Assessment of Tuberous Sclerosis-Associated Neuropsychiatric Disorders Using the MINI-KID tool: A Pediatric Cohort Study

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Research

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Abstract

Background: The tuberous sclerosis-associated neuropsychiatric disorders (TAND) has not been studied before in China. We aimed to assess TAND using the Mini International Neuropsychiatric Interview for Children (MINI-KID) in China.

Results: A total of 81.05% of patients (77/95) had at least one TAND, and 70.53% (67/95) had an intellectual disability. The MINI-KID tool diagnosed a total of 15 neuropsychiatric diseases, the most common of which were attention-deficit/hyperactivity disorder (ADHD) (51.58%, 49/95) and social anxiety disorder (41.05%, 39/95). The number of children with neuropsychiatric diseases in the TSC group was significantly greater than the numbers in the normal development group (P <0.0001). Epilepsy before the age of 2 years, an epilepsy duration exceeding 2 years, a seizure frequency of more than once a month, and use of more than 2 antiepileptic drugs were closely associated the occurrence of TAND.

Conclusion: The MINI-KID can be used for the screening and diagnosis of TAND in children with TSC aged 6-16 years. The incidence of neuropsychiatric diseases in children with TSC can arrive at 81.05%. Early onset of epilepsy, long duration of epilepsy, frequent seizures, and refractory epilepsy are risk factors for TAND. Early, reasonable, and rapid control of seizures may reduce the risk of neuropsychiatric illness in children with epilepsy.

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease characterized by the formation of hamartomas in multiple organ systems and has a variety of symptoms and degrees of severity. The currently known pathogenic genes are the *TSC1* (9q34) and *TSC2* (16p13.3) genes [1]. Since 1990, research on the global disease burden has ranked mental disorders as among the most serious diseases in the world [2, 3]. Neurological and psychiatric complications and kidney disease are often the greatest burdens imposed by TSC [4, 5], but they have not been given enough attention. A 2010 survey of members of the British Tuberous Sclerosis Association revealed that only 18% of TSC patients had been assessed or treated for neuropsychiatric disorders. TSC-associated neuropsychiatric disorders (TAND) were proposed by the neuropsychiatric expert group of the 2012 TSC International Consensus Conference [6]. The majority of studies on the incidence and pattern of TAND to date have come from relatively small studies and case reports [7, 8]. Data on TAND in children with TSC are even scarcer [9].

Therefore, in view of the simplicity, reliability and effectiveness of the Mini International Neuropsychiatric Interview for Children (MINI-KID) [10-13], this study intends to use the MINI-KID (parent version) tool to investigate TAND in a Chinese pediatric cohort and to compare with a normally developing population. As far as we know, this is at present the largest-sample TAND assessment of children in China, and it is also the first TAND study using the MINI-KID.

Results

Characteristics of the study population

Our TSC cohort had a total of 291 patients, of which 117 (40.21%) were 6-16 years old. After excluding 16 cases, 86.32% (101/117) parents signed the informed consent, but 6 cases did not complete all the questionnaires (withdrew halfway). 95 cases (81.20%, 95/117) completed the questionnaire, including 46 females (48.42%) and 49 male (51.58%), whose average age was 10.02±3.10 years old. All of them are Han people (Table 1). In addition, 95 children with normal development (male: female = 51:44, age 10.3±2.4 years) were recruited (Table 1).

Table 1
Sociodemographic comparison of TSC patients and normal controls

Sociodemographic feature	TSC	NC	χ^2/F	*P* value
N	95	95		
Male	49 (51.58)	51 (53.68)	0.08	0.17
Age at interview (years)	10.12±3.10	10.32±2.41	1.66	036
Paternal education (years)			0.33	0.72*
≤9	35 (36.84)	35 (36.84)		
9-12	20 (21.05)	23 (24.21)		
>12	40 (42.11)	37 (38.95)		
Maternal education (years)			2.75	0.57
≤9	38 (40.00)	30 (31.58)		
9-12	18 (18.95)	27 (28.42)		
>12	39 (41.05)	38 (40.00)		
Family income (RMB)			3.42	0.09
<5000	16 (16.84)	5 (5.26)		
5000-10000	51 (53.68)	63 (66.32)		
>10000	28 (29.47)	27 (28.42)		
Residence			1.37	0.11
Suburban or rural	50 (52.63)	58 (61.05)		
Urban	45 (47.37)	37 (38.95)		

TSC: tuberous sclerosis complex; NC: normal controls (children with normal nervous system development);

Data were presented as mean ± SD and n (%).

