Neuropsychiatric Manifestations of Tuberous Sclerosis and Management Options:

A Narrative Review

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Abstract

Importance: Tuberous sclerosis is an autosomal dominant genetic disorder that affects multiple organ systems and causes a wide range of physical manifestations. It commonly involves the brain, skin, heart, eyes, kidneys, and lungs. Individuals mostly present with neuropsychiatric symptoms, comprising a noteworthy source of morbidity and mortality.

Observation: Ninety percent of individuals with tuberous sclerosis have associated neuropsychiatric manifestations including attention-deficit/hyperactivity disorder, autism spectrum disorder, and intellectual disability, which are typically underidentified and undertreated.

Conclusion and Relevance: Lack of specific guidelines for management add to the significant burden of care. An individualized, multifaceted perspective, with particular focus on cognitive and psychosocial comorbidities, is key for managing tuberous sclerosis.

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Tuberous sclerosis (TSC), also known as Bourneville disease,[1] is a rare genetic autosomal-dominant disorder. The prevalence of TSC was reported to be 6.8–12.4 per 100,000 population, with no differences in male or female sex. The incidence of TSC is approximately 1 in 6,000 at birth.[2] TSC influences multiple organs and is associated with various physical manifestations with an age-related expression. Around 90% of patients with TSC are impacted by neuropsychiatric symptoms. These disorders/symptoms are often grouped under the umbrella term *tuberous sclerosis–associated neuropsychiatric disorders* (TAND). Despite the high prevalence of neuropsychiatric manifestations, they are often missed and hence undertreated. For those patients in whom comorbidity is identified, the challenge remains due to a lack of specific treatment guidelines.[3] Therefore, we conducted a narrative review of the currently available treatment protocols for the management of TAND to summarize the literature and propose treatment guidelines.

METHODS

An electronic search was carried out in various databases for peer-reviewed published articles using PubMed, Google Scholar, and Cochrane library as well as a wide range of keywords such as *tuberous sclerosis*, *TAND*, *neuropsychiatric manifestation*, *management*, *challenges*, *tuberous sclerosis complex*, *epilepsy*, *neuropsychiatric disorders*, *seizure*, and *antipsychotics* in different combinations. Articles published from 2000 to 2023 in English were considered. Wherever possible, cross-references were also thoroughly screened before final inclusion. After initial screening by all 3 authors and removal of duplicates, 50 articles were found to be relevant to the topic of interest. Of the 50 articles, 25 articles were included in the final review.

CLINICAL MANIFESTATIONS

TSC has the potential to affect any organ system of the body. Individuals with TSC seek medical care mainly due to seizures, aggressiveness, social behavior, and self-harming behavior.

NEUROLOGIC MANIFESTATIONS

Seizures are the most common neurologic sign in TSC. They occur in around 70%–90% of individuals, mostly

Clinical Points

- Patients with tuberous sclerosis have a high prevalence of psychiatric comorbidity, which should not be overlooked while managing these patients.
- Early recognition of psychiatric manifestations through screening and periodic assessment for tuberous sclerosis–associated neuropsychiatric disorders (TAND) and prompt treatment are crucial.
- There remains a need for evidence-based management guidelines for TAND.

within the first 3 years of life.[3] About 50% of patients with TSC have epileptic spasms, also known as infantile spasm, in their childhood.[4] Worsening of cognitive status is often associated with the outcome of continuous epileptic spasm or another variety of seizures. Individuals may present with tonic-clonic, tonic, or atonic seizures, and around two-thirds of individuals may have refractory seizures.[5] Neuropathological lesions affecting the nervous system include cortical or subcortical tubers, subependymal nodules, migration lines of white matter, and subependymal giant cell astrocytoma (SEGA). These pathological lesions are correlated with neurologic and neuropsychiatric disorders.[6]

A tuber is the hallmark feature of TSC, characterized by the brain's structural defect resulting from abnormal movement of neurons during brain development. Tubers represent focal cortical development malformations seen in around 80% of individuals with TSC.[7] Subependymal nodules are the intraventricular projections of abnormal cells usually seen in the lateral ventricles, which may be calcified and found in around 90% of individuals with TSC. Slow-growing glioneuronal tumors are observed in the caudothalamic groove near the foramen of Monro. These tumors may result in obstruction and are seen in around 10%–20% of individuals with TSC.[8]

