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SEVERE PSYCHIATRIC COMORBIDITIES IN AN ADOLESCENT WITH TUBEROUS SCLEROSIS COMPLEX: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by hamartomatous lesions affecting multiple organs. Beyond its neurological manifestations, TSC is frequently associated with a broad spectrum of neuropsychiatric disorders, collectively referred to as TSC-associated neuropsychiatric disorders (TAND), including autism spectrum disorder (ASD), intellectual disability (ID), behavioural disturbances, and psychiatric comorbidities. These manifestations represent a major source of disability but remain under-recognized and often undertreated.

Case presentation: We report the case of a 13-year-old boy, the youngest of three siblings, born to non-consanguineous parents with no family history of TSC or neurodevelopmental disorders. Early psychomotor development was initially reassuring, with emergence of expressive language and reciprocal social interaction before two years of age. He subsequently developed recurrent seizures that never achieved sustained control despite several successive antiseizure-medication combinations, evolving into drug-resistant epilepsy (currently generalized tonic-clonic seizures). Developmental regression followed, with loss of language, impaired social communication, stereotyped behaviours, and marked intolerance to change. Brain magnetic resonance imaging (MRI) revealed multiple cortical tubers and subependymal nodules, and dermatological examination identified hypomelanotic macules, confetti skin lesions, and facial angiofibromas, fulfilling the 2021 International TSC clinical diagnostic criteria for definite TSC; molecular genetic testing was not performed. At three

years of age, ASD (DSM-5, supported by ADI-R and ADOS) and severe ID (uniformly very low adaptive functioning on the Vineland Adaptive Behavior Scales) were diagnosed. Despite intensive multidisciplinary rehabilitation, clinical improvement remained minimal. During adolescence, the clinical picture became dominated by severe TAND: non-verbal ASD, persistent intellectual disability, repetitive head-banging requiring protective measures, and frequent heteroaggression. Management was particularly challenging because drug-resistant epilepsy limited pharmacological options, while serial follow-up MRI demonstrated progression of cerebral lesions, leading to evaluation for epilepsy surgery.

Conclusion: This case highlights the complex interplay between progressive TSC, early drug-resistant epilepsy, developmental regression, and severe neuropsychiatric comorbidities. It emphasizes that TAND may become the predominant source of long-term disability and underscores the need for early multidisciplinary assessment, systematic psychiatric evaluation, and individualized therapeutic strategies in children with TSC.

KEYWORDS: Tuberous Sclerosis Complex; Tand; Autism Spectrum Disorder; Intellectual Disability; Drug-Resistant Epilepsy; Self-Injurious Behaviour; Case Report.

1. INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare multisystem autosomal dominant genetic disorder caused by pathogenic variants in the TSC1 or TSC2 genes, which encode hamartin and tuberin, respectively. These proteins regulate the mechanistic target of rapamycin (mTOR) signalling pathway, and loss of their function results in constitutive mTOR activation, abnormal cellular proliferation, and formation of hamartomatous lesions in multiple organs, including the brain, skin, kidneys, heart, lungs, and eyes (1,2). Although the estimated incidence of TSC ranges from 1 in 6,000 to 1 in 10,000 live births, its clinical presentation is highly heterogeneous, even among members of the same family (1,2).

Neurological involvement is the major determinant of morbidity in TSC. Epilepsy affects approximately 80–90% of patients and often begins during the first years of life, with infantile spasms and focal seizures being the most common seizure types (1,9). Early seizure onset and drug-resistant epilepsy have consistently been associated with poor neurodevelopmental outcomes, including developmental delay, intellectual disability, autism spectrum disorder (ASD), and behavioural disturbances (3,8,9). Increasing evidence suggests that the combination of cortical malformations, persistent epileptic activity, and mTOR-

pathway dysregulation disrupts normal brain maturation during critical developmental periods, contributing to long-term cognitive and psychiatric impairment (2,3,8).

