ORIGINAL ARTICLE

Clinical Characteristics, Types of Epilepsy, Electrophysiological Profile and Neuroimaging Features of Neurocutaneous Syndrome: Experience in a Tertiary Care Hospital

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ABSTRACT

Objective: The neurocutaneous syndromes encompass disorders that primarily impact integumentary system and the central nervous system (CNS). Objective of this study is to conduct an in-depth patient history review and thorough neurocutaneous examination that may prove instrumental in establishing an accurate diagnosis, thereby enabling the formulation of appropriate treatment plan.

Study Design: Descriptive, observational hospital-based study.

Place and Duration of Study: Study was conducted at Department of Pediatric Neurology, Children's Hospital Lahore, Pakistan from March, 2023 to September 2023

Material and Methods: Children from either gender, from 1 month to 15 years diagnosed on the basis of diagnostic standard criteria for different neurocutaneous syndromes, were enrolled. Clinical history, examination, neuroimaging, electroencephalography was taken into account.

Results: Out of 33 children, 51.5% were female with mean age of 46±42.59 months. The majority patients belong to 1 to 5 years (45.5%). According to neurocutaneous distribution, 60.6% had tuberous sclerosis, 18.2% Sturge-Weber syndrome and Neurofibromatosis type-1 each and 3% had ataxia telangiectasia. The clinical features include seizures in 90.9% predominantly generalized tonic clonic seizures in 51.5%. While the hypopigmented patches (33.3%) was the most common cutaneous finding. Most common EEG recordings were generalized epileptiform discharges 51.5%, while the frequently observed neuroimaging findings were subependymal nodules in 30.3%.

Conclusion: Neurocutaneous syndromes encompass a multitude of different clinical presentations, with epilepsy being the most common manifestation. Skin lesions can serve as an early detectable indicator to ascertain the cause of epilepsy aiding in reaching a definitive diagnosis.

Key Words: *Epilepsy, Tuberous sclerosis, Sturge-weber syndrome, Neurofibromatosis 1, Neurocutaneous Syndrome, Electroencephalography, Magnetic resonance imaging.*

INTRODUCTION

The neurocutaneous syndromes encompass a diverse array of disorders that primarily impact both the integumentary system and the central nervous system (CNS), accompanied by distinct dysmorphic facial features as well as anomalies within the dermatologic, cardiac, ophthalmic, musculoskeletal, and genitourinary systems. Among the neurocutaneous disorders that have been identified are neurofibromatosis 1 (NF1), tuberous sclerosis complex (TSC), von Hippel Lindau (VHL) disease, Sturge-weber syndrome (SWS), ataxia-telangiectasia (AT), PHACE syndrome, linear nevus syndrome (LNS), hypomelanosis of Ito, and incontinentia pigmenti (IP).[1-2] Neurofibromatosis (NF), tuberous sclerosis complex (TSC), and Sturge-Weber syndrome are examples of the most prevalent disorders among the various neurocutaneous syndromes.[3]

The number of neurocutaneous disorders is estimated to be between 30 and 40 in total. Most neurocutaneous syndromes fall under the classification of single-gene disorders, even though they exhibit different inheritance patterns such as autosomal dominant, autosomal recessive, or X-linked. The remaining neurocutaneous disorders are considered rare diseases, as they occur with an incidence lower than 1:2,000 individuals in the general population.[4,5]

These conditions represent a complex and multifaceted group of pathologies, each characterized by their own unique set of clinical features and associated genetic mutations, making diagnosis and treatment a challenging endeavor for healthcare practitioners. As our understanding of these syndromes continues to evolve, it is crucial that further research is conducted to elucidate the underlying mechanisms and develop more effective therapeutic interventions for individuals affected by these debilitating conditions.[1,2]

