Neuropsychological profile in tuberous sclerosis complex: a study of clinical and cognitive variables in a cohort from Brazil

Perfil neuropsicológico no complexo da esclerose tuberosa: estudo de variáveis clínicas e cognitivas em uma coorte do Brasil

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Abstract

Background Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with a wide clinical, cognitive, and behavioral expressivity.

Objective To assess the neuropsychological profile of individuals clinically diagnosed with TSC and the factors that could significantly impact their cognitive development.

Methods A total of 62 individuals with ages ranging from 3 to 38 years were followed up in a tertiary attention hospital in Southern Brazil, and they were assessed using a standard battery and the Vineland Adaptive Behavior Scales, when intellectual disability was observed.

Results History of epilepsy was found in 56 participants (90.3%), and 31 (50%) presented an intellectual disability. Among the other half of TSC individuals without intellectual disability, 8 (12.9%) presented borderline classification, 20 (32.2%) presented average scores, and 3 (4.8%) were above average. In total, 17 participants (27.4%) fulfilled the diagnostic criteria for autism spectrum disorder. The results of the multiple linear regression analysis suggested that seizures, age at diagnosis, visual perception, and general attention significantly impact cognitive performance indexes.

Conclusion The present study suggests that the occurrence of epileptic seizures and older age at diagnosis contribute to higher impairment in the domains of cognitive development, underlining the importance of early diagnosis and the prevention of epileptic seizures or their rapid control. The development of attentional skills, visual perception, and executive functions must be followed up.

Keywords
- Tuberous Sclerosis
- Neurocutaneous Syndromes
- Neuropsychology
- Cognition

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Resumo

Antecedentes O complexo da esclerose tuberosa (CET) é uma doença genética autossômica dominante com ampla expressividade clínica, cognitiva e comportamental.

Objetivo Avaliar o perfil neuropsicológico de indivíduos com diagnóstico clínico de CET e os fatores que poderiam impactar significativamente o seu desenvolvimento cognitivo.

Métodos Ao todo, 62 indivíduos com idades entre 3 e 38 anos foram acompanhados em um hospital terciário do Sul do Brasil e avaliados por meio de uma bateria padrão e das Escalas de Comportamento Adaptativo Vineland, quando observada deficiência intelectual.

Resultados Encontrou-se histórico de epilepsia em 56 participantes (90,3%) e de deficiência intelectual em 31 (50%). Quanto à outra metade dos indivíduos com CET sem deficiência intelectual, 8 (12,9%) apresentaram classificação limítrofe, 20 (32,2%) apresentaram pontuações médias e 3 (4,8%) estavam acima da média. No total, 17 participantes (27,4%) preenchiam os critérios diagnósticos para o transtorno do espectro autista. Os resultados da análise de regressão linear múltipla sugeriram que as crises epilépticas, a idade ao diagnóstico, a percepção visual e a atenção geral impactam significativamente os índices de desempenho cognitivo.

Conclusão Este estudo sugere que a ocorrência de crises epilépticas e a maior idade ao diagnóstico contribuem para um maior comprometimento nos domínios do desenvolvimento cognitivo, e destaca-se a importância do diagnóstico precoce e da prevenção das crises epilépticas ou do seu rápido controle. O desenvolvimento de habilidades de atenção, percepção visual e funções executivas deve ser acompanhado.

Palavras-chave

- Esclerose Tuberosa
- Síndromes Neurocutâneas
- Neuropsicologia
- Cognição

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with variable expressivity,[1,2] and an estimated prevalence of nearly 1:6 thousand live births.[2,3] The pathophysiology of the disease relates to pathogenic DNA variants in either the *TSC1* (OMIM 605284; 9q34) or *TSC2* (OMIM 191092; 16p13.3) genes, commonly identified in 80 to 90% of patients.[1,4,5]