Beyond epilepsy, TSC is increasingly recognized as a neurodevelopmental and neuropsychiatric disorder. The International TSC Consensus introduced the concept of TSC-associated neuropsychiatric disorders (TAND) to describe the broad spectrum of behavioural, psychiatric, intellectual, academic, neuropsychological, and psychosocial manifestations observed across the lifespan (1,4). It has been estimated that nearly every individual with TSC experiences one or more TAND manifestations; however, these disorders remain substantially underdiagnosed and undertreated in routine practice (4,6,7).

ASD is one of the most prevalent psychiatric comorbidities in TSC, with reported frequencies of approximately 25% to 50%, substantially exceeding those observed in the general population (3,6). Likewise, intellectual disability affects nearly half of affected individuals, with severity closely related to seizure burden, age at seizure onset, and extent of cortical involvement (3,6,8). Developmental regression, particularly after the onset of epilepsy during infancy, has also been described and may represent a critical turning point leading to severe neurodevelopmental impairment (8,10).

Behavioural manifestations constitute another major component of TAND and include stereotyped behaviours, behavioural rigidity, anxiety, attention-deficit/hyperactivity disorder, mood disorders, aggression, and self-injurious behaviour (4,7). These symptoms frequently have a greater impact on functional outcome and caregiver burden than many systemic manifestations of TSC (4,6,7). Nevertheless, psychiatric manifestations are often overlooked during neurological follow-up, delaying appropriate assessment and intervention.

Managing severe behavioural disorders in patients with TSC is particularly challenging when they coexist with drug-resistant epilepsy. International recommendations emphasize that behavioural changes should be assessed comprehensively to identify potentially reversible medical or environmental contributors before initiating psychotropic treatment (1,4). Pharmacological management requires careful consideration of possible interactions with antiseizure medications and of the potential effects of psychotropic agents on seizure threshold. Consequently, optimal management relies on close collaboration between paediatric neurologists, child psychiatrists, psychologists, rehabilitation specialists, neurosurgeons, and caregivers (1,11,13).

We report the case of a 13-year-old adolescent with definite TSC who developed early-onset drug-resistant epilepsy followed by developmental regression, non-verbal ASD, severe intellectual disability, recurrent self-injurious behaviour, and heteroaggression, in the absence

of major renal or cardiac involvement. This case illustrates the profound psychiatric burden associated with TSC and the complex diagnostic and therapeutic challenges encountered in severe TAND. Through a narrative review of the current literature, we discuss the relationship between early epilepsy, developmental regression, psychiatric comorbidities, and the limitations of current therapeutic strategies.

2. Case Presentation

Patient information

A 13-year-old Moroccan boy, the youngest of three siblings, was referred to the Department of Child and Adolescent Psychiatry, Ar-Razi University Psychiatric Hospital, for assessment and management of severe behavioural disturbances. He was born at term after an uneventful pregnancy and normal vaginal delivery; birth weight and neonatal adaptation were normal. The parents were non-consanguineous, with no known family history of TSC, epilepsy, ASD, intellectual disability, or other hereditary neurological or psychiatric disorders.

Early development

During infancy, psychomotor development appeared normal. The patient achieved motor milestones within the expected age range and acquired early language skills, including a few meaningful words before two years of age. Reciprocal social interaction was present, with appropriate eye contact, social smiling, and interest in family members. No developmental concerns were reported during the first months of life.

Neurological history

Before the age of two years, the patient developed recurrent epileptic seizures. The precise semiology at onset is not documented in the available records; the epilepsy currently presents as generalized tonic-clonic seizures (most likely focal seizures with bilateral tonic-clonic evolution, consistent with the focal, tuber-related origin of epilepsy in TSC). Despite paediatric-neurology follow-up and several successive antiseizure-medication regimens and combinations, seizure control was never achieved, and the epilepsy progressively evolved into drug-resistant epilepsy.

Following seizure onset, the parents reported progressive developmental regression. Previously acquired language disappeared completely, and the child gradually lost social reciprocity and communicative abilities. Eye contact became inconsistent, social interaction markedly decreased, and repetitive motor stereotypies progressively emerged. Behavioural rigidity became increasingly evident, with severe intolerance to changes in daily routine and environmental transitions.