The clinical features required for the diagnosis of neurofibromatosis 1 (NF1) are when two or more of the following features are present: six or more café-au-lait macules (over 5 mm in diameter in prepubertal individuals and greatest 15 mm in diameter in post pubertal individuals), two or more neurofibromas or 1 plexiform neurofibroma, inguinal or axillary freckling, optic glioma, two or more Lisch nodules, a distinctive osseous lesion, and a first degree relative with NF1.[2]

Clinical criteria of tuberous sclerosis include 11 major and 6 minor-features, Major features: Hypomelanotic macules (at least 5mm diameter), angiofibroma's, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), angiomyo-lipoma. Minor features: confetti skin lesions, dental pits (>3), intraoral fibromas, retinal achromic patch, multiple renal cysts, and nonrenal hamartomas. For definite diagnosis one should have two major or one major and two minor features.[6]

Sturge-Weber syndrome manifested as presence of port wine stain on the face associated with leptomeningeal angiomatosis in brain that can lead to seizures, stroke and glaucoma. The leptomeningeal involvement can occur with or without port wine stain.[2]

These conditions are present from birth and are lifelong, with no current available treatments for correction[4,5,7] but their presentation may vary depending on the developmental age of the child, though skin lesions are found in 90% of patients of all age groups.[8] The first commencement of seizures noticed between 6 months and 12 years of age, which aligns with findings from a separate investigation.[9,10]

There exist various research studies that explore into the diverse forms of neurocutaneous syndromes, however, a comprehensive investigation focusing exclusively on the pediatric population remains limited in scope. It is worth noting that Pakistan, being a country with a high prevalence of consanguinity, may experience an elevated incidence of such syndromes within its population.

Our objective is to conduct an in-depth patient history review and thorough neurocutaneous examination that may prove instrumental in establishing an accurate diagnosis, thereby enabling the formulation of appropriate treatment plan, anticipating potential complications, and offering genetic counselling to affected families. Moreover, we aspire to facilitate the development of programs aimed at delivering appropriate

neurological rehabilitation for affected in individuals in the future.

MATERIAL AND METHODS

The study conducted at the Pediatric Neurology Department Indoor and Outpatient Clinic at the University of Child Health and Children's Hospital, Lahore, from March to September 2023 after obtaining ethics approval from the institutional review board (certificate number: 2023-727-CHICH). It was a descriptive, observational hospital-based study. In order to be included in this study, the children had to fulfill the criteria of diagnosis of specific neurocutaneous syndromes, between the ages of 1 month and 15 years. Any children over the age of 15, Skin disorder that cannot be explained under neurocutaneous syndromes and also parents or guardians who refused to participate were excluded from the study. Sample size was taken as 33 using 95% confidence interval and 5% margin of error taking prevalence of neurocutaneous syndromes as 1:6000 population using Openepi.net.[11] Sampling technique was non-probability consecutive.

Prior to enrollment, written informed consent was obtained from all parents or guardians of each participant included in this study. The data collected for this study was recorded on a semi-structured questionnaire. This included demographic features and a thorough clinical history of the patients, encompassing seizures, motor delay, skin lesions and headache. Additionally, a comprehensive clinical examination was conducted, encompassing general, systematic, and detailed neurological examinations, as well as a dermatological examination. Furthermore, CT and/or MRI brain scans and electroencephalography (EEG) were performed on all patients.

Motor delay, refers to a child who has not gained the developmental skills expected of him or her, compared to the others of the same age.

Microcephaly was defined as a head circumference greater than two standard deviation below the mean for gender and age, while Macrocephaly was defined as when head circumference is greater than two standard deviation above the mean for gender and age.

To ensure confidentiality, the participants' information was kept secure. Data collection was carried out by a single investigator. The collected data was subjected to analysis using the Statistical Package for Social Science (SPSS) v26. A Value of $p \leq 0.05$ was considered to be statistically significant. Chi-square test was used for calculating association between neurocutaneous syndrome and different variables including Age, headache, seizure onset, seizures types and association between seizures types including cutaneous and EEG findings. Frequencies and percentages were calculated for qualitative variables such as clinical presentations, including the types and frequency of seizures, as well as skin lesions, EEG, and CT and/or MRI brain findings. On the other hand, mean and standard deviation were calculated for continuous variables like age.

