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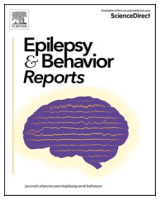

Neuropsychiatric disorders in Chinese pediatric tuberous sclerosis complex patients associated with drug-resistant epilepsy: A TAND checklist-based survey

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal-dominant genetic disorder frequently accompanied by neuropsychiatric disorders, especially in patients who have drug-resistant epilepsy (DRE). This study aimed to evaluate the distribution of neuropsychiatric disorders in Chinese children with TSC-related epilepsy using the TAND (Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders) checklist, comparing those with DRE to those achieving seizure freedom. A total of 47 children, aged 6 to 18 years, diagnosed with TSC at Peking University People's Hospital, participated in this cross-sectional study. All participants met the latest diagnostic criteria for TSC. Based on the definition of drug-resistant epilepsy, participants were categorized into DRE group and seizure-free group. Neurodevelopmental disorders were evaluated using the TAND checklist. The study found that 66 % of participants exhibited varying degrees of intellectual disability, with the DRE group demonstrating significantly poorer performance in intelligence, behavior, neuropsychological, and learning skills compared to the seizure-free group. The DRE group also had higher rates of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), alongside greater impairments in psychosocial functioning. This study indicates that DRE is strongly associated with neuropsychiatric development in children with TSC, but also that all children with TSC are at increased risk of TAND. Our findings highlight the importance of regular assessment and intervention to support TAND and improve quality of life in this vulnerable group.

1. Introduction

Tuberous sclerosis complex (TSC) is a hereditary neurocutaneous syndrome that affects multiple organs, with an incidence rate of 1 in 10,000 to 1 in 6,000, primarily observed in children. The condition affects males and females equally [1,2]. *TSC1* and *TSC2* genes are identified as causative genes for this disease. Clinical manifestations of TSC are complex and varied, most notably involving hamartomas across multiple organs, along with neuropsychiatric symptoms including seizures, autism, and intellectual disability [2].

About 90 % of patients with TSC encounter a variety of behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial challenges, imposing significant burdens on both the patients and their families. In 2012, the concept of tuberous sclerosis complex associated neuropsychiatric disorder (TAND) was formally introduced to improve the comprehension and management of neuropsychiatric diseases associated with TSC patients. TAND aims to improve clinical identification and gaps in treatment and management [3]. The TAND checklist has since been developed to provide a standardized "shared language" for the assessment and screening of various degrees of neuropsychiatric disorders in individuals with TSC [4].

Epilepsy represents a significant neurological manifestation of TSC, impacting around 70 %-90 % of children with the condition, with around two-thirds of these cases classified as drug-resistant epilepsy (DRE) [5–7]. Several studies have shown that epilepsy correlates with an increased risk of neuropsychiatric disorders [8–11]. Early-onset refractory epilepsy is associated with a greater risk of impaired cognitive development [12,13]. The TuberOus SClerosis registry to increase disease Awareness (TOSCA) highlighted that factors such as infantile spasms, DRE, and *TSC2* gene mutations elevate the risk of cognitive impairment and autism spectrum disorder (ASD) among patients with TSC [14]. Consistent with these findings, earlier recognition and

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treatment of epilepsy correlate with improved long-term neurological outcomes [15].

The International TSC Consensus Conference recommends assessing the presence and severity of TAND symptoms at least annually for patients with TSC [16]. However, routine evaluations for TSC patients remain infrequent, leading to gaps in the understanding and treatment of these patients during follow-up. A comprehensive scoping review of previous TAND studies published in 2022 described the landscape of TAND research, indicating that more than 80 % of these studies were conducted in high-income countries, predominantly in the United States and the United Kingdom [17]. Despite unique socioeconomic, cultural, and contextual factors within Chinese populations, their representation is inadequate, primarily based on international multi-site studies and individual clinical case reports [18]. In 2021, Ding et al. utilized Mini International Neuropsychiatric Interview for Children (MINI-KID) to assess psychiatric disorders in pediatric patients with TSC [19]. Currently, there are few studies that use the recommended TAND checklist to assess all TAND symptoms in children with TSC in China.

This study aimed to evaluate the rates of neuropsychiatric disorders in pediatric TSC patients with epilepsy using the Chinese version of the TAND checklist. It also compared TAND outcomes between children with DRE and those with well-controlled epilepsy.

