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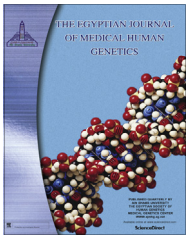

ORIGINAL ARTICLE

Multidisciplinary approach for evaluation of neurocutaneous disorders in children in Sohag University Hospital, Upper Egypt

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KEYWORDS

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Autism

Abstract *Background:* Neurocutaneous syndromes (NCS) are a broad term for a group of neurologic disorders that involve the nervous system and the skin. The most common examples are neurofibromatosis type 1 (NF-1) and type 2 (NF-2), tuberous sclerosis (TS), Sturge–Weber syndrome (SWS), ataxia telangiectasia (AT), and Von Hippel Lindau disease (VHL). These disorders are characterized clinically by neurological manifestations such as convulsions, mental retardation and learning disabilities in addition to cutaneous manifestations, and lastly tubers (benign growths found in different organs of the body).

Aim of the study: This study aimed to identify clinical, imaging, and neurophysiological profiles of neurocutaneous disorders. Children presented to the Pediatric neurology and Dermatology clinics, Sohag University Hospital who fulfilled the criteria for diagnosis of specific neurocutaneous syndromes were eligible for this study.

Patients and methods: All studied patients were subjected to thorough clinical history, full clinical examination, developmental assessment, and dermatological examination. Computed tomography of the brain (CT) and electroencephalography (EEG), ophthalmic, and phoniatric evaluation were also done for all children. Echocardiography was done for only twenty children.

Results: During the period of the study we diagnosed 27 cases with neurocutaneous disorders, tuberous sclerosis represented the majority of cases as it was detected in 12 cases (44.45%). The main complaint was convulsions in 19 cases (70.37%), whereas skin pigmentation was detected in 18 cases (66.66%). Developmental assessment showed that global developmental delay was found in 20 cases (74%). CT of the brain showed that 15 cases (55.55%) had intracranial calcifications and abnormal EEG findings were detected in 23 cases (85.2%). 85% of the studied children had various degrees of mental retardation. Echocardiography showed that three cases (15%) had ventricular wall tumor mostly rhabdomyoma.

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Conclusion: Neurocutaneous disorders had multiple clinical presentations and required a team work approach including various specialties in their evaluation and management.

1. Introduction

Neurocutaneous syndromes are a broad term for a group of neurologic disorders that involve the nervous system and the skin. These syndromes are due to defects in differentiation of the primitive ectoderm and usually life-long conditions that can predispose to malignancies. The most common examples are neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2), tuberous sclerosis (TS), Sturge–Weber syndrome (SWS), ataxia telangiectasia (AT), and Von Hippel Lindau disease (VHL) [1]. Neurocutaneous disorders are relatively common and could be seen in different societies with different incidences for example, NF-1 affects one in every 4000 births while NF-2 affects one in every 60,000 births in the United Kingdom [2] while in other countries NF-1 has a birth incidence of 1 in 2500 to 1 in 3000 [3,4]. Tuberous sclerosis affects one every 6000–9000 births and nearly one million people worldwide are known to have tuberous sclerosis [5]. Sturge–Weber syndrome, ataxia telangiectasia and the Von Hippel Lindau disease are rare disorders.

These disorders are characterized clinically by neurological manifestations as convulsions, mental retardation and learning disabilities [6], in addition to cutaneous manifestations including café au lait patches, port-wine stain (facial birth mark covering one upper eyelid and forehead), telangiectasia (tiny red spider-like blood vessels), and tubers (benign growths found on different organs as brain, eyes, heart, skin, kidneys and lungs) [6,7]. These manifestations are present in various combinations according to the type of syndrome allowing clinical diagnosis in most of the cases.

Clinical features required for diagnosis of NF-1 are; (1) one to six or more café-au-lait spots over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals, (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) Freckling in the axillary or inguinal regions, (4) optic glioma, (5) two or more lisch nodules (iris hamartomas), (6) osseous lesions such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis, (7) first degree relative affection (-parent, sibling, or offspring) with NF-1 by the above criteria with discovered mutations of the NF-1 gene, which is located at chromosome 17q11.2. Two of these seven "cardinal clinical features" are required for positive diagnosis [8].

