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Case Series

Cutaneous and neurological profile of tuberous sclerosis complex in children: A case series and literature review

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ABSTRACT

Introduction: Tuberous sclerosis complex (TSC) is a rare genetic disease, belongs to the group of the neurocutaneous syndrome. The consequence of genetic mutation is inadequate inhibition of the mammalian target of rapamycin (mTOR) signal pathway that results in the inactivation of regulated cells growth and formation of dysgenic tissues/ hamartomas in multiple systems. The updated version of diagnostic criteria for TSC and management has been laid down after the second International Tuberous Sclerosis Complex Consensus Conference (2012).
Aims: To describe the clinico-neuroradiological profile and aspects of the antiepileptic treatment of " definite" TSC cases
Materials and Methods : We report a case series of four TSC cases attended in a teaching hospital. The " definite" TSC cases are diagnosed by updated diagnostic criteria (2012) and data obtained retrospectively from records. We discuss the present series in light of the current literature.
Result: We report three female and one male TSC patient. The "definite" TSC is diagnosed by two major criteria - one or more cutaneous lesions and neuropathological lesions by neuroimaging. No family history of TSCs has been reported in the series.
Hypomelanotic macules were observed in all (n=4) patients. Two TSC patients (n=2) had facial angiofibroma and one TSC had (n=1) shagreen patch. In neuroimaging studies, subependymal nodules were reported in three TSC patients (n=3) and one TSC had cortical dysplasias.
The most common neurological manifestation in the TCS series is epilepsy; three TSC patients (n=3) had epilepsy. One TSC patient (n=1) did not present with epilepsy. Infantile spasms, tonic-clonic seizure, and focal seizure were the phenotype of seizures. Vigabatrin, valproate, and phenobarbitone have been prescribed in TSC patients. Scholastic performance was normal in one TSC patient (n=1) and subnormal in another patient(n=1).
Conclusion: TSC -associated cutaneous lesions, the major features for diagnosis, develop an age-dependant manner. The prospective evaluation with neuroimaging is an integral part of TSC management. Infantile spasm, focal seizure are the first manifested seizures with a subtle presentation. The first-contact physicians must be well knowledgeable about updated 2012 diagnostic criteria, so timely management could be advocated. Vigabatrin is the first choice for infantile spasms in TSC patients as well as for focal seizures. Cognitive outcome/ scholastic performance may vary in TSC patients.

1. Introduction

Neurocutaneous syndromes (NCS) are a heterogeneous group of genetic diseases with similar characteristics:

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primitive ectodermal development defect and multi-organ involvement.[1] Tuberous sclerosis complex (TSC) is one of the most common NCS.[1]

TCS is caused by a mutation of the tumor suppressor gene - TSC1 (modulates encoding hamartin) or TSC2 gene (modulates encoding tuberin).[2]

TCS is diagnosed by a consensus, evidence-based tool " 2012 International Tuberous Sclerosis Complex Diagnostic Criteria".[3] (Table 1) The incidence of TCS patients is 1:17.785 per live births after using the 2012 diagnostic criteria.[2]

We report the cliniconeurological features of four "definite' TCS children fulfilled two major features of the 2012 International TSC Diagnostic Criteria with a focused review of the literature.

The "definite" TCS is considered when fulfilling two major features or one major with two/more minor features. And "possible" TCS needs to fulfill one major feature or two or more minor features.[3]

2. Materials and Methods

This is case series of four cases of TCS. The series is a descriptive study design. TCS cases are diagnosed by the 2012 international Tuberous sclerosis complex updated diagnostic criteria. The four patients presented at a tertiary care teaching hospital in Kolkata, India, from 2010 to 2013. The medical records have been reviewed retrospectively and the analysis of the records described in Table 2.

