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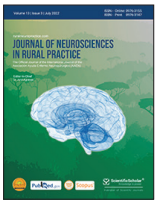

Original Article

The profile of epilepsy and its characteristics in children with neurocutaneous syndromes

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ABSTRACT

Objectives: The profile of seizures in neurocutaneous syndromes is variable. We aimed to define the characteristics of epilepsy in children with neurocutaneous syndromes.

Materials and Methods: Cross-sectional study over 18 months at a tertiary care pediatric hospital, including children with neurocutaneous syndromes aged between 1 and 15 years, using the 2017-International League Against Epilepsy classification.

Results: In 119 children with neurocutaneous syndromes, 94 (79%) had epilepsy. In eight children with neurofibromatosis one with epilepsy, 5 (62.5%) had generalized motor tonic-clonic seizures, 1 (12.5%) had generalized motor epileptic spasms, 1 (12.5%) had generalized motor automatism, and 1 (12.5%) had a focal seizure. In 69 children with tuberous sclerosis complex with epilepsy, 30 (43.5%) had generalized motor epileptic spasms, 23 (33.3%) had focal seizures, and nine (13.0%) had generalized motor tonic-clonic seizures. In 14 children with Sturge–Weber syndrome with epilepsy, 13 (92.8%) had focal seizures, and 1 (7.2%) had generalized motor tonic seizures. Statistically significant associations were found between epilepsy and intellectual disability ($P = 0.02$) and behavioral problems ($P = 0.00$).

Conclusion: Profiling seizures in children with neurocutaneous syndromes are paramount in devising target-specific treatments as the epileptogenesis in each syndrome differs in the molecular pathways leading to the hyperexcitability state. Further multicentric studies are required to unravel better insights into the epilepsy profile of neurocutaneous syndromes.

Keywords: Epilepsy, Neurocutaneous syndromes, Neurofibromatosis 1, Tuberous sclerosis complex, Sturge–Weber syndrome

INTRODUCTION

Neurocutaneous syndromes are a group of inherited disorders with a multitude of abnormalities involving the central nervous system, skin, and visceral organs. Neurofibromatosis 1 (NF1), tuberous sclerosis complex (TSC), and Sturge–Weber syndrome (SWS) are the prototypical neurocutaneous syndromes with genetic mutations in cell growth regulation pathways.[1] Neurological presentation ranges from mild behavioral abnormalities to drug-resistant epilepsy.[2-5] In these children, there is a high prevalence of neurodevelopmental disorders and epilepsy.[6,7] The frequency of epilepsy is estimated at 6–10% in NF1, 70–90% in TSC, and 70–90% in SWS.[1,3-5,8,9] Although the mechanisms resulting in epileptogenesis differ between the neurocutaneous disorders, there is an overlap in the molecular pathways, especially mammalian targets of rapamycin (mTOR) signaling pathways.[1] The possible contributors to cellular hyperexcitability in NF1 can be cortical malformations, neurotransmitter defects, alterations in ion channels, or synaptic plasticity.[10] The epileptogenesis in TSC is due to the dysfunction of mTOR signaling pathways resulting in abnormal cellular excitation and hyperexcitable circuits due to neuropathological substrates.[11,12] The possible contributors to cellular hyperexcitability in TSC are neuron dysplasia, dendritic spine dysgenesis, reduced GABAergic inhibition, increased glutamatergic excitation, and glial dysgenesis.[1] In SWS, the possible contributors are blood vessel dysgenesis, calcification, and cell death.[13] In these children, seizures can cause sleep disturbances which, in turn, cause behavioral issues and further reduce the threshold of seizures.[14] The management is challenging as these children have significant comorbidities that impact their quality of life. With a better molecular understanding of the mechanisms, therapy can be targeted with the help of "Precision medicine" based on unique molecular pathways. The profile of seizures in children with

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neurocutaneous syndromes is variable, and this study aimed to evaluate the characteristics of epilepsy in these children.

MATERIALS AND METHODS

This cross-sectional study was conducted for an 18-month study period in the Department of Pediatrics at a North Indian tertiary care referral hospital after obtaining prior ethical approval.

Inclusion criteria

Children with neurocutaneous syndromes aged between 1 and 15 years.

Exclusion criteria

Children with ages <1 year and >15 years were excluded from the study.

