

Original Research Article

Tuberous sclerosis complex associated neuropsychiatric disorder in children: experience sharing from a tertiary care hospital

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ABSTRACT

Background: Tuberous sclerosis complex (TSC) is a genetic disorder where there is multisystem involvement. Most important manifestations are neurological and psychiatric disorders. These disorders should be detected timely and addressed adequately. The common psychiatric disorders are autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), learning disorder etc. This study has been done to describe the pattern of psychiatric disorders in children with TSC.

Methods: This is an observational study taken place in a tertiary care hospital taken place on Children of 0-18 years of age. The study subjects were 84 patients with TSC. Detail history and physical examination had been done along with neuroimaging, EEG and target organs screening. Different psychometric tool was used for psychiatric evaluation.

Results: Total 84 patients were included in this study, mean age was 7+3.96 years, 54% were female. Physical finding were as follows: ash leaf spot, shagreen patch, adenoma sebaceum, cafe au lait spot, rhabdomyoma, renal cyst and angiomyolipoma etc. Seventy patients had epilepsy, most common being focal epilepsy (45.7%), 17.1% had epileptic spasm. Fifty percent patients had developmental delay. Regarding psychiatric disorders, most common disorder was ADHD in 27.38%, ASD in 23.81% and both in 10.71%. ID was found in 20.24% study subjects. Early onset of seizure was associated with more psychiatric disorders.

Conclusions: Neuropsychiatric manifestations of TSC are diverse and often are poorly addressed. The most commonly found disorders in this study were ADHD, ASD and ID. Early onset of seizure was associated with the psychiatric disorders in TSC.

Keywords: Tuberous sclerosis complex, Neuropsychiatric disorder, Children

INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder where there is involvement of multiple organs usually. The target organs are brain, lung, kidney, eyes and heart. The lesions are caused by the mutation of either the TSC1 or TSC2 gene.^{1,2} The characteristic lesions are benign hamartomas in brain which causes epilepsy and other neurological disorders.³ Apart from the physical

manifestations, patients with TSC present with a good number of neuropsychiatric disorders which are often under-recognized and poorly addressed.^{4,5}

It is here to mention that TSC-associated neuropsychiatric disorders (TAND) is an umbrella term coined by the Neuropsychiatry panel of the 2012 International Consensus Conference for TSC, and encompasses a range

of neuropsychiatric manifestations across various levels of investigation.^{3,6,7}

The spectrum of neuropsychiatric disorders in TSC is wide. There are behavioral, psychiatric, academic, neuropsychological, intellectual and psychosocial disorders observed in patients with TSC.^{8,9} There is hypothesis that these neuropsychiatric disorders are caused by dysregulation of mammalian target of rapamycin (mTOR). Thus, mTOR inhibitors might be targeted for the treatment of these disorders which is under study now.^{2,10}

As TSC is relatively a rare disorder, limited studies have been done on TSC associated neuropsychiatric manifestations particularly in children. Also, there are controversies regarding which gene mutation contribute significantly on these disorders. In TOSCA study it has been seen that the pattern of psychiatric disorders is bit different in children than in adults. Children showed hyperactivity and impulsivity while adults showed more anxiety, depression, psychosis, hallucination and mood swings.⁷ This study was designed to describe the pattern of psychiatric disorders in children with TSC and highlight the association of psychiatric disorders with seizure.

METHODS

Subject and place of study

This was an observational study taken place in a tertiary care hospital. Most of the patients were referred for neurodevelopmental evaluation. Patients with TSC with other neurological disorders were evaluated for psychiatric and behavioural disorders. Children of 0-18 years of age were included, the duration of the study was from January 2011 to October 2019. TSC was diagnosed as per TSC clinical diagnostic criteria.¹¹ The study subjects were 84 patients with TSC.

Method

Clinical history of the subjects was taken and noted in preformed data sheet. In every patient the presenting complaints, birth history, family history, developmental history, treatment history, social and personal history were taken. Most of the patients had epilepsy, thus elaborate history of seizure semiology was recorded. In every patient, comorbidities and rare manifestations were noted. Physical examination of every patient was done and noted in the questionnaire.

Detailed developmental assessment and psychological assessment were done in all patients. In every patient, a formal ophthalmological evaluation was done by an expert child ophthalmologist.

