Infantile spasms of unknown cause: predictors of outcome and genotype-phenotype correlation

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Background: No large-scale studies have specifically evaluated the outcomes of infantile spasms (IS) of unknown cause, previously known as cryptogenic or idiopathic. The Epilepsy Phenome/Genome Project (EPGP) aimed to characterize IS of unknown cause by phenotype and genotype analysis. Methods: We undertook a retrospective multicenter observational cohort of 133 individuals within the EPGP database meeting criteria for IS of unknown cause with at least 6 months of follow-up data. Clinical medical records, imaging, and electroencephalography were examined. Results: Normal development occurred in only 15% of IS of unknown cause. The majority (85%) had clinically documented developmental delay (15% mild, 20% moderate, and 50% severe) at last assessment (median 2.7 years; interquartile interval 1.71-6.25 years). Predictors of positive developmental outcomes included no delay prior to IS (\(P < .001\)), older age of IS onset (median 6 months old), and resolution of IS after initial treatment (\(P < .001\)). Additional seizures after IS occurred in 67%, with predictors being seizures prior to IS (\(P = .018\)), earlier age of IS onset (median 5 months old), and refractory IS (\(P = .008\)). On a research basis, whole exome sequencing identified 15% with de novo variants in known epilepsy genes. Individuals with a genetic finding were more likely to have poor developmental outcomes (\(P = .035\)). Conclusions: The current study highlights the predominately unfavorable developmental outcomes and that subsequent seizures are common in children with IS of unknown cause. Ongoing genetic evaluation of IS of seemingly unknown cause is likely to yield a diagnosis and provide valuable prognostic information.

Commentary

Infantile spasms (IS), a subset of epileptic spasms, is a common epilepsy encephalopathy, occurring in 2 to 4/10,000 live births. When the diagnosis is made, parents often have 2 questions: Why is my child having spasms? What will happen to my child? This prompts the physician to ask similar questions: What is the best way to evaluate this patient? What is the best treatment? Can I predict the outcome?

Unfortunately, the outcome is typically poor. Spasms often do not respond to treatment or relapse. Children with IS often develop additional seizure types and have developmental disabilities. A multicenter prospective observational cohort study demonstrated response rates of 55% to adrenocorticotropic hormone (ACTH), 39% to oral corticosteroids, 36% to vigabatrin, and 9% to all other treatments.\(^1\) Furthermore, 18% of responders later relapsed.\(^1\) Additional analysis demonstrated that the presence or absence of hypersrhythmia did not affect response to treatment.\(^2\) The greatest predictor of response in either analysis was choice of treatment, not underlying etiology. However, this study does provide further support that there are preferred treatments for IS: ACTH, corticosteroids, and vigabatrin.

Given that seizure control in IS is more dependent on treatment than etiology, is an evaluation for etiology necessary? Children with IS due to tuberous sclerosis complex (TSC) have a greater likelihood of seizure freedom when treated with vigabatrin.\(^3\) Therefore, diagnosing TSC guides the decision of hormonal versus vigabatrin initial therapy. Do we need to go beyond clinical exam and neuroimaging to diagnose the presence or absence of TSC?

Although specific underlying etiologies do not appear to predict outcome in IS, the presence or absence of identifiable etiology does. Meta-analysis demonstrated overall good developmental outcome in 54.3% in patients with IS of unknown etiology but only 12.5% in IS patients with identifiable etiology.\(^4\) Seizure relapse, including epileptic spasms, has been reported to occur more often in those with known etiology.\(^5\) A retrospective review of 71 infants with IS demonstrated that seizure relapse was common (66% overall), but much less so in unknown (29%) than known (75%) etiology.\(^5\) Furthermore, infants with no identified etiology treated with hormonal treatment may have improved development compared to those treated with vigabatrin.\(^6\) It is now recommended that hormonal...
therapy be considered preferentially over vigabatrin for treatment of IS of unknown cause to improve developmental outcome.7

