Neurodevelopmental Outcomes of a Cohort of Children with Tuberous Sclerosis Complex with Epileptic Spasms

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Abstract

The neurodevelopmental outcomes in children with tuberous sclerosis complex (TSC) with epileptic spasms remain underdiagnosed and might be responsible for significant morbidity and mortality burdens, even after spasms abate. The study was a cross-sectional study over 18 months at a tertiary care pediatric hospital, involving 30 children with TSC who had epileptic spasms. They were assessed with Diagnostic and Statistical Manual of Mental Disorders-5 criteria for autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual disability (ID), and childhood psychopathology measurement schedule (CPMS) for behavioral disorders. The median age at onset of epileptic spasms was 6.5 (1–12) months, and the age at enrolment was 5 (1–15) years. Of 30 children, 2 (6.7%) had only ADHD, 15 (50%) had only ID/GDD (global developmental delay), 4 (13.3%) had ASD and ID/GDD, 3 (10%) had ADHD and ID/GDD, and 6 (20%) had none. The median intelligence quotient/development quotient (IQ/DQ) score was 60.5 (20–105). CPMS assessment revealed significant behavioral abnormalities in almost half the children. Eight (26.7%) patients were completely seizure-free for at least 2 years, 8 (26.7%) had generalized tonic-clonic seizures, 11 (36.6%) had focal epilepsy, and 3 (10%) had evolved into Lennox-Gastaut syndrome. A high proportion of neurodevelopment disorders, including ASD, ADHD, ID/GDD, and behavioral disorders were seen in this pilot study with a small cohort of children with TSC with epileptic spasms.

Keywords

- neurodevelopmental outcomes
- tuberous sclerosis complex
- epileptic spasms

Introduction

Tuberous sclerosis complex (TSC), also known as "Bourneville disease" was first described by Désiré-Magloire Bourneville, a French neurologist, in 1880.[1] TSC has an autosomal dominant (AD) mode of Mendelian inheritance arising from mutations in the *TSC1* (OMIM* 605284) on chromosome 9q34.13 encoding hamartin and the *TSC2* gene (OMIM* 191092) on chromosome 16p13.3 encoding tuberin, both

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involved in the regulation of cell division and proliferation.[2] These inactivation mutations result in the loss of the mammalian target of rapamycin inhibition signaling cascade, leading to the formation of hamartomas.[3] The incidence of TSC is estimated at 1 per 6000 to 1 per 10,000 live births, and the overall prevalence is estimated at 1 in 20,000.[4] In TSC, epilepsy often develops in the first few months of life and occurs in up to 90% of patients.[5] Early-onset seizures in TSC with epileptic spasms, in particular, are associated with increased risk for poor long-term outcomes in terms of neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), and also behavioral problems.[6,7] For epileptic spasms with TSC, vigabatrin is Food and Drug Administration-approved first-line recommendation as monotherapy for 1 month to 2 years of age.[8] Early diagnosis and interruption of epileptic spasms at the very onset with vigabatrin prevent subsequent epileptic encephalopathy and reduce the risk of poor neurodevelopmental and behavioral outcomes but does not assure a normal cognitive outcome in children with TSC.[9] However, the neurodevelopmental outcomes remain underdiagnosed and represent significant morbidity and mortality burdens. This pilot study aimed to determine the neurodevelopmental outcomes of Indian children with epileptic spasms in TSC.

Methods

This was a cross-sectional study conducted over 18 months (January 2018 to June 2019) in the department of pediatrics at a tertiary care center after obtaining ethical approval (INT/IEC/2018/000349).

Inclusion Criteria

Children with TSC with epileptic spasms aged between 1 and 15 years attending the pediatric epilepsy clinic. For the diagnosis of TSC, the updated criteria of the '2012 International Tuberous Sclerosis Complex Consensus Conference' was used.[3]

Exclusion Criteria

Children with diagnostic dilemmas where it was not reliably ascertained at the time of enrolment. Informed written assent and consent were obtained from each participant and parent or guardian before inclusion in the study. The basic demographic data were recorded in a prestructured proforma. Children fulfilling the inclusion criteria were assessed with the American Psychiatric Association's "Diagnostic and Statistical Manual of Mental Disorders - 5" (DSM-5) criteria for ASD, ADHD, and ID.[10] Intelligence quotient (IQ) was assessed in children more than 5 years of age by using Malin's Intelligence Scale for Indian Children (MISIC), adapted for Indian children from Wechsler Intelligence Scale for Children. Development quotient (DQ) was assessed in children less than 5 years of age using development profile 3 (DP3).[11,12] Behavioral disorders were assessed by using the childhood psychopathology measurement schedule (CPMS).[13]

Results

Demographic Profile

A total of 72 children with TSC were assessed, and 30 children with TSC with epileptic spasms were included in the study. In the study, 16 (53%) were males, and 14 (47%) were females.