2. Methods

Structured interviews were conducted at Peking University People's Hospital utilizing the TAND checklist, and participants were monitored regularly for neurological disorders, dermatological symptoms, or lesions in other organs.

2.1. Participants

We conducted a retrospective analysis of clinical data from children with TSC admitted to the Department of Pediatric Neurology at Peking University People's Hospital between September 2023 and September 2024. The inclusion criteria were: ① Age ranging from 6 to 18 years; ② Diagnosis based on the 2021 updated TSC diagnostic criteria described by the International Tuberous Sclerosis Complex Consensus Group [16]; ③ Obtained informed and signed consent from family members for research participation. Patients not meeting these criteria were excluded. This retrospective cohort study received approval from the ethics committee of our hospital.

2.2. Evaluation of medical history

Demographic and clinical data, including gender, age, genotype, epilepsy history, and history of infantile epileptic spasms syndrome (IESS) were collected from electronic medical records. This study utilized the 2010 definition of DRE established by the International League Against Epilepsy (ILAE) [20]. DRE is diagnosed when a patient fails to achieve a seizure-free duration of three times the interseizure interval or one year, whichever is longer, following trials with two tolerated, appropriately chosen, and adequately administered anti-seizure medications. Patients who satisfy this definition were categorized into the DRE group, whereas those without clinical seizures for at least one year were classified into the seizure-free group.

2.3. TAND screening

Experienced neuropsychologists assessed participants for neurodevelopmental disorders, involving intelligence levels, attention deficit/hyperactivity disorder (ADHD), and ASD. The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) was utilized for the evaluation of intelligence, and diagnoses of neurodevelopmental disorders were conducted in alignment with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Parents or caregivers of the participants were interviewed with the TAND checklist, a validated screening tool in English, aimed at assisting families and clinicians in identifying TAND [21]. Since the official Chinese version of the TAND checklist was not available at the time of data collection, we initially used a research team-generated translation based on the original English checklist to interview families. After the authorized version was published in January 2025, we conducted a detailed comparison and supplemented the interviews to address any discrepancies and ensure data consistency. The official Chinese version of the TAND checklist can be accessed at https://tandconsortium.org/checklists/.

The TAND-L checklist encompasses six dimensions: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial functioning [4]. It contains 12 sets of questions, the majority of which (e.g., Questions 3 to 8) are answered by the family members of TSC patients with binary 'yes/no' responses, while Questions 10 and 11 require narrative responses (see Table 1) [4]. Each interview took approximately 15–30 min.

Question 3 of the TAND checklist includes 19 items covering the subdomains of "hyperactivity" and "social communication". A significant positive correlation was identified between the overall score in the behavioral area of the checklist and the total difficulty score on the Strengths and Difficulties Questionnaire (SDQ). Additionally, items and scores within the social communication subfield showed a clear linear correlation to the overall score on the Social Communication Questionnaire (SCQ) [21]. Notably, the subdomain of social communication (items 3 h-3 m) is categorized as an autism-like cluster within the natural TAND cluster [22]. The severity of symptoms in the behavioral domain was quantified by calculating the total number of "Yes" responses across the 19 items, while the social communication subdomain was assessed based on the number of "Yes" responses to 6 items (3 h to 3 m) related to social communication. In Question 9 of the TAND checklist, participants or caregivers assessed the impact of these neuropsychiatric disorders on the overall subjective experience of the patient and their family, using a scale from 1 to 10. Thus, scores in these domains serve as criteria to gauge the severity of the related problems, with higher scores indicating more pronounced neuropsychiatric symptoms.

2.4. Statistical methods

Following the method for validating the TAND checklist, to assess the severity within the behavioral level of Question 3, we calculated the number of "yes" responses overall and specifically in the "social communication" subdomain (3 h-3 m) to determine whether the patient exhibited autism-like symptoms [21].

Statistical analysis utilized SPSS 25.0 software. Quantitative data that follow a normal distribution are represented as mean ± standard deviation (mean ± SD), whereas non-normally distributed quantitative data are represented as median (interquartile range, IQR). Binary variables were presented as counts and percentages, and were analyzed

Table 1
TAND Checklist-structure [4].