Clinical diagnostic criteria for TS include 11 major features and six minor features. Major features include: hypomelanotic macules ($\geqslant 3$, at least five-mm diameter), angiofibromas ($\geqslant 3$), ungual fibromas ($\geqslant 2$), shagreen patch, multiple retinal hamartomas, cortical dysplasias (includes tubers and cerebral white matter radial migration lines), subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), and angiomyolipomas ($\geqslant 2$). Minor features include; "confetti" skin lesions, dental enamel pits (> 3), intraoral fibromas ($\geqslant 2$), retinal achromic patch, multiple renal cysts, and nonrenal hamartomas. Definite diagnosis should include two major features or one major feature with $\geqslant$ two minor features and possible diagnosis: either one major feature or $\geqslant$ two minor features [9].

Sturge–Weber syndrome (SWS) is a congenital non inherited neurocutaneous disorder. It is characterized by cutaneous manifestations, neurological abnormalities, and eye affection [10]. Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder. There is an impairment of skin ability to repair damage from ultraviolet light, leading to early skin changes, and eye damage [11].

Early diagnosis of these disorders is very important as it allows early treatment, proper follow up and genetic counseling. This requires the integrated work of pediatricians, dermatologists, ophthalmologists and other specialties to make appropriate diagnosis and management strategy. To the best of our knowledge a few studies were done in Upper Egypt to clarify this topic so our aim was to identify clinical, imaging, and neurophysiological profiles of neurocutaneous disorders in Sohag, Upper Egypt.

2. Patients and methods

2.1. Study design

This is an observational hospital based study, done in the Pediatric neurology and Dermatology clinics at the Sohag University Hospital, Upper Egypt, during the period from December 2012 through November 2013. All children from birth up to 15 years old who fulfilled the criteria for diagnosis of specific neurocutaneous syndromes were eligible for this study. Informed consent of the parents of the children was taken to conduct this research in addition to the approval of the Faculty of Medicine, Sohag University Ethics committee. The work has been carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) for experiments on humans.

2.2. Methods

All studied patients were subjected to thorough clinical history including detailed history of the presenting symptoms like seizures and developmental history. Autistic symptoms, hyperactivity symptoms, and a family history of similar conditions such as presence of epilepsy, mental retardation or global developmental delay were also clarified.

Full clinical examination (general, systematic, and detailed neurological examinations), developmental assessment, and dermatological examination were done. Computed tomography of the brain (CT) and electroencephalography (EEG) were done for all patients. Echocardiography was done for only 20 children. All patients were referred to the Phoniatric Unit and were subjected to language evaluation as well as assessment of passive and active vocabulary. Also evaluation of the autistic

features using the American Psychiatric Association diagnostic criteria for autism [12], and Childhood Autism Rating Scale (CARS) was done. The degree of autistic disorders was set as 30 serving as the diagnostic point for autism [13]. Mentality was assessed by Vineland Adaptive Behavior Scales [14], and Stanford–Binet Intelligence Scales [15]. Ophthalmological and fundus examination were done to detect any eye affection.

3. Results

3.1. Descriptive data of the studied patients

During the study period, 27 children were diagnosed as having different types of neurocutaneous syndromes by clinical examination and neuroradiological studies (CT Brain). The mean age of the whole studied group was 5.27 ± 4.11 years. Fifteen children (56%) were males and 12 (44%) were females. It was found that tuberous sclerosis cases were 12 cases (44.45%) constituting the majority of the cases followed by neurofibromatosis, and xeroderma pigmentosum were detected in four cases (14.82%) for each. Sturge–Weber syndrome cases were detected in three cases (11.11%) and lastly incontinentia pigmenti and hypomelanosis of ito were detected in two cases (7.40%) for each (Table 1).

3.2. Clinical features

The main complaint was convulsions which was detected in 19 children (70.37%) whereas skin pigmentations were detected in 18 cases (66.66%), delayed motor development was detected in 6 cases (22.22%), and autistic features were detected in four children (14.8%) (Fig. 1).

As regards seizures, eleven children (58%) started to experience seizures at the age of 1 month–1 year. Twelve children (63%) had generalized seizures including the 6 children (tuberous sclerosis cases) who had infantile spasms, and seven children (37%) who had focal seizures. Seizures were variable in frequency where seven children (37%) experienced seizures monthly, six children (36.5%) weekly. Response to treatment varied as well, where seven children (37%) were controlled and twelve children (63.15%) were not controlled (Table 2).