ANOVA F-test for continuous variables, chi-square test for categorical values.

All 95 children were genetically tested, and the TSC1:TSC2: NMI (no mutation identified) ratio was 27:58:10. There were more sporadic cases than familial cases (n = 55 VS n = 40). Sixty-seven children had an intellectual disability (IQ≤70) (70.53%), 34 (35.79%) had mild to moderate intellectual disability (IQ 35-70), and 33 (34.74%) had severe intellectual disability (IQ<35). Of the 95 children, 76 had epilepsy (80.00%). The average age at seizure onset was 2.50±3.59 years, and the duration was 7.65±4.37 years. Eighty-seven patients had cortical tubers, 86 children had subependymal nodules (SENs), and 3 patients had subependymal giant cell astrocytoma (SEGA).

Incidence of neuropsychiatric disorders in TSC patients and normal controls

A total of 77 (81.05%) children with TSC developed TAND. Among children with TAND, the male: female ratio was 39:38. A total of 85.19% (23/27) of the *TSC1* gene mutation group, 81.03% (47/58) of the *TSC2* gene mutation group and 70.00% (7/10) of NMI group had neuropsychiatric disorders, but there was no significant difference (*p = 0.578*). 11 cases (11.58%) occurred in control group. It was significantly lower than in the TSC group (*P <0.001*).

A total of 15 neuropsychiatric diseases were diagnosed, the most common of which was attention-deficit/hyperactivity disorder (ADHD) (51.58%, 49/95), followed by social anxiety disorder (41.05%, 39/95), panic disorder (26.32%, 25/95), specific phobia (26.32%, 25/95), (mild) manic episodes (22.11%, 21/95), agoraphobia (16.84%, 16/95), tic disorder (15.79%, 15/95) and separation anxiety disorder (10.53%, 10/95) (Table 2). ADHD, social anxiety disorder, panic disorder, specific phobia, (mild) manic episodes, agoraphobia, tic disorder, separation anxiety disorder, major depressive episode, suicide and obsessive-compulsive disorder were significantly different between the TSC and the control group (*p<0.05)*Table 2). Among TSC patients, 70.53% had two or more TAND. Patients with TSC1/TSC2 mutations were more likely to have multiple TAND (≥2) than children with NMI (*p = 0.004*).

Table 2
Distribution of neuropsychiatric disorders of TSC patients and normal controls

Neuropsychiatric disorders	TSC	Normal	p value
N	95	95	
ADHD	49（51.58）	6 （6.32）	<0.01
Inattentive type	27（28.43）	3（3.16）	
Combined type	13（13.68）	2（2.11）	
Hyperactive impulsive	9（9.47）	1（1.05）	
Social anxiety disorder	39（41.05）	2（2.11）	<0.01
Panic disorder	25（26.32）	0（0.00）	<0.01
Specific phobia	25（26.32）	1（1.05）	<0.01
(Mild) manic episodes	21（22.11）	0（0.00）	<0.01
Agoraphobia	16（16.84）	0（0.00）	<0.01
Tic disorder	15（15.79）	0（0.00）	<0.01
Separation anxiety disorder	10（10.53）	1（1.05）	0.01
Oppositional defiant disorder	7（7.37）	1（1.05）	0.07
Major depressive episode	6（6.32）	0（0.00）	0.03
Suicide	6（6.32）	0（0.00）	0.03
Obsessive-compulsive disorder	6（6.32）	0（0.00）	0.03
Dysthymia	4（4.21）	0（0.00）	0.12
Posttraumatic stress disorder	3（3.16）	0（0.00）	0.25
Conduct disorder	1（1.05）	0（0.00）	0.32

ADHD: attention-deficit/hyperactivity disorder; Normal: children with normal nervous system development

Data were presented as n (%). Chi-square or Fisher's exact tests for categorical values.

Analysis of TAND-related risk factors

Ninety-five children with TSC were divided into a combined TAND group and an uncombined TAND group. Logistic regression models found that earlier age of onset (<2 years) (*P = 0.019*), longer duration of epilepsy (≥ 2 years) (*P = 0.003*), more frequent seizure frequency (more than once a month) (*P = 0.024*) and use of a greater number of antiepileptic drugs (≥2) (*P = 0.029*) were closely related to the occurrence

of TAND (Table 3). We additionally adjusted for gender (male/female), maternal education (years) (≤9/9-12/>12), paternal education (years) (≤9/9-12/>12), family income (RMB) (<5000/5000-10000/>10000) and residence (suburban or rural/urban) (Table 4). However, there was no significant correlation with seizure type, TSC gene type, hypomelanotic macules, angiofibromas, shagreen patches, ungual fibromas, cardiac rhabdomyomas, renal angiomyolipoma, or lymphangioleiomyomatosis (LAM). No significant correlation was found with neoplastic disease, cortical tubers, SENs, or SEGA (*p>0.05*) (Table 3).