Item	Level of Investigation
Question 1	Basic developmental milestones
Question 2	Current level of functioning
Question 3	Behavioral concerns
Question 4	Psychiatric disorders diagnosed
Question 5	Intellectual ability
Question 6	Academic skills
Question 7	Neuropsychological skills
Question 8	Psychosocial functioning
Question 9	Parent, caregiver, or self-rating of the impact of TAND
Question 10	Prioritizing list
Question 11	Additional concerns
Question 12	Health-care professional rating of the impact of TAND

TAND: tuberous sclerosis complex associated neuropsychiatric disorders.

using the chi-square test or Fisher's exact test. The Mann-Whitney *U* test was employed to analyze ordinal variables. $P < 0.05$ was set as statistically significant.

3. Results

3.1. Demographic and clinical features

Table 2 presents the demographic characteristics of the study participants. The study comprised 47 TSC patients, including 30 males and 17 females. Among these participants, 26 (55 %) had DRE, and 23 (48.94 %) had the *TSC2* gene mutations. There were no statistically significant differences between the two groups regarding gender, age, or genotype distribution ($p = 0.805$, $p = 0.808$, and $p = 0.098$, respectively). At baseline, 9 patients (34.62 %) with TSC-associated DRE had a history of IESS, compared to 2 patients (9.52 %) in the seizure-free cohort. The difference was statistically significant ($p < 0.05$), suggesting an increased probability of IESS history in patients with TSC-associated DRE.

3.2. The survey results of the TAND checklist

Among the patients with TSC-associated epilepsy, 66 % exhibited various levels of intellectual disability, ranging from mild to extremely severe. As displayed in Fig. 1, in the seizure-free group, 13 patients (61.90 %) had normal or borderline intellectual functioning, 8 patients (38.10 %) had mild or moderate intellectual disability, and no severe or profound intellectual disability were found ($p < 0.001$). In contrast, within the DRE group, only 3 patients (11.54 %) had normal or nearly normal intelligence, 9 patients (34.62 %) had mild intellectual disability, 10 patients (38.46 %) had moderate intellectual disability, and 4 patients (15.39 %) exhibited severe to profound intellectual disability (Table 3).

At the behavioral level, the most prevalent symptoms included temper tantrums ($n = 35$, 74.47 %), difficulty paying attention or concentrating ($n = 34$, 72.34 %), mood swings ($n = 32$, 68.09 %), language absent or delay ($n = 29$, 61.70 %), and difficulties in getting along with peers($n = 25$, 53.19 %). In comparing the DRE group with the seizure-free group, only the DRE group exhibited self-injury and eating abnormalities. Notable differences were detected between the two groups regarding the following symptoms: depressed mood ($p = 0.003$), extreme shyness ($p = 0.002$), mood swings ($p = 0.007$), aggressive outbursts ($p = 0.002$), temper tantrums ($p = 0.014$), language absent or delay ($p = 0.017$), repetitive speech ($p = 0.012$), poor eye contact ($p < 0.001$), difficulties in getting along with peers ($p < 0.001$), repetitive behavior ($p < 0.001$), rigid behavior ($p = 0.002$), overactivity/hyperactivity ($p = 0.037$), and inattention ($p = 0.036$). Results are presented in Table 3.

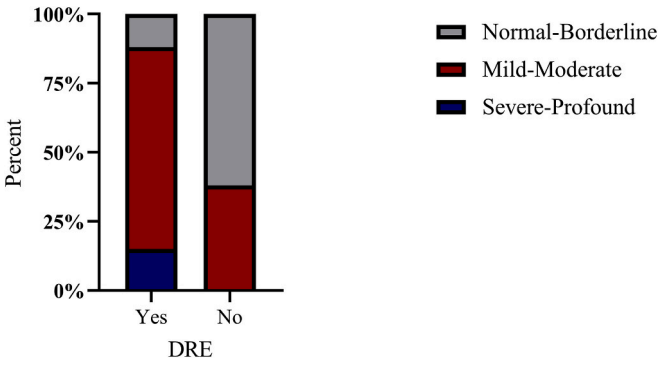

Fig. 1. Intelligence level in the DRE group and seizure-freedom group. DRE: drug-resistant epilepsy

The most diagnosed psychiatric disorder was ADHD ($n = 14$, 29.79 %), followed by ASD ($n = 13$, 27.66 %). Both ADHD and ASD showed a significant association with DRE ($p < 0.001$ and $p = 0.012$, respectively). Obsessive-compulsive disorder, depression, and other psychotic disorders, including bipolar disorder, were observed exclusively in the DRE group.