Delayed motor, language, and social development were noted in 20 children (74%). This means that they had global developmental delay. Eight children had sphincteric abnormalities.

As regards general examinations; six children (22%) had microcephaly, two children (7.4%) had dysmorphic features, one patient (3.7%) had macrocephaly and one patient (3.7%) had teeth abnormalities and alopecia.

Neurological examination of the studied children showed that; 20 children (74.07%) had delayed speech, one child (3.70%) had stuttering, and one child (3.70%) had a squint. Seventeen children (63%) had generalized hypotonia and hyperreflexia, and two children (7.4%) had hemi paresis, hypotonia and hyperreflexia. Movement disorders were detected in 6 children; three children (11%) had ataxia, two children (7.4%) had athetosis and one child (3.7%) had tremors (Fig. 2).

Table 1 Distribution of neurocutaneous syndromes.

Type	No. of patients	Percentage (%)
Tuberous sclerosis	12	44.45
Neurofibromatosis	4	14.81
Xeroderma pigmentosa (XP)	4	14.81
Sturge–Weber syndrome (SWS)	3	11.11
Incontenentia pigmenti (IP)	2	7.41
Hypomelanosis of ito (HI)	2	7.41

Table 2 Seizure characteristics in the studied children.

Variable	$N = 19$	Percentages (%)
Age of onset		
1 month–1 year	11	57.89
1year–5year	5	26.32
5year–12year	3	15.79
Type of seizures		
Generalized seizures	12	63.16
Partial (focal) seizures	7	36.84
Frequency of seizures		
Monthly	7	36.84
Weekly	6	31.58
Daily	3	15.79
Very frequent (⩾3/day)	3	15.79
Response to treatment		
Non controlled	12	63.15
Controlled	7	36.84

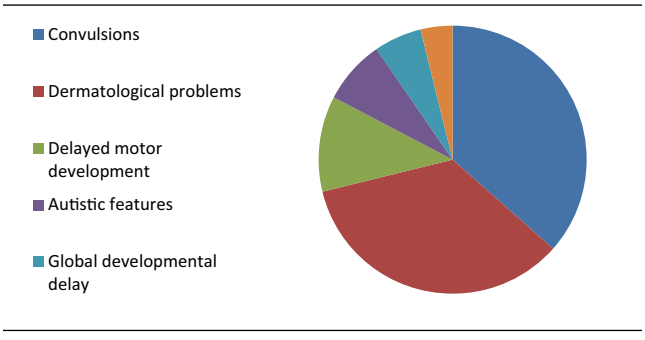

Figure 1 Main complaint in the studied children.

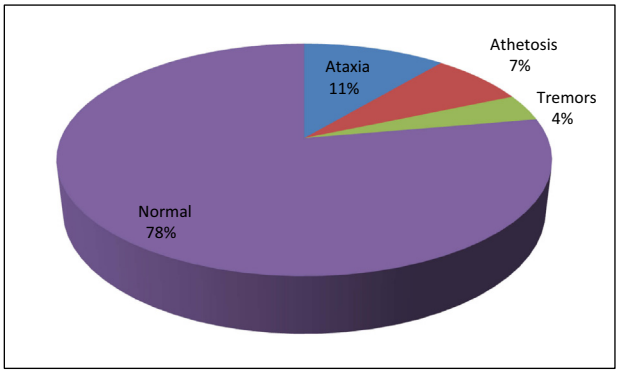

Figure 2 Movement disorders in the studied children.

Dermatological examination showed that seven children (25.93%) had asch-leaf macules, five children (18.52%) had asch-leaf macules, shagreen patches and angiofibromatosis of the face, and lastly four children (14.81%) had café au-lait patches (Table 3 and Figs. 4–11).

3.3. Ophthalmological and fundus examination

By ophthalmological and fundus examination; it was found that 22 children (81.4%) had normal fundus examination, two children (7.4%) had papilledema with optic atrophy and retinopathy. Iris lisch nodules were detected in one case (3.75%), pale optic disc in one case, and high intraocular pressure (IOP) in one case (3.75%).

Table 3 Dermatological manifestations of the studied children.