Loss of *TSC1* or *TSC2* function disrupts the TSC1/2-TBC1D7 complex, often causing abnormal cell growth[6] that results in benign tumors in multiple organs, known as hamartomas,[7] which are most frequently found on the skin (hypomelanotic macules, facial angiofibromas, shagreen patch), the brain (subependymal nodules and subependymal giant-cell astrocytomas, SEGAs), the heart (cardiac rhabdomyomas), the kidney (angiomyolipomas), and the retina (hamartomas and achromia).[8]

Recently, the definite genetic diagnosis of TSC has been reaffirmed, and major and minor features were further reviewed for the clinical diagnosis. Among eleven major and seven minor features, a clinically-definite diagnosis can be established with the observation of the presence of two major features or one major feature plus at least two minor features. If either one major feature or two or more minor features are identified, a possible diagnosis is established.[2]

The neuropsychiatric manifestations commonly associated with TSC include learning disabilities and behavioral problems,[9] and they have led to the introduction of the term *TSC-associated neuropsychiatric disorders* – TAND.[10] The diversity of cognitive phenotypes is an important characteristic of TSC.[11,12] While some patients present intellectual disability (ID),[9] others present intellectual performance within average levels.[8,11,13] The latter group, however, can present deficits in specific cognitive functions.[11,14]

Once the diagnosis is established, patients with TSC should receive multidisciplinary clinical care. In this context, neuropsychological assessment is a valuable instrument for the identification of cognitive, behavioral, and emotional features, with the objective of studying their interrelationships.[15] The neuropsychological assessment can inform the development of clinical rehabilitation and educational programs.

The present study aimed to evaluate the neuropsychological profile of patients from Southern Brazil diagnosed with definite TSC, and to identify clinical and morphological factors that could have a significant impact on cognitive development in this cohort.

METHODS

Study design

We conducted an observational, analytical, cross-sectional study with prospective data collection from 2015 to 2017. The present study is part of a multiisciplinry research and was approved by the Ethics Research Committees of the university hospital of Universidade Federal do Paraná (UFPR)

(CAAE: 45059915.8.0000.0096), and the Institute of Biosciences of Universidade de São Paulo (USP) (CAAE: 125729112.3.000.5464 and CAEE: 48259715.2.0000.5464), and it complied with the international ethical requirements for research involving human subjects. All of the patients and/or their families signed informed consent forms.

Study subjects

The subjects were selected from UFPR and other health and educational centers of the states of Paraná and Santa Catarina, in Southern Brazil. A definite clinical diagnosis of TSC was the only inclusion criterion. The exclusion criterion was the impossibility of answering a standard assessment of intelligence level or an adaptive behavior scale.

Neuropsychological study protocol

The standard neuropsychological assessment was composed of the following instruments: the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)[16] and for Adults – Third Edition (WAIS-III);[17] one version of the Snijders-Oomen nonverbal intelligence test, the SON-R $2^1/_2$-7[a];[18]the Psychological Battery for Attention Assessment (BPA);[19] the Rey-Osterrieth Complex Figure Test;[20] and the Wisconsin Card Sorting Test (WCST).[21] The Vineland Adaptive Behavior Scales[22] were administered to parents/caregivers when the participant did not answer the standard assessment due to significant cognitive impairment.

The participants were screened for autism spectrum disorder (ASD) with the Childhood Autism Rating Scale (CARS).[23] The cut-off score for the present study was of 30 (30 to 36: mild-to-moderate symptoms; $\geq$ 37: severe symptoms). A CARS validation study[23] conducted in Brazil comprised participants aged from 3 to 17 years; however, there is evidence the scale can be used in adults as well.[23]

Clinical characteristics

Data on TSC diagnosis, medical history, seizures, imaging exams, and sociodemographic status were collected using semistructured interviews with the participants and their parents/caregivers, and medical records when available.

Genetic tests were performed by extracting DNA from peripheral blood samples of 55 participants to identify the *TSC1* (NM_000368.4) or *TSC2* (NM_000548.3) genes (Dufner-Almeida et al., in preparation).