At the academic level, more than 90 % of children with TSC-associated epilepsy experience varying degrees of difficulties with academic skills. Specifically, 42 (89.36 %) had difficulties in mathematics, 37 (78.72 %) in writing, 36 (76.60 %) in reading, and 30 (63.83 %) in spelling. The presence of academic difficulties among children with TSC was significantly correlated with DRE, as shown in Table 3.

At the neuropsychological level, dual/multitasking difficulties were the most common issue, affecting 34 participants (72.34 %), followed by attention deficits in 33 (70.21 %) and impaired executive skills in 32 (68.09 %). In the DRE group, attention deficits ($p = 0.016$), dual/multitasking difficulties ($p = 0.006$), visual-spatial task issues ($p = 0.001$), impaired executive skill ($p < 0.001$), and disorientation ($p = 0.015$) were statistically significant.

At the psychosocial level, over half of the children with TSC-associated epilepsy experienced low self-esteem, while family stress ($p = 0.005$) and strained parental relationships ($p = 0.001$) were more frequently reported in the DRE group compared to the seizure-free group.

Table 2
Demographic characteristics of TSC patients with epilepsy.

Variable	All (%)	DRE (%)		P value
	n = 47	Yes, n = 26 (55 %)	No, n = 21 (48.94 %)	
Gender				0.805
Male	30 (63.83)	17 (65.38)	13 (61.90)	
Female	17 (36.17)	9 (34.62)	8 (38.10)	
Age (years)				0.808
6–12	35 (74.47)	19 (73.08)	16 (76.19)	
>12	12 (25.53)	7 (26.92)	5 (23.81)	
Genotype				0.098
TSC1	10 (21.28)	3 (11.54)	7 (33.33)	
TSC2	23 (48.94)	16 (61.54)	7 (33.33)	
NMI/ND	14 (29.79)	7 (26.92)	7 (33.33)	
IESS				0.043
Yes	11 (23.40)	9 (34.62)	2 (9.52)	
No	36 (76.60)	17 (65.38)	19 (90.48)	

Data are presented as numbers (%).
DRE: drug-resistant epilepsy; IESS: infantile epileptic spasms syndrome; NMI: no mutation identified; ND: not done.

Table 3
TAND results of the study group (n = 47) stratified by DRE.