Diagnosis of tuberous sclerosis complex

At two years of age, brain MRI demonstrated multiple cortical tubers associated with subependymal nodules. Dermatological examination revealed several hypomelanotic macules ("ash-leaf" lesions), confetti skin lesions, and disseminated facial angiofibromas. Molecular genetic testing (TSC1/TSC2) was not available; the diagnosis therefore rested on the clinical and neuroimaging criteria. According to the 2021 International TSC Consensus Conference clinical criteria, these findings fulfilled the criteria for definite TSC (1) (Table 1). Comprehensive systemic evaluation did not reveal clinically significant renal angiomyolipomas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis, or ophthalmological involvement.

Table 1. 2021 International TSC clinical diagnostic criteria and the patient's features.

Feature	Category	Present in patient
Cortical dysplasias (tubers / radial migration lines)	Major	**Yes**
Subependymal nodules	Major	**Yes**
Subependymal giant cell astrocytoma (SEGA)	Major	No
Hypomelanotic macules (≥3, ≥5 mm)	Major	**Yes**
Angiofibromas (≥3) or fibrous cephalic plaque	Major	**Yes (facial angiofibromas)**
Ungual fibromas (≥2)	Major	No
Shagreen patch	Major	No
Multiple retinal hamartomas	Major	No
Cardiac rhabdomyoma	Major	No
Lymphangioleiomyomatosis	Major	No
Angiomyolipomas (≥2)	Major	No
Confetti skin lesions	Minor	**Yes**
Dental enamel pits (>3)	Minor	Not assessed
Intraoral fibromas (≥2)	Minor	No
Retinal achromic patch	Minor	No
Multiple renal cysts	Minor	No
Non-renal hamartomas	Minor	No

Definite TSC requires either two major features or one major feature plus at least two minor features. The patient presented four major features (cortical tubers, subependymal nodules, ≥3 hypomelanotic macules, ≥3 facial angiofibromas) and one minor feature (confetti lesions), fulfilling the criteria for definite TSC on clinical and imaging grounds alone.

Psychiatric and neurodevelopmental assessment

At three years of age, comprehensive developmental and psychiatric assessment established a diagnosis of ASD according to DSM-5 criteria, supported by the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). The patient also met criteria for severe intellectual disability; adaptive functioning, assessed with the Vineland Adaptive Behavior Scales, was uniformly very low across all domains (communication, daily-living skills, and socialization), indicating a homogeneous and profound adaptive impairment. Over time, language failed to develop further and the patient remained completely non-verbal; functional communication was extremely limited and relied mainly on non-specific gestures and behavioural expressions. At the most recent evaluation he demonstrated persistent deficits in social reciprocity, absent functional verbal communication, restricted interests, repetitive motor stereotypies, marked insistence on sameness, and profound adaptive impairment, consistent with severe TAND.

Behavioural phenotype

Challenging behaviours progressively became the predominant clinical concern. The patient exhibited frequent episodes of heteroaggression directed towards caregivers, particularly during frustration, interruption of preferred activities, or changes in routine. Recurrent self-injurious behaviour was another major challenge: the principal form consisted of repetitive head-banging against walls, resulting in repeated cranial trauma. Environmental safety measures, including continuous supervision and protective headgear, were implemented to reduce the risk of serious injury.

Therapeutic interventions

The patient received long-term multidisciplinary management, including paediatric-neurology follow-up, antiseizure medications, speech and language therapy, psychomotor rehabilitation, psychoeducational interventions, and Applied Behavior Analysis (ABA). Despite years of continuous intervention, developmental progress remained minimal, with persistent severe communication deficits, ongoing behavioural disturbances, and profound functional dependence.