Statistical analysis

The statistical analysis was based on the descriptive evaluation of the data and the multiple linear regression analysis. The following Wechsler scale index scores were selected as dependent variables: full-scale intelligence quotient (IQ), verbal comprehension index, working memory index, processing speed index, and perceptual reasoning index. The following independent variables were selected: gender, age, age at diagnosis, age at the onset of the first symptoms, number of medications used at the time of the assessment, presence and type of epileptic seizures, number of neurological lesions, presence of cortical tubers, presence of subcortical lesions, presence of SEGAs, the raw scores on the copy, short-term, and long-term memory of the Rey-Osterrieth Complex Figure Test, the raw scores on the BPA –general attention index, the number of perseverative errors (standard score) on the WCST, and the interaction between age and establishment of the diagnosis. The process of variable selection, in which variables with non-significant impact were removed in each new model, was applied aiming at an appropriate model that fitted well with the data. In all models, the behavior of the residuals was satisfactory, so the validity assumptions for the linear regression model were not violated in any of the cases. The Statistica 7 (TIBCO Software Inc., Palo Alto, CA, United States) software was used for the statistical analysis, and the significance threshold was set at 0.05.

RESULTS

Clinical characteristics of the participants

A total of 62 participants with a definite TSC clinical diagnosis was assessed; 36 of them were male (58.1%; ►**Table 1**), and the median age at enrollment was of 180.0 (41.0–458.0) months (range: 3 to 38 years). The median age at diagnosis was of 24.0 (0.0–360.0) months, and at the onset of the first sign or symptom, it was of 6 (0.0–108.0) months. Epileptic seizures were the most frequent cause that led participants to first seek TSC-related medical assistance (71%), followed by hypomelanotic macules (35.5%) and fetal cardiac rhabdomyomas. The median of the difference between age at first sign/symptom onset and age at diagnosis was of 6.0 (0.0–288.0) months. Among the 61 individuals submitted to DNA testing, 55 had pathogenic variants identified, 5 (9%) in the

Table 1 Clinical and demographic data of the sample

Variable		n = 62	(%)
Age: median (months)		180.0	
Range		(41.0–458.0)	
Gender	Male	36/62	(58.1)
	Female	26/62	(41.9)
Positive family history		7/62	(11.3)
Hypomelanotic macules		60/62	(96.8)
Angiofibroma		52/62	(83.9)
Shagreen patch		26/62	(41.9)
“Confetti” skin lesions		22/62	(35.5)
Ungual fibromas		19/62	(30.6)
Fibrous cephalic plaque		17/62	(27.4)
Angiomyolipomas		22/50	(44.0)
Multiple renal cysts		10/50	(20.0)
Cardiac rhabdomyoma		17/48	(35.4)
Multiple retinal hamartomas		7/37	(19.4)
Retinal achromic patch		1/37	(2.7)

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Table 2 Standard assessment results from the individuals with definite diagnosis of tuberous sclerosis complex

Wechsler scales ($n = 36$)	Index	Score: mean ± SD
	Full-scale IQ	81.7 ± 17.6
	Verbal comprehension index	83.8 ± 15.5
	Perceptual reasoning index	86.5 ± 16.5
	Working memory index	79.9 ± 18.1
	Processing speed index	87.8 ± 18.5
SON-R $2^1/^2$-7[a] ($n = 3$)	**Index**	**Score: mean ± SD**
	Total IQ	116.3 ± 17.8
	Reasoning scale (raw score)	109.0 ± 12.2
	Execution scale (raw score)	120.0 ± 25.2
Rey-Osterrieth Complex Figure Test ($n = 33$)	**Index**	**Score: median (min.–max.)**
	Copy	20.0 (1.5–34.0)
	Short-term memory	8.0 (0.5–60.0)
	Long-term memory	7.5 (0.5–16.0)
BPA ($n = 27$)	**Index**	**Score: median (min.–max.)**
	General attention	171.0 (25.0–313.0)
	Sustained attention	61.0 (9.0–118.0)
	Divided attention	50.0 (-22.0–109.0)
	Alternate attention	64.0 (30.0–113.0)
WCST ($n = 20$)	**Index**	**Score: mean ± SD**
	Total correct	60.1 ± 20.3
	Total errors	79.3 ± 15.7
	Perseverative errors	76.2 ± 20.2
	Number of categories completed	2.9 ± 1.9

Abbreviations: BPA, Psychological Battery for Attention Assessment; IQ, intelligence quotient; max., maximum; min., minimum; SD, standard deviation; SON-R $2^1/^2$-7[a], a version of the Snijders-Oomen non-verbal intelligence test; WCST, Wisconsin Card Sorting Test.
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TSC1 gene and 50 (91%) in the *TSC2* gene, leading to a *TSC1*: *TSC2* alteration ratio of 1:10 (Dufner-Almeida et. al., in preparation).