Our study included 119 children. Seizures were classified using 2017 International League Against Epilepsy (ILAE) classification.[15] For assessing the neurodevelopmental disorders," Diagnostic and statistical manual of mental disorders (DSM-5) criteria for Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), and intellectual disability (ID) were used.[16] For assessing the intelligence quotient (IQ), Malin's Intelligence Scale for Indian Children (MISIC)[17] was used, or the development quotient was assessed using developmental profile 3 (DP-3).[18]"MISIC has 11 subsets measuring verbal, performance, and total IQ. The areas measured in MISIC are similarities, vocabulary, digit span, picture completion, picture arrangement, block design, object assessment, coding, information, comprehension, arithmetic, and mazes. DP-3 is a standardized scoring system to measure child development. DP-3 utilizes inputs from parents or caregivers to provide scores in five key areas of development, including physical, adaptive behavior, social-emotional, cognitive, and communication, with each scale with 34–38 items. A general development score is provided, that is a composite of all the five areas. The Childhood Psychopathology Measurement Schedule (CPMS) was used to assess behavioral abnormality, and a score of >10 was considered significant.[19] CPMS measures psychopathology in the form of total score and type of psychopathology in the form of eight factorial derived syndromes. Children with a score of 10 or more are likely to be disturbed psychiatrically. Descriptive statistics, including frequencies and percentages for categorical variables and mean and standard deviation/median and interquartile range (as appropriate) for continuous variables, was used.

RESULTS

Of 119 children with neurocutaneous syndromes, 94 (79%) had epilepsy, 8/21 (38.1%) children with NF1 had epilepsy, 69/72 (95.8%) children with TSC had epilepsy, 14/16 (87.5%) children with SWS had epilepsy, and 26/119 (21.8%) children fulfilled the criteria of West Syndrome [Table 1].

Syndrome-wise profile of seizures - ILAE 2017 classification

NF1

Of eight children with NF1 with epilepsy, 5 (62.5%) had generalized motor tonic-clonic seizures, 1 (12.5%) had generalized motor epileptic spasms, 1 (12.5%) had generalized motor automatism, and 1 (12.5%) had focal onset impaired awareness non-motor behavioral arrest.

TSC

Of 69 children with TSC with epilepsy, 30 (43.5%) had generalized motor epileptic spasms, 9 (13%) had generalized motor tonic-clonic seizures, 5 (7.3%) had focal onset impaired awareness motor clonic seizures, 3 (4.3%) had generalized motor atonic seizures, 3 (4.3%) generalized non-motor atypical type, 3 (4.3%) had focal-onset aware motor automatism, 3 (4.3%) had focal onset impaired awareness motor epileptic spasms, 3 (4.3%) had focal onset impaired awareness non-motor behavioral arrest, 2 (2.9%) had focal onset aware motor tonic seizure, 2 (2.9%) had focal onset aware motor clonic seizures, 2 (2.9%) had focal onset impaired awareness motor tonic seizures, 1 (1.5%) had generalized non-motor typical type, 1 (1.5%) had focal onset aware motor myoclonic seizures, 1 (1.5%) had focal onset aware motor atonic seizures, and 1 (1.5%) had focal onset impaired awareness non-motor emotional type.

SWS

Of 14 children with SWS with epilepsy, 7 (50%) had focal onset impaired awareness motor clonic seizures, 2 (14.2%) had focal onset impaired awareness motor tonic seizures, 2 (14.2%) had focal onset aware motor clonic seizures, 1 (7.2%) had focal onset aware motor clonic seizures, 1 (7.2%)

Table 1: Prevalence of seizures in neurocutaneous syndromes.

Neurocutaneous syndromes	Seizures		Total
	Present	Absent	
NF 1	8	13	21
TSC	69	3	72
SWS	14	2	16
Others*	3	7	10
Total	94	25	119

*Others: Linear nevus sebaceous syndrome, Hypomelanosis of Ito, Von Hippel Lindau Syndrome, Ataxia Telangiectasia, McCune Albright Syndrome, Megalencephaly Capillary Malformation Syndrome.
NF1: Neurofibromatosis 1, TSC: Tuberous sclerosis complex, SWS: Sturge–Weber syndrome

had focal onset impaired awareness motor epileptic spasms, and 1 (7.2%) had a generalized motor tonic seizure.

Relation of epilepsy and neurodevelopment in neurocutaneous syndromes

ASD

Out of 94 children with epilepsy, 13 had fulfilled the DSM-5 diagnostic criteria for ASD. However, the association between these two variables was not statistically significant ($P = 0.81$). On determining the syndrome-wise association of ASD with epilepsy, it was significant in TSC ($P = 0.02$) but not in NF1 ($P = 0.42$) and SWS ($P = 0.47$).

ADHD

Out of 94 children with epilepsy, 12 (81.3%) fulfilled the DSM-5 diagnostic criteria for ADHD. No association was found between ADHD and epilepsy in the study population ($P = 0.06$). On determining the syndrome-wise association of ADHD with epilepsy, it was not significant in NF1 ($P = 0.19$), TSC ($P = 0.50$), and SWS ($P = 0.69$).