RESULTS

Total 33 children with neurocutaneous syndromes were included. Among 33 children, 48.5%[16] were males and 51.5%[17] were females. Mean age of children was 46 ± 42.59 months. According to age distribution, the majority of patients presented to us within age group of 1 to 5 years 45.5%,[15] and had significant association between presence of skin manifestations with p-value <0.014.

According to neurocutaneous syndrome distribution, it was found that tuberous sclerosis cases were 60.6%[20] constituting the majority of cases followed by Sturge-Weber syndrome 18.2%,[6] neurofibromatosis type-1 18.2%[6] and, ataxia telangiectasia 3%.[1] Regarding the distribution of different diagnosis according to gender, there was significant male predominance seen in patients with Sturge weber syndrome, while in others no significant difference recorded in studied population. We found seizures, headache, motor delay and skin lesions to be the most commonly presenting feature in our clinic. Among these children, seizures in 30 cases (90.9%) and seizures were the main presenting complaint in all tuberous sclerosis patients, whereas motor delay was found in 16 cases (48.5%), headache in 5 cases (15.2%), and skin lesions were detected in 3 cases (9.1%) as presenting complaint**.** Among 5 patients, 3 patients with neurofibromatosis 1 presented with headache only. There was significant association between neurocutaneous syndrome and headache with a p-value <0.003. Patient clinical characteristics shown in table 1.

As regards general examination, 19 (57.6%) had normal head size, 13 (39.4%) had microcephaly and remaining 1 (3.0%) had macrocephaly. There

was significant association between head size and motor delay with a p-value <0.001.

TABLE 1: Patient characteristics

Characteristics	Values (%)
Mean age, months	46 ± 42.59
Gender, n (%)	
Female	17 (51.5)
Male	16 (48.5)
Neurocutaneous syndromes n (%)	33 (100.0)
Tuberous sclerosis	20 (60.6)
Neurofibromatosis type-1	6 (18.2)
Sturge-weber syndrome	6 (18.2)
Ataxia telangiectasia	1 (3.0)
Presenting Complaint	
Seizures	30 (90.9)
Motor delay	16 (48.5)
Headache	5 (15.2)
Skin lesion	3 (9.1)

As regards seizures, generalized tonic clonic seizures were the most common type reported in half of the patients (51.5%), while focal seizures 5 (15.2%) and infantile spasm 5 (15.2%), then followed by myoclonic seizures 3 (9.1%) and 3 (9.1%) had no seizures with a significant p-value <0.005. All patients with tuberous sclerosis and Sturge-weber syndrome had seizures, while no seizures have been reported in Ataxia telangiectasia with a significant p-value <0.001.

Frequency of types of seizures and frequency among specific neurocutaneous syndrome. Are shown in fig 1 & 2.