History of epilepsy was found in 56 (90.3%) participants, with a median age at seizure onset of 6 (0.0–144.0) months. Twenty-five (44.6%) had a history of West syndrome (WS). Among the 56 participants with epilepsy history, 38 (67.8%) had achieved seizure control at the time of the evaluation, 16 (28.6%) presented generalized onset seizures, 14 (25.0%) had focal aware seizures, 11 (19.6%) had focal to bilateral tonic-clonic seizures, and 3 (5.3%) had focal impaired awareness seizures.

The results of imaging exams were available for 61 (98.4%) participants: all of them (100%) presented subependymal nodules, 47 (77.0%), cortical tubers, 32 (52.4%), subcortical lesions, 11 (18.0%), SEGAs, and 8 (13.0%), migration lines.

Neuropsychological profile

A total of 39 participants (62.9%; age: 89–458 months) answered the standard assessment of intelligence level (Wechsler scales or SON-R). However, some patients completed only part of the other tests of the battery, as follows: the BPA was completed by 27 participants, the Rey-Osterrieth Complex Figure Test, by 33, and the WCST, by 20 participants (►**Table 2**). The remaining 23 patients (37.1%; age: 41–262 months) were assessed with the Vineland Adaptive Behavior Scales; all presented features of global intellectual delay, suggestive of ID.

In the analysis of the entire sample ($n = 62$), 31 participants (50.0%) scored as presenting ID, 8 were detected by the Wechsler scales, and 23 individuals were assessed by the Vineland Adaptive Behavior Scales. Other individuals assessed by Wechsler scales were classified as follows: 8 (12.9%) as borderline, 20 (32.2%) presented scores within average (lower average, average or upper average), and 3 (4.8%) had above-average scores (superior or very superior).

In total, 17 subjects (27.4%) had CARS results suggestive of ASD. Concerning this subgroup, 7 (41.2%) individuals presented mild or moderate symptoms, and 10 (58.5%) presented severe symptoms. The significant results of the multiple linear regression analysis are presented in ►**Table 3**.

Table 3 Significant results of multiple linear regression models

Index	Variable	Estimated (β)	*p*-value
Full scale IQ	Presence of epileptic seizures	-26.98	0.01*
	Age at diagnosis	-0.43	0.01*
	General BPA (raw score)	0.11	0.01*
VCI IQ	Presence of epileptic seizures	-23.55	0.03*
	Age at diagnosis	-0.43	0.01*
	General BPA (raw score)	0.08	0.04*
WMI IQ	Presence of epileptic seizures	-31.25	0.00*
	Age at diagnosis	-0.43	0.01*
	General BPA (raw score)	0.07	0.05*
PSI IQ	Presence of epileptic seizures	-16.78	0.01*
	General BPA (raw score)	0.21	0.00*
PRI IQ	ROCF – copy	0.84	0.00*

