Assessment of tuberous sclerosis-associated neuropsychiatric disorders using the MINI-KID tool: a pediatric cohort study

Yifeng Ding
Department of Neurology, Children's Hospital of Fudan University https://orcid.org/0000-0002-4185-6628

Ji Wang
Department of Neurology, Children's Hospital of Fudan University

Hao Zhou
Department of Pediatrics, Guizhou Provincial People's Hospital, Medical College of Guizhou University

Taoli Li
Department of Neurology, Xi'an Chlidren' Hospital

Shuizhen Zhou
Department of Neurology, Children's Hospital of Fudan University

Yi Wang (yiwang@shmu.edu.cn)
Department of Neurology, Children's Hospital of Fudan University https://orcid.org/0000-0002-7051-3739

Research

Keywords: TSC, TAND, child, MINI-KID, ADHD, mental disorders

Posted Date: January 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-32617/v2

Version of Record: A version of this preprint was published at Orphanet Journal of Rare Diseases on April 17th, 2021. See the published version at https://doi.org/10.1186/s13023-021-01814-4.

Abstract

Background: Tuberous sclerosis-associated neuropsychiatric disorders (TANDs) have not been studied before in China. We aimed to assess the psychiatric level of TAND using the Mini International Neuropsychiatric Interview for Children (MINI-KID) in China.

Results: A total of 83.16% of patients (79/95) had at least one TAND, and 70.53% (67/95) had an intellectual disability. The MINI-KID tool diagnosed a total of 16 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 number in the normal development group ($p < 0.0001$). Epilepsy before the age of 2 years, a seizure frequency of more than once a month, and the use of more than 2 antiepileptic drugs were closely associated with the occurrence of TAND.

Conclusion: The MINI-KID can be used as a standardized tool to examine the psychiatric level of TANDs in children with TSC aged 6-16 years. The rate of neuropsychiatric diseases in children with TSC reached 83.16%. Early onset of epilepsy, frequent seizures, and refractory epilepsy are risk factors for TAND. Early, reasonable, and rapid control of seizures is related to reducing 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]. In addition to the physical manifestations of multiple organs, children with TSC may also suffer from a wide array of neurodevelopmental, behavioral, psychiatric, and psychosocial difficulties. The Neuropsychiatry Panel proposed the term TSC-associated neuropsychiatric disorders (TAND) as an umbrella term to include the full range of mental health issues. The panel defined six levels of investigation: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial level[2, 3]. Neurological and psychiatric complications and kidney disease are often the greatest burdens imposed by TSC, but TAND have not been given enough attention[4, 5]. 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[6]. With the exception of the TOSCA study with a larger sample size of 1400 children (possibly including some Chinese pediatric patients)[7], there are very few studies on the incidence and pattern of TANDs in children with TSC, and none have been reported in China[8].

As a structured diagnostic interview, the MINI-International Neuropsychiatric Interview for Children (MINI-KID) was developed based on DSM-IV and ICD-10 criteria for the assessment and diagnosis of psychiatric disorders[9]. In view of the simplicity, reliability and effectiveness of the MINI-KID [9-12], 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. To the best of our knowledge, 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. Sixteen people declined to participate, 86.32% (101/117) of parents signed informed consent, but 6 patients did not complete all the questionnaires (withdrew halfway). Ninety-five patients (81.20%, 95/117) completed the questionnaire, including 46 females (48.42%) and 49 males (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).

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 a history of epilepsy (80.00%), and 49 of the patients with TSC and epilepsy developed drug-resistant epilepsy (64.47%). 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).

Rate of neuropsychiatric disorders in TSC patients and normal controls

A total of 79 (83.16%) children with TSC developed TANDs. Among children with TANDs, the male:female ratio was 41:38. A total of 85.19% (23/27) of the *TSC1* gene mutation group, 84.48% (49/58) of the *TSC2* gene mutation group and 70.00% (7/10) of the NMI group had neuropsychiatric disorders, but there was no significant difference ($p = 0.546$). 11 cases (11.58%) occurred in control group. It was significantly lower than in the TSC group ($p < 0.001$).

A total of 16 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), pervasive developmental disorder (PDD) (22.11%, 21/95), (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, PDD, (mild) manic episodes, agoraphobia, tic disorder, separation anxiety disorder, major depressive episode, suicide and obsessive-compulsive disorder were significantly different between the TSC and control groups ($p<0.05$) (Table 2). Among TSC patients, 73.68% had two or more TANDs. The rates of psychiatric disorders in those with different levels of ID and different genotypes are shown in Supplementary Table 1 and Supplementary Table 2.

