

Review article

TUBEROUS SCLEROSIS: ITS NEUROLOGICAL AND NEUROPSYCHIATRIC ASPECTS AND A CASE REPORT

Jithu Jacob Varghese¹, Soumya P Thomas^{2*}, Roy Abraham Kallivayalil³

¹Junior Resident, Department of Psychiatry, Pushpagiri Institute of Medical Sciences, Thiruvalla

²Senior resident, Department of Psychiatry, Pushpagiri Institute of Medical Sciences, Thiruvalla

³Professor and Head, Department of Psychiatry, Pushpagiri Institute of Medical Sciences, Thiruvalla

*Correspondence: soumyasujin@rediffmail.com

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ABSTRACT

Tuberous sclerosis (TS) is an autosomal dominant, neurocutaneous disorder. Mutations of TSC1 and TSC2 genes which lead to the mechanistic target of rapamycin (mTOR) pathway dysregulation have been identified. In addition to the neurological and neuropsychiatric manifestations the disease can have many other systemic manifestations affecting skin, kidneys, lungs, heart and eyes. The psychiatric manifestations can be broadly considered under neurodevelopmental, behavioural, intellectual, and psychosocial symptoms. The diagnosis is often confirmed after a detailed evaluation. Treatment options include symptomatic management, prevention of loss of function of the affected organs and the etiological approach through mTOR inhibitors. Researches are being conducted using mTOR inhibitors like Rapamycin, everolimus and sirolimus on this regard. A case of organic delusional disorder with paranoid schizophrenia like symptomatology in a patient with TS is also described at the end.

Keywords: tuberous sclerosis, TSC-Associated Neuropsychiatric disorders (TAND), mTOR inhibitors

INTRODUCTION

TS or Bourneville disease is an autosomal dominant, neurocutaneous disorder. It's a multisystem disorder characterised by cellular hyperplasia and tissue dysplasia. The disorder has a birth incidence of approximately 1:6000. The central nervous system (CNS) is affected in more than 90% of individuals with many

radiologically evident pathological lesions (cortical or subcortical tubers, sub ependymal nodules, giant cell astrocytomas, and white matter migration lines). The clinical signs of these structural lesions can be epilepsy and neuropsychiatric disorders. The most common extra-neurological manifestations of TS are dermatological, renal, pulmonary, cardiac, and ophthalmological. The characteristic triad of TS

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(Vogt triad) includes facial angifibroma, epilepsy, and mental retardation.¹

PATHOPHYSIOLOGY

A mutation has been identified in the TSC1 (chromosome 9q34) or TSC2 (chromosome 16p13) genes. About 90% of cases are due to mutation of the TSC2 gene, however both the mutations can produce the same phenotype with individual variations. TSC1, TSC2 and a third protein, TBC1D7, together form the TS protein complex acting as a negative regulator of the mTOR complex i.e. mTORC1 (a serine/threonine kinase) which regulates cell growth and proliferation. Loss-of-function mutations in either TSC1 or TSC2 lead to mTORC1 activation and active mTORC1 signalling thus constitutes the molecular basis of TS.²

CLINICAL FEATURES

TS is a protean disease with clinical manifestations often being age dependent. Neurological and neuropsychiatric manifestations are the major source of morbidity and mortality, but TS can affect almost any organ system, including the skin, kidneys, heart, lungs, liver, and eyes.³ The discussion of clinical features will be carried out under separate headings: neurological, neuropsychiatric and non-neurological manifestations.

NEUROLOGICAL MANIFESTATIONS

The main neurological manifestation of TS is epilepsy, occurring in 70 to 90% of the individuals and this is the most common sign with which a diagnosis of TS is considered.

Seizures typically present as infantile spasms and focal seizures within the first three years of life, however any semiological variety can be seen and in two-thirds of the cases there is focal refractory epilepsy.^{4,5}

The neuropathological findings of TS include cortical dysplasia (including tubers and white matter migration lines), subependymal nodules, and subependymal giant cell astrocytomas (SEGA).⁵ Tubers are characterised by loss of the hexalaminar cortical architecture, presence of an excessive number of astrocytes, dysmorphic neurons, giant cells and represents focal malformations of cortical development. Tubers and the perituberal cortex have been implicated to have a key role in epileptogenesis. An mTOR dysregulation alone as observed from tuber free animal models may also produce seizures.

White matter involvement can vary from the very evident radial migration lines to apparently normal appearing areas and the extend of involvement influences the severity of neurological symptoms.