Follow-up

Brain MRI was initially performed for diagnosis and has since been repeated regularly to monitor disease evolution. The most recent study, performed a few months ago, showed progression of cerebral involvement compared with previous examinations. Because subependymal nodules are congenital and do not increase in number over time, this change most likely reflects enlargement of pre-existing lesions and/or increased lesion conspicuity; it

mandates close surveillance to exclude an evolving subependymal giant cell astrocytoma (SEGA) should a lesion adjacent to the foramen of Monro enlarge. In view of persistent drug-resistant epilepsy despite optimized medical treatment, together with this radiological progression, the patient is currently being evaluated for epilepsy surgery, the multidisciplinary team weighing the potential functional benefits against the surgical risks. At the time of writing, the major determinants of disability are no longer the dermatological manifestations of TSC but the combination of drug-resistant epilepsy, severe ASD, profound intellectual disability, self-injurious behaviour, and heteroaggression, which impose a substantial burden on the patient and his caregivers.

3. DISCUSSION

3.1. Tuberous sclerosis complex: beyond a multisystem genetic disorder

TSC has long been regarded as a multisystem genetic disorder characterized by hamartomatous lesions of the brain, skin, kidneys, heart, lungs, and eyes. Advances in clinical and translational research have progressively reframed it as a neurodevelopmental disorder in which neurological and psychiatric manifestations frequently determine long-term prognosis more than extracerebral organ involvement (1,2).

The discovery of pathogenic TSC1/TSC2 variants clarified the central role of dysregulated mTOR signalling in TSC pathogenesis. Hyperactivation of this pathway not only promotes hamartoma formation but also interferes with neuronal migration, dendritic development, synaptic plasticity, and cortical network organization; abnormal brain development therefore begins during fetal life, long before clinically detectable seizures or behavioural abnormalities appear (2,3). This framework explains why many patients with TSC develop neurodevelopmental disorders independently of structural disease burden. Nevertheless, epilepsy—particularly when severe and uncontrolled—appears to amplify these developmental abnormalities, leading to a more severe neuropsychiatric phenotype (1,3).

Our patient illustrates this evolution. Although his TSC diagnosis rested on characteristic neuroimaging and dermatological findings, the most disabling manifestations during adolescence were neither dermatological nor systemic but psychiatric: severe ASD, profound intellectual disability, recurrent self-injury, heteroaggression, and complete dependence became the principal determinants of disability and quality of life.

3.2. TSC-associated neuropsychiatric disorders (TAND): a comprehensive framework

Recognition of the wide spectrum of neuropsychiatric manifestations in TSC led to the TAND concept, introduced by de Vries and colleagues and subsequently incorporated into

the International TSC Consensus recommendations (1,4). Rather than treating autism, intellectual disability, behavioural disorders, anxiety, and learning difficulties as isolated conditions, the TAND framework emphasizes that these manifestations are interconnected dimensions of a common neurodevelopmental phenotype.

TAND encompasses six domains—behavioural, psychiatric, intellectual, academic, neuropsychological, and psychosocial—and international recommendations advise systematic assessment of each domain at diagnosis and throughout follow-up using the TAND Checklist (4,5). Despite these recommendations, registry data indicate that TAND remains substantially under-recognized in routine practice, and many patients never receive formal psychiatric evaluation (6,7).

Our patient fulfilled criteria across nearly all TAND domains (Table 3). Behaviourally, he exhibited stereotyped movements, marked insistence on sameness, severe self-injurious behaviour, and recurrent heteroaggression; psychiatrically, he met DSM-5 criteria for ASD; intellectually, he had severe intellectual disability with profound adaptive impairment; neuropsychologically, he showed developmental regression after seizure onset; and psychosocially, his condition imposed considerable caregiver burden because of complete dependence and the need for continuous supervision. This broad profile illustrates the usefulness of the TAND framework in capturing the complexity of psychiatric morbidity in TSC.

3.3. Early drug-resistant epilepsy and developmental regression

Epilepsy is one of the earliest and most prevalent manifestations of TSC, affecting up to 90% of individuals (1). Numerous studies have identified early seizure onset and drug-resistant epilepsy as major predictors of poor neurodevelopmental outcome (8,9,10).

