EPILEPSY CURRENTS

Current Literature
In Clinical Science

STXBP1-Related EOEE – Early Onset Epilepsy AND Encephalopathy, or is it Early Onset Epileptic Encephalopathy?

STXBP1 Encephalopathy: A Neurodevelopmental Disorder Including Epilepsy.

Stamberger H, Nikanorova M, Willemsen MH, Accorsi P, Angriman M, Baier H, Benkel-Herrenbrueck I, Benoit V, Budetta M, Caliebe A, Cantalupo G, Capovilla G, Casara G, Courage C, Deprez M, Destrée A, Dilena R, Erasmus CE, Fannemel M, Fjær R, Giordano L, Helbig KL, Heyne HO, Klepper J, Kluger GJ, Lederer D, Lodi M, Maier O, Merkenschlager A, Michelberger N, Minetti C, Muhle H, Phalin J, Ramsey K, Romeo A, Schallner J, Schanze I, Shinawi M, Sleegers K, Sterbova K, Syrbe S, Traverso M, Tzschach A, Uldall P, Van Coster R, Verhelst H, Viri M, Winter S, Wolff M, Zenker M, Zoccante L, De Jonghe P, Helbig I, Striano P, Lemke JR, Møller RS, Weckhuysen S. *Neurology* 2016;86:954–952.

OBJECTIVE: To give a comprehensive overview of the phenotypic and genetic spectrum of STXBP1 encephalopathy (STXBP1-E) by systematically reviewing newly diagnosed and previously reported patients. METHODS: We recruited newly diagnosed patients with STXBP1 mutations through an international network of clinicians and geneticists. Furthermore, we performed a systematic literature search to review the phenotypes of all previously reported patients. RESULTS: We describe the phenotypic features of 147 patients with STXBP1-E including 45 previously unreported patients with 33 novel STXBP1 mutations. All patients have intellectual disability (ID), which is mostly severe to profound (88%). Ninety-five percent of patients have epilepsy. While one-third of patients presented with Ohtahara syndrome (21%) or West syndrome (9.5%), the majority has a nonsyndromic early-onset epilepsy and encephalopathy (53%) with epileptic spasms or tonic seizures as main seizure type. We found no correlation between severity of seizures and severity of ID or between mutation type and seizure characteristics or cognitive outcome. Neurologic comorbidities including autistic features and movement disorders are frequent. We also report 2 previously unreported adult patients with prominent extrapyramidal features. CONCLUSION: De novo STXBP1 mutations are among the most frequent causes of epilepsy and encephalopathy. Most patients have severe to profound ID with little correlation among seizure onset, seizure severity, and the degree of ID. Accordingly, we hypothesize that seizure severity and ID present 2 independent dimensions of the STXBP1-E phenotype. STXBP1-E may be conceptualized as a complex neurodevelopmental disorder rather than a primary epileptic encephalopathy.

Commentary

Early onset epileptic encephalopathy is an electroclinical concept that embodies the notion that the epileptic activity itself may contribute to the severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and this can worsen over time. In other words, even for the same pathology (etiology), a child with early onset intractable epilepsy and interictal-ictal continuum of epileptiform abnormalities is likely to show more severe and likely progressive intellectual disability (ID) (1). However, some etiologies such as the syntaxin-binding protein 1 gene (*STXBP1*)-related neurological disease may per se directly lead to severe epilepsy and profound ID as two independent dimensions of a severe phenotype and the notion that epileptic activity is a predominant driver of ID may not apply. Early onset epilepsy and encephalopathy (EOEE) may be a more appropriate term, and is an argument made in Stamberger et al.'s report. Authors studied genotype-phenotype spectrum of a large cohort of 147 (includes 45 previously known but unreported) patients with *STXBP1* epilepsy-encephalopathy (*STXBP1*-EE) using a network of collaborating clinicians and geneticists. Authors also reviewed published reports.

STXBP1-EE is caused by mutations in the *STXBP1* gene, a membrane-trafficking protein predominantly expressed in the brain and plays an important role in the vesicular docking and fusion, a necessary mechanism for neurotransmitter secretion. *STXBP1* knockout mice showed neurodegeneration after an initially normal synaptic assembly indicating that functional *STXBP1* is crucial to synaptic maintenance and function (2). In the case of *STXBP1* haploinsufficiency, reduced *STXBP1* was shown to increase synaptic depression at both GABAergic and

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glutamatergic synapses with a greater impact on GABAergic interneurons resulting in the net hyperexcitability and epileptic activity (3).