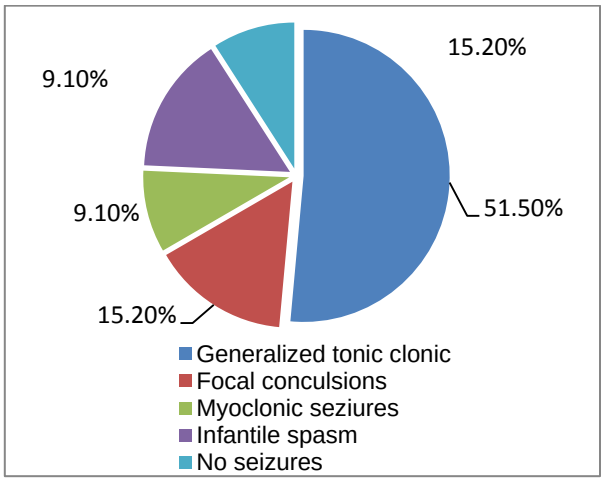
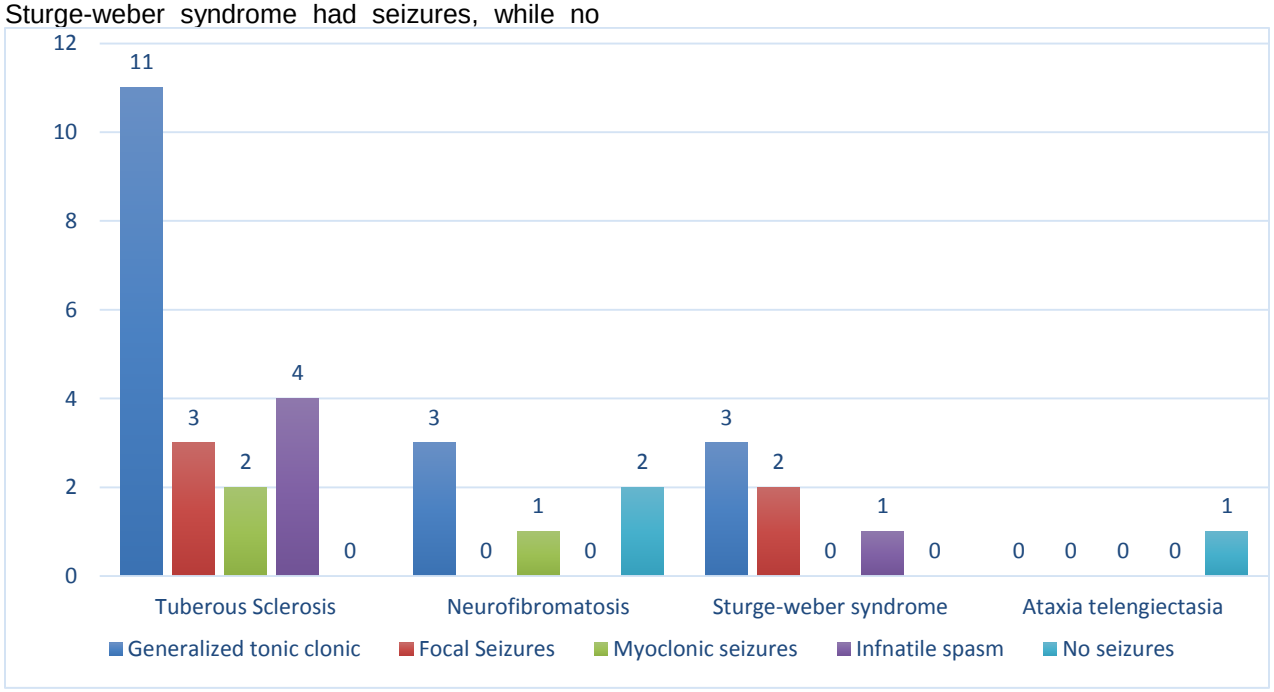


Fig 1: Distribution of types of seizures among studued children



p-value: 0.005

Fig 2: Frequency of seizures among specific neurocutaneous syndrome

Majority of the patients showed skin manifestations, hypopigmented patches in 11 (33.3%) was the most common finding. 6 (18.2%) had port wine stain then café au lait patches and shagreen patches equally in 4 patients (12.1%). Ash leaf macules in 2 (6.1%), plexiform neuroma in 1 (3.1%) and, while no skin pigmentation seen in 1 (3.1%) as shown in table 2 & fig 3-4 There was significant association between skin manifestation and seizures types with a p-value <0.007.