Dermatological examination	Number	Percentages (%)
Asch-leaf macules	7	(25.93)
Asch-leaf macules, shagreen patches, angiofibromatosis of the face	5	(18.52)
Café au-lait patches	4	(14.81)
Axillary, inguinal freckles	4	(14.81)
Sun exposed freckles	3	11.11
Port-wine stain	3	11.11
Bizzar shaped hypo pigmentations	2	(7.40)
Bizzar shaped hyper pigmentations	2	(7.40)

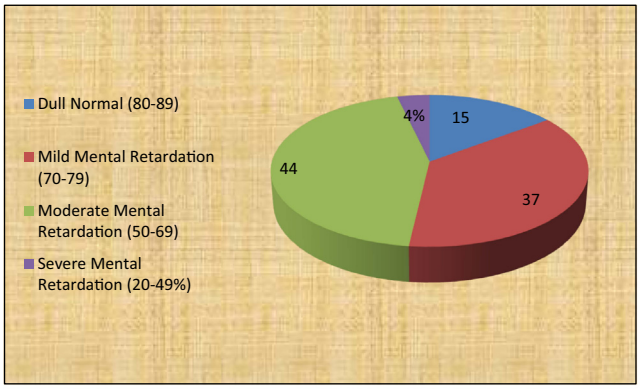

Figure 3 IQ findings in the studied children.

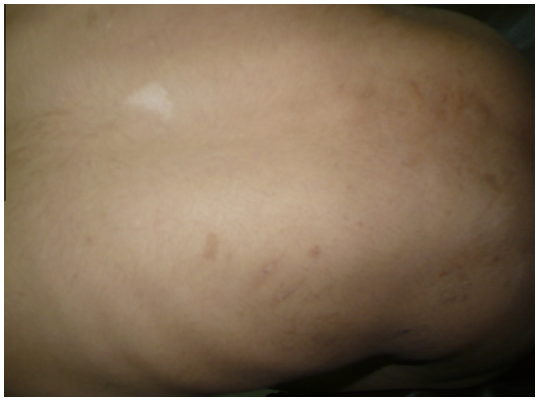

Figure 4 Ash-leave macules and shagreen patch in the back in a child with tuberous sclerosis.

Figure 5 Angiofibromatosis of the face in a child having tuberous sclerosis.

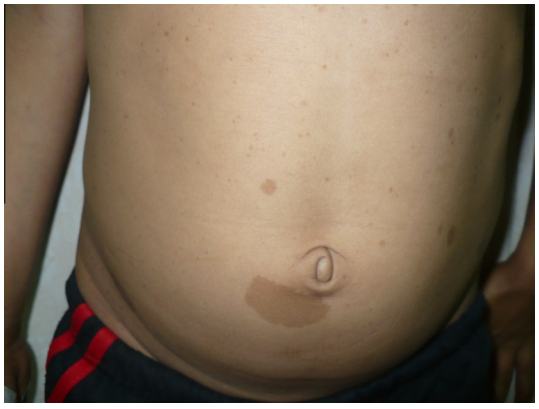

Figure 6 Café au lait patches in neurofibromatosis type 1 child.

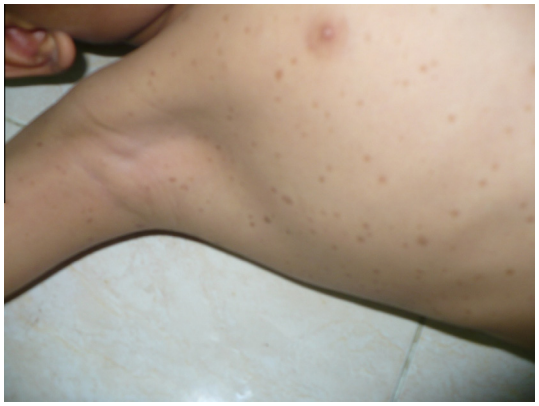

Figure 7 Axillary freckles in a child had neurofibromatosis type 1.

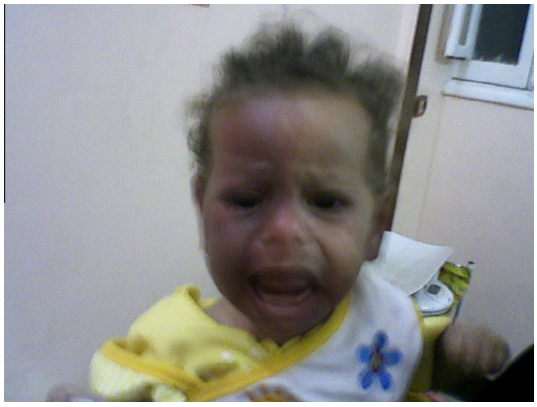

Figure 8 Port-wine stain in a girl having the Sturge–Weber syndrome.