ID

Among the 119 patients, 69 (58%) had IQ scores <70. The ID was present in 54/90 (60%) children in the study population with epilepsy, and the association was statistically significant ($P = 0.02$).

Behavioral problems

For determining behavioral abnormality, CPMS was used. Among the 75 children with epilepsy, 46 (61.3%) had a statistically significant association with behavioral abnormalities ($P = 0.00$).

The relationship of epilepsy with neurodevelopmental comorbidities in neurocutaneous syndromes is summarized in Table 2.

Table 2: Relation of epilepsy with neurodevelopmental comorbidities in neurocutaneous syndromes.

	Seizures		Total	*P*-value
	Present	Absent		
ASD				
Present	13	3	16	0.81
Absent	81	22	103	
Total	94	25	119	
ADHD				
Present	12	0	12	0.06
Absent	82	25	107	
Total	94	25	119	
ID				
Present	54	8	62	0.02*
Absent	40	17	57	
Total	94	25	119	

ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; ID: Intellectual disability. *P<0.05: Statistically significant. The total numbers differ due to the presence of an overlap of neurodevelopmental disorders in the same patient.

DISCUSSION

The higher proportion of epilepsy in our study population may be due to the enrollment of patients from neurodevelopment and epilepsy clinics with significant neurological comorbidities. In a study by Santoro *et al.*,[20] seizures were found in 4.3% of the general population, and in Hsieh *et al.*,[21] the prevalence was 5.87%. The most common seizure type in the index study was generalized tonic-clonic seizure (GTCS) (23.8%). In the previous studies, focal seizures were more common, followed by GTCS.

Among the studies on NF1, Khair *et al.* reported epilepsy in 13.5% of their cohort of children with NF1, with focal onset seizures in 11 patients, followed by GTCS in five patients.[5] In a retrospective study by Hsieh *et al.* with 630 children and adults, focal-onset seizures in 2.6% and GTCS in 2.4% of the cohort.[21] In a study by Santoro *et al.* on NF1 children, 11/19 (58%) had focal seizures; however, 10/19 children with seizures had structural epilepsy, all of whom had focal seizures.[20] In the index study, all children had non-structural seizures and among the children with NF1, generalized motor tonic-clonic seizures were the most common type (62.5%).

Among the studies on TSC, Nabbout *et al.* reported a prevalence of epilepsy in 83.6%, with 38.9% presenting with epileptic spasms and 67.5% with focal seizures.[22] In another study by Vignoli *et al.*, epilepsy was reported in 72.5% with TSC.[23] In another study by Chu-Shore *et al.*, 85.2% of 291 patients with TSC had seizures, with focal onset seizures in 76%.[24] Similar to the previous studies, focal seizures and generalized onset epileptic spasms were the most common seizure types in the index study. In a study by Alkonyi *et al.*, all 110 patients with SWS enrolled had seizures.[25]

In our cohort, 26/119 (21.8%) children fulfilled the criteria of West syndrome. Five children were follow-up cases of West syndrome more than 10 years old and continued to have epileptic spasms. Many patients might have had West syndrome before enrolment in our study and might have evolved into another type of seizure, as reported in the previous studies.[26] In a study by Fukushima *et al.* with 50 TSC patients monitored and analyzed after 10 years, the outcome was unfavorable for patients with generalized seizures.[26] Capal *et al.* reported that in patients with epileptic spasms, developmental outcomes were poor on assessments at 12, 18, and 24 months of age.[27]

Among the studies on SWS, the prevalence of epilepsy reported was 90% in patients with bilateral cerebral involvement.[1] The common seizure type reported in SWS was focal seizures.[1] In the index study, more than 90% of children with SWS had focal seizures, in concordance with the previous studies.

Among the 16 children with ASD, 13 (81.3%) had epilepsy, but the association was not statistically significant in our study population. In the index study, there was a significant association between epilepsy and ASD in children with TSC ($P < 0.01$), similar to the study by Vignoli *et al*., where epilepsy has been considered a significant risk factor for ASD in TSC.[28] The higher proportion in our cohort can be attributed to more children presenting with epilepsy in the pediatric neurology clinic. The index study found statistically significant associations between epilepsy and ID ($P = 0.02$) and behavioral problems ($P = 0.00$).

Limitations

In the index study, the epilepsy profile of only the common neurocutaneous syndromes was studied.

CONCLUSION

The prevalence of epilepsy in neurocutaneous syndromes is very high. Profiling seizures in children with neurocutaneous syndromes is paramount in devising target-specific treatments as the epileptogenesis in each syndrome differs in the molecular pathways leading to the hyperexcitability state.

Ethical approval

A prior ethical approval was obtained, and the study complied with the Helsinki Declaration of 1964.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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