TABLE 2: Cutaneous Manifestation in Studied Children

Skin examination findings	Number	Percentage
Hypopigmented patches	11	33.3
Port wine stain	6	18.2
Café au-lait patches	4	12.1
Shagreen patch	4	12.1
Ash-leaf macules	2	6.1
Asch-leaf macules and hypopigmented patches	2	6.1
Neurofibroma	1	3.0
Inguinal and axillary freckles	1	3.0
Adenoma sabecum	1	3.0
Normal	1	3.0

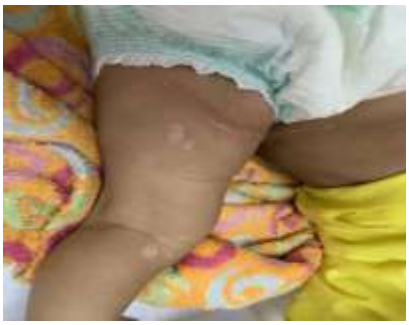


Fig 3

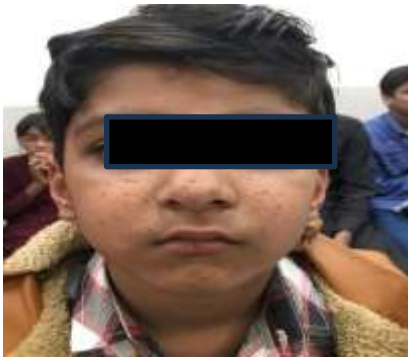


Fig 4
Fig 3 & 4: Angiofibroma on the face

Multiple Hypomelanotic patches over legs of a child having Tuberous sclerosis

Fig 5

Fig 6
Fig 5 & 6: Plexiform neurofibroma of the right Port wine Stain Over Right Half of the Face upper limb

EEG was done to all patients, showed that 16 (48.5%) had generalized epileptiform discharges, 8 (24.2%) had normal EEG findings, while hypsarrhythmia seen in 5 (15.2%), and 4 (12.1%) had focal epileptic discharges. Types of seizures had significant association with EEG findings (p-value <0.014). As shown in fig 6.

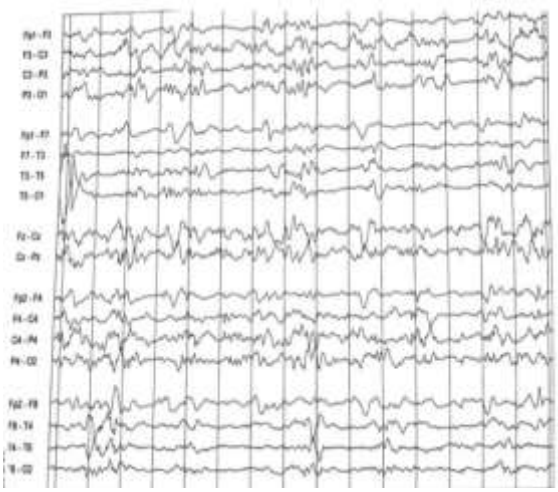


Fig 6: Multifocal epileptiform discharges

Neuroimaging either CT or MRI brain was done in all patients and showed that 10 children (30.3%) had subependymal nodules, normal seen in 6 (18.2%) children, and 5 children (15.2%) had cortical tubers. One child with ataxia telangiectasia had cerebellar atrophy and one child as neurofibromatosis presented with headache had hydrocephalus as shown in table 3. There was significant association between the types of neurocutaneous syndrome and their imaging findings with a p-value <0.001, also there was a strong association between neuroimaging findings and occurrence of seizures with a significant p-value <0.006.

TABLE 3: Frequency distribution of neuroimaging findings

Neuroimaging findings	Fre-quency	Percen-tage
Subependymal nodules	10	30.3
Normal	6	18.2
Cortical tubers	5	15.2
Calcifications (scattered or periventricular)	3	9.1
White matter changes	2	6.1
Cerebral hemi atrophy	2	6.1
Tram line calcifications	2	6.1
Serpentine calcifications	1	3.0
Hydrocephalus	1	3.0
Cerebellar atrophy	1	3.0
Total	**33**	**100.0**

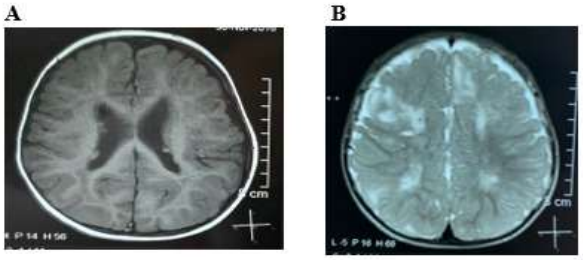


Fig 8: MRI Scan of Child with Tuberous Sclerosis.