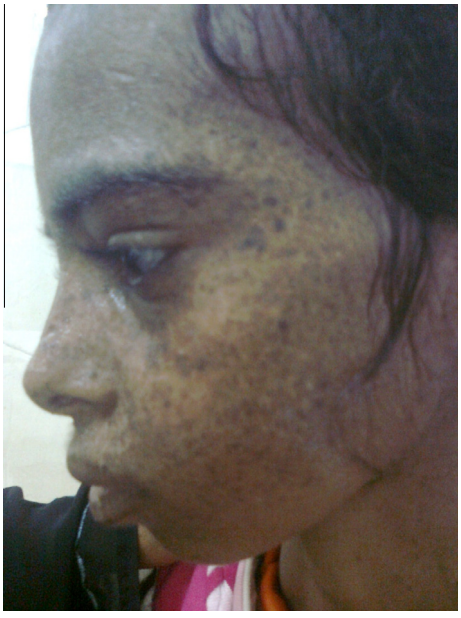

Figure 9 Freckles with hypo and hyper pigmentation in the face in a girl with xeroderma pigmentosa.

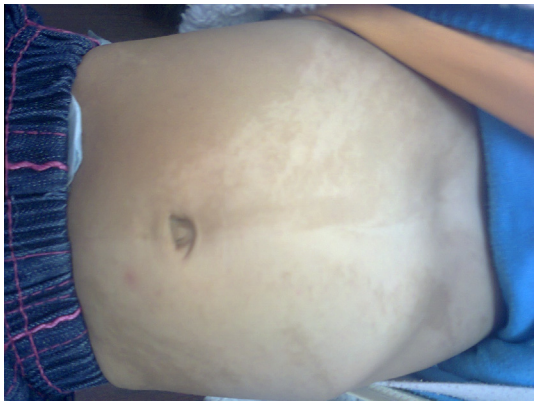

Figure 10 Whorly pattern of hypo pigmentation in a child with hypomelanosis of ito.

3.4. CT brain

CT brain was done to all studied children and showed that 12 children (44.44%) had multiple foci of calcifications (scattered or periventricular), and three children (11.11%) had serpentine calcifications. In one child with neurofibromatosis there was a brain tumor which correlates with astrocytoma and confirmed by magnetic resonance imaging (MRI) of the brain (Table 4 and Figs. 11–13).

3.5. EEG findings

EEG was done to all children and we found that nine children (33.33%) had focal epileptic discharges, eight children (29.62%) had generalized epileptic discharges, six children (22.22%) had hypsarrhythmia, and four children (14.81%) had normal EEG findings (Table 5).

3.6. IQ findings

Intelligence Quotient (IQ) assessment showed that 12 children (44.4%) had moderate mental retardation (MR), ten children (37%) had mild MR Fig. 3).

3.7. Echocardiography findings

Echocardiography was done to 20 children and revealed that 16 children (80%) had normal echo findings, three children (15%) had a ventricular wall mass (mostly rhabdomyoma), and one child (5%) had arrhythmia confirmed by electrocardiography (ECG). Children with positive echocardiographic findings were belonging to tuberous sclerosis complex group.

4. Discussion

Neurocutaneous syndromes are a group of disorders that lead to the growth of tumors in various parts of the body including the nervous system and skin. While some can be diagnosed at birth; others do not produce symptoms until later in life. Although neurocutaneous syndromes cannot be cured, treatments can help to manage symptoms and any health problems that occur [1].

The present study performed a clinical analysis and prospectively collected the data of 27 children having NCS. The mean age was 5.2 ± 4.11 years which was nearly similar to other studies [16,17], and lower than the results of Sun et al., study where the mean age was 14.7 ± 10.5 years as their study included a wide range of age 2 months–58 years [18]. In our study, neurocutaneous disorders were slightly more common in males and this agrees with the study of Purkait et al. [16].

