

Brief Communication

Cognitive and neuro-psychiatric profile in adult patients with epilepsy secondary to Tuberous Sclerosis Complex

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ABSTRACT

Introduction: Tuberous Sclerosis Complex (TSC) is a neurocutaneous disorder associated with epilepsy (70–90% of cases) and neuropsychiatric symptoms (NPS). However, the influence of epilepsy on NPS remains unclear.

Objectives: This study aimed to describe the presence of NPS in our cohort and to establish their relationship with epilepsy severity and other clinical characteristics (genetic, neuroimaging, and EEG findings).

Patients and methods: Descriptive, cross-sectional, single-centre study of adults (18–65 years) with TSC, without significant intellectual disability. Patients underwent comprehensive neurological and neuropsychological assessment, which included cognitive, depression, and quality of life evaluations, alongside the TAND-checklist for NPS.

Results: Twenty-eight patients with TSC were included (19 women, 44.7 ± 14.4 years). Seven patients had *TSC1* variants and 11 had *TSC2* variants. Nineteen (67.86 %) patients had epilepsy, 7 (36.84 %) of them exhibiting drug-resistant epilepsy. Five (17.86 %) presented Infantile Spasms in the past. Regarding TAND-L, the most frequent NPS were: mood swings (80 %), excessive shyness (70 %), sleep/attention disorders (60 %) and low self-esteem (50 %). A longer duration of epilepsy and a higher number of anti-seizure medications (ASM) trials correlated with poorer total IQ –Intelligence Quotient– (Pearson correlation = -0.53 , significant at 0.007 and -0.45 , significant at 0.03, respectively). Patients carrying a *TSC2* variant or with a history of Infantile Spasms had higher intellectual disability and worse TAND scores ($p < 0.05$). Despite the high prevalence of NPS, only 4 (14.28 %) patients had received specific psychiatric care.

Conclusion: Patients with TSC and severe epilepsy showed worse neuropsychiatric outcomes. The high prevalence of NPS underscores the need for specific protocols for early detection and intervention.

1. Introduction

Tuberous Sclerosis Complex (TSC) is a rare disease, with an approximate incidence of 1 in 6000/10000 live births [1], standing out as one of the most disabling multisystemic disorders. The underlying mechanism involves a pathogenic variant in the *TSC1* gene

(chromosome 9q34) or in the *TSC2* gene (chromosome 16p13.3), encoding the hamartin and tuberin proteins respectively, in approximately 75–85 % of cases, with clinical features sufficient for the diagnosis [2]. Both proteins are part of a complex that leads to overactivation of the mTOR (mammalian target of rapamycin) pathway, resulting in uncontrolled cell growth, disturbances in differentiation,

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metabolism, and autophagy, and ultimately leading to the formation of hamartomatous dysplasia in multiple organs, including the brain [1,2]. However, there is significant clinical heterogeneity in terms of severity and phenotypic expression, as well as an age-dependent evolution of symptoms [3].

Around 80–90 % of TSC patients have epilepsy [1,4,5], with infantile spasms in 45 % (especially in TSC2) [4] and other types of seizures, such as focal or secondarily generalized seizures, also being common [6]. Although the onset of epilepsy typically occurs within the first two years (0.4 years for infantile spasms) [4], adults are not exempt, with > 12 % experiencing new-onset epilepsy [7]. Epilepsy is often drug-resistant [8] with only 30–40 % of patients achieving good seizure control [7,9].

Beyond epilepsy, most individuals with TSC experience neuropsychiatric symptoms (NPS) at some point in their lives (up to 90 %) [10]. In 2012, NPS were collectively termed “TAND; TSC-associated neuropsychiatric disorders” [3]. Consequently, the “TAND-checklist” was developed to assess NPS, comprising six distinct domains (Behavioural, Intellectual, Developmental, Academic, Neuropsychological, and Psychosocial) [11]. Current guidelines recommend an annual screening of NPS. However, NPS remain underexplored in clinical practice, with fewer than 20 % of patients receiving the support they require [12].

Moreover, identifying risk factors or biomarkers for the development of NPS is essential. Some studies have shown that early onset and the severity of epilepsy are linked to these symptoms, while others have demonstrated that treating tumours and epilepsy can improve NPS [4,12–14]. Nevertheless, this research is limited and does not systematically investigate the complete NPS dimensions.

This work focuses on two main objectives: first, to offer a more detailed description of NPS in adult patients with TSC; and second, to better understand the relationship between epilepsy and NPS as well as other clinical characteristics, such as epilepsy severity, genotype, tuber localisation and EEG abnormalities.

