COMMENTARY

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Enhancing the utility of tuberous sclerosis complex-associated neuropsychiatric disorders checklist in China

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INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by abnormalities affecting various organ systems, including the skin, brain, kidneys, heart, lungs, and eyes. It presents with a diverse range of physical manifestations, necessitating continuous assessment, monitoring, and treatment.[1] The incidence of TSC is estimated to range between 1:6000 and 1:10 000 live births.[2] *TSC2* pathogenic variants typically result in a more severe phenotype compared to *TSC1* pathogenic variants.[3] The diagnosis of TSC is confirmed in a proband through genetic diagnostic criteria, which involves identifying a heterozygous pathogenic variant in either *TSC1* or *TSC2* using molecular genetic testing. Alternatively, clinical diagnostic criteria can be employed based on the presence and quantity of major and minor clinical features. Regular evaluation and monitoring are essential for the comprehensive management of individuals affected by TSC.[2]

The neuropsychiatric panel convened during the 2012 TSC Consensus Conference proposed the definition of TSC-associated neuropsychiatric disorders (TAND),

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encompassing a range of difficulties across many levels including behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial. These encompass a spectrum of conditions, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), learning and cognitive impairments, disruptive behaviors, and emotional issues, among others.[4] It is noteworthy that while the general population has an approximate 2% risk of ASD,[5] individuals with TSC face a significantly elevated risk ranging from 16% to 61%.[6–13] Despite more than 90% of TSC individuals experiencing one or more TAND-related disorders in their lifetime, only 20% have undergone evaluation and intervention for these challenges.[14,15] To address this, it is recommended that TAND screening be conducted at least annually, with a comprehensive formal evaluation performed at crucial developmental stages in the life of a TSC patient.[15] Seeking the expertise of qualified professionals is paramount for the proper management of TAND, which may involve consideration of medication for individuals with ADHD.[16,17]

Vanclooster et al.[18] conducted a comprehensive review of articles related to TAND, revealing that despite an increase in recent research on TAND, there is still a lack of adequate assessment, treatment, and research for TAND patients. There is room for improvement in human-related studies, which can guide future research on TAND. de Vries et al.[19] put forth the International Consensus Recommendations for the Identification and Treatment of TAND in 2023, offering valuable guidance for the effective management of TAND. The overall suggestion is to "screen" for TAND at least annually, proceed with appropriate follow-up steps for assessment and treatment, take action, and "repeat" this process to ensure early identification and intervention using the most appropriate biological, psychological, and social evidence-informed approaches to support TSC patients and their families.[19]

This commentary article aims to achieve three primary objectives. First, it seeks to delineate the characteristics of the TAND Checklist along with the pertinent research findings. Secondly, it endeavors to facilitate the accessibility of the TAND Checklist in China. Lastly, it aims to advocate for the adoption and recognition of the TAND Checklist within the Chinese TSC patient community.

TAND CHECKLIST

Background and development of the TAND Checklist

The prevalence of TAND over the course of the lifetime of a TSC patient is notably high. However, research has indicated that a significant proportion of individuals with TSC have not undergone comprehensive assessments or received targeted treatments for TAND. Addressing this gap, the neuropsychiatric panel at the 2012 Consensus Conference recommended the development of straightforward tools to aid clinical teams and families in screening individuals with TAND and subsequently offering in-depth evaluations or treatments.[15] To systematically address TAND, de Vries et al.[15] pioneered the TAND Checklist. Following two rounds of pilot validation, this checklist has proven to be clear, thorough, and user-friendly, establishing its efficacy as an efficient screening tool in clinical settings.

In a study of 2093 patients in the TuberOus SClerosis registry to increase disease Awareness (TOSCA) cohort, it was found that diagnoses of TAND were often delayed, with 30%–50% of patients not undergoing evaluation.[13] A pilot study of the TAND Checklist, involving 20 professionals and 62 parents and caregivers from 28 countries, found that 93% of participants experienced four or more lifetime TAND behavioral difficulties.[20] A study utilizing questionnaires with disease-specific questions on the burden of illness (BOI) and validated quality of life questionnaires, analyzed individual outcomes of 143 participants in the TOSCA study, emphasizing the burden of TSC on the personal lives of TSC patients and their families. The findings indicated high BOI and low quality of life within this population, underscoring the importance of early identification and intervention for TAND to enhance the quality of life for these individuals.[21] Therefore, the TAND Checklist should serve as a valuable resource for identifying and evaluating TAND-related disorders, contributing to the enhancement of care and management for individuals with TSC.[15,20]

In 2023, Heunis et al.[22] introduced a self-report quantified TAND Checklist (TAND-SQ), distinct from the clinician-completed lifetime version (TAND-L). The TAND-SQ Checklist allows for completion by caregivers or individuals with TSC, quantifying TAND difficulties. However, further advancements and external validation of the checklist are necessary to incorporate it into evidence-informed consensus recommendations for smartphone applications.[22]