Abbreviations: BPA, Psychological Battery for Attention Assessment; IQ, intelligence quotient; PSI, processing speed index; PRI, perceptual reasoning index; ROCF, Rey-Osterrieth Complex Figure; VCI, verbal comprehension index; WMI, working memory index;.
Note: Statistically significant results ($p \leq 0.05$).
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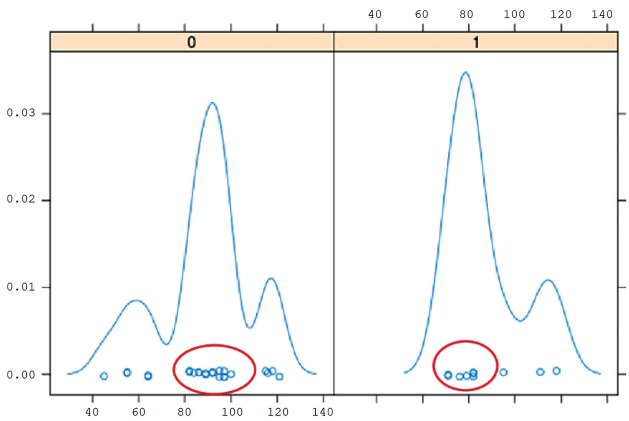

Abbreviations: IQ, intelligence quotient; WS, West syndrome. Notes: 0–group without WS; 1–group with WS. **Source:** Reproduced with permission from publisher.[40]
Figure 1 Distribution of processing speed index in the groups of participants with and without WS.

Overall, 10 out of 25 participants with WS answered the standard assessment and demonstrated a distribution of density plots similar to the group without the syndrome regarding the full-scale IQ, verbal comprehension index, perceptual reasoning index, and working memory index results. However, in relation to the processing speed index, the results of most of the sample with WS were between 60 and 80, while in the group without WS the scores ranged from 80 to 100 (►**Figure 1**).

DISCUSSION

The present study aimed to determine the neuropsychological profile of patients from Southern Brazil clinically diagnosed with definite TSC, and to identify the factors with a significant impact on cognitive development in this cohort. In a previous study by our group,[24] a high prevalence of epilepsy (95%), cognitive impairment (45%), and psychiatric manifestations was found, which is consistent with the descriptions in the literature. Intellectual impairment has been associated with a greater number of drugs used to control epilepsy and autism ($p < 0.05$).

Regarding clinical features, epileptic seizures were the symptom that most frequently led participants to seek medical assistance. Like our previous study,[24] almost the totality of the sample presented epilepsy. Subependymal nodules were the most frequent brain lesion, and radial migration lines were the least prevalent. Among the participants with genetic alterations identified (55/61), most (91%) had *TSC2* pathogenic alterations. Although mutations in the *TSC2* gene have been described more frequently than in the *TSC1* gene among the most severe cases of TSC,[25] our cohort was not predominantly composed of severe cases (►**Table 2**). However, and in agreement with our work, the *TSC2* pathogenic variant is at high risk of significant developmental delays.[26]

In relation to cognitive characteristics, the sample followed a bimodal distribution of intellectual level, with 50% of the participants presenting ID. This bimodal pattern was pointed out by other authors.[27] Other studies,[28,29] however, have suggested a unimodal distribution. The presence of epileptic seizures, the age at diagnosis, and attention were the factors that influenced the intelligence indexes the most (►**Table 3**).

In the present study, the frequency of subjects with epilepsy diagnosis (90.3%) was similar to that described by Jansen et al. (90%),[30] but slightly higher than that described by Humphrey et al. (80%).[31] The presence of epileptic seizures had a statistically significant negative impact on the full-scale IQ, verbal comprehension index, and working memory index (►**Table 3**). This finding indicates that, in

this group of participants, IQ tends to be lower, and that epileptic seizures may influence cognitive development. These results are in accordance with what has been pointed out by other authors regarding the presence of epilepsy.[30,32–34] A significant part of the participants with WS (16/25; 64%) showed some degree of ID, corroborating what other studies have described.[30,33] On the other hand, the subgroup of WS participants who answered the standard assessment ($n = 10$) had a performance in the Wechsler scale indexes similar to non-WS individuals who also completed the standard assessment, except with regard to the processing speed index.

A tendency towards better results in the perceptual reasoning index and the processing speed index was observed in the standard assessment. Ridler et al.[35] demonstrated that a group of patients with TSC showed fewer deficits in inhibition, processing speed, and visuospatial abilities in comparison to other cognitive functions. Diversely, de Vries et al.[13] found low performance in processing speed measures, and Jeste et al.[36] identified a specific deficit in non-verbal IQ in a TSC group, which could be secondary to problems in visual reception and fine motor function. The significant impact of visual perception, evaluated by the copy of the Rey-Osterrieth Complex Figure test, on the perceptual reasoning index reinforces the importance of visual information reception for posterior execution.