2. Methods

2.1. Study population

We undertook a descriptive, prospective, cross-sectional and single-centre study of adult patients with TSC followed at Hospital de la Santa Creu i Sant Pau (HSCiSP) from February 2023 to July 2024. Patients were included according to the following criteria: 1) Clinical and/or molecular diagnosis of TSC; 2) Aged 18–65 years; 3) If epilepsy was present, it had to meet the ILAE criteria[15]; 4) MRI performed within the last three years; 5) EEG performed within the past year. We excluded patients with moderate-severe intellectual disability, defined as an Intelligence quotient (IQ) < 50 due to their inability to read and understand the informed consent and to complete the required neuropsychological tests.

The study was approved by the Ethics Committee of HSCiSP.

We recorded the following variables: age; genetic testing; history of Infantile Spasms; current seizure status (active if seizures occurred within the last year); types of seizures; drug-resistance criteria; epilepsy duration (years); number of total antiseizure medications (ASM) prescribed to date; number of current ASM; localisation of cortical tubers (frontal/parietal/temporal/occipital lobes) on the latest brain MRI; and EEG findings in the most recent EEG (epileptiform versus non-epileptiform abnormalities, such as slow background activity or focal or diffuse slowing).

A structured interview was conducted using the TAND Checklist (TAND-L) [11], alongside the following scales: Montreal Cognitive Assessment (MoCA) for cognitive screening, with an impairment cutoff of < 26; Hospital Anxiety Scale (HADS-A) and Hospital Depression Scale (HADS-D), with a cutoff of ≥11; EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) [16] for health-related quality of life, with each dimension evaluated at three levels: no problems, some problems, extreme problems; Quality of Life in Epilepsy Inventory-10 (QOLIE-10) [17], where each item

assesses an aspect of quality of life, with responses ranging from 1 (least affected) to 5 (most affected); Thermometer Test (TERMO) for subjective health assessment, with responses ranging from 0 (worst imaginable) and 10 (best possible); and Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) for cognitive ability evaluation, with subtest scores expressed as scaled values (10 ± 3) and indices with coefficient scores (100 ± 15).

2.2. Statistical analysis

Means and standard deviations (±SD) were used to compare quantitative variables between patients with and without epilepsy; the mean values allowed us to assess the magnitude of the difference and its significance. For variables with a non-normal distribution, the Mann-Whitney *U* test was applied. The Chi-Square test was used for categorical variables, like TAND-L, allowing us to obtain the percentage separately for both groups and assess its potential significance. To study the correlation between two quantitative variables, such as duration of epilepsy and IQ, the Pearson test was employed.

Statistical significance was established at a *p*-value of 0.05 (two-sided). Statistical analysis was conducted using IBM SPSS (Statistical Package for the Social Sciences) software, version 29.0.

3. Results

A total of 34 patients with TSC were identified. Six patients were excluded due to moderate-severe intellectual disability (IQ < 50). Thus, 28 patients were included (mean age: 44.68 ± 14.42 years). Baseline characteristics are detailed in Table 1.

Regarding cognitive performance, 18/28 patients were evaluated

Table 1
Baseline characteristics of the patients (n = 28). Descriptive statistics are presented with means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Age (years), mean (SD)	44.68 (14.42)
Sex (female), n (%)	19 (67.86)
West syndrome history, n (%)	5 (17.86)
Epilepsy, n (%)	19 (67.96)
Active epilepsy, n (%)*	10 (52.63)
Epilepsy time of evolution (years), mean (SD)*	20.95 (16.45)
Current ASM (n°), mean (SD)*	1.58 (1.22)
History of ASM (n°), mean (SD)*	2.79 (1.87)
Drug-resistant epilepsy, n (%)*	7 (36.84)
Most frequent types of epileptic seizure, n (%)*	
- Focal without impaired awareness	3 (15.79)
- Focal with impaired awareness	12 (63.16)
- Bilateral tonic-clonic or other generalized	8 (42.11)
Available genetic testing, n (%)	18 (64.29)
- TSC1**	7 (38.89)
- TSC2**	11 (61.11)
Number of tubers, n (%)	
- <3	6 (21.43)
- 3–6	8 (28.57)
- 6–10	5 (17.86)
- >10	9 (32.14)
Tubers location, n (%)	
- Frontal	23 (82.14)
- Temporal	16 (57.14)
- Parietal	19 (67.86)
- Occipital	11 (39.29)
EEG abnormalities (availability of EEG < 1 year), n (%)***	
- Normal	17 (68)
- Pathologic but non-epileptiform activity	4 (16)
- Epileptiform activity	4 (16)
*Excludes 9 patients without epilepsy	
**Excludes 10 patients without available genetic test	
***Excludes 3 patients without a recent EEG (within the last year)	