Analysis of TAND-related risk factors

Ninety-five children with TSC were divided into the TAND group (n=79) and the without TAND group (n=16). Multivariate logistic regression models found that earlier age of onset (<2 years) (*p = 0.03*), more frequent seizure frequency (more than once a month) (*p =0.04*) and use of a greater number of antiepileptic drugs (≥2) (*p = 0.04*) were closely related to the occurrence of TANDs (Table 3). No significant correlation was found with neoplastic disease (RAML, LAM and cardiac rhabdomyomas), cortical tubers, SENs, or SEGA (*p>0.05*) (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 (spasm, generalized and focal seizures), TSC gene type, hypomelanotic macules, angiofibromas, shagreen patches, ungual fibromas, cardiac rhabdomyomas, renal angiomyolipoma (RAML), or lymphangioleiomyomatosis (LAM).

Discussion

To make screening for TANDs easy and convenient, the Neuropsychiatry Panel offers the TAND Checklist, which is a simple framework for a conversation about TANDs. Its results are used to indicate a possible clinical diagnosis to guide patients in further evaluation and in seeking more specialized treatment[3]. Unfortunately, there is currently no Chinese version of the TAND Checklist available. Therefore, the Chinese version of the MINI-KID, which has been well validated in terms of reliability and validity, would be a very useful attempt in the area of psychiatric disorders.

To our knowledge, this is the first cross-sectional study of TANDs using the MINI-KID, and it is also the largest-sample TAND cohort study in China. As one of the large advanced pediatric neurological disease centers in China, the Children's Hospital of Fudan University mainly receives TSC children with epilepsy or even drug-refractory epilepsy and other complications from all over China. The rate (70%) of children with ID is slightly higher than that previously reported (44%-64%)[13-15] but close to that reported by Chinese scholars (72%)[16]. The rate of neuropsychiatric disorders in children with TSC is significantly higher than that in patients with normal neurodevelopment. As in previous studies, TANDs can exist in childhood and adolescence [3, 4, 17, 18]. The lifetime prevalence of TANDs is approximately 90% [3]. Anxiety, depression, and ADHD are more common in TSC patients [18]. In our cohort, a total of 77 TSC children had neuropsychiatric disorders, for a rate 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 TANDs data is high. This demonstrates that TANDs are not adequately identified and processed even at TSC specialty centers [18]. 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 & de Vries et al. [19, 20], autistic spectrum disorder (ASD) and ADHD are the most common TANDs 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%[21-24]. The MINI-KID serves as a short, standardized, universal assessment tool to systematically assess parent reports of health-related neuropsychiatric disorders in children with chronic diseases [25-27]. To our knowledge, this report is the first application of the MINI-KID tool in a TSC cohort to accurately screen and diagnose TANDs. We found that ADHD, social anxiety disorder, panic disorder, PDD and specific phobia were the most common in this group. The rate of ADHD in our cohort was significantly higher than that in the TOSCA cohort (51.58% vs. 22.4%)[7], 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.

Although the rate of anxiety was very high in previous cohorts [7, 17, 18], the diagnosis rate of anxiety was lower in our study (25.80%-56.00% vs. 10.53%), while the rate 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 [8].

We sought to identify the risk factors associated with the occurrence of TANDs and found that an earlier onset age (<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 TANDs. These are similar to previous studies[7, 17, 19]. It is therefore recommended that epilepsy be diagnosed as early as possible and controlled as soon as possible to reduce the risk of neuropsychological disorders, but it does not seem to stop TAND completely[28]. Although the statistics showed that children with a *TSC1/TSC2* gene mutation are more likely to have multiple TANDs (≥ 2) than children with NMI *($p = 0.004$)*, all children with TSC are at significantly increased risk of TAND and should therefore be screened[2].

This study presents several limitations. This 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.

Conclusion

The MINI-KID scale can be used as a standardized tool to examine the psychiatric level of TANDs in children with TSC aged 6-16 years. The rate of neuropsychiatric diseases in children with TSC is very high, reaching 83.16%, which is significantly higher than that in normally developing children. ADHD is the most common psychiatric disorder identified with the MINI-KID in this study and can occur in 51.58%

of children. Epilepsy onset before the age of 2 years, seizures of more than once a month, and the use of more than 2 antiepileptic drugs are closely related to the occurrence of TANDs. Early screening, diagnosis and intervention are critical for early-onset epilepsy. In addition, controlling seizures as soon as possible and rational use of anti-epileptic drugs are related to reducing 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 [2] 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 in the health examination center of Children's Hospital of Fudan University and matched them by age and sex. 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 diabetes, asthma or cancer); and (4) no family history of mental illness in first-degree relatives. 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.

1.1 Data collection

Standardized questionnaire

After providing informed consent, parents or guardians were 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. Cognitive assessment was performed using the Wechsler Intelligence Scale for Children in Chinese (WISC-C). 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 the 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 [29] and that the parent version is more sensitive than the child version [30, 31].