Age at diagnosis also had a significantly negative impact on the full-scale IQ, verbal comprehension index, and working memory index, highlighting that, the earlier the diagnosis was established and the treatment implemented, the better were the results in these domains. Van Eeghen et al.,[32] studying the association between epilepsy variables and development results, suggested that early diagnosis and treatment of epilepsy favored prevention of encephalopathic damages as well as improved developmental outcomes in patients with TSC.

The statistically significant positive impact observed of the general attention score on most of the dependent variables shows an association with performance in general intelligence, verbal comprehension, working memory, and information processing speed. Lezak et al.[15] classify attentional functions as mental activity variables that maintain the activity of other cognitive functions. This understanding reinforces the importance of care in cognitive development and in the daily activity of patients with TSC. In the present study, the lowest median score on the BPA was observed in divided attention (►**Table 2**). A similar result was found in another study,[13] which described consistent impairment in divided attention in children with TSC.

The number of participants that screened positive for ASD in our cohort is consistent with the evidence in the literature.[37] It is important to assess ASD with caution and precision due to the high percentage of individuals with TSC that present indicative signs of the disorder.

Poor performance was identified in visual perception and short- and long-term visual memory, as well as in the working memory index (in which the subjects presented the lowest index mean). Ridler et al.[35] described significant impairment in different tests of long-term memory, verbal working memory, and spatial working memory in TSC patients.

In addition, the low scores on the WCST indicated a deficit in cognitive flexibility, which is part of executive functioning and contributes to involvement in complex, independent, intentional, and self-directed behaviors.[15] It is also worth mentioning the clinical qualitative observations. Adult participants showed difficulty in maintaining jobs or finishing graduation courses. Children demonstrated difficulty in changing inadequate behaviors, in flexibility during tasks, and in organizing their activities. These characteristics are suggestive of deficits in organization, planning, self-regulation, and goal setting. The difficulties observed in social skills, including making friends, may be related to executive functioning impairment.

Corroborating the outcomes of the present study, de Vries and Watson[38] emphasize neuropsychological deficits in attention and executive functions in TSC patients, even when the global intellectual abilities are within normal limits, and there are no diagnostic criteria for other developmental disorders, such as attention-deficit hyperactivity disorder, considering this clinical group. The attentional, memory, and executive function deficits described in the present research are consistent with frontal lobe impairment at the level of the third functional unit, according to Luria's theory.[39] Although we had limited exploration of neuroimaging data, the functional deficits observed in the current report were similar to those observed in previous[11] studies that revealed a high predominance of TSC cortical lesions in the frontal lobe.

For individuals diagnosed with TSC, it is recommended that visual and practical resources be available in academic and professional contexts to facilitate learning. In the school setting, the time to complete tasks should be flexible, and short-term objectives should be proposed within long-term activities. Strategies to organize daily activities should be encouraged, such as the regular use of calendars, planners, and reminders. Playtime with peers and group activities are also important for cognitive and social development.

Since TSC has a wide variety of expressions, it is difficult to propose a single neuropsychological assessment plan for the whole group. It is indicated that the first evaluation prioritizes the differential diagnosis of ID using a combination of instruments that assess functioning, and brief instruments for global cognitive performance. Further assessments of specific cognitive functions, such as attention, long- and short-term visual and verbal memory, and visual perception, should require specific tests.

The present study has certain limitations. Firstly, the small cohort of children and younger participants, including infants and toddlers. It is suggested that age-appropriate instruments for cognitive evaluation be used, as well as the performance of an investigation of social skills and other variables, such as lifestyle characteristics, familial context, and substance use. The neuropsychological assessment of individuals with TSC enables the identification of the cognitive deficits and strengths of this population. Furthermore, early assessment and intervention can encourage this group of individuals to step out of an unprivileged intellectual

condition that is associated with social and academic impairment. Secondly, we did not use neuroimaging to understand injuries related to cognitive development. Finally, more accurate instruments were not used for the diagnosis of ASD and ID.