In TSC, epilepsy typically begins during the first year of life, most often as focal seizures and/or epileptic (infantile) spasms, which may occur separately or together, with focal seizures frequently preceding or accompanying the spasms (1,9). Because seizures arise from epileptogenic cortical tubers and the surrounding cortex, the epilepsy is fundamentally focal in origin, and apparently “generalized” tonic-clonic seizures usually represent focal seizures with bilateral tonic-clonic evolution. Over time, many patients develop multiple seizure types and a subset progress to a developmental and epileptic encephalopathy such as Lennox-Gastaut syndrome, with drug resistance in approximately 60% (1,9,11). In our patient, the current generalized tonic-clonic pattern most plausibly reflects this evolution from earlier focal or spasm-type seizures, although the onset semiology could not be confirmed from the available records.

Our patient's trajectory closely mirrors this pattern. Early development was marked by acquisition of language and reciprocal social interaction, suggesting relatively preserved neurodevelopment during infancy. However, the onset of recurrent generalized tonic-clonic seizures before two years of age was followed by progressive regression, loss of expressive language, deterioration of social communication, emergence of stereotypies, and increasing behavioural rigidity. This temporal sequence has been repeatedly reported in longitudinal TSC studies: persistent epileptic activity during periods of rapid brain maturation is thought to disrupt synaptic development, cortical connectivity, and functional network organization, increasing the likelihood of ASD, intellectual disability, and severe adaptive impairment (3,8). Although the underlying mTOR dysfunction contributes to abnormal neurodevelopment from early fetal life, epilepsy appears to accelerate and exacerbate these abnormalities.

Drug-resistant epilepsy may further contribute to psychiatric morbidity through recurrent epileptic discharges, cumulative antiseizure-medication exposure, sleep disruption, and reduced opportunities for learning and environmental interaction. Consequently, early seizure control has become a major therapeutic objective in TSC, not only to reduce seizure frequency but also to improve long-term neurodevelopmental outcome (1,11,12).

3.4. Severe psychiatric comorbidities: ASD, severe intellectual disability, self-injury, and aggression

Psychiatric symptoms are among the most disabling dimensions of TSC, often affecting long-term functioning and family quality of life more than systemic features (3,4). Although epilepsy has historically been regarded as the hallmark neurological feature, increasing attention is now directed towards the high prevalence of ASD, intellectual disability, behavioural disorders, anxiety, ADHD, and mood disorders collectively referred to as TAND (1,4).

Our patient presented one of the most severe TAND phenotypes, combining non-verbal autism, severe intellectual disability, developmental regression, stereotyped behaviours, behavioural rigidity, recurrent self-injurious behaviour, and heteroaggression. Such a combination has been described in severe forms of TSC but remains relatively uncommon, particularly when all these manifestations coexist in the same patient (3,4).

ASD is reported in roughly one-quarter to one-half of individuals with TSC, making it one of the genetic disorders most strongly associated with autism (4,6). Consistently identified risk factors include early seizure onset, infantile spasms, drug-resistant epilepsy, high cortical-tuber burden, and pathogenic TSC2 variants (3,6). Although genetic testing was not available

in our patient, his clinical evolution closely followed this recognized pattern: normal early development followed by epilepsy, developmental regression, and the subsequent emergence of severe autistic symptoms.

An important feature is the complete loss of expressive language after seizure onset, followed by absence of further language acquisition despite years of rehabilitation. Language regression has been described in children with TSC, particularly with persistent epileptic activity during the first years of life (8,9), supporting the hypothesis that uncontrolled epilepsy may interfere with cortical-network maturation during critical developmental windows.

Severe intellectual disability further contributed to functional dependence. TOSCA data indicate that intellectual disability affects about half of individuals with TSC, with severity closely associated with seizure burden and early epilepsy (6). In our patient, adaptive functioning remained profoundly impaired despite continuous educational and rehabilitation interventions, highlighting the cumulative effects of early epilepsy, developmental regression, and abnormal cortical development (10).

Behavioural disturbances became the predominant reason for psychiatric referral during adolescence. Self-injury consisted mainly of repetitive head-banging, whereas heteroaggression was directed primarily towards caregivers during frustration, interruption of preferred routines, or environmental change. Similar behaviours are described in severe ASD with profound intellectual disability, in whom aggression and self-injury frequently represent maladaptive forms of communication rather than primary psychiatric disorders (4,7). The absence of functional verbal communication further complicated behavioural assessment: in non-verbal individuals, challenging behaviours may reflect pain, sensory overload, anxiety, frustration, sleep disturbance, gastrointestinal discomfort, or seizure-related phenomena. International recommendations therefore emphasize a biopsychosocial evaluation before considering psychotropic medication (1,4,13).