PSYCHIATRIC MANIFESTATIONS

TSC complex is correlated with various psychiatric manifestations across the behavioral, cognitive, and psychosocial domains. The cluster of cognitive and behavioral problems imposes a significant burden on individuals with TSC and their caregivers.[9] The time between onset of symptoms and seeking medical care for individuals with TAND was similar to the HIV approach, wherein the primary focus was also on physical effects.[10] HIV-associated neurocognitive disorders (HAND) served as the model for the umbrella term TAND.[11]

According to the literature, about 90% of children with TSC have TAND.[12] At the behavioral level, symptoms are aggressiveness, temper outburst, anxiety, sad mood, injury to self, inattention, impaired social interaction, and difficulty in sleep pattern. In adolescents suffering from TSC, anxiety and depression are frequent.[13]

On average, 40%–50% of young children with TSC have autism spectrum disorder, and 30%–50% have attention-deficit/hyperactivity disorder (ADHD)[14]; 50%–60% of individuals with TSC have associated intellectual disability. Approximately 30% of school-aged children with TSC experience difficulty in reading, writing, spelling, and arithmetic. In individuals with TSC, specific deficits have been found even in those who had ordinary or above-average intelligence. These deficits include executive impairments, notably in cognitive flexibility and complicated spatial working memory task, as well as attention deficits, mostly while performing dual tasks, and impairment in memory, specifically in recalling memory.[15] Evidence of an impact on self-confidence, functioning of family, stress to parents, and peer interactions has been identified at the psychological level.[6] These neuropsychiatric manifestations are often underidentified.

ASSESSMENT OF TAND

Current evidence suggests that monitoring for TAND in those with TSC should include annual screening for TAND by validated screening tools like the TAND Checklist.[16] If any concerns are identified by screening, further evaluation by appropriate professionals is required. A thorough formal assessment for TAND is recommended at critical developmental time points including infancy (0–2 years), preschool (3–6 years), pre-middle school (7–9 years), adolescence (10–17 years), early adulthood (18–25 years), and as needed thereafter.[17]

In addition to assessment for TAND, based on recommendations of a consensus panel at a TSC brain/behavior workshop, cognitive and behavioral profiles of individuals with TSC should be evaluated in a planned approach at regular intervals.[18] Figure 1 summarizes the guidelines as suggested by this panel.

MANAGEMENT

At any stage when TAND has been detected in patients with TSC, general principles to be followed for management and treatment are as follows[17,19]:

(1) Refer to appropriate professionals for the management/intervention of relevant TAND manifestations.

(2) Personalize interventions according to each individual's TAND profile and based on evidence-based practice guideline parameters for individual manifestations (eg, autism spectrum disorder, ADHD, anxiety disorder).

(3) Aim for early identification of TAND manifestations and early intervention.

(4) Consider an individual educational program for scholastic difficulties.

(5) Initiate prompt physical evaluation to look

Figure 1.
Guidelines for Management of Tuberous Sclerosis–Associated Neuropsychiatric Disorders[a]

[a]Based on de Vries et al.[18]

at potential medical causes (eg, SEGA, seizures, renal disease, medications) if a sudden and unexpected change in behavior occurs.

(6) Provide psychological and social support to families and caregivers and ensure strategies are in place to support caregiver well-being.

(7) Continue to provide parent/caregiver education and training about TAND to ensure families know what to look for in emerging TAND manifestations across the lifespan.

TREATMENT OF TAND

mTOR Inhibitors

mTOR inhibitors provided a breakthrough in the management of TSC because of their ability to correct molecular defects. Many clinical studies and animal models have shown that not all TSC-related manifestations benefit equally from mTOR inhibitors.[20] Research is ongoing to optimize mTOR inhibitors for each symptom and other pharmacologic and nonpharmacologic interventions that can be used to address the therapeutic challenges of TSC.[21]

Treatment of Epilepsy

Corticosteroids and other antiepileptic medications such as benzodiazepines and vigabatrin (GABA inhibitor) are traditionally used to treat epileptic spasms associated with TSC. Vigabatrin has demonstrated effectiveness and is recommended as a primary line of management in individuals with TSC.[22] However, vigabatrin is associated with indefinite visual field defects, complicating the selection of management for seizure in these patients.[23] The risk of developing medically refractory epilepsy is high. Surgery can be a choice of treatment for symptomatic focal cortical lesions.[22]

Treatment of Neuropsychiatric Manifestations

Neuropsychiatric manifestations related to TSC should be managed with a multifaceted approach concentrated on enhancing the patient's psychosocial and neurocognitive functioning. Only 20% or fewer individuals with TAND were treated for cognitive and behavioral symptoms despite significantly contributing to care burden.[2,24]

Table 1.