Subependymal nodules occur in about 80% of individuals with TS and are often detectable prenatally.⁶ These nodules usually arise along the wall of the lateral and third ventricle. Nodules located near the foramen of Monro, larger than 5 mm in diameter with contrast enhancement on MRI are at high risk of transforming into SEGA.

SEGA are typically slow growing tumours of different cell lineages, seen in at least 5–15% of individuals with TS. They are histologically benign, but their location and tendency to grow can lead to obstructive hydrocephalus. MRI brain is recommended every 1–3 years in all individuals with TS up to age 25 years (especially for those who can't indicate the signs of increased intra cranial tension) for early

detection of SEGA growth. The risk of getting SEGA substantially decreases after this age.

TUBEROUS SCLEROSIS ASSOCIATED NEUROPSYCHIATRIC DISORDERS (TAND)

TAND brings together different levels of involvement related to the neurobiological, psychological, and social aspects of TS. The term was brought in to capture all the possible manifestations, complications, and sequelae of TS with respect to behaviour, psychiatric disorders, academic, intellectual, neurodevelopmental, neuropsychological, and psychosocial abilities. The expectation is that the use of the term will immediately indicate and communicate the different domains of interest. A minority of the TS patients may not have TAND problems at the early stages but may arise later in life after many years of apparent well-functioning.

TAND can present with behavioural, intellectual, and psychosocial manifestations. The behavioural symptoms can include aggression, tantrums, anxiety, depressed mood, self-injury, and attention, social, and sleep difficulties. The behavioural level often represents the “reasons for referral” for a next-step evaluation by primary care or a specialist team.

Behaviours of concern are evaluated on a bio psychosocial background and if meeting the specified intensity and duration, and causes distress or impairment to the individual, a psychiatric disorder can be diagnosed based on diagnostic systems such as the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5), or the International

Classification of Diseases, tenth edition.³ Neurodevelopmental disorders such as autism spectrum disorder (40–50%) and attention deficit hyperactivity disorder (30–50%) are the common psychiatric diagnoses made.⁹ TS is one of the medical disorders most strongly associated with autism. Anxiety and depressive disorders (30–60%) are diagnosed from early in adolescence and into adulthood. Children with TS referred for possible OCD (Obsessive Compulsive Disorder) often met criteria for autism spectrum disorders rather than OCD and hence the exact prevalence of OCD is not known. The prevalence of psychotic disorders is the same as that occurs in the general population (about 1%). Hallucinations and delusions are explained based on tubers impinging upon various limbic structures and causing dopaminergic dysfunction, they can also be associated with seizure disorders, particularly temporal lobe discharges.

About 50% of individuals with TS have normal intellectual capacity, and the remainder has varying levels of intellectual disability. Severe and profound intellectual disability has got a higher incidence in TS than with other medical disorders.⁵ The intellectual level is defined by formal measures of intellectual ability (IQ tests) and assessment of adaptive behaviours (such as selfcare, daily living skills, communication, and social abilities in daily life). As otherwise, individuals with intellectual disability have a 4–5-fold increase in the rates of psychiatric disorders. At least 30% of children with TS are at risk of having learning difficulties with reading, writing, spelling, and arithmetic skills.¹⁰ Neuropsychological problems like attentional deficits, especially with dual-task performance; memory deficits, particularly in recall memory; and executive dysfunctions, particularly complex spatial working

TABLE 1. *Clinical criteria for the diagnosis of tuberous sclerosis complex*

Major criteria	Minor criteria
Hypomelanotic macules (≥ 3 , ≥ 5 mm in diameter)	“Confetti” skin lesions
Angiofibromas (≥ 3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungual fibromas (≥ 2)	Intraoral fibroma (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasia	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangiomyomatosis	
Angiomyolipomas (≥ 2)	

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memory tasks are seen in those having a normal intellectual functioning. Neuropsychological functioning has got correlation with many psychiatric disorders and with intellectual or academic ability. At a psychosocial level the disease can have a negative impact on the individual’s self-esteem, family functioning, and peer relationships.