This case reinforces the importance of comprehensive psychiatric assessment in all individuals with TSC, regardless of the severity of systemic manifestations. Although our patient developed no major renal, cardiac, or pulmonary complications, psychiatric manifestations became the principal determinants of disability, caregiver burden, and healthcare utilization, supporting the view that TAND should be considered a core manifestation of TSC rather than a secondary complication (1,4,7).

3.5. Therapeutic challenges: when drug-resistant epilepsy limits psychiatric management

Managing severe behavioural disorders in TSC is especially difficult, because treatment decisions must simultaneously address neurological and psychiatric needs. Current recommendations advocate a multidisciplinary approach integrating paediatric neurology, child psychiatry, psychology, rehabilitation medicine, behavioural therapy, and family support (1,11).

Our patient underwent long-term multidisciplinary management, including speech and language therapy, psychomotor rehabilitation, psychoeducational interventions, and ABA. Despite sustained participation, functional improvement remained minimal—probably reflecting the severity of the underlying neurodevelopmental disorder rather than inadequate therapeutic intensity. Developmental outcomes are strongly influenced by the timing of epilepsy onset and seizure control, and behavioural interventions are less effective when profound intellectual disability and persistent epilepsy coexist (8,10).

Pharmacological management posed another major challenge. Second-generation antipsychotics such as risperidone and aripiprazole are recommended for severe irritability and aggression in ASD (13). However, in drug-resistant epilepsy, treatment must be individualized, because psychotropic agents may interact with antiseizure drugs, modify serum concentrations, increase adverse effects, or influence seizure control; the risk–benefit balance must therefore be evaluated carefully. In our patient, recurrent self-injury required immediate protective interventions—environmental modification, continuous supervision, and protective headgear—to reduce the risk of traumatic brain injury while avoiding unnecessary pharmacological escalation, consistent with guidelines recommending non-pharmacological interventions as first-line treatment whenever possible (11,16).

A further consideration is the ongoing evaluation for epilepsy surgery. The International TSC Consensus recommends early consideration of surgery in selected patients with medically refractory epilepsy after multidisciplinary assessment (1). Although surgery primarily aims to improve seizure control, successful seizure reduction may also improve attention, adaptive functioning, behaviour, and caregiver quality of life; nevertheless, outcomes remain variable, particularly with extensive bilateral cortical involvement or established severe neurodevelopmental impairment (14).

3.6. Clinical implications and what this case adds

Although TSC is classically recognized as a multisystem genetic disorder, this case illustrates that neuropsychiatric manifestations may become the predominant source of disability during

adolescence. While cortical tubers, epilepsy, and dermatological lesions are essential for diagnosis, this patient's long-term prognosis was driven by the progressive accumulation of TAND—ASD, severe intellectual disability, self-injury, and heteroaggression (1,8,9).

The case demonstrates the temporal relationship between early-onset drug-resistant epilepsy and developmental regression, and the predominance of psychiatric manifestations despite the absence of clinically significant renal, cardiac, pulmonary, or ophthalmological involvement. This reinforces recommendations advocating routine TAND screening at diagnosis and during follow-up, irrespective of the severity of extracerebral disease (1,4,7). The coexistence of recurrent head-banging, heteroaggression, severe behavioural rigidity, non-verbal autism, and profound intellectual disability represents one of the most disabling expressions of TAND, and its minimal response to prolonged rehabilitation likely reflects the cumulative effects of abnormal cortical development, developmental regression, and persistent epileptic activity. Overall, this report supports considering TSC a lifelong neuropsychiatric disorder and integrating child psychiatry into its long-term management (14).