What is the best way to evaluate for etiology? When epilepsy and seizure classifications were being revised, the concept of “cryptogenic” epilepsy was appropriately challenged. Previously, cryptogenic epilepsy had been loosely defined as “presumed symptomatic,” but primarily meant no lesion identified on neuroimaging.8 We now understand that epilepsy etiology goes well beyond neuroimaging and family history. The prospective database of the National Infantile Spasms Consortium (NISC) was able to identify the highest yield, most cost-effective studies. Of the cases who underwent magnetic resonance imaging (MRI) with seizure protocol, a causal abnormality was identified in 40.9%, making this the highest yield test. In those without a structural cause, the next highest yield was genetic testing; combining comparative genomic hybridization array (aCGH) and epilepsy gene panel provided a definitive diagnosis in >40%.9

Overall, a cause was identified in 64.4% of patients in the NISC cohort, including 57.6% identified with MRI and genetic testing alone, highlighting the importance of these evaluations.9 However, approximately 1/3 of patients with IS had no identifiable etiology. What tests should be done next? The NISC cohort did not identify an etiology through whole exome sequencing, but only 3 patients underwent this analysis.9 The multicenter Epilepsy Phenome/Genome Project (EPGP) database identified 126 patients with IS of unknown cause. Of these, 100 underwent whole exome sequencing. Pathogenic de novo variants were identified in 15 individuals; 105 de novo variants were identified in 62 patients, but most of these were of unknown significance. In contrast, evaluation for metabolic cause identified an etiology in only 4.8% of the NISC cohort.9 Therefore, investigations for etiology in children with IS should include clinical evaluation, MRI, aCGH, and epilepsy gene panel, as previously recommended. If no cause is identified, whole exome sequencing should be strongly considered.

To return to our original questions, we have evidence supporting preferred evaluation with MRI and genetic testing. We have evidence to treat with vigabatrin, ACTH, or corticosteroids, using vigabatrin preferentially in patients with TSC and ACTH in patients with unknown etiology. Can we predict who will do better?

Thus far, children with IS of unknown cause are thought to have better outcomes. However, as testing improves, the concept of “unknown etiology” appears to be a moving target. Even within this large multicenter EPGP cohort, additional evaluation provided an etiology in nearly 15%. Can children have IS without etiology? Is the lack of identifiable cause a marker for less severe disease? In those without an obvious cause at the time of IS diagnosis in the NISC cohort, an etiology was more likely to be identified if there was severe developmental delay. An etiology was identified in 32.5% of patients with clearly abnormal development versus 8.3% with normal development.9 The EPGP study also supports this. Overall, 67% had seizures after IS, consistent with previous studies. Predictors of subsequent seizures were consistent with markers for more severe disease: earlier age of IS onset, seizures prior to IS onset, and IS refractory to initial treatment.

In the EPGP study, only 15% had no developmental delays at follow-up, although another 15% had only mild delays. Overall, this would be 30% with good developmental outcome and not significantly different than previous reports. Furthermore, this includes the 15 patients for whom a genetic cause was identified; 14 of these had severe delays. Predictors of developmental disability were nearly identical to those for subsequent seizures. However, shorter time from IS onset to treatment and the use of first-line medication were predictors of IS freedom but not predictors of developmental outcomes. This most important predictors of good developmental outcome were older age at IS onset, normal development prior to IS, and IS freedom after first medication.

All of these findings support the importance of identifying an etiology to help guide treatment, but also to provide information on expected seizure and developmental outcomes, but still raise the question of whether there actually is a subset of children who truly have no identifiable etiology for spasms. In the 39 infants who had normal development prior to IS onset and achieved IS freedom with first medication, 64.1% had normal development at last follow-up. It is possible that this very small group is the group that truly has IS of unknown etiology. I remain hopeful that further advances in genetic and imaging evaluations will allow us to identify this group and better counsel parents on expected outcomes.

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