A) T1W plain showing hypointense lesion in the left parietal area (cortical tubers) and sub ependymal nodules.

B) T2W images showing cortical tubers

DISCUSSION

Neurocutaneous syndromes encompass a diverse collection of disorders denoted by anomalies in both the integumentary system and the central nervous system. These syndromes can be managed through therapeutic interventions aimed at mitigating symptoms and addressing emerging healthcare concerns. Family history played a crucial role in making the diagnosis, however two third of cases with tuberous sclerosis may arise indistinctively.[12] Remarkably, the mean age of diagnosis was 46±42.59 months, which was nearly similar to other study.[2,13)]

However, in our study male and female almost equally affected, in contrast to other studies where neurocutaneous syndromes were slightly more common in males.[2,14]

In the present study, the majority of collected cases were Tuberous Sclerosis (60.6%), followed by neurofibromatosis 1 and Sturge Weber syndrome. In the year 2019, a comprehensive investigation was conducted in Bangladesh, which spanned over the course of an entire year. The study specifically focused on the prevalence of tuberous sclerosis, that affects 13 (48.1%) individuals out of total 27 children that included in study.[15]

Similar findings observed in study done by Diaconu et al,[16] while in contrast to results seen in study done by Purkait et al., where neurofibromatosis 1 were the most common.[2] In

the present investigation, the predominant grievance reported by the subjects was seizures, which were observed in a significant proportion (90.9%), this was much higher than the results of other researchers Diaconu et al. and Sadek, et al. who recorded seizures 39.1% and 70.3%, in their respective studies.[14,16] According to the research conducted by Radheshyam et al., it was found that seizures were documented in approximately 78.2% of the patients under investigation.[2] This prevalence rate was slightly higher compared to a similar study carried out in Egypt, which reported seizures in 70% of the patients, and another study conducted in Pakistan, where seizures were observed in 65% of the patients, making it the most common presenting complaint in both cases (table 4).

The disparity in the incidence of seizures among these studies might be attributed to different types of neurocutaneous syndromes that were investigated.[14,17]

TABLE 4: Association of neurocutaneous syndrome and seizures

	Seizures among studied children			
	Yes	No	Total	p-value
Tuberous sclerosis	20	0	20	0.001
Neurofibromatosis	4	2	6	
Sturge Weber syndrome	6	0	6	
Ataxia telangiectasia	0	1	1	
	30	3	33	

Another study focused specifically on tuberous sclerosis patients and revealed that epileptic seizures serve as a hallmark characteristic of this condition. Notably, focal seizures were reported as the most common type of seizure, accounting for approximately 67% of cases, followed by epileptic infantile spasms, which were documented in 38% to 49% of the patients. [(18)]In cases with tuberous sclerosis, 88.9% of children had generalized seizures, while 60% experienced focal seizures. The onset of seizures often occurred during the early years of life, which aligns with findings from previous research.[19,20]

In our study, generalized tonic clonic seizures were the most common type reported in half of the patients (51.5%), this was slightly lower than the results of Oshi et al., where generalized tonic clonic seizures were recorded (65%), and results were similar in other study done by Sadek, et al. with regards to types of seizures.[14,21] These results disagree with Diaconu et al. study, where the commonest type of seizures was complex partial type.[16] It is important to note that the variability in rates may be influenced by the severity of brain involvement depending on age groups and by the size of populations included in each study. In tuberous sclerosis, all children had seizures which were generalized tonic clonic in 55%, focal in 15% and infantile spasms were observed in 20%, this was much lower than the study of Sadek, et al.[14] All 6 cases of Sturge-Weber syndrome in our study had seizures and this agrees with other study.[21]

