE for epilepsy features, intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder using standardized neuropsychological instruments. We performed exome analysis (whole exome sequencing) filtered on epilepsy and neuropsychiatric gene sets to identify genetic etiologies. Results: We analyzed 101 patients with MAE (70% male). The median age of seizure onset was 34 months (range = 6-72 months). The main seizure types were myoclonic atonic or atonic in 100%, generalized tonic-clonic in 72%, myoclonic in 69%, absence in 60%, and tonic seizures in 19% of patients. We observed intellectual disability in 62% of patients, with extremely low adaptive behavioral scores in 69%. In addition, 24% exhibited symptoms of autism and 37% exhibited attention-deficit/hyperactivity symptoms. We discovered pathogenic variants in 12 (14%) of 85 patients, including 5 previously published patients. These were pathogenic genetic variants in SYNGAP1 (n = 3), KIAA2022 (n = 2), and SLC6A1 (n = 2), as well as KCNA2, SCN2A, STX1B, KCNB1, and MECP2 (n = 1 each). We also identified 3 new candidate genes, ASH1L, CHD4, and SMARCA2 in 1 patient each. Significance: MAE is associated with significant neurodevelopmental impairment. MAE is genetically heterogeneous, and we identified a pathogenic genetic etiology in 14% of this cohort by exome analysis. These findings suggest that MAE is a manifestation of several etiologies rather than a discrete syndromic entity.

Commentary

Epilepsy with myoclonic atonic seizures (EMAS), previously known as myoclonic-astatic epilepsy (MAE) or Doose syndrome, was initially described by Dr Hermann Doose in 1970.[1] He asserted EMAS should be considered to be a primary generalized epilepsy, in the same family as the absence epilepsies and juvenile myoclonic epilepsy—syndromes of presumed genetic etiology.[1] Due to the high incidence of seizures and abnormal electroencephalograms (EEGs) in family members of patients with EMAS, Doose stated "a genetic predisposition to seizures of early childhood onset is the decisive factor in the pathogenesis of MAE."[1(p.166)] Indeed, Doose reported a family history of seizures in 32% of probands.[1] Similarly, subsequent studies have reported a positive family history in 33% to 44%.[2,3] By comparison, a family history of epilepsy has been reported in 13% to 27% of probands with idiopathic generalized epilepsy (IGE).[4,5]

Decades later, we have seen tremendous growth in our understanding of the genetic basis of many epilepsy syndromes. While the genetics behind some epilepsies are so well-known that they are now listed by the genetic change, such as CDKL5 disorder, definitive understanding of the genetic cause of many childhood onset generalized epilepsy syndromes, including EMAS, is not clear. Despite the high rate of positive family history in patients with EMAS, even higher than the "presumed genetic" idiopathic generalized epilepsy syndromes, the yield of genetic testing thus far has been quite low.[6] In a study of 77 patients with EMAS, 59 of whom had at least one genetic test performed, a definitive molecular diagnosis was identified in only 10%. This low rate was partially attributed to the need for updated testing, including wider use of whole exome/genome sequencing.[6] However, in a recent study of 101 patients with EMAS who underwent whole exome sequencing, a pathogenic etiology was identified in only 14%.[7]

It is suggested that this is due to multifactorial inheritance.[8] However, it is more likely that this is not only a disease with multifactorial inheritance but that the broad phenotype of this electroclinical syndrome is the final common pathway of multiple etiologies, as was suggested by Tang et al.[7] This is consistent with original assertions in the study by Doose, where he described it as being a "multifactorial disease" and stated that it was not his "intention to present MAE as a rigidly defined syndrome."[1]

Regardless of whether EMAS is a multifactorial disease or a single disease of multifactorial inheritance, the low yield of genetic testing suggests EMAS is an electroclinical syndrome that relies on phenotype to make the diagnosis. Unfortunately, there is significant disagreement in the literature regarding the details of that phenotype. The broad descriptions of this electroclinical syndrome may also be limiting our ability to determine clear genetic etiologies.

Doose initially characterized EMAS as being a rare epilepsy syndrome affecting children between 1 and 5 years. Development is expected to be "mostly normal" without neurological deficits prior to seizure onset without neurometabolic or degenerative diseases.[1] The International League Against Epilepsy (ILAE) now describes EMAS as occurring between 6 months and 6 years with normal development and cognition prior to seizure onset, followed by possible impairments occurring at or after seizure onset, similar to the initial description (Epilepsy Diagnosis.org).[9] However, 21% of patients in the study by Tang et al were reported to have developmental delay prior to epilepsy onset.[7] Similarly, a recent survey of diagnosis and treatment of EMAS showed only 50% to 79% of respondents felt developmental delay prior to seizure onset was an exclusionary criterion for the diagnosis of EMAS.[10]

Initial seizure types included myoclonic, atonic-astatic, myoclonic-astatic (now known as myoclonic atonic), absence, absence or nonconvulsive status epilepticus, and generalized tonic clonic seizures. Nocturnal tonic seizures, as well as rare focal seizures, were also seen.[1] The ILAE now reports a history of epileptic spasms or focal seizures as being exclusionary for a diagnosis of EMAS (EpilepsyDiagnosis.org).[9] Similarly, a history of epileptic spasms, focal seizures, and focal EEG abnormalities were felt to be strong or modest exclusionary criteria in the survey.[10] However, focal seizures have been reported in children with EMAS, including in the recent study.[7]

Finally, most studies agree there is a variable course for children with EMAS. Doose noted onset in the first or second year of life, absence status epilepticus, and tonic seizures were poor prognostic indicators.[1] Since that time, potential prognostic indicators have included family history (good or bad outcome reported), tonic and absence seizures, myoclonic, convulsive, absence, or nonconvulsive status epilepticus, generalized tonic-clonic seizures in the first 2 years of life, sleep onset seizures, and persistence of abnormal background EEG rhythms.[2,3,8] Overall, it was felt there were identifiable, but not reproducible risk factors that could be identified and that the risk factors may not be present at onset.[2]

Therefore, our lack of understanding of the genetic basis of EMAS, even in the setting of high incidence of family history of epilepsy, is likely due to a combination of multifactorial inheritance, multifactorial disease, and our failure to identify clear clinical diagnostic criteria. Further research is needed to better define this electroclinical syndrome if we want to make more progress in understanding its causes.

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