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[9, 12]. 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[9, 12]. 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. Multivariate logistic regression models were performed with each TAND risk factor as an independent variable. Those known risk or protective factors of TAND were included in our analysis regression models. We 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) in the adjusted model. 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 provided 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 have any conflicts of interest to disclose.

Funding

This study was supported by grants from the Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX01) and ZJLab); omics-based precision medicine of epilepsy was entrusted by the Key Research Project of the Ministry of Science and Technology of China (Grant No. 2016YFC0904400).

Authors' contributions

YF.D. and Y.W. designed the research. YF.D., J.W. and SZ.Z. The patients were interviewed, and patient clinical records were collected. 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.

Acknowledgments

We gratefully acknowledge the participants and their parents in our study for their support. Special thanks go to Dr X Wang for statistical support.

References

1. Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers 2016: 2: 16035.

2. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013: 49: 243-254.
3. de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn D, Ess KC, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. *Pediatr Neurol*. (2015)

52:25-35. doi: 10.1016/j.pediatrneurol.2014.10.004

4. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015. 14(7): 733-45.
5. Ding Y, Wang J, Zhou Y, Yu L, Zhang L, Zhou S, et al. Quality of life in children with tuberous sclerosis complex: A pediatric cohort study. CNS Neurosci Ther. 2020.
6. de Vries PJ, Hunt A, Bolton PF. The psychopathologies of children and adolescents with tuberous sclerosis complex (TSC): a postal survey of UK families. *Eur Child Adolesc Psychiatry*. (2007) 16:16-24. doi: 10.1007/s00787-006-0570-3
7. de Vries PJ, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOSCA natural history study. Orphanet J Rare Dis. 2018;13(1):157.
8. Toldo I, Brasson V, Miscioscia M et al. Tuberous sclerosis-associated neuropsychiatric disorders: a paediatric cohort study. Dev Med Child Neurol 2018 .
9. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. (1998) 59 Suppl 20:22-33;quiz 34-57.
10. Duncan L, Georgiades K, Wang L, Van Lieshout RJ, MacMillan HL, Ferro MA, et al. Psychometric evaluation of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *Psychol Assess*. (2018) 30:916-28. doi: 10.1037/pas0000541
11. Högberg C, Billstedt E, Björck C, Björck PO, Ehlers S, Gustle LH, et al. Diagnostic validity of the MINI-KID disorder classifications in specialized child and adolescent psychiatric outpatient clinics in Sweden. *BMC Psychiatry*. (2019) 19:142. doi: 10.1186/s12888-019-2121-8
12. Sheehan DV, Sheehan KH, Shytle RD et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 2010: 71: 313-326.
13. van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Genotype and cognitive phenotype of patients with tuberous sclerosis complex. Eur J Hum Genet. 2012;20(5):510-5.
14. Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. Neurology. 2005;65(2):235-8.
15. Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med. 2003;33(2):335-44.
16. Yang G, Shi ZN, Meng Y, Shi XY, Pang LY, Ma SF, et al. Phenotypic and genotypic characterization of Chinese children diagnosed with tuberous sclerosis complex. Clin Genet. 2017;91(5):764-8.
17. de Vries PJ, Wilde L, de Vries MC, Moavero R, Pearson DA, Curatolo P. A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). Am J Med Genet C Semin Med Genet. 2018.

18. Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. TuberOus SClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. *Orphanet J Rare Dis*. (2017) 12:2. doi: 10.1186/s13023-016-0553-5
19. Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. *J Child Neurol*. (2004) 19:666-74. doi: 10.1177/08830738040190090601
20. de Vries PJ, Gardiner J, Bolton PF. Neuropsychological attention deficits in tuberous sclerosis complex (TSC). Am J Med Genet A. 2009;149A(3):387-95.
21. Hunt A. Development, behaviour and seizures in 300 cases of tuberous sclerosis. *J Intellect Disabil Res*. (1993) 37 (Pt 1):41-51. doi: 10.1111/j.1365-2788.1993.tb00868.x
22. Gillberg IC, Gillberg C, Ahlsén G. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. Dev Med Child Neurol. 1994;36(1):50-6.
23. Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. Epilepsy Behav. 2007;11(4):506-13.
24. D'Agati E, Moavero R, Cerminara C, Curatolo P. Attention-deficit hyperactivity disorder (ADHD) and tuberous sclerosis complex. J Child Neurol. 2009;24(10):1282-7.
25. Mordal J, Gundersen O, Bramness JG. Norwegian version of the Mini-International Neuropsychiatric Interview: feasibility, acceptability and test-retest reliability in an acute psychiatric ward. *Eur Psychiatry*. (2010) 25:172-7. doi: 10.1016/j.eurpsy.2009.02.004
26. Pettersson A, Modin S, Wahlström R, Af Winklerfelt Hammarberg S, Krakau I. The Mini-International Neuropsychiatric Interview is useful and well accepted as part of the clinical assessment for depression and anxiety in primary care: a mixed-methods study. *BMC Fam Pract*. (2018) 19:19. doi: 10.1186/s12875-017-0674-5
27. van Vliet IM, de Beurs E. [The MINI-International Neuropsychiatric Interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders]. *Tijdschr Psychiatr*. (2007) 49:393-7.
28. Moavero R, Benvenuto A, Emberti Gialloreti L, Siracusano M, Kotulska K, Weschke B, et al. Early Clinical Predictors of Autism Spectrum Disorder in Infants with Tuberous Sclerosis Complex: Results from the EPISTOP Study. J Clin Med. 2019;8(6).
29. Liu YX, Liu J, Wang YF. Reliability and validity of Chinese version of the Mini International Neuropsychiatric Interview for Children and Adolescents (Parent Version). Chin Ment Health J 2010: Volume 25: Pages 921-925.
30. Liu YX, Liu J, Wang YF. Reliability and validity of Chinese version of the Mini International Neuropsychiatric Interview for Children and Adolescents (Child Version). Chin Ment Health J 2011: 25: 8-13.
31. Van Lieshout RJ, Savoy CD, Ferro MA, Krzeczkowski JE, Colman I. Macrosomia and psychiatric risk in adolescence. *Eur Child Adolesc Psychiatry*. (2020) . doi: 10.1007/s00787-019-01466-7