TAND Feature	All(%) n = 47	DRE(%) Yes, n = 26	No, n = 21	X^2	P value
Behavioral level					
Anxiety	17(36.17)	12(46.15)	5 (23.81)	2.512	0.113
Depressed mood	15 (31.91)	13 (50.00)	2 (9.52)	8.759	0.003
Extreme shyness	23 (48.94)	18 (69.23)	5 (23.81)	9.591	0.002
Mood swings	32 (68.09)	22 (84.62)	10 (47.62)	7.318	0.007
Aggressive outbursts	13 (27.66)	12 (46.15)	1 (4.76)	9.947	0.002
Temper Tantrums	35 (74.47)	23 (88.46)	12 (57.14)	5.993	0.014
Self-injury	6 (12.77)	6 (23.08)	0 (0.00)	5.555	0.018
Absent or delayed speech	29 (61.70)	20 (76.92)	9 (42.86)	5.705	0.017
Repeating words or phrases	23 (48.94)	17 (65.38)	6 (28.57)	6.300	0.012
Poor eye contact	15 (31.91)	14 (53.85)	1 (4.76)	12.881	<0.001
Difficulties getting on with other people of similar age	25 (53.19)	22 (84.62)	3 (14.29)	23.078	<0.001
Repetitive behaviors	18 (38.30)	16 (61.54)	2 (9.52)	13.301	<0.001
Very rigid or inflexible about how to do things	23 (48.94)	18 (69.23)	5 (23.81)	9.591	0.002
hyperactivity	19 (40.43)	14 (53.85)	5 (23.81)	4.352	0.037
Difficulties paying attention	34 (72.34)	22 (84.62)	12 (57.14)	4.382	0.036
Restlessness or fidgetiness	15 (31.91)	11 (42.31)	4 (19.05)	2.892	0.089
Impulsivity	11 (23.40)	8 (30.77)	3 (14.29)	1.761	0.185
Difficulties with eating	12 (25.53)	12 (46.15)	0 (0.00)	13.015	<0.001
Sleep difficulties	5 (10.64)	4 (15.38)	1 (4.76)	1.379	0.240
Psychiatric level					
ASD	13(27.66)	11(42.31)	2(9.52)	6.240	0.012
ADHD	14(29.79)	13(50.00)	1 (4.76)	11.367	<0.001
Anxiety disorder	5(10.64)	4(15.38)	1 (4.76)	0.488	0.485
Depressive disorder	2 (4.26)	2 (7.69)	0 (0.00)	–	0.495
Obsessive Compulsive Disorder	2 (4.26)	2 (7.69)	0 (0.00)	–	0.495
Psychotic disorder	2 (4.26)	2 (7.69)	0 (0.00)	–	0.495
Intellectual ability				−3.695	<0.001
Normal-Borderline	16 (34.04)	3 (11.54)	13 (61.90)		
Mild	14 (29.79)	9 (34.r62)	5 (23.81)		
Moderate	13 (27.66)	10 (38.46)	3 (14.29)		
Severe	3 (6.38)	3 (11.54)	0 (0.00)		
Profound	1 (2.13)	1 (3.85)	0 (0.00)		
Academic level					
Reading	36 (76.60)	25 (96.15)	11 (52.38)	12.417	<0.001
Writing	37 (78.72)	26 (100.00)	11 (52.38)	15.727	<0.001
Spelling	30 (63.83)	23 (88.46)	7 (33.33)	15.292	<0.001
Mathematics	42 (89.36)	26 (100.00)	16 (76.19)	6.927	0.008
Neuropsychological level					
Memory	15 (31.91)	11 (42.31)	4 (19.05)	2.892	0.089
Attention	33 (70.21)	22 (84.62)	11 (52.38)	5.771	0.016
Dual/ multi-tasking	34 (72.34)	23 (88.46)	11 (52.38)	7.558	0.006
Visuo-spatial tasks	19 (40.43)	16 (61.54)	3 (14.29)	10.770	0.001
Executive skills	32 (68.09)	24 (92.31)	8 (38.10)	15.713	<0.001
Getting disoriented	18 (38.30)	14 (53.85)	4 (19.05)	5.953	0.015
Psychosocial level					
Low self-esteem of the patient	26(55.32)	17(65.38)	9 (42.86)	2.385	0.122
Family stress	17 (36.17)	14 (53.85)	3 (14.29)	7.875	0.005
relationship difficulties between parents	17 (36.17)	15 (57.69)	2 (9.52)	11.675	0.001

Data are presented as numbers (%).
TAND: tuberous sclerosis complex associated neuropsychiatric disorders; DRE: drug-resistant epilepsy; ASD: autism spectrum disorder, ADHD: attention-deficit hyperactivity disorder.

3.3. Comparison of TAND domains between patients with DRE and those with seizure freedom

Fig. 2 demonstrates that the overall TAND score, behavioral score, and social communication (autism-liked cluster) score were significantly higher in the DRE group, exhibiting statistically significant differences between the two groups ($p < 0.001$). Detailed results are provided in Table 4.

3.4. Other concerns of caregivers of children with TSC-associated epilepsy

In Questions 10 and 11, we conducted in-depth interviews with parents of TSC patients. Nearly all parents in the DRE group emphasized that controlling seizure was their highest priority. They also expressed concern about improving their child's self-care abilities and cognitive development. In contrast, most parents in the seizure-free group were more focused on their child's intellectual and learning abilities, particularly on improving attention, academic skills, and social interaction with peers.

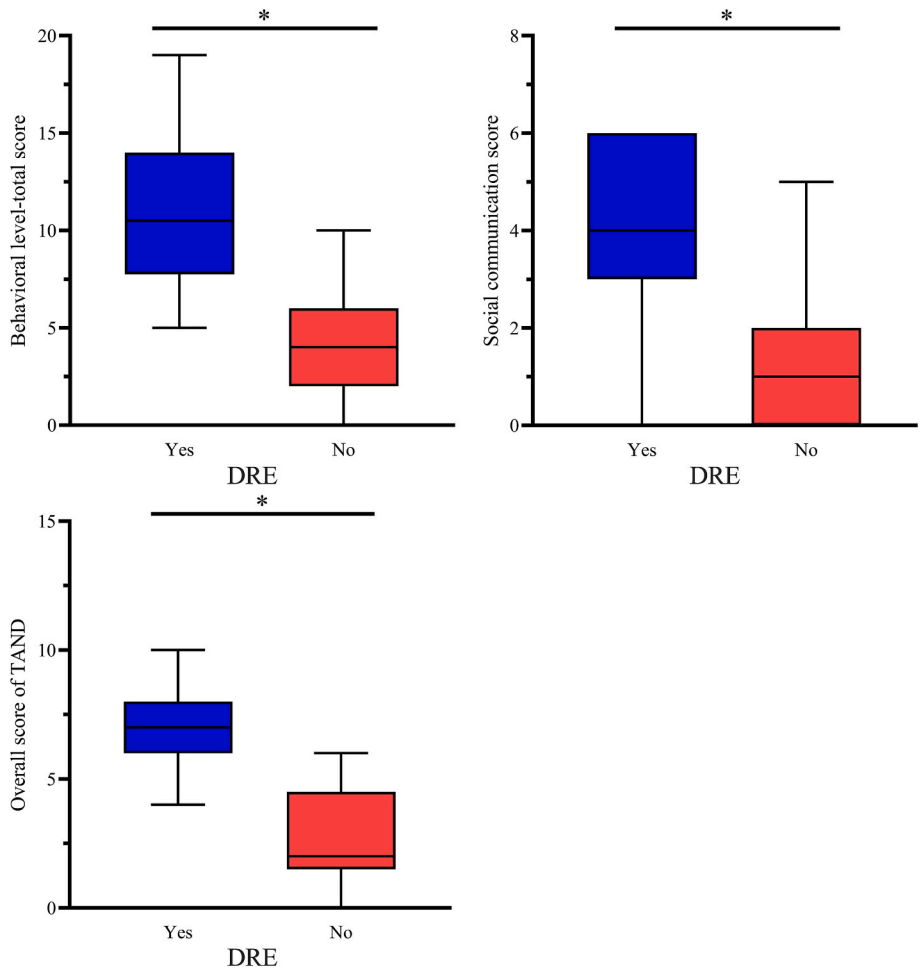

Fig. 2. Comparison of TAND domains between the DRE group and the seizure-free group, with higher scores indicating more severe neuropsychiatric symptoms at that level. The Overall score of TAND refers to the caregiver's rating of the overall impact of neuropsychiatric symptoms using a visual analogue scale ranging from 1 to 10 (TAND Checklist, Question 9); the Behavioral level-total score represents the total number of affirmative ("Yes") responses to the 19 behavioral items assessed in Question 3 of the TAND Checklist; the Social communication score denotes the number of affirmative ("Yes") responses to items 3 h-3 m of the behavioral level, corresponding to the autism-like symptom cluster. TAND: tuberous sclerosis complex associated neuropsychiatric disorders; DRE: drug-resistant epilepsy.

Table 4
Scores of different TAND domains between the two groups.

	DRE		P value
	Yes (n = 26)	No (n = 21)	
Overall score, median (IQR)	7.00 (6.00, 8.00)	2.00 (1.50,4.50)	<0.001
Behavioral level, median (IQR)			
Total score	10.50 (8.00,14.00)	4.00 (2.00,6.00)	<0.001
Social communication score	4.00 (3.00, 6.00)	1.00 (0.00,2.00)	<0.001

DRE: drug-resistant epilepsy; IQR: inter-quartile range.

4. Discussion

This study, conducted with 47 TSC patients with epilepsy, provided a comprehensive evaluation of neuropsychiatric disorders in children with TSC, with a particular focus on differences between those with DRE and those achieving seizure freedom. The findings highlight the importance of using the TAND checklist for thorough assessment. Results indicated that the DRE group showed significantly worse performance compared to the seizure freedom group across multiple neuropsychiatric domains. Previous studies have similarly demonstrated a higher incidence of TAND symptoms, particularly intellectual and behavioral disorders, in patients with epilepsy [8,9,23,24]. This study further elucidates the association between DRE and cognitive and behavioral development in children with TSC. The findings emphasize the need for comprehensive clinical evaluation and timely intervention targeting neuropsychiatric manifestations in this vulnerable cohort.

The TOSCA study identified a correlation between the epileptic seizure and an increased incidence of intellectual disability [24]. A longitudinal study by Tye et al. investigated long-term cognitive outcomes for those with TSC, revealing that early seizures, a history of IESS, and severe seizures are significantly linked to impaired intellectual development [25]. Humphrey et al. discovered that the onset and duration of IESS are correlated with significant intellectual developmental impairments [26]. The incidence of IESS was substantially higher in the DRE group compared to the seizure-free group in our study, suggesting a potential association between IESS and long-term intellectual developmental deficits. Our study found that 66 % of children with TSC-related epilepsy exhibited intellectual disability, while only 11.54 % of patients in the DRE group demonstrated normal or borderline intelligence. Early seizure control may be critical for the promotion of intellectual development, as seizure freedom has been related to higher intellectual functioning [27].

Our research revealed that more than 90 % of children with TSC displayed behavioral issues, including temper tantrums, diminished attention, mood swings, speech delays, and difficulties in relationships with peers. Patients with DRE had significantly elevated rates of mood

swings, aggressive behaviors, and abnormal social communication. The comparison of total behavioral scores and social communication subdomain scores between the two groups illustrates that DRE is correlated with increased behavioral dysregulation and developmental language disorder. Prior research suggests that epilepsy in children might impact language development, with severity, the quantity of ASMs, and therapeutic efficacy closely associated with language outcomes [10,28,29]. Early language deficits in TSC patients frequently indicate the presence of ASD [28].

Prather and de Vries et al. assert that ASD and ADHD are the most prevalent neuropsychiatric problems in children with TSC, whereas anxiety and mood disorders are predominant in adults [30,31]. Our results corroborate previous studies, indicating that ADHD (29.79 %) and ASD (27.66 %) are the most common psychiatric disorders, with a higher occurrence of psychotic disorders in children with DRE [18]. Additionally, psychological stress, social isolation, and the side effects of medications associated with recurrent seizures might aggravate behavioral and emotional abnormalities in children with TSC-related DRE. The challenges not only impair daily functioning and social interactions, which may intensify feelings of isolation and reduced self-esteem, but also increase psychological burdens within families, potentially leading to elevated familial stress and strained parental relationships, as evidenced by our psychosocial findings. We compared the overall TAND impact scores on patients or families, as rated by parents or caregivers (TAND checklist-Question 9), and found that the DRE group had considerably higher scores than the epilepsy control group (7.00 vs. 2.00).

Academic difficulties are more evident in children than in adults with TSC. Among patients with normal intelligence, 36 % of school-aged children face an increased danger of experiencing learning difficulties in reading, writing, and mathematics [32,33]. Epilepsy and intellectual disability were strongly associated with learning difficulties [34]. In our study, the presence of difficulties in multiple academic skills was markedly correlated with DRE. More than 90 % of patients in DRE group demonstrated notable deficits in reading, writing, and mathematics, a proportion far greater than previously documented for TSC-related epilepsy [14,35]. Recurrent seizures impair vital cognitive abilities, including memory, attention, information processing, and executive function, which are required for learning [36–39]. Additionally, the potential impact of social and environmental factors on TAND should be considered. The age range of our study population (6 to 18 years) encompasses a critical educational period for children in China, during which the academic pressures stemming from intense competition may influence symptom reporting.

Our research indicates that DRE substantially affects multiple neuropsychological functions in TSC patients, encompassing attention, dual/multi-tasking, visuo-spatial tasks, executive skills, and disorientation. These findings correspond with Cardozo et al.'s discoveries that seizure frequency and age are inversely related to cognitive function [37]. Previous research indicates that cognitive impairment tends to be exacerbated with a higher quantity of ASMs administered [38].