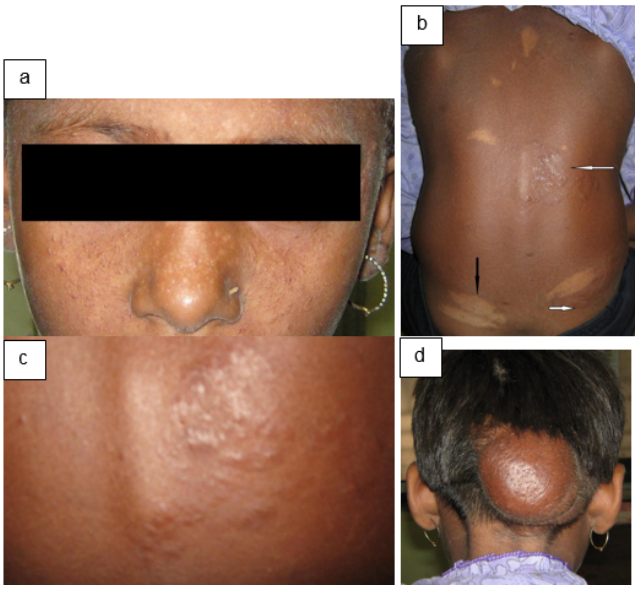

Fig. 1: a: Facial Angiofibromas; **b:** black arrows - Hypomelanotic macule, white arrows-Shagreen patch; **c:** Shagreen patch; **d:** Soft, non-fluctuating mass at occipetal region.

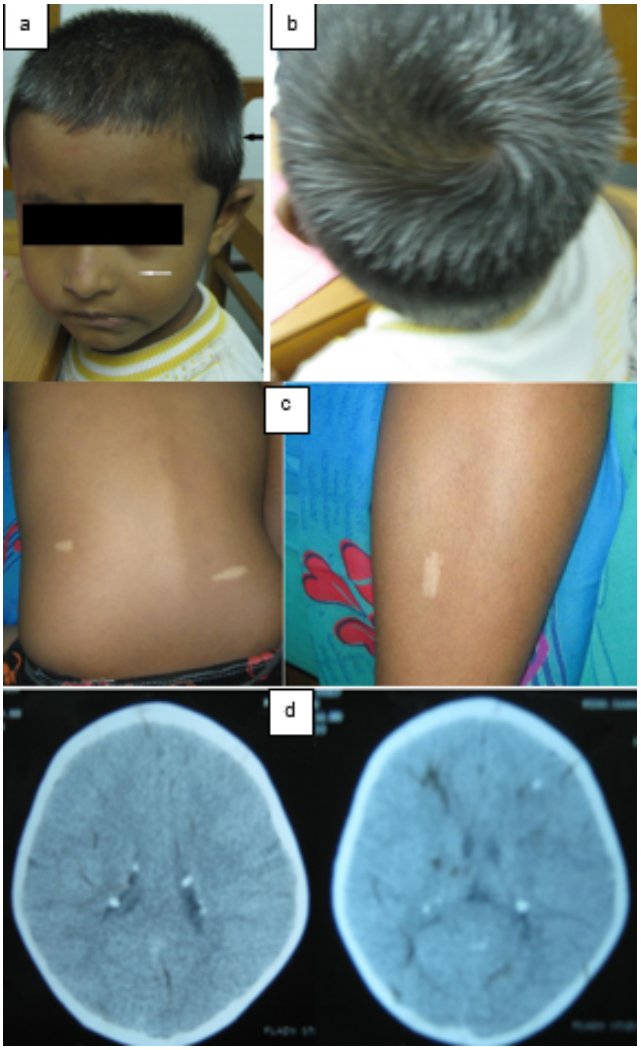

Fig. 2: a: white arrow - Facial Angifibroma, black arrow hypomelanotic of hair; **b:** Poliosis / hypomelanosis of hair; **c:** Hypomelanotic patches; **d:** Multiple bilateral subependymal nodules