Summary of Pharmacologic Management Strategies Available for Tuberous Sclerosis–Associated Neuropsychiatric Disorders (TAND) Management

Sources	Drugs/Therapy	Results	Evidence Base
Słowińska and Jóźwiak[27] Mizuguchi et al[28] Samanta[29] Samanta[30] Luo et al[31] Franz and Capal[32] Capal and Franz[33] Overwater et al[34] de Vries[35] Hwang et al[36]	mTOR inhibitors (sirolimus and everolimus)	Role of mTOR: pathway in causation of autism and behavioral abnormalities proved Animal studies: improvements in learning and social deficits in mice and rat models were seen Human studies: • Open-label study showed improvement of some neurocognitive functions • Randomized controlled trial (RCT) on cognitive deficits in elderly TSC patients yielded negative results • RCT of a small subgroup of Japanese patients showed improvement of autistic behavior with everolimus • 2 RCTs in children noted no change in autistic behavior Epilepsy: • US Food and Drug Administration approval of everolimus as an adjuvant treatment for TSC-associated epilepsy • Everolimus as monotherapy to control epilepsy in certain patients Case reports: • Improvement of behavioral deficits with short-term therapy • Child with TSC and difficult-to-treat selective mutism, who was exposed to everolimus as a treatment protocol for her subependymal giant cell astrocytoma (SEGA), showed improvement in mutism	• Inconclusive about definite utility/need for further human studies/RCTs in neurocognitive functions, social deficits, and autism • Studies need to evaluate whether the positive evidence in neurocognitive functions is secondary to epilepsy control or not • Definitive evidence for use in epilepsy as adjunct and monotherapy • Prior to starting an mTOR inhibitor, one should obtain screening laboratories that include fasting lipid panel, liver function tests, and hemoglobin A_{1c}
Salussolia et al[37] Luo et al[31]	Rapamycin	Animal studies: Recent studies have shown that treating mutant mice with rapamycin at postnatal day 7 or at 6 weeks of age rescued not only the social deficits but also the structural and electrophysiologic changes in the cerebellar Purkinje cells lacking Tsc1 Human studies: Phase II-III trials, which are still ongoing, to assess efficacy and safety in epilepsy prevention and autism; 1 RCT showed efficacy and safety in autism; rapamycin as an alternative to everolimus in the adjuvant treatment of epilepsy	Preliminary animal studies: Hypothesize that the timing of therapeutic intervention is crucial in mediating the neurodevelopmental sequelae of TSC Evidence from human studies: Inconclusive as trials are limited in number and ongoing; further studies are needed
Chakravarty et al[38] Pokharel et al[39] Samanta[30]	Antipsychotics (quetiapine-low dose, fluphenazine), risperidone, aripiprazole	Case reports: Significant reduction in psychotic symptoms over short term For challenging or repetitive behaviors in children with autism	Moderate-high efficacy noted Adverse effects risk is high Evidence from controlled trials is lacking
Haq et al[40] Akuly et al[41]	Mood stabilizers	Many patients with TSC have renal damage from disease or surgical intervention and are unable to tolerate lithium, a first-line treatment for bipolar disorder Other first-line agents, such as divalproex/ and second-generation antipsychotics, carbamazepine plus haloperidol, are better tolerated	Although case reports suggest utilization and efficacy of mood stabilizers similar to other patients, evidence from controlled trials is lacking
Samanta[30]	Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine)	Repetitive behaviors in autism	No high-level evidence exists
Uysal and Şahin[24] Schubert-Bast and Strzelczyk[42] Canevini et al[43]	Vigabatrin or antiepileptics to prevent seizure	Human studies: RCT showed early treatment with vigabatrin to prevent seizure prevents development of neurocognitive impairments/social deficits in children Animal studies: Correlations between seizure frequency and social deficits; improved by early treatment of epilepsy	Modest evidence suggesting prevention or early treatment of epilepsy as protection for development of TAND
Uysal and Şahin[24] Singh et al[44] Connolly et al[45] Canevini et al[43] Wang and Fallah[46]	Antiepileptics for seizures	Infantile spasms • Vigabatrin is the best choice • Adrenocorticotropic hormone is an alternative in cases with insufficient response Epilepsy • Most antiseizure medications can be used • Selection by seizure type, medication interactions, side effect profile, and tolerability • Focal seizures: valproate, lamotrigine, levetiracetam, brivaracetam, carbamazepine, oxcarbazepine, topiramate, zonisamide, lacosamide, and perampanel • Alternative options include surgery (tuberectomy or larger perituberal resection or corpus callosotomy), ketogenic low-glycemic index diet, and vagal nerve stimulation • EXIST-3 trial: showed the benefit of everolimus in patients with treatment-resistant focal seizures	For medications: Definitive evidence from RCTs is present; further studies needed in patients with treatment-refractory seizures For alternative therapies: Although existing studies show positive findings regarding safety and efficacy, further studies are needed, as research is in the preliminary stage
Singh et al[44] Schubert-Bast and Strzelczyk[42]	Synthetic cannabinoids (epidiolex)	RCTs showed reduction of seizure frequency when used as adjunct treatment	Preliminary positive evidence; consider the patient's other antiseizure medications and often adjust the concurrent medication doses, as epidiolex affects the metabolism of several medications and can exacerbate their side effects