For diagnosis of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was used. Intellectual abilities were categorized

as normal (IQ>70), mild ID (IQ 51-70), moderate ID (IQ 36-50), severe ID (IQ 20-35), and profound ID (IQ<20), according to DSM-5.¹² An expert clinical child psychologist did the assessments.

Investigations

For target organ screening and laboratory support of the diagnosis in every patient certain investigations had been done. A brain CT scan or MRI was done in every patient and evaluated by radiologist who have expertise in this field. Electroencephalography (EEG) in awake and sleep state has been done in all the subjects. Other investigations taken place were color doppler echo, ultrasonogram (USG) of whole abdomen, X-ray chest etc. Genetic tests were suggested but most of the patients could not do it due to financial constraints.

Data was analyzed using SPSS (statistical package for social science) program version 22 for windows and for all the analysis a p value<0.05 was considered statistically significant. Ethical clearance was taken from the institutional review board of the institution.

RESULTS

In this study 84 patients were included in a total duration of eight years. Mean age of the study subject was 7±3.96 years. About 54% of the study subjects were female and more than two third of the patients were from rural community (Table 1).

Table 1: Demographic characteristics of the study subjects (N=84).

Demographic characteristics	Frequency (%)
Age: Mean ±SD	7±3.96
Range	0-18 years
Sex	
Female	46 (54.76)
Male	38 (45.23)
Place of residence	
Rural	56 (66.66)
Urban	28 (33.33)

Regarding the clinical features, the most important feature for diagnosis of TSC was skin findings and was present in all the patients. Most commonly occurring skin manifestation was ash leaf spot presenting in 27.38% while other findings were shagreen patch (22.62%), adenoma sebaceum (20.24%), cafe au lait spot (10.71%) and multiple skin features in 19.05% patients. (Table 2).

Other less commonly occurring manifestations were cataract and optic atrophy in eye. The cardiac features were rhabdomyoma, tricuspid regurgitation and arrhythmia while hepatic cyst, oral hamartoma was found in some patients and in 2 patients there was renal involvement (renal angiomyolipoma and cyst) (Table 2) (Figure 1).

Table 2: Distribution of the study subjects by clinical features (N=84).

Clinical features	Frequency (%)
Skin manifestations	
Ash leaf spot	23 (27.38)
Shagreen patch	19 (22.62)
Adenoma sebaceum	17 (20.24)
Café au lait spot	9 (10.71)
Multiple skin manifestations	16 (19.05)
Eye findings	
Normal	81 (96.43)
Cataract	2 (2.38)
Optic atrophy	1 (1.19)
Cardiac manifestations	
Rhabdomyoma	4 (4.76)
Tricuspid regurgitation	1 (1.19)
Arrhythmia	1 (1.19)
Gastrointestinal manifestation	
Hepatic cyst	2 (2.38)
Oral hamartoma	1 (1.19)
Renal manifestation	
Angiomyolipomas	1 (1.19)
Renal cyst	1 (1.19)

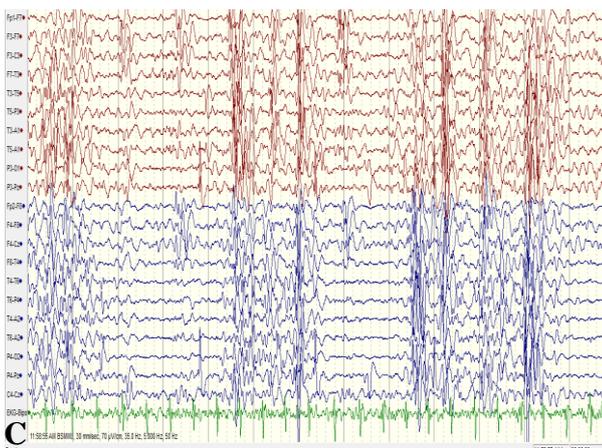
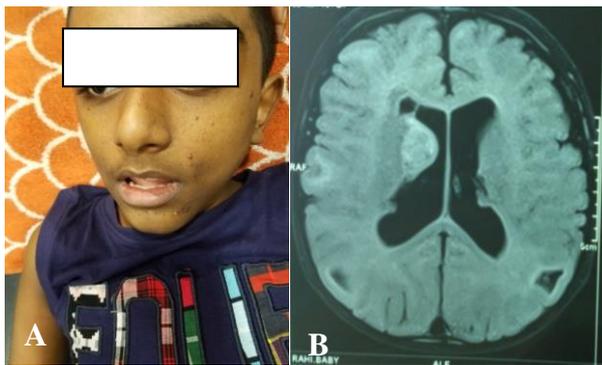


Figure 1: (A) adenoma sebaceum in the face of a patient with TSC with ADHD and epilepsy; (B) MRI of brain of a TSC patient showing multiple cortical tuber, subependymal nodules and SEGA; (C) EEG of a patient with TSC showing hypsarrhythmia (modified).