In our study we found that the majority of the collected cases were tuberous sclerosis (44.44%) followed by neurofibromatosis type1 and xeroderma pigmentosum (XP). This was in accordance to the study of Diaconu et al. [19], and in contrast to the results of Purkait et al., where NF-1 were the most common [16].

In the present study the most common presentation of NCS was convulsions in 70.37% of the studied children, this was slightly lower than the result of Jóźwiak et al., where seizures were recorded in 95% of the patients [20], and much higher

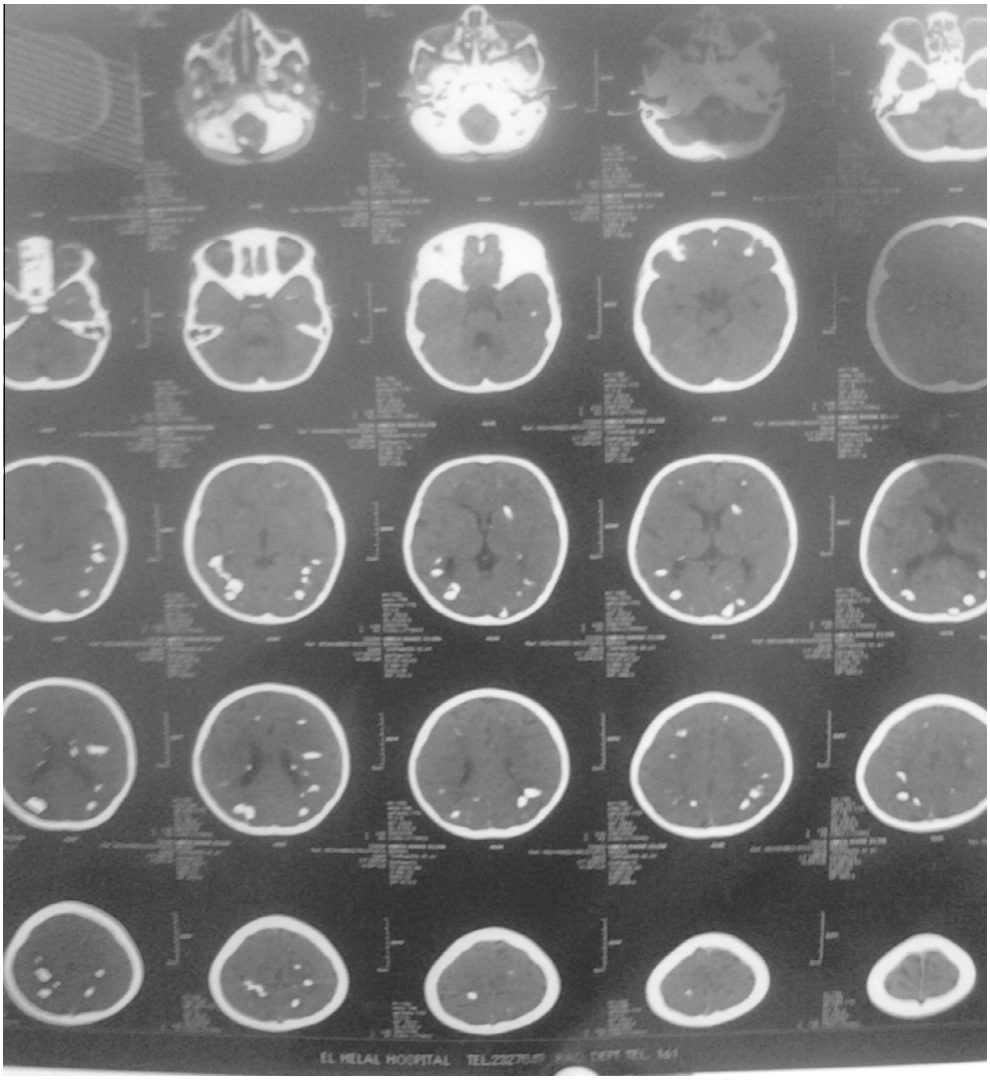

Figure 11 CT brain showed multiple cortical calcifications in a child with tuberous sclerosis.

Table 4 CT brain findings in the studied children.