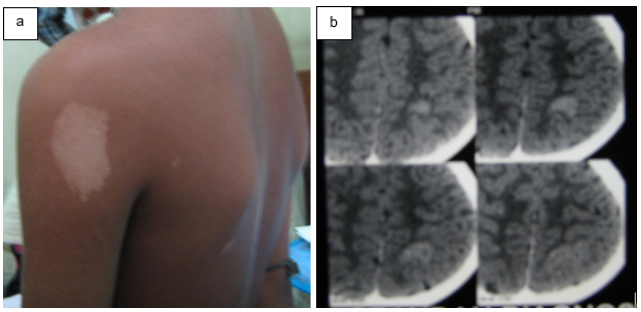

Fig. 3: a: large >10cm Hypomelanotic patches; **b:** MRI: focal signal changes changes in high parietal regions

Table 1: The International TCS Diagnostic Criteria Updated on 2012

Major criteria	Minor features
1. Hypomelanotic macules (three in number or more than three , minimum five mm diameter)	1. 'Confetti' skin lesions
2. Angiofibromas (three in number or more than three) or fibrous cephalic plaque	2. Dental enamel pits ((three in number or more than three)
3. Ungual fibromas (two in number or more than two)	3. Intraoral fibromas ((two in number or more than two))
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias (The cortical tubers and cerebral radial white matter migration lines in cortex are considered as cortical dysplasia)	6. Non-renal hamartomas.
7. Subependymal nodules (SENs)	
8. Subependymal giant cell astrocytoma (SEGA)	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis	
11. Angiomyolipomas (≥2) (The presence of lymphangioleiomyomatosis together with angiomyolipomas and no other features of TCS - does not considered as TCS.)	

Table 2: Description of four Tuberous Sclerosis Complex children

Final diagnosis	Age	Gender	Clinical manifestation and Neuroimaging studies
TCS Case no. 1	7yr	F	Facial Angiofibroma .(Figure 1a). Hypomelanotic macule on trank (Figure 1b). Shagreen patch.(Figure 1b & c). A soft, non-fluctuating mass at occipetal region (Figure 1d). Epilepsy - Tonic Clonic convulsion Non-contrast CT scan: Bilateral multiple small subependymal calcified nodules seen. Multiple small subcortical cystic lesions are noted in right frontal and bilateral parietal areas suggestive of tuberous sclerosis in CT scan. A well-defined soft tissue density lesion is seen in occipital area at subcutaneous plane measuring 6.04 cm nature could not be identified.
TCS Case No. 2	3yr 6 Months	F	Facial Angiofibroma .(Figure 2a). Poliosis / hypomelanosis of hair (Figure 2a. & b). Hypomelanotic patches (Figure 2c). Presented for only Skin lesions, Had no seizure episode till the date of study Non-contrast CT scan: Multiple bilateral subependymal nodules (Figure 2 d).
TCS Case No. 3	7yr	F	Hypomelanotic patches in face , trunk and limbs since birth, Multiple (total number 14) Maximum size approx 10 cm on left arm (Figure 3a) one on face above 1.5 cm Epilepsy- Mixed type - head nodding in clusters persists for2 to 3 seconds; several episodes rapid eye blinking and twitching of angle of mouth - 10 to 15 episodes per day without generalization) T2 weighted FLAIR MRI: focal signal changes changes in high parietal regions (Figure 3b) and frontal lobe CT (plain & contrast): small areas of increased signal intensity without enhancement or edema or calcification or mass effect in the grey - white matter junction of the left parietal and frontal lobes - cortical dysplasias Awake Video EEG: Frequent paroxysms of High amplitude generalized spike wave discharges
TCS Case no 4	11 Months	M	Hypomelanotic patch in trunk multiple ((Figure 4a) Epilepsy- focal seizure Non contrast CT : Periventricular multifocal calcific subependymal nodules noted.(Figure 4b) Multifocal hypodense lesion in Cerebral cortex and subcortical white matter EEG : intermittent bilateral discharges of sharp waves and spike suggestive of paroxysmal generalized dysrhythmia

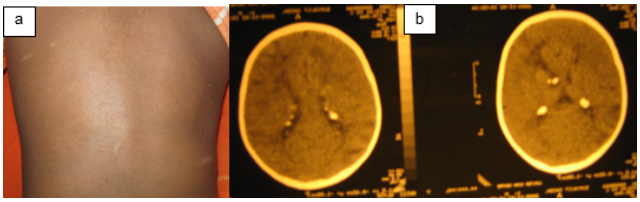

Fig. 4: a: Hypomelanotic pathes; **b:** Periventricular multifocal calcific subependymal nodules

3. Discussion

TSC is a multisystem disease caused by a genetic mutation that causes the development of dysgenic tissues and the formation of hamartomas in different organs. However, approximately 20% of TCS patients do not have a mutation, and just 12.5% of the first-degree relative of TCS patients were affected by TSC.[2] The mutational changes are neither treated by genetic approaches as standard management nor required as a diagnostic tool according to updated 2012 diagnostic criteria of TCS.[3–5]

Hypomelanotic macules were observed at the time of the birth by the parents of case no. 3 and 4 in this series. And the parents of the case no 1 and 2 have reported hypomelanotic macules before three months and six months of age, respectively.

Four TCS children (n=4) of the series were “Possible” TSC either at birth or before six months. The age of the first clinical expression of TCS is variable.[2,5,6] An epidemiological study showed the age range of the first diagnosis of TCS patients is birth to 69 years with a median age of one year.[6] However, a " possible" TCS could be diagnosed five months before birth with the detection of cardiac rhabdomyoma by antenatal ultrasonography.[2] And when the antenatal sonography was a part of the study design, the number of antenatal ”possible” TCS patients raised from 5.9%[6] to 22.1%.[2] And prospective management can start from birth.

In this TCS series, three were female, and one was male. A female preponderance (F: M:: 51.8: 48.2) has been seen in the database.[6]

Hypomelanotic macules are the most common (90%) skin lesions of TCS; often the first skin lesion in TCS.[7,8] These are hypopigmented areas observed in more than 50% of infants at birth, and it develops almost in every child (100%) before two years of age.[7,8]

Hypomelanotic macules are asymmetric oval, medium to long 1 to 12 cm in diameter[5] (required size in diagnostic criteria - five mm)[3] and mostly on the trunk and the face.[5] The lesion looks like the leaf of the ash tree (found in India, North America) - oval-shaped with rounded and tapered end - called “ash leaf” spots.[5]

Poliosis/hypomelanotic of hair is counted as hypomelanotic macules diagnostic criterion.[3] Case no. 2 of the series had hypomelanotic hair (Figure 2a & b) since birth and four hypomelanotic macules.

In this TCS series, four patients (n=4) had hypomelanotic patches as one “major” feature - three or more in numbers and > 5 mm diameter. Case no 3 had the maximum numbers of hypomelanotic macules - fourteen with a diameter of 10 cm(Figure 3a).

Confetti-skin lesions, a minor feature, are multiple, hypopigmented, small (1- 3 mm), typically scattered over limbs. No patient in the series had confetti-like skin lesions.

Facial angiofibromas are the most prominent visual skin lesions.[5]

Previously, these are erroneously called adenoma sebaceum. Facial angiofibromas are dark-brown to red-brown, papulonodular (roughly 5 mm diameter), smooth surface with visible capillaries, and usually in a cluster with butterfly-like distribution on the face.[5]

The presence of a minimum of three facial angiofibroma is considered a major criterion.[3] Two TCS patients (case no. 1 and 2) in the series had more than three facial angiofibroma. (Figure 1a.&Figure 2a.)

Case no. 2 and 3 in this series age of three years six months and seven years, respectively, had no facial angiofibroma till during study. Facial angiofibromas appear typically from 2 to 5 years of age and grow in approximately 75% of TCS patients.[3,7]

Shagreen patches, a major feature of diagnostic criteria, manifest as a large irregular and elevated plaque with orange peel-like surface[3] and specific for TCS[3] Shagreen patch develops characteristically in the first decade of life on the lumbar-sacral region in 50% of TCS patients.[5,7]

Shagreen patch grows due to developmental defects in the inner layers of skin.[3]

One patient (case no.1) in the present TCS series had a shagreen patch typically on the lower back.(Figure 1b &.c)

Fibrous cephalic plaque (instead of previous terminology forehead plaque) is seen in 25% of TCS. The plaque is the most specific cutaneous lesion of TSC patients.[3] This is located anywhere on the scalp unilateral, and histologically similar to angiofibromas. We did not find a typical fibrous cephalic plaque in the present TCS series.

Two or more angiomyolipomas are counted as a major feature for TCS diagnosis. These are benign tumors composed of vascular tissue, muscle, and fatty tissue and are comparatively specific for TCS. They are found most frequently in kidneys and other sites (pulmonary, adrenal gland) also. Every TSC patient in the series (n=4) had undergone serial renal ultrasonography to detect early renal mass; no patients had renal lesion.

Case no.1 of this series presented with a mass at the midline in the occipital region. The mass was soft, nonfluctuant and large-sized (6 cm).(Figure 1d.) CT Scan revealed this is a subcutaneous mass but did not detect the nature. The histological nature of the mass has not to be

revealed as the parent refused for biopsy).

Cutaneous lesions require treatment with topical mammalian target of rapamycin (mTOR) inhibitors or laser therapy when lesions are severe, rapidly enlarging, and disfiguring.[5]

Epilepsy is the most common presentation of central nervous system involvement.[3,9]

At least one episode of seizure occurs from 83.6%[9] to 85.2%[10] of TSC patients'. The estimated prevalence of epilepsy in TCS patients is 62%[11] to as high as 93%.[12] In this series, the three TCS patients (n=3) out of four had epilepsy.

In the present series, cases 1, 3, and 4 presented with a first seizure at the age of two years, six years, and six months, respectively. Epilepsy manifested in 80 % of TSC patients before three years of age.[9,10]

Case no 2 (three years six months) had cutaneous lesions without a history of seizure till date of the present study, neuroimaging showed SENs in the brain.

TCS patients may have any type of seizures like or tonic or tonic-clonic seizures, atonic and tonic[13] The early onset seizures are focal seizure and/or infantile spasm.[13] Infantile spasms usually manifested from 1 to 30 years age of TCS patients and focal and multiple type seizure occurred from 1 to 66 years in TCS patients.[9]

Infantile spasms have been documented in 37.8%[10] to 38.9%,[9] and persisted as a single-type seizure in 3.6% of TSC patients' life.[10] The multiple/ mixed types without an episode of infantile spasms have been recorded 54.1%[9] of TCS patients with epilepsy. Focal seizures were observed in 67.5%[9] to 93.2% of TSC patients alone or with multiple types.[10]

The clinical diagnosis of seizures phenotype is difficult in TCS patients as they have subtle manifestations like infantile spasms / focal onset and mixed with other phenotype. The case of 3 in the series was difficult to characterize epilepsy as with a mixed phenotype - infantile spasm and focal seizures. Case no 1 had a tonic-clonic convulsion, and case 4 had focal seizures. The EEG reports of two patients (case 3 and 4) of the present series were obtained and showed bilateral spike-wave discharge in both patients.