Tables

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	0.36
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 the mean ± SD and n (%).

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

Table 2. Distribution of neuropsychiatric disorders in 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
Pervasive developmental disorder	21（22.11）	0（0.00）	<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
No neuropsychiatric disorders	16 (16.84)	78 (82.11)	<0.0001

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.

Table 3. Analysis of factors associated with TAND incidence

Predictor	TAND	Without TAND	*p* value
N	77	18	
Male	39（50.65）	10（55.56）	0.71
Paternal education (years)			0.74
≤9	29（37.66）	6（33.33）	
9~12	17（20.08）	3（16.67）	
>12	31（40.26）	9（50.00）	
Maternal education (years)			0.94
≤9	31（40.26）	7（38.89）	
9~12	15（19.48）	3（16.67）	
>12	31（40.26）	8（44.44）	
Family income (RMB)			0.36
<5000	11（14.29）	5（27.78）	
5000-10000	42（54.55）	9（50.00）	
>10000	24（31.17）	4（22.22）	
Residence			0.07
Suburban or rural	37（48.05）	13（72.22）	
Urban	40（51.95）	5（27.78）	
Epilepsy	64（83.12）	12（66.67）	0.12
Age at seizure onset（<2y）	45（58.44）	5（27.78）	0.03
Seizure frequency ≥ 1/month	30（38.96）	2（11.11）	0.04
Spasm	20（25.97）	1（5.56）	0.14
Gene			0.50
NMI	7（9.09）	3（16.67）	
TSC1	23（29.87）	4（22.22）	
TSC2	47（61.04）	11（61.11）	
Family history	36（46.75）	4（22.22）	0.13
Mutation type			0.51
Nonsense	20（25.97）	6（33.33）	
Missense	16（20.78）	3（16.67）	
Frame shift	21（27.27）	3（16.67）	
Splicing	7（9.09）	2（11.11）	
Small deletion	2（2.60）	1（5.56）	
Large deletion	4（5.19）	0（0）	
Polytherapy（≥2 AEDs）	55（71.43）	8（44.44）	0.04
Hypomelanotic macules	72（93.51）	18（100.00）	0.30
Angiofibromas	32（41.56）	8（44.44）	0.48
Shagreen patches	39（50.65）	12（66.67）	0.19
Ungual fibromas	7（9.09）	0（0）	0.22
RAMLs	52（67.53）	13（72.22）	0.98
Cardiac rhabdomyomas	64（83.12）	14（77.78）	0.42
LAM	17（22.08）	7（38.89）	0.06
SENs	69（89.61）	17（94.44）	0.63
Cortical tubers	70（90.91）	17（94.44）	0.73
SEGA	3（3.90）	0（0）	0.43

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	Crude	Adjusted
		OR (95% CI)	OR (95% CI) *
Age at seizure onset			
>2y	33 (41.77)	Ref.	Ref.
<2y	46 (58.23)	4.18 (1.24, 14.12)	6.53 (1.16, 36.80)
Seizure frequency			
< 1/month	49 (62.02)	Ref.	Ref.
≥ 1/month	30 (37.98)	9.18 (1.15, 73.11)	21.28 (1.14, 59.24)
Polytherapy			
<2 AED	42 (53.17)	Ref.	Ref.
≥2 AEDs	37 (46.84)	3.82 (1.01, 14.45)	15.28 (1.65, 41.64)

TAND: tuberous sclerosis-associated neuropsychiatric disorders;
Data were presented as n (%).
*: 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).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx