Tuberous Sclerosis Complex

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Case Vignette

DC is a 2-year-old young boy with tuberous sclerosis complex (TSC) with restless sleep in his new bedroom. His restlessness is worsened by illness. His father's goal for DC's sleep is that he would not scream and wake up frequently as his parents' sleep is being interrupted when they awaken to console him. DC also has epilepsy treated with vigabatrin and has been seizure-free since infancy. An EEG obtained to determine if his restlessness was due to subtle seizure activity was negative, and he was referred to our center's Sleep Clinic for further evaluation and recommendations.

DC was diagnosed with parasomnias, unusual events occurring during or around sleep. Night terrors are a kind of parasomnia during which children cry out and appear markedly frightened during sleep. As such, his family was advised that the events would improve over time with adjustment to his new environment. It was recommended that they not enter his room to intervene and consider adjusting his bedtime to 30 min earlier. Iron labs, ordered to rule out a potential etiology of restless sleep, were normal. Three months later, his restless sleep resolved.

Introduction

Tuberous sclerosis complex (TSC) is a genetic syndrome occurring in 1/6000 live births that may either be inherited in an autosomal dominant manner or develop spontaneously. It is classified as a neurocutaneous disorder due to the predominance of brain and skin manifestations and is clinically diagnosed based upon the presence of major and minor features (Table 19.1) [1]. Autism (61%) [2, 3], intellectual disability (45%) [4], and epilepsy (up to 90%) [5–7] are comorbidities linked to this condition. The neurobiology of TSC lies in loss of regulation of the protein kinase mammalian target of rapamycin (mTOR). Typically, the genes *TSC1* and *TSC2* encoding hamartin and tuberin, respectively, form a complex that functionally serves to activate and deactivate mTOR, a protein that mediates cell growth among other functions. An inherited or spontaneous mutation in either *TSC1* or *TSC2* renders mTOR constitutively active. It is this excessive activity of mTOR that has been linked to the major and minor features as well as the comorbidities associated with TSC [8]. The effects of mTOR on the brain are multiplicative (Fig. 19.1) [9–16]. In terms of sleep dysfunction in TSC, the disruption of the balance of gamma-aminobutyric acid (GABA) and glutamate, the brain's most abundant neurotransmitters, is of particular interest. GABA mediates inhibition, while glutamate is responsible for excitation in the synaptic activity of the brain. An appropriate balance is necessary to achieve optimal learning and maintain freedom from seizures [17, 18]. Preclinical evidence suggests that GABA activity is too low in TSC [14, 19–21]. In addition to epilepsy it is plausible that this imbalance may also result in the sleep disturbances so commonly observed in this population. Fortunately, there are targeted therapies for TSC; however, they have not been studied primarily for sleep disturbances in this population to date.

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Table 19.1 Tuberous sclerosis complex – major and minor features

Major features	Minor features
Cortical dysplasias >3	Dental enamel pits
Subependymal nodules >2	Hamartomatous rectal polyps
Subependymal giant cell astrocytoma	Cerebral white matter radial migration lines
Hypomelanotic macules (3 or more)	Gingival fibromas
Shagreen patch	Nonrenal hamartoma
Facial angiofibromas >3 or cephalic plaque	Retinal achromatic patches
Multiple renal nodular hamartomas	"Confetti" skin lesions
Nontraumatic ungual fibromas >2	Multiple renal cysts
Cardiac rhabdomyoma	
Pulmonary lymphangioleiomyomatosis (LAM) and/or renal angiomyolipomas[a]	

Definite TSC, 2 major or 1 major plus 2 minor features; possible TSC, 1 major or >2 minor features
[a]When both pulmonary LAM and renal angiomyolipomas are present, they are counted as one major feature of TSC

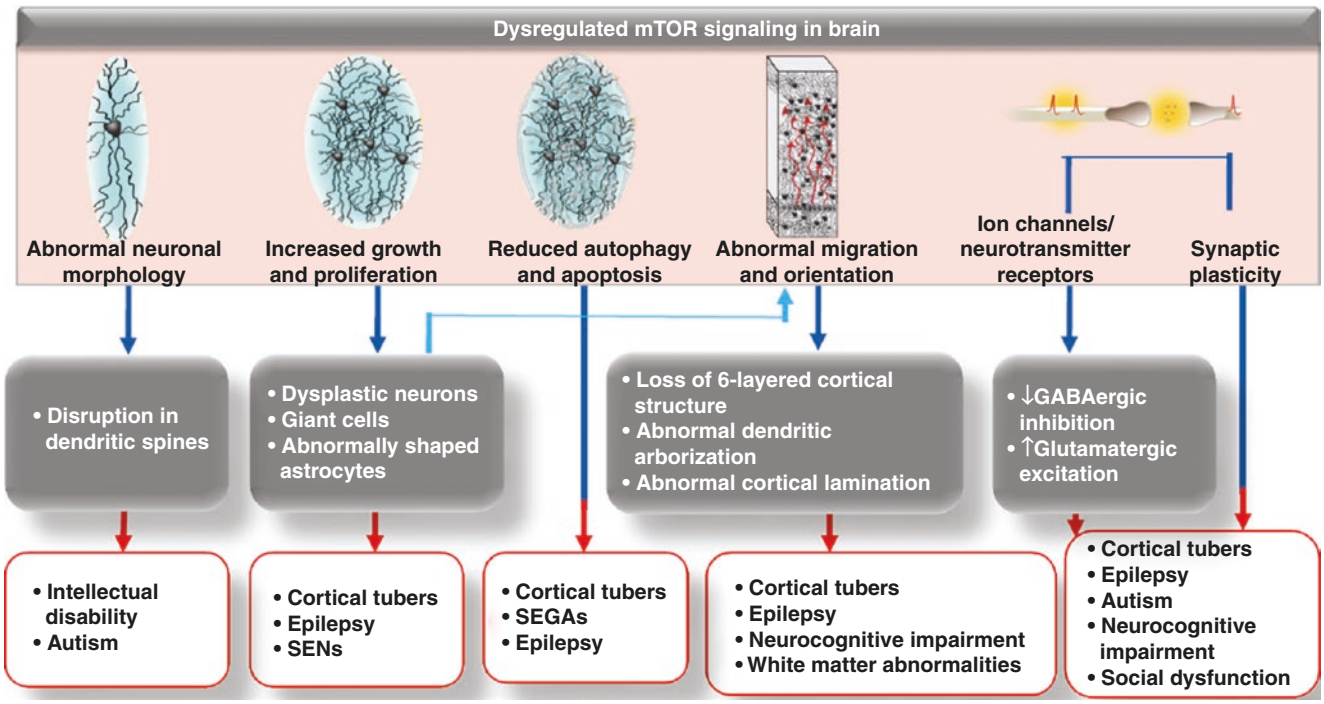

Fig. 19.1 Illustration depicting the neurobiological impact of dysregulated mTOR (mammalian target of rapamycin) (© 2018 Novartis AG)

Evidence Base

Diagnosis

Clinicallydefinite TSC is characterized by the presence of the combination of two major *or* one major and two minor features. Clinically possible TSC is present when there is one major *or* two minor features. Genetic testing is useful in determining whether there is a mutation in *TSC1* or *TSC2*; however, there are individuals with no mutation identified who have a clinical diagnosis of TSC. To date, the literature suggests that mutations in *TSC2* as compared to those in *TSC1*, and spontaneous as opposed to inherited mutations, are associated with greater phenotypic severity [22, 23]. A correlation between the protein effects of these mutations and cognitive outcomes was discovered in a recent review [24].

After confirmation of a TSC, diagnosis begins a lifelong schedule of surveillance studies as the major and minor features of TSC can appear throughout life. Guidance exists for the frequency of surveillance studies [25]. Among the recommendations, neuroimaging is warranted as individuals are at risk for the development of three different types of brain

lesions – subependymal nodules, cortical tubers, and subependymal giant cell tumors (SEGT). Subependymal nodules line the ventricles of the brain and have not been often associated with pathology. SEGTs often initially appear to be subependymal nodules but are distinguished by their contrast enhancement on brain MRI and localization near the foramen of Monro. Although benign and slow-growing, enlargement often leads to obstruction of CSF resulting in hydrocephalus, headaches, and seizures. Cortical tubers are abnormal aggregations of neuronal and glial cells that often appear early on but are most prominent after the age of 2 years when myelination is mostly complete (Fig. 19.2). These lesions have been associated with epilepsy and neurodevelopmental outcome [27–31]. Abdominal imaging is mandated for life as individuals may commonly develop renal lesions – cysts, carcinoma, and/or angiomyolipoma.

Benign growths have also been reported in other solid organs. At least two cases of insulinoma have been reported in TSC [32, 33]. Sleepiness associated with increased seizure frequency was reported in one of them emphasizing the need for heightened vigilance for unusual causes of sleep disorders in this population [32]. In another case, calcified subependymal nodules in the brainstem were associated with central and obstructive sleep apnea associated with hypoxia-induced seizures [34]. Further, a young girl with TSC, high-functioning autism, and expressive language delay was found to have electrical status epilepticus during sleep (ESES) emanating from the temporal lobe on sleep EEG [35]. REM interictal epileptiform discharges were associated with the ictal EEG and largest tuber with good outcomes noticed after epilepsy surgery in another individual with TSC [36].

In addition to neurological diagnostics, evaluations are also indicated by ophthalmology, genetics, dentistry, nephrology and/or urology, dermatology, and cardiology.

Management

Ongoing, timely surveillance and early treatment with targeted therapeutics for the known features and associated comorbidities of TSC are the primary aims of management in this population.

Sleep Disturbances in TSC

In adults with TSC, the majority had epilepsy, and 31% reported a sleep disorder in a questionnaire-based study. Insomnia was associated with obstructive sleep apnea and restless legs syndrome. Daytime sleepiness correlated with the presence of mental health medications, depression, and antisocial behavior. Using medications for epilepsy correlated with daytime sleepiness, anxiety, and inattention [37]. In a series of pediatric patients with TSC who underwent two overnight polysomnographic studies, consistent sleep abnormalities included decreased REM sleep, shorter total sleep time, higher number of awakenings and stage transitions, reduced sleep efficiency, and increased wakefulness after sleep onset and stage 1. Epileptic events related to sleep and large temporal or bifrontal tubers were associated with these abnormalities [38].

We employ a three-in-one approach (functional, symptomatic, and organic) to assessing sleep difficulties in individuals with TSC. A functional assessment, often administered by behavioral professionals, seeks to identify if there are any variables in the environment that may maintain the sleep dysfunction [39]. For example, a child who gets up from bed and is given a cup of milk for soothing may stay up later to seek the attention of this interaction with the parent. Symptomatic assessments in TSC focus on the severity and adequacy of treatment of epilepsy as seizures often interrupt sleep in this population. Finally, an organic assessment relates to the identification and treatment for TSC-specific features, such as subependymal giant cell tumors.

Epilepsy

Epilepsy occurs in as many as 90% of individuals with TSC and may often be refractory [40–42]. Infantile spasms, a catastrophic type of epilepsy, have been treated with vigabatrin [26, 43–48]. This medication is an irreversible inhibitor of GABA transaminase and thus functions to restore GABA levels that are abnormally low in this population likely explaining its higher rate of efficacy among those with TSC. Further, evidence supports a role for vigabatrin in refractory complex partial seizures associated with TSC [49]. Clobazam also functions to target abnormally low GABA levels and has also been found to be helpful in this group [50].

SEGAs and Renal Angiomyolipomas

Subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas have been historically monitored until growth was associated with either increased in intracranial pressure or hematuria, respectively. However, everolimus has now been FDA-approved and indicated for both tumors allowing medical management when tumors are as small as 3 cm [51, 52]. Trials are ongoing to determine if everolimus is useful for epilepsy [53]. Sirolimus, another mTOR inhibitor, has been approved for the treatment of pulmonary lymphangioleiomyomatosis [54]. A clinical trial of a topical version of sirolimus for facial angiofibromas has been completed and is awaiting an FDA decision [55].

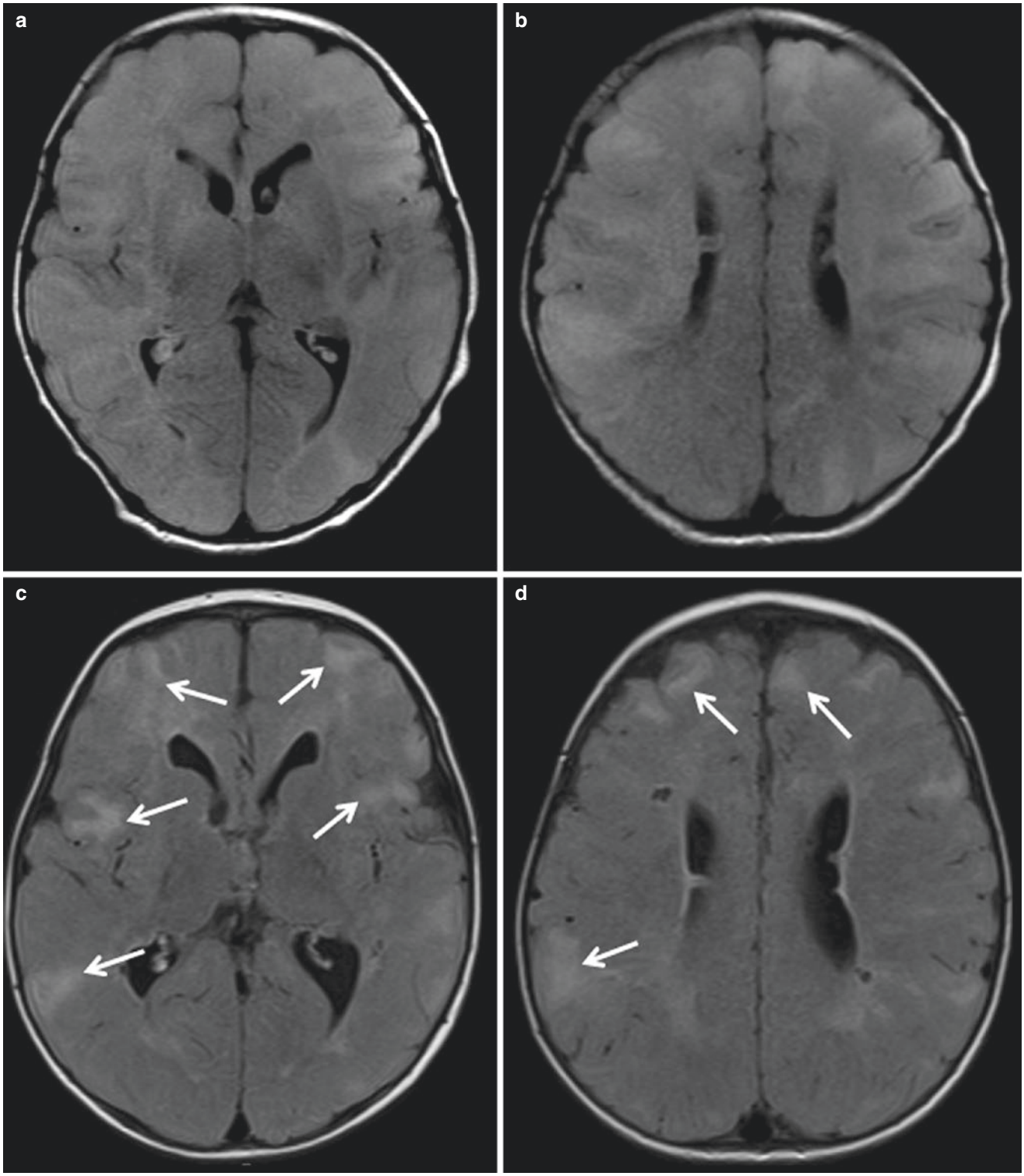

Fig. 19.2 (**a**) and (**b**) Axial FLAIR (fluid attenuated inversion recovery) images of a 1-month-old infant with tuberous sclerosis complex reveal multiple FLAIR hyperintense lesions representing tubers and involving the cortical and subcortical white matter of the bilateral frontal and parietal lobes. Additionally, multiple subependymal nodules were observed in the body of the lateral ventricles and the left foramen of Monro (not illustrated). (**c**) and (**d**) Matching, axial FLAIR images of the same child at 14 months of age reveal again multiple cortical and subcortical FLAIR hyperintense tubers within the bilateral frontal and parietal lobes (white arrows in (**c**) and (**d**)) (From Gipson et al. [26]. Reprinted with permission from Elsevier Limited)

Areas of Uncertainty (Future Directions)

Diagnosis

As sleep in TSC is not commonly studied, future studies are needed to focus on best practices for the effective screening and diagnostic evaluation of sleep disorders in this population. Validation of measures such as the TAND checklist [56] and the three-in-one approach used in our center could prove useful for screening. Diagnostic evaluation may require a comprehensive approach to include polysomnogram, EEG, or a combined study as well as a thorough investigation for both rare and common tumors associated with TSC. It is uncertain if this should be applied uniformly to the entire population at discrete intervals or just as difficulties arise.

Management

The applicability of traditional behavioral and sleep interventions to individuals with TSC warrants further study. Melatonin, for example, seems to work as a simple sedative in children and adults with TSC but does not correct any abnormalities in secretion of melatonin [57]. Prolonged-release melatonin tested in a group of individuals with neurodevelopmental disorders including a few with TSC was well tolerated in the majority of patients and positively impacted multiple facets of sleep – sleep latency, duration, quality, and frequency of awakenings [58]. In a randomized, placebo-controlled trial with crossover of seven individuals with TSC with sleep disorders compounded by epilepsy and learning difficulties, increased total sleep time and a trend toward better sleep onset time was associated with treatment using 5 mg of melatonin [59]. Contrastingly, melatonin improved not only total sleep time and sleep latency but also decreased the number of night awakenings in a study of individuals with intellectual disabilities including some with TSC using a dose range of 0.5–9 mg [60].

Using vigabatrin or everolimus to target the potential mechanism of sleep disturbances in TSC by restoring the imbalance of GABA/glutamate is a unique opportunity for this population and worthy of study in well-designed clinical trials.

Guidelines

The clinical consensus guidelines for TSC have recently been updated for medical management and cognition [1, 25].

Conclusions and Recommendations

Clinicians treating individuals with TSC should be vigilant in monitoring for the development of sleep disturbances. Although sleep disturbances in TSC are very common, they are infrequently studied. Therefore, the approach for screening, diagnosis, and treatment does not differ from the general population. However, the burden and localization of neurologic disease and the impact of epilepsy and rare tumors are unique aspects of TSC that must be considered during the diagnostic work-up. Fortunately, neurobiologically targeted medications are available for TSC and may provide an opportunity for actual disease *modification*. Therefore, well-designed clinical trials are warranted.

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