Variables	Number	Percent (%)
Multiple foci of calcifications	6	(22.22)
Periventricular calcifications	6	(22.22)
Serpentine calcifications	3	(11.11)
Involutional changes	2	(7.41)
Hydrocephalus	2	(7.41)
White matter disease	1	(3.7)
Tumor (Astrocytoma)	1	(3.7)
Normal	6	(22.22)

than the study of Diaconu et al., where convulsions were detected in 39.13% of cases [19].This variation between studies could be related to variations in the types of NCS.

The age of onset of convulsions was from 1 month to 12 years; this was similar to the study of Diaconu et al., where the age of onset of seizures was 4 months to 15 years. According to our study convulsions of most cases of NCS were generalized seizures especially infantile spasms and frequently occurred, this disagrees with Diaconu et al., study where the commonest type of seizures was complex partial type, not frequent. In our study patient's response to treatment was variable (good, partial and poor response), this was similar to the study of Diaconu et al. [19]. In tuberous sclerosis, all children were complaining of convulsions which were generalized in 66.67% and focal in 33.33%, these results agree with the study of Söğüt et al. [17]. In 58.33% of TS cases, convulsions started in the first year of life and this agrees with the study of Jóźwiak et al. [21]. Infantile spasms were observed in 50% of TS cases and this was much higher than the study of Jóźwiak et al., where infantile spasms were observed in 21% of cases [21]. Epileptic discharges in EEG were detected in 91.7% and this was similar to Ulate-Campos et al., where epileptic discharges in EEG were detected in 91% [22].

In tuberous sclerosis, cutaneous manifestations were the most characteristic features which presented as initial manifestations of the disease in 100% of cases and were helpful in early diagnosis. We observed in our study that hypo pigmented (Asch-leaf) macules were the most frequent sign as they could be found in all children with TS, this was similar to other

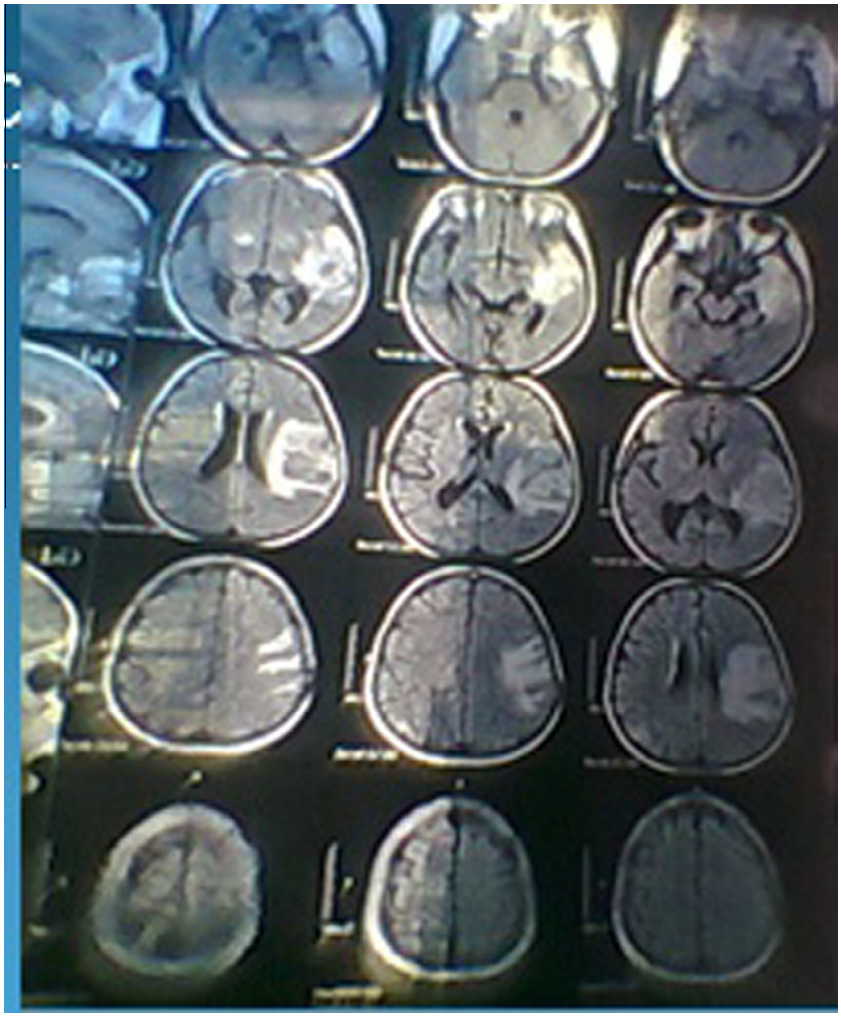

Figure 12 MRI brain showed tumor correlated with astrocytoma.