The majority of the 134 children (phenotype unknown in 13) with *STXBP1*-EE presented with epilepsy of infantile onset at a median age of 6 weeks (1 day–12 years) and were diagnosed with EOEE (53%), Ohtahara syndrome (21%), or infantile spasms (IS; 10%). Most (27/28; 96%) infants with Ohtahara syndrome evolved into IS. Uncommonly, children presented with intellectual disability (ID) with nonsyndromic epilepsy (6%). Nine patients (7%) presented only with ID without epilepsy. Median age at the time of study inclusion was 5.75 (0.5–56) years, and interestingly few patients further elucidated the adult phenotype.

Core seizures types in *STXBP1*-EE were IS (65%) frequently coexisting with focal (58%) and tonic seizures (41%). EEG showed multiregional epileptiform activity in 64%, frequently with hypsarrhythmia (40%) and burst-suppression (36%) patterns noted at some point during the disease. In 104 with available treatment information, 53% were on more than three antiepileptic drugs. Epilepsy remission was reported in 44% during the available follow-up period; however, this was not well studied as systematic documentation was lacking. One patient was reported to be seizure-free after corpus callosotomy (4). Another 2-year old with a normal brain MRI had greatly reduced seizures (>90% improvement) with continuing short series of IS post operatively (unknown follow-up duration) after resection of the right temporal and disconnection of the occipital lobe (focal cortical dysplasia type 1A) (5).

Brain MRI (*N*=117) was normal (47%) or showed diffuse volume loss (33%), hypoplastic corpus callosum or aberrant/delayed/hypomyelination (32%). EEG and MRI phenotypes were nonspecific as reported in many EOEE (6). However, MRI findings should be cautiously interpreted due to dissimilarities in the MRI protocols, lack of consistent readers, and age-related complexities due to 'evolving' gray and white matter signal changes during infancy.

In 121 patients with ID information, 107 (88%) were classified as severe to profound ID. Despite early onset of epilepsy in most, some degree of developmental delay was noted prior to the onset of epilepsy. Regression was rarely reported, and did not always followed epilepsy onset. More detailed information on developmental milestones was available in the 45 previously unreported cohort in which 64% had pre-existing developmental delay when epilepsy began after neonatal (>30 days) period. Only 2 of 45 walked independently but lost ambulation later, while 21 were reported to take few steps independently between the ages of 14 months and 6 years. Language development was limited to few words in only seven patients. There has been a patient with *STXBP1*-EE with a mild phenotype limited to learning disabilities (7). ID assessment in the study, is an estimate at best, as developmental assessment in severe childhood epilepsies is often gauged from parental assessments that tend to overestimate child's development. Other neurological findings described were autistic features, hypotonia, ataxia, tremors, stereotypies, spasticity, dyskinesia, and dystonia. With a biased identification of cases from pediatric epilepsy clinics, it is reasonable to state that most *STXBP1*-EE diagnosed in infancy are expected to have profound ID. However, it is not implausible that a milder phenotype may exist and will unfold itself when a full clinical spectrum of *STXBP1*-related disorders is realized. The cohort had 12 patients older than 12 years of age. Two had prominent extrapyramidal features and hypomimic facies, and both were older than 20 years of age. Juvenile onset parkinsonism has been described as a feature of *STXBP1*-EE later in life (8).

Genotypically, *STXBP1* mutations were missense (38%) and truncating (62%) mutations including nonsense, splice site, and frame-shift mutations, partial or whole gene deletions, and larger microdeletions. There were no mutation hot spots across the gene. When inheritance information was available, most mutations were de novo.

Genotype-phenotype correlation was complex, which is in line with other genetic epilepsies. No significant correlation was found between mutation type (missense vs truncating) and cognitive outcome, age of seizure onset, and seizure outcome. Furthermore, there was no correlation between epilepsy phenotype (age of onset, duration of epilepsy, seizure outcome) and ID (mild, moderate, or profound) leading authors to conclude that severe epilepsy and profound ID are two independent clinical expressions of *STXBP1*-EE rather than epilepsy being the primary driver of the degree of ID.

This study outlines the clinical and genetic spectrum of *STXBP1*-EE, and illustrates the power of collaboration in rare epilepsies that may eventually turn out to be not so rare once milder unrecognized phenotypes are discovered. More importantly, it argues against the concept of 'epileptic encephalopathy' as being a sweeping generalization that may not collectively apply to genetic or infantile onset epilepsies. The study has limitations due to retrospective data, variability in reporting, and missing data points in many patients. Genotype-phenotype correlation and importance of each mutation in this study should be cautiously interpreted in the absence of a segregation analysis. In the future systematic longitudinal clinical, electrophysiological, and imaging studies may identify "phenotypical clues" that may make *STXBP1*-EE recognition easier. Our next frontier is to look beyond aggressive epilepsy treatment in EOEE by identifying specific disease-modifying treatments and biomarkers based on the genetic pathobiology.

by Ajay Gupta, MD

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