4. CONCLUSION

TSC is increasingly recognized as a neurodevelopmental disorder in which psychiatric manifestations substantially contribute to long-term disability. We reported a 13-year-old adolescent with definite TSC who developed early-onset drug-resistant epilepsy followed by developmental regression, non-verbal ASD, severe intellectual disability, recurrent self-injurious behaviour, and heteroaggression. The case illustrates the profound impact of persistent epileptic activity on neurodevelopment and the usefulness of the TAND framework, and shows that psychiatric symptoms may become the principal determinant of functional impairment even without significant extracerebral involvement. Management proved especially difficult: drug-resistant epilepsy limited pharmacological options, and intensive rehabilitation produced only modest improvement. Greater awareness of TAND, systematic psychiatric screening throughout follow-up, and earlier comprehensive multidisciplinary intervention may improve quality of life for patients and caregivers. Further longitudinal studies are needed to identify predictors of severe psychiatric phenotypes and to optimize therapeutic strategies in TSC.

Learning points

- TSC should be considered a neurodevelopmental disorder in which psychiatric manifestations may become the principal source of long-term disability.
- Early-onset drug-resistant epilepsy is strongly associated with developmental regression, ASD, and severe intellectual disability in TSC.
- The TAND framework provides a comprehensive structure for evaluating behavioural, psychiatric, cognitive, and psychosocial manifestations and should be assessed systematically throughout follow-up.
- Managing severe self-injurious behaviour and heteroaggression in TSC requires a multidisciplinary approach combining behavioural interventions, environmental adaptation, neurological management, and individualized psychiatric treatment.
- In medically refractory epilepsy, early referral to an epilepsy-surgery centre should be considered according to international recommendations.

Ethics and consent

Written informed consent for publication of this anonymized case was obtained from the patient's parents/legal guardians. [Confirm and complete institutional-review/ethics statement as required by the target journal.]

Table 2. Clinical timeline.

Age	Clinical findings
Birth	Full-term pregnancy, uncomplicated delivery
Infancy	Normal psychomotor development; early language and reciprocal social interaction before 2 years
Before 2 years	Onset of recurrent seizures (onset semiology not documented; currently generalized tonic-clonic)
Shortly after seizure onset	Developmental regression with loss of language and social reciprocity
2 years	Brain MRI: cortical tubers and subependymal nodules; dermatological findings (hypomelanotic macules, confetti lesions, facial angiofibromas); diagnosis of definite TSC (clinical criteria; genetic testing not performed)
3 years	Diagnosis of ASD (DSM-5, ADI-R, ADOS) and severe intellectual disability
Childhood	Speech therapy, psychomotor therapy, and ABA initiated
Follow-up	Drug-resistant epilepsy despite multiple antiseizure-medication combinations; progressive abnormalities on serial MRI; discussion of

Age	Clinical findings
	epilepsy surgery
13 years	Non-verbal ASD, severe intellectual disability, self-injury, heteroaggression, profound functional dependence

Table 3. Neuropsychiatric manifestations according to the TAND framework.

TAND domain	Findings in our patient
Behavioural	Head-banging, heteroaggression, stereotypies, behavioural rigidity
Psychiatric	Autism spectrum disorder (DSM-5; ADI-R, ADOS)
Intellectual	Severe intellectual disability
Neuropsychological	Developmental regression following seizure onset
Academic	Absence of functional academic skills
Psychosocial	Complete dependence, marked caregiver burden

Table 4. Major diagnostic and therapeutic challenges.

Challenge	Clinical impact	Management implications
Drug-resistant epilepsy	Persistent seizures	Limited therapeutic options; consideration of epilepsy surgery
Developmental regression	Loss of acquired language and social abilities	Long-term multidisciplinary rehabilitation
Non-verbal autism	Severe communication impairment	Difficult behavioural assessment
Severe intellectual disability	Complete functional dependence	Continuous caregiver support
Self-injurious behaviour	Risk of traumatic head injury	Environmental adaptation and protective headgear
Heteroaggression	Family burden and safety concerns	Behavioural interventions and individualized psychiatric management
Progressive cerebral lesions	Risk of neurological deterioration	Regular MRI surveillance and multidisciplinary evaluation