For attention deficits and autistic behavior, therapy that improves behavior is indicated. Educational and behavioral therapy measures can strengthen prosocial behaviors, reduce deviant behaviors, and help develop verbal and nonverbal communication skills. Combining oral medication and psychosocial intervention is recommended for autistic symptoms. Psychotropic agents can be helpful as a companion to psychosocial measurement to address target symptoms such as aggressiveness, impulsive behavior, self-injurious behavior, decreased tolerance for frustration, hyperactivity, and obsessive-compulsive symptoms.[22]

Obsessive-compulsive, stereotyped behaviors and mood disorders like depression and anxiety, which can aggravate behavioral disturbances, may be addressed by selective serotonin reuptake inhibitors (SSRIs). At therapeutic doses, the seizure rate is low with newer antidepressants such as SSRIs and selective serotonin-norepinephrine reuptake inhibitors (venlafaxine).[23] In one study, favorable treatment of behavior symptoms, mood symptoms, compulsive thought, and anxiety were reported in 42% with escitalopram and bupropion.[25]

The use of psychotropic agents should be considered against the probable effect of decreasing the seizure threshold in patients with TSC. The exacerbation of seizures and reduced therapeutic efficacy may occur at the therapeutic dose of some psychotropic drugs due to pharmacodynamic interactions between psychotropic and antiepileptic medications. Antipsychotics, mainly new-generation agents such as olanzapine, quetiapine, aripiprazole, and risperidone, have low seizure rates at therapeutic doses. These atypical antipsychotics are reported to be efficacious in reducing aggression, hyperactivity, and self-harm in patients with TSC and have better side effect profiles than typical antipsychotics.[22,26] Study analysis of 157 patients revealed that beneficial treatment results of around 59%–65% for aggressive behavior were perceived with risperidone, quetiapine, aripiprazole, and olanzapine.[25] Nevertheless, no report provides guidance for how long antipsychotics should be continued. Side effects that may hinder treatment are always a possibility.

Antiepileptic drugs are used to prevent seizures in TSC patients, but these drugs also have notable effects on numerous psychiatric and behavioral manifestations. In one study,[25] valproic acid and lamotrigine were commonly prescribed, followed by benzodiazepines and oxcarbazepine with unspecified favorable outcomes. For ADHD, methylphenidate and dexmethylphenidate were most often used, whereas guanfacine and clonidine were reported to worsen symptoms.[25] A summary of pharmacologic management strategies available for TAND and its evidence base is provided in Table 1.

CONCLUSION

The identification of biomarkers specific to disease progression and management is needed. Further research into the neurobiology and genetic basis of TSC will allow for better understanding of the mechanism of associated epileptogenesis, intellectual disability, autism symptoms, and other neuropsychiatric conditions. An individualized, multifaceted perspective with particular attention to cognitive and psychosocial comorbidities is key to managing this disorder. Treatment of the neuropsychiatric aspects of TSC poses great challenges to patients, doctors, and caregivers. There is a need to develop specific treatment guidelines for the management of TSC to lessen the burden of care and improve patients' quality of life. Early detection and intervention are ideal and should aim to prevent the development of maladaptive behavioral patterns.

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