TAND symptoms remain prevalent in patients who have achieved seizure freedom. In this study, 48 % of TSC children who achieved seizure freedom displayed mood swings, 57 % exhibited temper tantrums, 43 % experienced absent or delayed speech, 57 % had difficulties paying attention, 76 % encountered difficulties in mathematics, and 52 % had problems with dual-task processing. Aside from epilepsy, certain risk markers may increase the likelihood of TAND manifestations, such as pathogenic variants in *TSC2* and *TSC1*, cortical tuber-related abnormalities and abnormal structural and functional connectivity. The *TSC2* genotype is highly associated with an increased risk of severe epilepsy, intellectual disability, and autism [40]. Farah et al. conducted a genotype-phenotype study involving 92 infants with TSC [41]. The results indicated that infants carrying pathogenic variants in *TSC2* exhibited significantly lower Mullen Scales of Early Learning scores at 24 months, independent of seizures. The degree of reduction in *TSC2* levels, as observed in hypomorphic conditional mice, correlated with behavioral abnormalities in anxiety, social interaction, and learning assays [42]. Hulshof et al. found that early brain MRI showing a higher tuber-brain ratio was associated with lower cognitive and motor development quotients at 2 years, regardless of the presence of TSC gene mutations or epilepsy [43]. The symptoms of TAND arise not from abnormalities in specific brain regions but from disorders in functional connectivity, indicative of network damage. Research shows a correlation between behavioral problems and autistic characteristics with the white matter in the limbic system, the anterior limb of the internal capsule, and the corpus callosum [44]. Early identification allows for timely intervention, and environmental enrichment during the critical developmental period can improve joint engagement, attention, and social interaction in toddlers at high risk of ASD [45]. Therefore, the emergence of TAND reflects the complex interplay of genetic, neurodevelopmental and environmental factors at multiple levels.

At present, limited research has investigated the priorities of demands by parents or caregivers (TAND checklist-Question 10). Previous studies have primarily concentrated on the quality of life and disease burden experienced by patients and caregivers, often considering the needs of parents across all TSC phenotypes as a unified group without stratifying by seizure control status [46,47]. This study addresses the existing gap. Interview findings reveal that parents of patients with DRE emphasize the need of seizure control and the enhancement of self-care and cognitive abilities, reflecting a major concern for fundamental health and life skills, alongside an extreme psychological burden. Conversely, parents or caregivers in the seizure-free group concentrate on intellectual, academic, and social skills, indicating elevated expectations for overall development.

5. Limitations

While this cross-sectional study offers valuable insights into neuropsychiatric disorders in DRE associated with TSC, several limitations should be noted. The limited sample size and single-center design constrain the applicability of the results. Subsequent research including larger sample sizes and multi-center collaboration is essential to validate these findings. Additionally, the absence of TSC children without epilepsy as a control group may be attributed to the recruitment source (pediatric neurology). The study population comprised children aged 6 to 18 years, excluding infants and preschool-aged children, which limits conclusions about younger age groups. Future research should include additional risk factors, such as age of onset, types of seizures (e.g., focal, spasms, and generalized seizures), neuroimaging-related variables (e.g., tuber burden and location), electroencephalogram characteristics (such as interictal epileptiform discharges), and sociodemographic factors (such as age at the initial clinical assessment). The integration of these variables will help explain the persistence of certain TAND domains despite seizure control, thereby improving the risk stratification model for TAND. In addition, the newly developed TAND-SQ, once translated into Chinese, could serve as a valuable self-report tool for quantifying neuropsychiatric difficulties in TSC. Unlike the clinician-completed TAND-L, it allows individuals with TSC and their caregivers to systematically document symptoms and severity [48]. As a structured and quantified tool, TAND-SQ enables a more detailed characterization of symptom burden across different TAND domains, potentially facilitating longitudinal monitoring and individualized management strategies.

6. Conclusions

This study examines neuropsychiatric disorders in children with TSC who also have epilepsy. Compared to the seizure-free group, DRE is associated with greater impacts on the intellectual and neuropsychiatric health of children with TSC, emphasizing the critical importance of epilepsy control for supporting their long-term neurodevelopment. By utilizing the TAND checklist, this study uncovers previously

unrecognized neuropsychological, psychiatric, and behavioral issues in Chinese children with TSC. Ultimately, these findings will contribute to the development of more comprehensive healthcare services for children affected by TSC.

Ethical statement

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study was approved by the Ethical Committee of Peking University People's Hospital (approval number: 2023PHB245-001).

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CRediT authorship contribution statement

Jie Fu: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qinrui Li:** Writing – review & editing, Investigation, Data curation. **Genfu Zhang:** Investigation, Data curation. **Zhixian Yang:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Jiong Qin:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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