We observed in our study that cutaneous manifestations were present in nearly all patients, and were helpful in making early diagnosis. In tuberous sclerosis, hypopigmented patches were the commonest finding in our study, and similar findings observed in study of Sadek, et al.[14] whereas study done in Bangladesh, where the facial angiofibroma were frequently seen and followed closely by the presence of hypomelanotic macule and shagreen patch. Interestingly, it was observed that those with neurofibromatosis type 1, demonstrated almost universal occurrence of café–au-lait macules (100%) and neurofibroma (100%) in their presentations.[15] In a separate study conducted in Egypt, the analysis focused on the presence of skin pigmentation abnormalities in patients. Although, it was discovered that 66.6% of the cases exhibited some form of skin pigmentation irregularity.[14]

It is noteworthy to mention that these variations with regards to fact that patients with skin manifestations tended to delay seeking medical advice in comparison to those presenting with neurological symptoms.[21] We found 48.5% had gross motor delay, this was much lower than the study of Sadek, et al.[14]

Furthermore, the researchers also analyzed the electroencephalogram (EEG) tests results, that indicated the abnormal EEG readings in majority of the cases, specifically in 85.2% of the participants,[14] nearly similar abnormal results observed 90.9% in our study and study done by Ulate-Campos et al.[22] These results shed light on

the various aspects of tuberous sclerosis and neurofibromatosis, providing valuable insights into the prevalence and clinical features of these complex conditions.[14] There was a strong association among types of seizures to EEG findings as shown in table 5.

TABLE 6: Stratification of types of Seizures with respect to EEG findings

Types of seizures	EEG findings among studied children				
	Normal	Focal epileptiform discharges	Generalized epileptiform discharges	Hypsarrhythmia	p-value
Generalized tonic clonic	3	0	12	2	
Focal seizures	1	3	1	0	
Myoclonic seizures	0	1	1	1	0.014
Infantile spasm	2	0	1	2	
No seizures	2	0	1	0	
Total	**8**	**4**	**16**	**5**	**33**

The type of discharges disagrees with other study of Sadek, et al., where the focal epileptiform discharges were common tracing 33.3%,[14] while we found generalized epileptiform discharges 48.5% in our study. Neuroimaging done in all our patients, the commonest finding discovered the presence of subependymal modules in 30.3%, this disagrees with other studies where brain calcifications 55.6% and 70% were the most common findings by Sadek, et al., and Sun et al.,[14,23] respectively.

Within the cohort of patients afflicted with neurocutaneous disorders, a prevailing pattern emerges, in which the most prevalent form of seizures in these children tends to be generalized in nature; indeed, this particular type of seizure predominates within the study group. Our patient clinic, upon careful examination, has determined that tuberous sclerosis holds the distinction of being the most frequently encountered neurocutaneous disorder. It is worth highlighting the significance of dermatological assessment in the timely identification and diagnosis of neurocutaneous disorders, for it serves as a crucial tool for early detection. By employing dermatological examination as a diagnostic strategy, healthcare professionals can effectively identify and intervene in the management of neurocutaneous syndromes, thereby ensuring optimal patient outcomes.

Limitations of study: Although this study has been conducted at the largest pediatric neurology department of the country which gives a broader insight about common neuro-cutaneous disorders. However, being a single centered study, results cannot be generalized.

CONCLUSION

Neurocutaneous syndromes encompass a multitude of clinical presentations, exhibiting a diverse array of manifestations. Tuberous sclerosis was the most common and frequent type of neurocutaneous syndrome. They may have high association with epilepsy. Consequently, our objective is to promptly identify the indications and manifestations associated with neurocutaneous syndrome, in order to provide effective and early intervention strategies.

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Conflict of interest: Nil

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