NON-NEUROLOGICAL MANIFESTATIONS

One may suspect TS for the first time because of the dermatological manifestations which include hypomelanotic macules (90%), angiofibromas (75%), fibrous cephalic plaques (25%), unguinal fibromas (20%), shagreen patches, and confetti skin lesions. Dermatological manifestations are not likely to be identified in the first few years of life because of the clear age-related expression except for hypomelanotic macules.¹¹

Cardiac rhabdomyomas occur in about 60% of individuals with TS and sometimes enable prenatal diagnosis. Rhabdomyomas can usually be detected on routine antenatal ultrasound after 20 weeks of gestation. Although, they can be detected as early as 17 gestational weeks, they typically undergo spontaneous regression during childhood.¹² They are mostly asymptomatic, but can sometimes lead to outflow obstruction, cardiac arrhythmias and Wolf-Parkinson White syndrome hence a cardiology follow-up is recommended for asymptomatic individuals.¹³

Renal manifestations in the form of angiomyolipomas and cysts (80% and 50% respectively) are a substantial source of morbidity and mortality.¹⁴ An abdominal MRI every one to three years, renal function and blood pressure monitoring annually are recommended as both of the lesions tend to increase in number and size with age. Renal cysts are sometimes detectable very early in life,

particularly in individuals with genetic deletions in TSC2.

Another condition that represents TS related morbidity is pulmonary lymphangiomyomatosis. The condition affects women almost exclusively, but less severe forms of the disease have been described in men.¹⁵ Among 47% of women, the condition is completely asymptomatic. Symptomatic lymphangiomyomatosis is characterized by dyspnoea, spontaneous pneumothorax, chylous effusion and haemoptysis.¹⁶ It can progress to cystic lung lesions and can sometimes even cause an abrupt reduction in lung function mandating periodic evaluations.

Other systemic manifestations of TS include dental enamel pits, intraoral fibromas, liver angiomyolipomas, retinal hamartomas, and retinal achromic patches.

DIAGNOSIS

The presence of two major criteria or one major and two minor criteria indicates a definitive diagnosis. A probable diagnosis is made with one major criterion or two or more minor criteria.

TS is often suspected and evaluated further after noticing the clinical signs that occur in the context of TS, other than that there are no specific symptoms to diagnose the condition. At least a three generational family history should be obtained, and genetic testing should be considered in cases where there is suspicion of TS or for family-planning. An individual can have a 50% chance of having the condition if one of the biological parents is affected and the risk remains unchanged even when multiple siblings are affected.

Antenatal detection of cardiac rhabdomyoma; the post-natal identification of hypo pigmented macules; seizures in childhood, particularly with spasms; autistic features, cognitive impairment

etc. should raise the diagnostic suspicion.¹ From a psychiatry point of view yearly screening for neuropsychiatric disorders and whenever clinically indicated is being recommended for early diagnosis. Fundoscopy, MRI brain, EEG, transthoracic echocardiogram, pulmonary function test, electrocardiogram, HRCT chest and abdominal imaging, particularly MRI, are all recommended to find out the extend of systemic involvement.⁸

TREATMENT

Being a systemic condition multidisciplinary approach is needed for the treatment of TS. The aim is to manage the symptoms caused by hamartomas and to prevent loss of function of the affected organs. After the discovery of the mTOR pathway in the pathogenesis of TS, mTORC1 inhibitors were highlighted to have some therapeutic role. Rapamycin is a natural macrolide isolated from *Streptomyces hygroscopicus* in 1965, that binds specifically to mTOR, causing inhibition of mTOR activity and eventually of cellular growth. Everolimus, a Rapamycin derivative has also been studied in TS patients and both were found to be effective for the treatment of renal angiomyolipomas, lymphangiomyomatosis, giant cell subependymal astrocytomas and cutaneous manifestations.¹⁷ Sirolimus is an mTOR inhibitor with antiangiogenic properties and has got superior effects on highly vascularized cutaneous tumours.

TAND is often underdiagnosed and undertreated. The International Tuberous Sclerosis Complex Consensus Panel recommends the use of clinical guidelines for individual disorders. An individual educational plan with additional support as needed, is recommended for school aged children. A few patients treated with mTOR inhibitor sirolimus

showed improvement in recall memory and executive skills and hence mTOR dysregulation is supported as a pathological mechanism.

Early treatment with antiepileptic agents is recommended for seizures, however there are no guidelines for the same except for infantile spasm where Vigabatrin is the recommended first line and ACTH is the second line agent. For refractory seizures other treatment options, such as surgery, a ketogenic diet, vagal nerve stimulation or mTOR inhibitors might be needed. Surgery remains the treatment option for SEGA, in acute cases CSF shunt may also be helpful. Pharmacological options include mTOR inhibitors.^{18,19}

For renal angiomyolipoma lesions larger than 3 cm mTOR inhibitors are the treatment of choice. Embolisation followed by corticosteroid treatment is another treatment option. Sirolimus may be useful for the lymphangiomyomatosis.²⁰ The interventions for angiofibromas include laser treatment, surgical excision, or topical mTOR preparations.