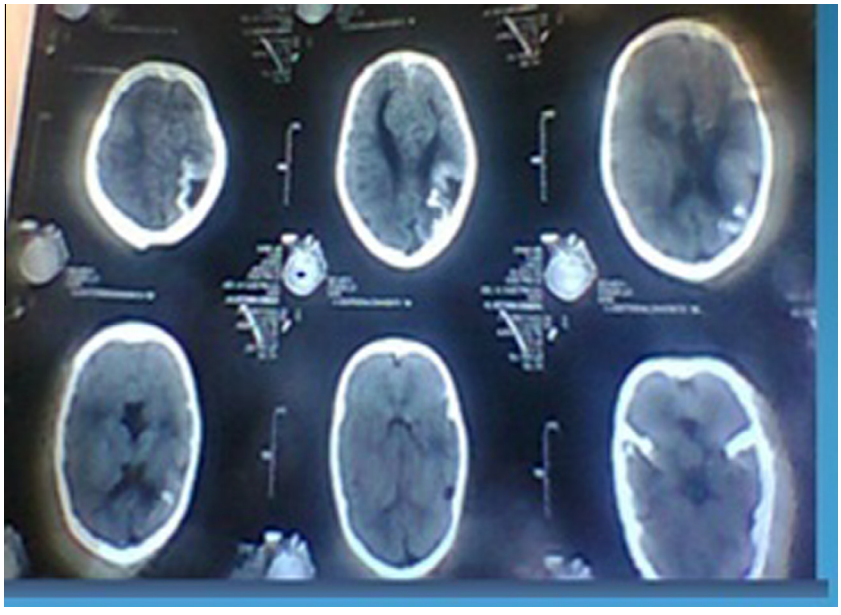

Figure 13 Serpentine calcification in a child having Sturge–Weber syndrome.

Table 5 EEG Findings in the studied children.

EEG findings	Number	Percentages (%)
Focal epileptic discharges	9	33.33
Generalized epileptic discharges	8	29.62
Hypsarrhythmia	6	22.22
Normal	4	14.81

studies [21,22]. All the cases of NF-1 presented with one consistent finding that was increasing number and size of café au lait macules (CALM) and axillary or inguinal freckling, these results agree with the study of Purkait et al. [16].

In our study, according to neurodevelopmental analysis of the studied children, we found 74% of them had delayed motor, social and language development, while by IQ testing we found 85.2% had mental retardation (MR), this was much higher than the results of Diaconu et al., study where only 21.73% of patients had mental retardation [19]. This could be explained that only severe cases seek medical evaluation. In tuberous sclerosis 33.33% of cases had autistic features. The association of autism with TS is well known, many studies agree with our findings and clarify this point [7,23–25].

CT brain in children with NCS revealed that 55.6% of the patients had scattered, periventricular, and serpentine calcifications, this result was less than found in Sun et al., study where brain calcifications were observed in 70%. This was because they studied only cases of TS [18]. Echocardiography showed that 25% of children with tuberous sclerosis had a ventricular wall mass (mostly rhabdomyoma); this was in accordance to other studies [18,26].

By ophthalmological and fundus examination; it was found that the majority had normal fundus (81.4%), other findings were papilledema with optic atrophy and retinopathy, iris lisch nodules, pale optic disc, and high Intraocular pressure (IOP). These ophthalmological findings agree with other studies [27,28].

5. Conclusion

Neurocutaneous disorders had multiple clinical presentations; tuberous sclerosis was the most frequent type of neurocutaneous disorders in our hospital. Epilepsy especially infantile spasms was the commonest presentation for those children. Language development and cognitive functions are significantly impaired in NCS so they should be assessed regularly for those patients. Early diagnosis and follow up of these disorders are important for appropriate management of seizures and early detection of malignancy. This requires a team work approach including pediatricians, neurologists, cardiologists, ophthalmologists, dermatologists, phoniatrician, radiologists, oncologists and other specialties in their evaluation and management.

Declaration

The authors declare that there was not any conflict of interest.

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