Seventy patients out of 84 had epilepsy in our study subjects. Most commonly occurring type of epilepsy was focal seizure (45.7%). While other types of epilepsy were generalized epilepsy (27.1%), epileptic spasm (17.1%) etc. Most of the patients had onset of seizure below 6 months (37.1%) and least patients had the onset between 1-5 years. In all patients having seizure, EEG was done. In 47.1% of the patients focal discharge was found, while in 24% of patients generalized discharge and in 14.3% patients hypsarrhythmia was found.

Epileptic encephalopathy other than Lennox gastaut syndrome (LGS) was found in 11.4% patients and in 2 patients EEG was suggestive of LGS (Table 3) (Figure 1).

Table 3: Distribution of study subjects in seizure manifestation (N=70).

Variables	Frequency (%)
Type of seizure	
Focal	32 (45.7)
Generalized	19 (27.1)
Epileptic spasm	12 (17.1)
Other	4 (5.7)
Epileptic spasm followed by focal	3 (4.3)
Age of onset	
<6 months	26 (37.1)
6-12 months	16 (23.0)
1-5 years	10 (14.0)
>5 years	18 (25.7)
Electroencephalogram (EEG)	
Focal discharge	33 (47.17)
Generalized discharge	17 (24.0)
Hypsarrhythmia	10 (14.3)
Epileptic encephalopathy (other than LGS)	8 (11.4)

About half (50%) of the study subjects had developmental delay, while 5.95% had regression of acquired developmental skills. The regression observed were in cognitive skills and motor skills. (Table 4).

Table 4: Developmental status of the studied subjects (N=84).

Developmental status	Number (%)
Developmental delay	42 (50)
Normal	37 (44.04)
Developmental regression	5 (5.95)

Neuroimaging (computed tomography scan or MRI of brain) were performed in all the studied subjects. About one third (32.14%) of the subjects had subependymal nodules (SEN), 20.24% had cortical tubers and 41.67% had both SEN and cortical tubers.

Other findings were arachnoid cyst, subependymal giant cell astrocytoma (SEGA) etc (Table 5) (Figure 1).

Table 5: Neuroimaging features of studied subjects (N=84).

Neuroimaging finding	Number (%)
Subependymal nodule (SEN)	27 (32.14)
Cortical tuber	17 (20.24)
SEN+cortical tuber	35 (41.67)
Arachnoid cyst	2 (2.38)
Subependymal giant cell astrocytoma (SEGA)	2 (2.38)
Multiple lesion	1 (1.19)

Only 30.95% of the study subjects had no psychiatric illness. Most commonly occurring psychiatric disorder in the study subjects were intellectual disability found in 20.24%. While about 16.67% had ADHD, 13.1% had ASD and 10.71% had both (Table 6). Other disorders observed were learning disorder, OCD and anxiety. An important association has been observed regarding the age of onset of seizure with that of psychiatric illnesses. The patients who had early onset of seizure had more psychiatric illnesses. Like children who had onset of seizure in less than 6 months had most of the psychiatric disorders (30.95%), here common disorders were ID, ADHD and ASD. There was slight decrease of psychiatric disorders in patients who had seizure onset between 6 months to 5 years.

Table 6: Psychiatric disorders in the studied subjects (N=84).

Psychiatric disorders	Number (%)
Normal	26 (30.95)
Intellectual disability	17 (20.24)
ADHD	14 (16.67)
ASD	12 (13.10)
ASD with ADHD	10 (10.71)
Learning disorder	3 (3.57)
Obsessive compulsive disorder (OCD)	1 (1.19)
Anxiety	1 (1.19)

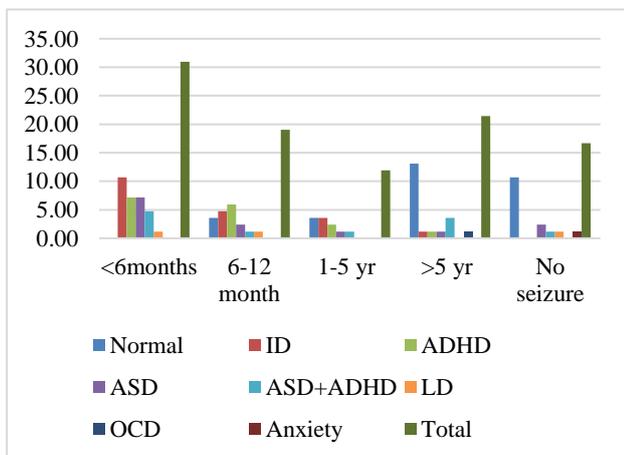


Figure 2: Association of onset of seizure with psychiatric disorders.