Table 3
Analysis of factors associated with TAND incidence

Predictor	TAND	Without TAND	*p* value
N	77	18	
Male	39（41.05）	10（10.53）	0.71
Paternal education (years)			0.74
≤9	29（30.53）	6（6.32）	
9~12	17（17.89）	3（3.16）	
>12	31（32.63）	9（9.47）	
Maternal education (years)			0.94
≤9	31（32.63）	7（7.37）	
9~12	15（15.79）	3（3.16）	
>12	31（32.63）	8（8.42）	
Family income (RMB)			0.36
<5000	11（11.58）	5（5.26）	
5000-10000	42（44.21）	9（9.47）	
>10000	24（25.26）	4（4.21）	
Residence			0.07*
Suburban or rural	37（38.95）	13（13.68）	
Urban	40（42.11）	5（5.26）	
Epilepsy	64（67.37）	12（12.63）	0.12
Age at seizure onset（<2y）	45（47.37）	5（5.26）	0.02
Duration of epilepsy（≥2y）	51（53.68）	5（5.26）	0.003
Seizure frequency ≥ 1/month	30（31.58）	2（2.11）	0.02
Spasm	20（26.32）	1（1.32）	0.1
Gene			0.58
NMI	7（7.37）	3（3.16）	
TSC1	23（24.21）	4（4.21）	
TSC2	47（49.47）	11（11.58）	
Family history	36（37.89）	4（4.21）	0.06

Mutation type			0.78
Nonsense	20（23.53）	6（7.06）	
Missense	16（18.82）	3（3.53）	
Frame shift	21（24.71）	3（3.53）	
Splicing	7（8.24）	2（2.35）	
Small deletion	2（2.35）	1（1.18）	
Large deletion	4（4.71）	0（0）	
Polytherapy（≥2 AEDs）	55（57.89）	8（8.42）	0.03
Hypomelanotic macules	72（75.79）	18（18.95）	0.27
Angiofibromas	32（33.68）	8（8.42）	0.82
Shagreen patches	39（41.05）	12（12.63）	0.22
Ungual fibromas	7（7.37）	0（0）	0.18
RAMLs	52（54.74）	13（13.68）	0.7
Cardiac rhabdomyomas	64（67.37）	14（14.74）	0.6
LAM	17（17.89）	7（7.37）	0.14
SENs	69（72.63）	17（17.89）	0.53
Cortical tubers	70（73.68）	17（17.89）	0.63
SEGA	3（3.16）	0（0）	0.4

TAND: tuberous sclerosis-associated neuropsychiatric disorders; TSC: tuberous sclerosis complex;

AED: antiepileptic drugs; NMI: no mutation identified; RAML: Renal angiomyolipoma; LAM: Lymphangioleiomyomatosis; SENs: Subependymal nodules; SEGA: Subependymal giant cell astrocytoma;

Data were presented as n (%). Logistic regression models were used to explore the risk factors for TAND.

Table 4
Risk factors associated with TAND

Predictor	TAND	Without TAND	Crude	Adjusted
			OR (95% CI)	OR (95% CI)*
Age at seizure onset（<2y）	45 （47.37）	5（5.26）	3.66 (1.19, 11.28)	4.17 (1.19, 14.66)
Duration of epilepsy（≥2y）	51 （53.68）	5（5.26）	5.10 (1.64, 15.86)	7.44 (1.92, 28.92)
Seizure frequency ≥ 1/month	30 （31.58）	2（2.11）	5.11 (1.10, 23.81)	4.94 (1.98, 24.86)
Polytherapy（≥2 AEDs）	55 （57.89）	8（8.42）	3.125 (1.09, 8.96)	2.98 (1.93, 9.46)

TAND: tuberous sclerosis-associated neuropsychiatric disorders;

Data were presented as n (%).

*: adjust for gender (male/female), maternal education (years) (≤9/9-12/>12), paternal education (years) (≤9/9-12/>12), family income (RMB) (<5000/5000-10000/>10000) and residence (suburban or rural/urban).