In conclusion, in the present study, we have observed clinical symptoms similar to those reported in the literature, and we have pointed out that the occurrence of epileptic seizures and a higher age at diagnosis contribute to higher impairment in the domains of cognitive development. The study reinforces the importance of early diagnosis, mainly aimed at the prevention of epileptic seizures or their rapid control. In addition, emphasis on the development of attentional skills, visual perception, and executive function is recommended.

Authors' Contributions

LFMC, APAP, SAA: conceptualization and design of the work, data acquisition, analysis, and interpretation, and writing and reviewing of the manuscript; MRS, LGDA, LAH, IB: data acquisition, analysis, and interpretation, and writing and reviewing the manuscript; All authors approved the final version of the manuscript and agree to be responsible for all aspects of the work.

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Conflict of Interest

The authors have no conflict of interest to declare.

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References

1 Rosset C, Netto CBO, Ashton-Prolla P. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. Genet Mol Biol 2017;40(01):69–79
2 Northrup H, Aronow ME, Bebin EM, et al; International Tuberous Sclerosis Complex Consensus Group. Update international Tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatr Neurol 2021;123:50–66
3 de Vries PJ, Belousova E, Benedik MP, et al; TOSCA Investigators. Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND): new findings on age, sex, and genotype in relation to intellectual phenotype. Front Neurol 2020;11(603):603
4 Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. Pediatr Neurol 2015;52(01):16–24
5 Rosengren T, Nanhoe S, de Almeida LGD, et al. Mutational analysis of TSC1 and TSC2 in Danish patients with tuberous sclerosis complex. Sci Rep 2020;10(01):9909
6 Dibble CC, Elis W, Menon S, et al. TBC1D7 is a third subunit of the TSC1-TSC2 complex upstream of mTORC1. Mol Cell 2012;47(04): 535–546
7 de Waele L, Lagae L, Mekahli D. Tuberous sclerosis complex: the past and the future. Pediatr Nephrol 2015;30(10):1771–1780
8 Krueger DA, Sadhwani A, Byars AW, et al. Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders. Ann Clin Transl Neurol 2017;4(12):877–887
9 Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol 2015; 14(07):733–745
10 Leclezio L, de Vries PJ. Towards an improved understanding of TSC-Associated Neuropsychiatric Disorders (TAND). Adv Autism. 2016;2(02):76–83
11 Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol 2004;19(09):666–674
12 Moavero R, Marciano S, Graziola F, Curatolo P. Combined targeted treatment in early onset epilepsy associated with tuberous sclerosis. Epilepsy Behav Case Rep 2016;5:13–16
13 de Vries PJ, Gardiner J, Bolton PF. Neuropsychological attention deficits in tuberous sclerosis complex (TSC). Am J Med Genet A 2009;149A(03):387–395
14 Both P, Ten Holt L, Mous S, et al. Tuberous sclerosis complex: Concerns and needs of patients and parents from the transitional period to adulthood. Epilepsy Behav 2018;83:13–21
15 Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York: Oxford University Press; 2012
16 Wechsler D. WISC IV: Escala de Inteligência Wechsler para Crianças: Manual. São Paulo: Casa do Psicólogo,; 2013
17 Wechsler D. WAIS III: Escala de Inteligência Wechsler para Adultos: Manual. São Paulo: Casa do Psicólogo,; 2004
18 Tellegen PJ, Laros JA, de Jesus GR, Karino CA. Manual teste não-verbal de inteligência SON-R 21/2-7 [a]. São Paulo: Hogrefe,; 2015
19 Rueda FJM. Bateria Psicológica para Avaliação da Atenção (BPA). São Paulo: Editora Vetor,; 2013
20 Oliveira MS, Rigoni MS. Figuras Complexas de Rey: teste de cópia e de reprodução de memória de figuras geométricas complexas. São Paulo: Casa do Psicólogo,; 2010
21 Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. Manual do Teste Wisconsin de Classificação de Cartas Adaptação e padronização brasileira. 1st ed. Cunha JA, Trentini CM, Argimon IL, Oliveira MS, Werlang BG, Prieb RG. São Paulo: Casa do Psicólogo,; 2005
22 Sparrow SS, Balla DA, Cicchetti DV. The Vineland Adaptive Behavior Scales. Circle Pines: American Guidance Services,; 1984
23 Pereira A, Riesgo RS, Wagner MB. Childhood autism: translation and validation of the Childhood Autism Rating Scale for use in Brazil. J Pediatr (Rio J) 2008;84(06):487–494
24 Schwind MR, Cardozo LFM, Antoniuk AS, et al. Perfil neuropsiquiátrico de crianças adolescentes e jovens adultos com complexo de esclerose tuberosa. Saúde e Desenvolvimento Humano. 2017;5(02):27–37
25 Sancak O, Nellist M, Goedbloed M, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. Eur J Hum Genet 2005;13(06):731–741
26 Farach LS, Pearson DA, Woodhouse JP, et al; TACERN Study Group. Tuberous Sclerosis Complex Genotypes and Developmental Phenotype. Pediatr Neurol 2019;96:58–63
27 Lyczkowski DA, Conant KD, Pulsifer MB, et al. Intrafamilial phenotypic variability in tuberous sclerosis complex. J Child Neurol 2007;22(12):1348–1355
28 Bolton PF, Clifford M, Tye C, et al; Tuberous Sclerosis 2000 Study Group. Intellectual abilities in tuberous sclerosis complex: risk factors and correlates from the Tuberous Sclerosis 2000 Study. Psychol Med 2015;45(11):2321–2331