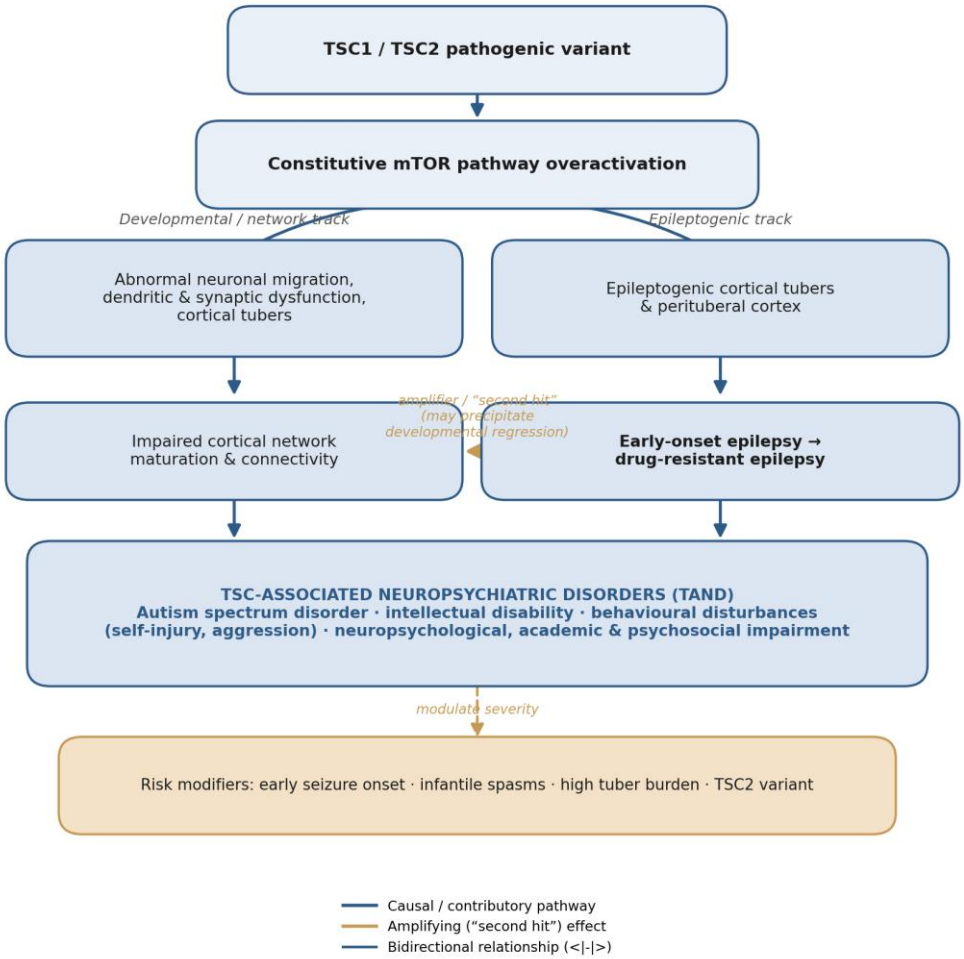

Figure 1. Proposed convergent two-track pathophysiological model of TSC-associated neuropsychiatric disorders (TAND).

In this model, constitutive mTOR overactivation drives two partly independent tracks. A developmental/network track (abnormal neuronal migration, dendritic and synaptic dysfunction, cortical tubers) impairs cortical maturation and leads directly to autism spectrum disorder and intellectual disability, independently of seizures. In parallel, an epileptogenic track (epileptogenic tubers and perituberal cortex) produces early-onset, frequently drug-resistant epilepsy. Epilepsy acts as an amplifying "second hit" on the developmental track and may precipitate developmental regression, as in the present case. The two tracks converge on TAND—the umbrella construct encompassing behavioural, psychiatric, intellectual, neuropsychological, academic and psychosocial manifestations—and their severity is modulated by early seizure onset, infantile spasms, high tuber burden and TSC2 genotype. Relationships between epilepsy and neurodevelopmental/psychiatric outcome are bidirectional rather than strictly linear.

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