Discussion

To our knowledge, this is the first cross-sectional study of TAND using the MINI-KID, and it is also the largest-sample TAND cohort study in China. The incidence of neuropsychiatric disorders in children with TSC is significantly higher than in patients with normal neurodevelopment. As in previous studies, TAND can exist in childhood and adolescence [4]. The lifetime prevalence of TAND is approximately 90% [14]. Anxiety, depression, and ADHD are more common in TSC patients [15]. In our cohort, a total of 77 TSC children had neuropsychiatric disorders, for an incidence of 81.05%, which far exceeded our expectation. However, clinicians pay far less attention to mental illness than neurological disorders (such as epilepsy and SEGA). As reported in previous studies, less than 40% of more than 2,000 patients from 31 countries have had an intelligence assessment, and the proportion of missing TAND data is high. This demonstrates that TAND are not adequately identified and processed even at TSC specialty centers [15]. Our study suggests that the disease burden of TSC is far greater than previously realized, which will serve as a basis for a better distribution of medical resources.

According to Prather P et al. [16], autistic spectrum disorder (ASD) and ADHD are the most common TAND in children, and anxiety/mood disorders are the most common in adults. The incidence of ADHD has varied by study method and diagnostic criteria from 30 to 60% [17]. The MINI-KID serves as a short, standardized, universal assessment tool to systematically assess parents' knowledge of health-related neuropsychiatric disorders in children with chronic diseases [18-20]. To our knowledge, this report is the first application of the MINI-KID tool in a TSC cohort to accurately screen and diagnose TAND. We found

that ADHD, social anxiety disorder, panic disorder and specific phobia are the most common in this group. The incidence of ADHD in our cohort was significantly higher than that in the TOSCA cohort (51.58% vs. 22.4%)[21], and we suggest the following possible reasons: (1) The age distribution of children in the TOSCA cohort was 0-18 years old, while the age distribution of children in our cohort was 6-16 years old, which was consistent with the high incidence age of ADHD diagnosis. (2) Our cohort included TSC patients from all over the country. In some areas, a comprehensive and systematic treatment standard has not been established, and clinicians do not even know enough about TAND to intervene in time. (3) Unlike the TAND Checklist method adopted by the TOSCA, the MINI-KID tool can be used for both screening and diagnosis in our cohort.

Although the incidence of anxiety was very high in previous cohorts [15], the diagnosis rate of anxiety was lower in our study (25.80% vs. 10.53%), while the incidence of depression was approximately the same (8.20% vs. 6.32%). In the future, attention should be paid to screening children for emotional disorders and anxiety responses. Our results are comparable to those of a cohort study of 32 samples in Italy [22].

We sought to identify the risk factors associated with the occurrence of TAND and found that an earlier onset age (<2 years), a longer seizure duration (≥ 2 years), more frequent seizures (more than 1 seizure per month), and the use of more antiepileptic drugs (≥2) are closely related to the occurrence of TAND. It is therefore recommended that epilepsy be diagnosed as early as possible and controlled as soon as possible to improve the neuropsychological prognosis. We also found that children with a *TSC1/TSC2* gene mutation are more likely to have multiple TAND (≥ 2) than children with NMI *($p = 0.004$)*, suggesting that more alertness to TAND in children with a *TSC1/TSC2* gene mutation is warranted and revealing an initial genotype-neuropsychiatric disease relationship. Of course, this relationship needs to be supported by a larger sample size.

This study presents several limitations. It was a cross-sectional study of a single center, and future multicenter prospective studies are needed to further verify the results. In addition, this study used only one method to explore the mental health of children with TSC and did not use the TAND checklist for comparison. The study population included children 6-16 years of age, excluding younger children. The MINI-KID scale does not screen and diagnose ASD.

Conclusion

The MINI-KID can be used for the screening and diagnosis of TAND in children with TSC aged 6-16 years. The incidence of neuropsychiatric diseases in children with TSC is very high, reaching 81.05%, which is significantly higher than that in children with non-neurological chronic diseases (such as asthma) and normally developing children. ADHD is the most common TAND and can occur in 51.58% of children. Epilepsy onset before the age of 2 years, a duration of epilepsy for more than 2 years, seizures more than once a month, and the use of more than 2 antiepileptic drugs are closely related to the occurrence of TAND. Early screening, diagnosis and intervention are critical for early-onset epilepsy. In addition,

controlling seizures as soon as possible and rational administration of antiepileptic drugs may reduce the risk of TAND.