29 Tye C, Thomas LE, Sampson JR, et al. Secular changes in severity of intellectual disability in tuberous sclerosis complex: A reflection of improved identification and treatment of epileptic spasms? Epilepsia Open 2018;3(02):276–280
30 Jansen FE, Van Huffelen AC, Van Rijen PC, et al; Dutch Collaborative Epilepsy Surgery Programme. Epilepsy surgery in tuberous sclerosis: the Dutch experience. Seizure 2007;16(05): 445–453
31 Humphrey A, MacLean C, Ploubidis GB, et al; Tuberous Sclerosis 2000 Study Group. Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis. Epilepsia 2014;55(01): 108–116
32 van Eeghen AM, Chu-Shore CJ, Pulsifer MB, Camposano SE, Thiele EA. Cognitive and adaptive development of patients with tuberous sclerosis complex: a retrospective, longitudinal investigation. Epilepsy Behav 2012;23(01):10–15
33 Overwater IE, Verhaar BJH, Lingsma HF, et al. Interdependence of clinical factors predicting cognition in children with tuberous sclerosis complex. J Neurol 2017;264(01):161–167
34 Uematsu M, Numata-Uematsu Y, Aihara Y, et al. Behavioral problems and family distress in tuberous sclerosis complex. Epilepsy Behav 2020;111:107321
35 Ridler K, Suckling J, Higgins NJ, et al. Neuroanatomical correlates of memory deficits in tuberous sclerosis complex. Cereb Cortex 2007;17(02):261–271
36 Jeste SS, Hirsch S, Vogel-Farley V, et al. Atypical face processing in children with tuberous sclerosis complex. J Child Neurol 2013;28 (12):1569–1576
37 Bolton PF, Park RJ, Higgins JNP, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain 2002;125(Pt 6):1247–1255
38 de Vries PJ, Watson P. Attention deficits in tuberous sclerosis complex (TSC): rethinking the pathways to the endstate. J Intellect Disabil Res 2008;52(Pt 4):348–357
39 Luria AR. Fundamento de Neuropsicologia. 1st ed. São Paulo: Editora da Universidade de São Paulo,; 1981
40 Cardozo LFM. Caracterização neuropsicológica de pacientes com Complexo da Esclerose Tuberosa [master's dissertation]. Curitiba: Federal University of Paraná; 2017