The central nervous systems (CNS) major features in updated 2012 TSC diagnostic criteria are 1) Cortical dysplasias, 2) Subependymal nodules, and 3)Subependymal giant cell astrocytoma.[3]

The cortical tubers have been documented in 90% of TCS patients.[3] Cortical tubers (hamartomas) are made of dysplastic, immature neurons and supporting glia without layers configuration of the cortex and mostly develop at the grey-white matter junction of the cerebral cortex.[14] Cerebral white matter migration lines are radially directed heterotopias inside the white matter.[14]

Multi-regional focal cortical dysplasia is only considered as one major feature in the diagnostic criteria as normal a single area of cortical dysplasia may have been seen in a normal person without clinical variables of TCS.[3]

SENs are benign growth of CNS cells that arise from the ependymal surface of ventricles presented in 80% of patients with TCS.[14] SEGA are originated from SENs around the foramen of Monro causing obstructive hydrocephalus, but not epileptogenic.[14] SENs and SEGA are calcified with time.[3]

Cortical dysplasias and SENs are epileptogenic and cortical tuber in the temporal lobe related to autism.[14]

In the present series, case no 3 had cortical dysplasias, and three TCS patients (case no. 1, 2, and 4) had multiple bilateral calcified Subependymal nodules. (Figure 2d, Figure 4b)

Antiepileptics are the mainstay for epilepsy management in TCS patients.[15]

And early treatment, after the first episode, might have been reduced the seizure-induced encephalopathy and intellectual disability.[13]

There are two studies have been done - i) prospective monitoring with electroencephalogram (EEG) to detect epileptic discharge before clinical seizure[13] and ii) prophylactic antiepileptic in TSC patients before clinical infantile spasm.[16] It has been revealed prophylactic antiepileptic did not provide any benefit, so yet not recommended.[15]

Vigabatrin is the treatment of choice in infantile spasm that is effective in 73% to 96% of infantile spasms[16] and also in focal seizure with TSC children.[15]

The principal action of vigabatrin is inhibition of gamma-aminobutyric acid (GABA) transaminase. So an inhibitory neurotransmitter (GABA)increases at the synapse. Moreover, vigabatrin inhibits the mTOR complex 1 pathway. So it may have modified the disease pathobiology and control seizures.[17]

At the time of the present study, Case no. 3 with mixed type of seizures, case no.1 with tonic-clonic convulsions and Case no. 4 with focal seizure were receiving vigabatrin, valproate, and phenobarbitone, respectively.

The most common first-line antiepileptics prescribed in epilepsy of TCS children are: 1. valproate (45%) 2. vigabatrin (25%) and 3. phenobarbitone (11%).[18] And epilepsy free period with monotherapy by valproate, vigabatrin and phenobarbitone achieved in respectively 70%, 78%, and 50% of children with TSC.[18]

The drug-refractory seizures in TSC patients are 70% which is much higher than general (30%).[10] The success rate of seizure control with antiepileptic has been observed in 76.3% of Infantile spasms and 58.2% of focal seizures.[13] The non-pharmacological methods for refractory epilepsy are : the ketogenic diet, vagus nerve stimulation, and subsequent surgical removal of

neuropathological lesions.[14] And surgical resection of epileptic focus have required in 69% of TCS patients.[10]

The case no. 3 had normal scholastic performance, and case 1 had subnormal compared to peers in school. Case 2 and 4 have normal development in four domains. Approximately 30% of school-going TCS patients are at risk of poor school performance.[14] and 50% of TCS patients have normal intellectual ability.[14]

4. Conclusions

Tuberous sclerosis complex (TSC) is a rare disease with the genetic mutational defects causing disordered the mammalian target of rapamycin (mTOR) signal pathway result in the development of benign tumor composed of various types of cells in different systems.

Neither mutational changes is required for diagnosis nor gene therapy is recommended.

Cutaneous lesions in TSC appear in different ages. Hypomelanotic macules are the earliest and most common skin marker.

Prospective evaluation with neuroimaging and the diagnosis of the first seizure is the essential part of updated (2012) diagnostic criteria.

Subependymal nodules and Cortical dysplasias are the commonest neuropathological lesions in neuroimaging.

Initial seizure types are infantile seizure or focal seizure and multiple seizures is the most common phenotype.

Vigabatrin is the antiepileptic of choice of infantile spasms and focal seizures in TSC children.

The prognosis in context with scholastic performance is variable in the patients of TSC.

5. Conflict of Interest

None.

6. Funding of Sources

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