Epileptic Spasms

The median age of onset of epileptic spasms was 6.5 months (1–12 months). However, the median age at enrolment in the study was 5 years (1–15 years). Among the 30 children with TSC with epileptic spasms, 23 (76.7%) children fulfilled the criteria for West syndrome.

Neurodevelopmental Profile and Behavioral Problems

On assessment using DSM-5 criteria for NDDs, no child had isolated ASD, 2 (6.7%) children had isolated ADHD, 15 (50%) children had isolated intellectual disability/global developmental delay (ID/GDD), 4 (13.3%) children had ASD and ID/GDD, 3 (10%) had ADHD and ID/GDD, and 6 children had none of the NDDs. Twenty-three (76.7%) children had ID/GDD either isolated or with other comorbid NDDs (►**Fig. 1**). Age-specific IQ testing using MISIC or DQ testing using DP3 revealed a median score of 60.5 (range: 20–105). Behavioral disorders assessment by CPMS revealed a clinically significant behavioral abnormality in almost half of the children with TSC with epileptic spasms.

Treatment Profile

Among the study cohort of 30 children, 21 (70%) had received vigabatrin, and the median duration was 2 years (range: 6 months to 3 years). Five (16.6%) children received oral steroids, 2 (6.7%) children received adrenocorticotropic hormone, and 2 (6.7%) children were only on anti-

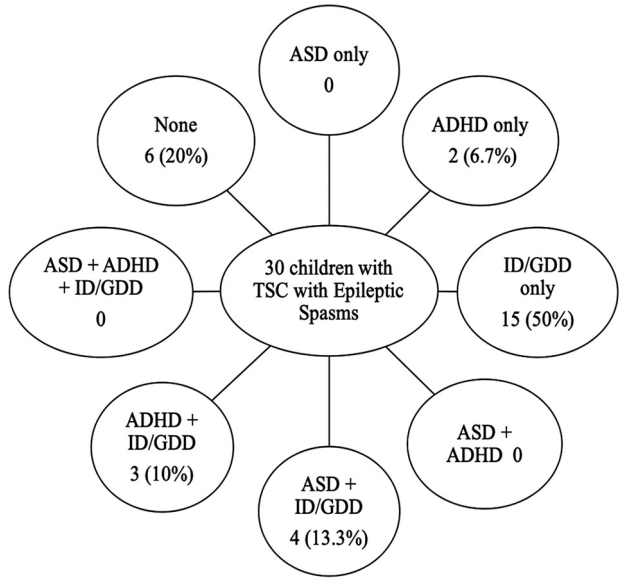

Fig. 1 Neurodevelopmental outcomes of the cohort. ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; ID, intellectual disability; GDD, global developmental delay; TSC, tuberous sclerosis complex.

seizure medications. At the time of enrolment in the study, 10 (33.3%) children continued to have drug-refractory epilepsy.

Outcome Profile

Of the 30 children, 8 (26.7%) children were completely seizure-free for at least 2 years. In 19 children, the epilepsy shifted from encephalopathy to symptomatic epilepsy. Eight (26.7%) children currently had generalized tonic–clonic seizures, 11 (36.6%) children had focal seizures, and 3 (10%) children had evolved into electroclinical syndrome suggestive of Lennox-Gastaut syndrome (LGS; ►**Table 1**).

Discussion

The association of early-onset epilepsy in TSC, particularly epileptic spasms and ID, was well established by Webb et al in a population-based prevalence study. Webb et al reported that the prevalence of epileptic spasms was more in males (33%) than females (18%), with a peak age of occurrence at 4 months.[14] There was a significant association between learning disorder and epileptic spasms ($p = 0.00$) and also with poor seizure control ($p < 0.01$).

In patients with TSC, different seizure semiologies are known to occur. The early-onset seizures with epileptic spasms, in particular, are associated with an increased risk for poor long-term outcomes. The prognosis of the cognitive outcome also depends on the age at the onset of spasms. In a study by Riikonen and Simell on the outcomes for 24 children with TSC with epileptic spasms, the short-term outcome seemed favorable, but the long-term outcome on a mean follow-up period of 8.2 years (range: 2.5–19 years) was worse. All 24 children had ID and most had behavioral abnormalities.[6]

Table 1 Demographics, treatment, and outcome of the cohort

Demographics ($n = 30$)	
Girls/boys	14 (47%) / 16 (53%)
Mean age at enrolment	5.7 years
Median age at enrolment (range)	5 (1–15) years
Mean age of onset of spasms	6.8 months
Median age of onset of spasms (range)	6.5 (1–12) months
Children with West Syndrome	23 (76.7%)
Treatment profile	
Children who received vigabatrin therapy	21 (70%)
Median duration of vigabatrin therapy (range)	2 (0.5–3) years
Seizure and outcomes	
Completely seizure-free (at least 2 years)	8 (26.7%)
Focal seizures	11 (36.6%)
Generalized tonic–clonic seizures	8 (26.7%)
EEG suggestive of Lennox-Gastaut syndrome	3 (10%)

Abbreviation: EEG, electroencephalogram.