Abbreviations

SD, standard deviation; ASM, antiseizure medications; TSC, Tuberous Sclerosis Complex; EEG, electroencephalogram.

using the WAIS-IV and MoCA (4/28 declined further evaluations and 6/28 were excluded because they exhibited mild intellectual disability- IQ 50–70; mean IQ: 59 ± 6.44). Among this group, the mean IQ was 92.29 ± 16.23 , and their cognitive index profile was as follows: Verbal Comprehension Index (VCI): 98.83 ± 14.52 ; Perceptual Reasoning Index (PRI): 92 ± 17.38 ; Working Memory Index (WMI): 84.33 ± 12.91 ; and Processing Speed Index (PSI): 94.89 ± 14.37 . As shown in Fig. 1, all cognitive indices demonstrated lower scores in patients with epilepsy (active or not) compared to those with no epilepsy.

The scaled scores for the WAIS-IV subtests yielded the following results: Block design: 8.22 ± 2.75 ; Similarities: 9.17 ± 2.74 ; Digit span: 7.44 ± 2.06 ; Matrix reasoning: 9.67 ± 4.00 ; Vocabulary: 10.72 ± 2.78 ; Arithmetic: 7.50 ± 2.7 ; Visual puzzles: 8.56 ± 3.20 ; Symbol Search: 9.39 ± 2.63 ; Information: 9.56 ± 3.07 ; and Coding: 8.67 ± 2.91 . The MoCA score was 24.89 ± 3.87 , with half of the patients scoring < 26 , suggesting cognitive impairment. Patients with epilepsy had lower scores in the MOCA test ($p = 0.01$).

Anxiety and depression were assessed in all 28 participants. The scores on HADS were as follows: HADS-A: 7.22 ± 4.88 ; HADS-D: 4.87 ± 4.11 . Five patients exceeded the score cutoff of 11 in the anxiety subscale, and three in the depression subscale.

Concerning the TAND-L checklist, the most frequent symptoms were mood swings (80 %), excessive shyness (70 %), sleep and attention disorders (60 %), and tantrums (50 %). Half of the patients reported low self-esteem.

In terms of quality of life, patients scored 6.70 ± 1.43 on the EQ-5D-3L, indicating mild impairment. In contrast, the score on the QOLIE-10 was 20.74 ± 8.08 , with higher scores observed in patients with active epilepsy (23.85 ± 4.00) compared to those without active epilepsy (19.07 ± 8.38). However, these differences were not statistically significant.

Patients evaluated their overall health perception using TERMO, with an average score of 6.81 ± 1.78 , suggesting an acceptable perception of their health status.

Comparing patients with and without epilepsy, a significant association was found between the presence of epilepsy and lower IQ ($p = 0.027$). Notably, a history of Infantile Spasms was related with both intellectual disability and higher TAND-L scores ($p = 0.047$), specifically in TAND-3 (behavioural problems) and TAND-6 (difficulties in school-related skills).

Furthermore, a longer duration of epilepsy and a higher number of ASM trials correlated with poorer total IQ (Pearson correlation = -0.53 , significant at 0.007 and -0.45 , significant at 0.03, respectively).

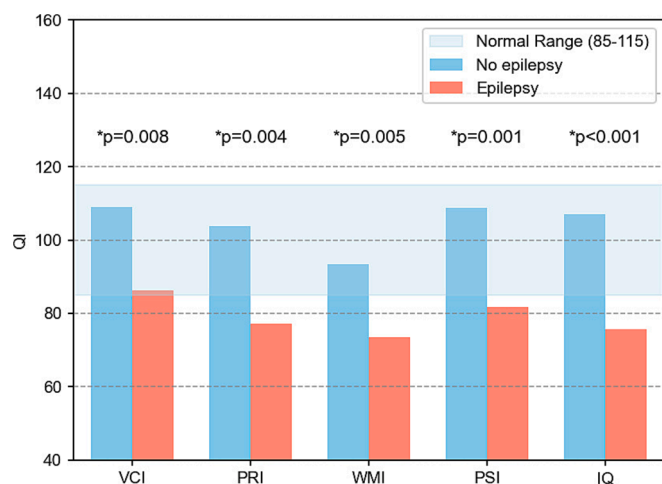


Fig. 1. Comparison of Cognitive Indices and associated p-values between Epilepsy and Non-Epilepsy patients. *Abbreviations:* VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; IQ, Intelligence Quotient.