However, the percentage of psychiatric disorders increased a bit after 5 years (21.43%). In patients with no seizure, in about 16.47% psychiatric illnesses were observed. The subjects with TSC without any psychiatric illness were most in more than 5 years group (10.71%) and then in no seizure group (9.41%) (Figure 2).

DISCUSSION

In the last decades, significant improvements have been achieved in treatment of neurological aspects of TSC particularly in epilepsy. But the neuropsychiatric disorders associated TSC are under-addressed and under-treated particularly in children.¹³ Patients with TSC have variable extent of psychiatric disorders. In some reports, it is as high as 90% with ASD and ID in 50% individual. Even people with normal intellectual abilities can develop impairment of academic, neuro-psychological and psychosocial domains.^{3,5,14} However, it is observed that there is significant gap in diagnosis and management of these psychiatric disorders. In one survey, they found that only 20% individual received an assessment or treatment for psychiatric disorders.¹⁵ Limited studies have been done in this particular aspect of TSC till date.

The psychiatric disorders in TSC are caused due to multifactorial and/or combined etiologies. Thus, there is wide variability in this disorder in different individuals and age. It is mainly attributable by structural brain lesions which are responsible for neurological disorders like seizure. Again, these lesions are caused by impaired signaling of TSC1 and TSC 2 gene.¹⁵ TSC1 and TSC2 encodes hamartin and tuber-in-protein respectively. Both the proteins regulate the protein complex, mTORC1, constituting a key cellular pathway important for protein synthesis and cell size regulation. This mTORC1 is again regulated by Rheb, a small GTPase. Hamartin and tuberin together act to negatively regulate Rheb thus they inhibit protein synthesis. In patients with TSC, there is inactivation of either TSC1 or TSC2 which lead to the over activation of Rheb and mTORC1 with a subsequent increase in protein production.¹⁶

In this study, the most commonly occurring psychiatric disorder was ID. It was observed in 20.24% of the children. Again 16.67% of the children had ADHD only, 13.10% had ASD and 10.71% had both ASD and ADHD. Other disorders were learning disorder, OCD and anxiety. Thus overall 60.95% of the studied subject had psychiatric disorders in this study. This finding has similarity with previous studies where 55% paediatric and 68% of the adult population with TSC had psychiatric manifestations.¹⁷ However, in later studies up to 90% of the TSC patients showed some TSC-associated neuropsychiatric disorders (TAND).³ In their study they found ID in 34% patients, ASD in 16% patients and ADHD in 7%. Age related variations have been observed in TSC associated psychiatric disorders. For instance, in adults 22% had ADHD while in adolescent 73% had ADHD.^{15,18}

The intellectual ability (IA) in TSC subjects is variable.¹⁹ Joinson et al has reported that 40-50% of patients with TSC have normal range of IQ. But they also have mentioned that mean IQ of the subjects with TSC was 12 points lower than unaffected siblings.^{13,19} In our study, ID was observed in 20.24% of the subjects. In some related studies, ID was observed in higher rates.²⁰⁻²² Variation may be due to large scale study, population based sample and psychiatric assessment tools. A genetic association of pattern of IA has been observed. Wong et al in their study found an association of profound ID with TSC2 mutation.²³ Again age-related change have been noticed in ID in TSC subjects. Van et al observed although IQ remained same over a period of time, there was considerable change in their study subjects.²² Here 9 out of 66 subject had significant improvement and 11 out of 66 had significant deterioration of IA. Moreover, there was significant decline of adaptive behavior in study population which is due to failure to achieve new skills.