In the TOSCA (TuberOus SClerosis registry to increase disease Awareness) study on TSC-associated neuropsychiatric disorders by de Vries et al, involving 1410 children (less than or equal to 18 years), 23.1% had ASD, and 22.4% had ADHD. Behavioral problems were noted in 94.3% of children. On IQ testing in 585 children, 56.5% of children had ID; of them, 31% had mild ID, 15.5% had moderate ID, 7.8% had severe ID, and 2.2% had severe ID.[5] In the TOSCA study, the neurodevelopmental outcomes were assessed in children with TSC with different seizure types. The index study showed fewer children with ASD at the time of assessment. The epileptic encephalopathy in our cohort could have contributed to the secondary autistic features, but the epileptic encephalopathy improved with treatment, thereby reducing the overall severity of ASD.

In children with TSC with epileptic spasms, vigabatrin has been recommended as the first-line monotherapy. The interval between the first symptom and initiation of therapy is important for the neurodevelopmental and behavioral outcomes. In a study by van der Poest Clement et al on the vigabatrin therapy for 21 children with TSC with epileptic spasms, tonic seizures, and status epilepticus, the mean age at vigabatrin initiation was 48 months (median: 27, range: 13–219 months), mean duration of receiving vigabatrin was 15 months (range: 2–33 months). In the study by van der Poest Clement, the response to therapy was assessed in children with epileptic spasms, eight patients were seizure-free and two had more than 90% improvement but were not seizure-free, and one had no improvement.[8] In the index study, eight children were completely seizure-free for at least 2 years on treatment, three children had evolved into LGS, eleven children had focal seizures, and eight children had generalized tonic–clonic seizures. The EPISTOP (EPIleptogenesiS in a genetic model of epilepsy – Tuberous sclerOsis comPlex) trial by Kotulska et al including 54 patients with TSC showed the possibility of changing its natural history by using preventive therapy with vigabatrin. Vigabatrin therapy delayed the onset of seizures and prevented infantile spasms, thereby improving the level of psychoneurodevelopment in these children with TSC.[15]

Prompt treatment aimed at controlling epileptic spasms at the earliest with vigabatrin may help reduce the risk of subsequent epileptic encephalopathy. Also, the timing of high-dose vigabatrin therapy may be relevant to the outcome. This may improve the neurodevelopmental and behavioral outcomes; however, a normal cognitive outcome may not be assured. Although our study represents a significant cohort of children with TSC with epileptic spasms in the Indian population, the sample size is small to derive conclusions.

Limitations of the Study

The index study had a small sample size of children with TSC. The different intervals between spasms onset and treatment initiation and duration of spasms persistence were not collected. The other factors that could have influenced the neurodevelopmental outcomes, including the genetic

distribution of TSC, neuroimaging, and electroencephalography characteristics, were not evaluated in all children.

Conclusion

A high proportion of NDDs, including ASD, ADHD, ID/GDD, and behavioral disorders, were seen in this pilot study with a small cohort of children with TSC with epileptic spasms. The epileptic spasms in children with TSC may hamper the long-term neurodevelopmental outcomes. Our study underscores the need for treatment initiation at the earliest onset of spasms that may increase the chances for favorable long-term neurodevelopmental outcomes; however, this needs to be validated with further multicentric studies in larger cohorts.

Highlights

- The prevalence of NDDs, including ASD, ADHD, ID/GDD, in children with TSC is high.
- Epileptic spasms in children with TSC may hamper the long-term neurodevelopmental outcomes.
- Early treatment for controlling epileptic spasms may help reduce the risk of subsequent epileptic encephalopathy.

Authors' Contributions

L.K. and S.M. helped in study design, writing, editing, and drafting. P.M., J.K.S., and N.S. contributed to intellectual content. L.S., S.M., P.K.G., P.M., A.G.S., R.S., I.K.S., R.S., J.K.S., and N.S. were involved in critical revision and final approval.

Note

The authors want to disclose that this research article is a part of larger study on children with neurocutaneous syndromes.

Ethical Statement

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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Conflict of Interest

None declared.

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