Regarding genetics, when comparing the 11 patients with TSC2 variants to the 7 patients with TSC1 variants, the TSC2 group showed a higher prevalence of psychiatric disorders included in TAND-4 ($p = 0.002$). Additionally, the TSC2 group performed worse in several subtests of the WAIS-IV, including digit span, arithmetic, block design, puzzles, coding, PRI, PSI, and total IQ. The mean total IQ was 83 (SD = 29.61) in the TSC2 group, compared to 86.57 (SD = 13.40) in the TSC1 group ($p = 0.002$).

As for the location of the tubers in the MRI, tubers in the frontal lobe (82.14 % of patients) and parietal lobe (67.86 % of patients) were significantly associated with TAND-6 (school-related skills) ($p = 0.043$ and 0.022 respectively). Parietal lesions were also related to TAND-3 (behavioural problems) and TAND-7 (difficulties in some specific brain skills) ($p = 0.030$ and 0.020 respectively). No significant differences were observed between TAND subcategories and lesions in the temporal and occipital lobes.

Lastly, regarding the EEG, 4/28 patients exhibited non-epileptiform abnormalities and 4/28 showed interictal epileptiform activity. There were no significant differences between EEG findings and intellectual disability or other NPS.

4. Discussion

This study suggest that adult patients with TSC exhibit a high prevalence of NPS, significantly affecting their quality of life, especially those with epilepsy. Overall, the results indicate that cognitive performance varied among patients (mean IQ of 92.29 ± 16.23), with particular deficits in working memory and processing speed. Behavioural symptoms were prevalent, underscoring the interplay between cognitive and emotional health in this cohort. Our findings reveal a notable association between epilepsy severity and lower IQ, emphasizing the impact of recurrent seizures on cognition. Remarkably, a history of Infantile Spasms seems to be linked with intellectual disability, behavioural issues, and genetic factors (TSC2 mutations correlated with poorer cognitive performance).

Our cohort had relatively mild epilepsy, with lower rates of Infantile Spasms (17.86 %) and drug-resistant epilepsy (36.84 %) compared to previous studies. This may suggest a reporting bias in diagnosing Infantile Spasms in adults, as well as a better control of epilepsy in later stages of the disease, compared to paediatric population. The acceptable quality of life reported by patients, could be attributed to this effective seizure control and a degree of anosognosia concerning their cognitive deficits.

Frontal and parietal lesions on MRI impacted on school-related skills and behavioural problems. A previous study correlated parietal and temporal lesions with higher occurrences of learning difficulties, mood disorders, anxiety, and extreme shyness [18]. The involvement of frontal and parietal regions may contribute to poorer outcomes given their critical roles in cognitive functions and spatial awareness, crucial for academic performance and social interactions. On the other hand, in our cohort, EEG findings were not related with NPS, possibly due to less specific alterations in adults with TSC compared to those with infantile TSC. In a retrospective study involving 103 participants aged 3 to 55 years [19], epileptiform activity was more prevalent in patients with autism spectrum disorders.

So far, most studies have focused on the paediatric or combined paediatric-adult populations. A recent Polish study assessed the TAND-checklist in 100 adults with TSC [20], revealing high frequency of NPS primarily in the behavioural domain, including extreme shyness, inflexibility, and sustained attention deficits, consistent with our results. The study also highlighted an association between epilepsy and increased NPS and disability, which also aligns with our observations. To our knowledge, the present study is the first to analyse the cognitive profile of adult patients using a complete neuropsychological battery. These results confirm the complexity of NPS in TSC and the need for further research across different age groups.

Our study has several limitations. First, the cross-sectional design restricts our ability to establish causality between NPS and epilepsy and it may limit the generalizability of our findings. Secondly, the small sample size of 28 patients reduces statistical power, potentially limiting the precision and robustness of our results. Future studies with larger cohorts and longitudinal designs are recommended to validate and expand upon these observations. Finally, there are limitations related to the TAND-checklist questionnaire. Its interpretation may be subjective, affecting the comparability across studies. It also does not specify when symptoms began or whether they persist, making it difficult to determine if NPS are temporally linked to active epilepsy or follow any age-related patterns.

In conclusion, in patients living with TSC, neurological care should transcend the mere management of epileptic seizures and it seems mandatory to adopt an integral strategy that incorporates the assessment of NPS.

CRedit authorship contribution statement

Clara Toscano-Prat: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Carmen García-Sánchez:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Victoria Ros-Castelló:** Writing – review & editing, Investigation, Conceptualization. **Ainara Barguilla-Arribas:** Writing – review & editing, Investigation, Conceptualization. **Ignasi Gich Saladich:** Software, Methodology, Investigation, Formal analysis. **Kevin Rodríguez-Clifford:** Project administration, Methodology, Investigation, Conceptualization. **Roser Torra-Balcells:** Writing – review & editing. **Susana Boronat:** Writing – review & editing. **Alba Sierra-Marcos:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, 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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