After having referred to a relatively low incidence of psychotic features in TS, we would like to report an interesting case.

CASE HISTORY

Mr. ST 22-year-old, single male of low middle-class socioeconomic status, hailing from a nuclear family in central Kerala presented to our OPD with complaints of hearing voices, suspiciousness, irritability, muttering to self, poor self-care and scholastic decline for a period of 6 years. The onset was insidious with no precipitating factors. He has undergone pharmacotherapy (was on risperidone at the time of his first visit and has already taken trifluoperazine in the past) but never had any significant improvement. Family history was

negative for any neurological or psychiatric disorder. He had delayed developmental milestones and had two attacks of generalized tonic-clonic seizures associated with fever before 3 years of

Figure 1.



age. However, he reportedly had good adaptive functioning and average scholastic performance.

Physical examination showed adenoma sebaceum over his face (fig.1) and ash leaf macule over his lower back (fig. 2).

Figure 2



Mental status examination revealed poor eye contact, decreased personal hygiene, restricted affect, delusions of reference and persecution, and 3rd person auditory hallucinations. Further evaluation revealed cortical tubers (fig: 3) and subependymal nodules on MRI, confirming TS. The score on IQ assessment was 65. Hence a diagnosis of Organic delusional (schizophrenia-like) disorder with a differential diagnosis of

paranoid schizophrenia, Mental retardation (MR) and Tuberous sclerosis was made.

He was evaluated in detail for the presence of other manifestations of the illness. He was started on clozapine (as the patient had already undergone trials with two antipsychotics belonging to two different classes), under antiepileptic coverage (suspecting the vulnerability to have seizures due to tuberous sclerosis per se especially with the addition of a seizurogenic drug) on which psychotic symptoms got under control. After discharge he is on regular follow up under a multidisciplinary team, and has an improvement in his hallucinations, delusions and personal care, but hasn't resumed back to studies.

DISCUSSION

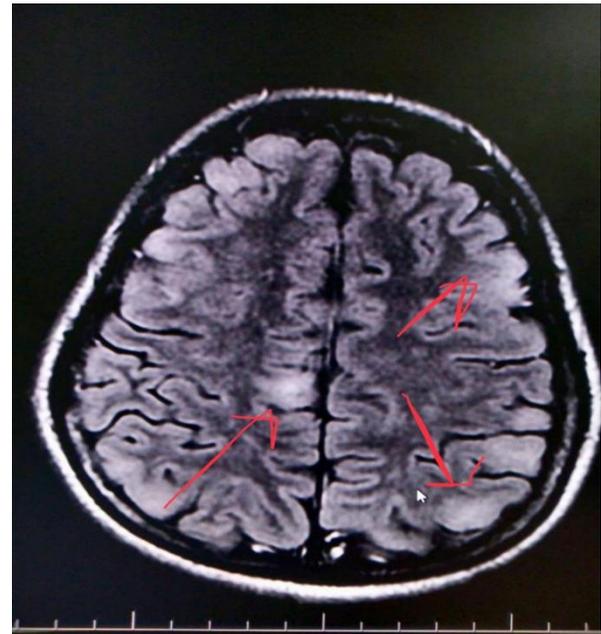
In our case the recognition was delayed till adulthood. Despite having the typical dermatological manifestations, the MR got overlooked and the seizure was labelled as "febrile". Also, there was a complete absence of family history in the three preceding generations, which is unexpected for the inheritance pattern, raising possibilities of alternative genetic explanations (random mutations or mosaicism). TS cases with psychosis and schizophrenia-like symptomatology have been reported very rarely and the knowledge about these connections in literature is limited. Our patient also had the paranoid type of schizophrenic symptoms as in the few previously reported cases of TS associated organic delusional disorder, however considering the fact that TS just has a population risk of having psychosis, a differential diagnosis of schizophrenia was also considered especially because of the presence of typical symptoms of the illness. Though the literature lacks specific treatment recommendations for psychosis in TS, antipsychotics with a low seizurogenic

potential tailored according to the patient profile may effectively manage the condition.

CONCLUSION

Neuropsychiatric symptoms may be equally or sometimes more important than physical manifestations of multi system disorders like TS, with additional impact on social and occupational functioning and quality of life.¹⁸ Careful history taking, detailed physical examination, and ancillary testing when indicated, may help in the rapid diagnosis of such conditions providing optimal care for patients.

Figure 3



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