About 30-50% of TSC subject had ADHD in different previous reports.^{15,17} In our study 16.67% of the study subjects had only ADHD and 10.71% had ADHD with ASD, in total 27.38% had ADHD. The pathogenesis of ADHD in TSC is unclear. Several factors may contribute namely frontal lobe epilepsy, structural defect, EEG abnormalities and TSC2 mutation.^{17,24} Studies suggest that core symptoms of ADHD such as inattention, hyperactivity and impulsivity are more severe in TSC patients. These patients also are less responsive to pharmacological and non-pharmacological management than non TSC ADHD.²⁵

ASD is another important psychiatric disorder in TSC occurring up to 61% of the patients.²⁶ In our study, it was present in about 23% of the subject. The risk factor is still controversial. The underlying etiology are epilepsy most importantly infantile spasm.²⁷ Another important risk factor is localization of the cortical tubers. Frontal and temporal lobe tubers are associated with ASD in TSC in previous reports.²⁸ Other underlying etiologies of ASD are ID and TSC2 mutation.^{29,30} In our study, we also found that children who had early epilepsy (<12 months) were mostly affected by ASD.

Learning disorder was found in 3.57% in our study subjects. In this relation Vries noted that 36% of school age children with TSC of normal IA had difficulty in academic performance in reading, writing and mathematics.³¹ While Carlisle et al reported that majority of children of TSC received special education.³²

Not only this, school refusal, anxiety to attend school and deficit in social skill, low self-esteem were observed significantly in them.^{8,33} These aspects were not studied in our study though. But we found 1.19% of our study subject had anxiety.

In our study, 70 out of 84 TSC children (83.33%) had epilepsy, most common form was focal epilepsy. In

previous reports epilepsy has been closely related to psychiatric morbidity in TSC. In case of ASD, it has been postulated that mTOR pathway confers a higher risk of both epilepsy and ASD. The underlying pathogenesis are alteration of synaptogenesis, long term potentiation, alteration of GABA/glutamate balance and range of putative intracellular aberrations.³⁴⁻³⁶ Early age of onset of seizure is an important indicator of psychiatric comorbidity which is also reflected in our study where earlier seizure onset was associated with more psychiatric comorbidities. Other important factors are higher seizure frequency, abnormal EEG, drug resistant epilepsy, gap to start treatment etc.^{19,37-39} Certain seizure pattern showed more association with psychiatric disorders particularly infantile spasm. This age-related seizure had association with cognitive impairment and ASD.^{34,40} Regarding the follow up, one study reported 34.2% were seizure free for at least 1 year, 22.8% had ongoing seizure.⁴¹

Both abnormal EEG and brain lesions are closely related to psychiatric morbidities in TSC.²⁹ In our study, the EEG changes were as follows focal discharge, generalized discharge, hypsarrhythmia, epileptic encephalopathy and EEG suggestive of LGS. All the 70 patients with epilepsy had EEG changes. Brain lesion in TSC mainly consists of cortical tubers, subependymal nodules (SEN) and subependymal giant cell astrocytomas (SEGA). Cortical tubers are responsible for both epilepsy and psychiatric disorders.⁴² In this study we have found cortical tubers in 61.91% patients, other lesion were SEN (73.81%), SEGA (2.38%) and arachnoid cyst (2.38%). Cortical tubers are responsible for focal cortical dysplasia causing disruption of cerebral function.⁴² The number of tubers and bilateral distribution are significantly associated with cognitive decline in TSC.⁴⁰

Regarding the demographic criteria, mean age of the studied subjects was 7±3.96 years, a slight female predominance was observed like other related study.⁴³ We depended upon skin, cardiac, renal, gastrointestinal and eye findings for diagnosis. Most characteristic clinical feature were the cutaneous features like ash leaf spot (27.38%), shagreen patch (22.62%), adenoma sebaceum (20.24%) and café au lait spot (10.71%). Other features were rhabdomyoma in heart, hepatic cyst, oral hamartoma, renal cyst and angiomyolipoma. Half of the studied subject had delay in one or more domains and 5.95% had regression mostly due to uncontrolled epilepsy.

CONCLUSION

Physical and neuropsychiatric manifestations of TSC are diverse and often are poorly addressed. We outlined the psychiatric morbidities in TSC in pediatric population. The most commonly found disorder was ADHD, ASD and ID. Early onset of seizure was associated with the psychiatric disorders in TSC. Thus, meticulous screening and surveillance for psychiatric manifestation is very important and should be done periodically. Moreover, further large scale studies are suggested involving the

genotype, epilepsy management and neuroimaging of TSC and their association with psychiatric disorders.

Limitations

Limitation of this study was that it was done in a tertiary care centre, so only referral cases were taken.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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