Methods

Study population

This cross-sectional study was carried out from September 2019 to November 2019. The TSC children were recruited from among all patients with TSC 6-16 years old who were treated in the Department of Neurology at the Children's Hospital of Fudan University. All patients met the latest diagnostic criteria for tuberous sclerosis [6] and were examined for the *TSC1/TSC2* genes. The exclusion criterion was refusal to participate.

We also recruited children with normal nervous systems as the control group and matched them by age and gender. The criteria for children with normal nervous system development were as follows: (1) normal motor and language development; (2) no history of seizures or other neurological diseases; (3) no other chronic diseases (such as epilepsy, diabetes, asthma or cancer); and (3) no family history of mental illness. The exclusion criterion was parental refusal to provide informed consent. Children with normal development were screened by the deputy chief physician and attending physician of the neurology department, who each had more than 5 years of experience.

Written informed consent was received from all participating families. This study was approved by the ethics committee of the Children’s Hospital of Fudan University.

Data collection

Standardized questionnaire

After providing informed consent, parents or guardians are invited to participate in interviews, and standardized questionnaires were used to obtain demographic and clinical data. The demographic data collected were date of birth, gender, ethnicity, parental education level, family income, and residence. The clinical data collected were growth and development, family history, age at onset of epilepsy, duration of epilepsy, current number of antiepileptic drugs, frequency of seizures, spasm, and TSC clinical manifestations.

MINI-KID (parent version)

Parents or guardians of the TSC children were interviewed using the MINI-KID (parent version) for children and adolescents. The Chinese version of the MINI-KID (parent version) 5.0 was translated by Liu YX and others from Peking University Institute of Mental Health in 2010. Liu YX’s study and other studies have confirmed that the Chinese version of the MINI-KID (parent version) has good reliability and validity [23] and that the parent version is more sensitive than the child version [24, 25].

The MINI-KID is a structured diagnostic scale designed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and the International Classification of Disease, 10th version (ICD-10). The scale has 25 modules to diagnose 24 mental illnesses and suicidal tendencies in children and adolescents between the ages of 6 and 16 years old [26]. Each module includes a screening questionnaire and a diagnostic questionnaire. The MINI-KID was administered in this study by highly trained neurologists (minimum 5 years of experience in the diagnosis of neuropsychiatric diseases in children), and the diagnosis was based solely on whether the responses to the screening questions were positive. All questions had a "yes/no" response format [26]. It took approximately 30-45 minutes to complete the assessment.

All parents of children in this study were administered the questionnaire face-to-face after signing the informed consent form.

Statistical Analysis

Continuous variables are presented as the mean and standard deviation (SD). Continuous variables were analyzed using ANOVA F-test, and categorical variables were analyzed using chi-square or Fisher's exact tests. Logistic regression models were used to explore the risk factors for TAND. We additionally adjusted for gender (male/female), maternal education (years) (≤9/9-12/>12), paternal education (years) (≤9/9-12/>12), family income (RMB) (<5000/5000-10000/>10000) and residence (suburban or rural/urban). Two-sided $p < 0.05$ was statistically significant. All analyses were performed by using JMP Pro 15.0.0 software (version 15.0.0, SAS Institute Inc., USA).

Abbreviations

TSC: tuberous sclerosis complex; TAND: tuberous sclerosis-associated neuropsychiatric disorders: MINI-KID: Mini International Neuropsychiatric Interview for Children; NMI: no mutation identified; SENs: subependymal nodules; SEGA: subependymal giant cell astrocytoma; RAML: Renal angiomyolipoma; LAM: Lymphangioleiomyomatosis; ADHD: attention-deficit/hyperactivity disorder; AED: antiepileptic drugs; ASD: autistic spectrum disorder.

Declarations

Ethics approval and consent to participate

This study was approved by the Children's Hospital of Fudan University Institutional Review Board prior to the recruitment of subjects (2018-No.26).

Consent for publication

All presentations of case reports have consent for publication.

Availability of data and material

The datasets used during and/or analyzed during the current study are available from the corresponding author on request.

Competing interests

None of the authors has any conflict of interest to disclose.

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Authors' contributions

YF.D. and Y.W. designed the research. YF.D., J.W. and SZ.Z. Interviewed the patients and collected patient clinical records. HZ and TL.L performed the collection and analysis of healthy children’s data. YF.D. and Y.W. designed the analysis and reviewed and revised the manuscript. All authors read and approved the manuscript.

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