TAND Checklist

The TAND Checklist encompasses six levels: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial. It is structured into 12 sections, each containing distinct questions, predominantly requiring a "yes" or "no" response. It can be completed within minutes by a clinician. Sections 1 and 2 are specifically designed to evaluate the current developmental level of the patient before delving into issues related to behavior. Section 3 addresses behavior-related concerns associated with TSC. Section 4, the checklist outlines the most prevalent psychiatric disorders diagnoses linked to TSC. Section 5 is dedicated to assessing delays in intellectual development. Section 6 focuses on learning abilities, highlighting proficiency or difficulties in standard learning skills related to reading, writing, math, or spelling. Section 7 is designated for identifying specific cognitive skill challenges, such as memory,

attention, and executive skills. Section 8 emphasizes core issues of psychosocial functioning, such as self-esteem, parental stress, and family relationships. Sections 9 and 12 inquire about the respondent's and interviewer's perceptions or judgments regarding the overall impact of TAND, respectively. Sections 10 and 11, which are descriptive in nature, prompt the TSC patient or interviewee to specify their top priority for TSC management and express any additional concerns about TAND. These sections provide a platform for the family or patient to communicate aspects not covered in the TAND Checklist but considered crucial to address.[15] The checklist assesses the presence of specific TAND-related symptoms but lacks scoring for evaluating disease progression or response to therapy, posing certain limitations.

Characteristics of the TAND Checklist

Individuals exhibit seemingly unique TAND profiles, prompting de Vries and his colleagues[23–25] to propose that identifying natural clusters within TAND could lead to personalized identification and treatment strategies. Two studies were conducted using hierarchical cluster analysis to comprehend the intricate items in the TAND Checklist.[23,24] In a substantial international dataset, de Vries et al.[25] collected information from 453 individuals' TAND checklists and identified seven distinct TAND clusters, demonstrating robustness through bootstrapping. Cluster analysis exhibited significant alignment with an exploratory factor analysis solution. The identified TAND clusters include scholastic, neuropsychological, ASD-like, dysregulated behavior, overactive/impulsive, mood/anxiety, and eat/sleep clusters.[25] In parallel research, Alperine et al.[26] analyzed a total of 1545 TAND checklists completed by 668 participants. Notably, approximately 90% of participants reported at least one TAND symptom, with neuropsychological symptoms emerging as the most prevalent. These findings underscore the potential for tailored interventions based on the specific TAND profile of each individual.

During the three-year study period, the prevalence of TAND-related disorders demonstrated overall stability. Children tended to manifest a higher frequency of behavioral symptoms, whereas adults exhibited a predilection for emotional symptoms, aligning with the outcomes of a global study involving 2216 patients conducted by the TOSCA study.[26,27]

TRANSLATED VERSIONS OF THE TAND CHECKLIST

The TAND Checklist has been translated into 20 languages, including Spanish, German, Portuguese, Japanese, and Korean, among others (https://tandconsortium.org/checklists/). However, notably absent from this roster is a Chinese translation. In an effort to enhance the accessibility and utility of the TAND Checklist within China, the TAND Checklist development team is working to translate its English version into both simplified Chinese and traditional Chinese. The complete TAND Checklist in Chinese versions will be available soon.

DIAGNOSIS AND TREATMENT OF TSC IN CHINA

Following the establishment of recommendations and standards by the 2012 International TSC Consensus Conference and the subsequent update of international TSC diagnostic criteria, along with surveillance and management recommendations in 2021, the scientific diagnosis and treatment of TSC have been effectively implemented and disseminated in China.[2] This successful translation of scientific research findings into clinical practice has notably improved the quality of life for patients with this rare disease in China. This achievement is a testament to the collaborative efforts and advocacy of Chinese healthcare professionals and patients alike. The TSC community in China has navigated the challenges of lacking a cure, and Chinese medical experts have gradually developed a set of proven diagnostic and treatment programs.[28] The translation of the TAND scale into Chinese reflects the recognition of the differences in language and culture that exist across the world. This is a significant step towards providing more effective care for individuals with TSC in China. However, it is important to acknowledge that there is still a pressing need for evidence-based guidelines that are specifically tailored to the Chinese population.

By continuing to refine and adapt these guidelines, we can ensure that the care and outcomes for individuals with TSC in China are optimized. This ongoing commitment to improving the guidelines will ultimately benefit those who are affected by this condition, and contribute to the overall advancement of healthcare in China.

In recent years, specialized TSC treatment centers have been established within medical institutions in China, offering comprehensive diagnostic and treatment services. Peking Union Medical College Hospital, Peking University First Hospital, Beijing Children's Hospital, Children's Hospital of Fudan University, Shenzhen Children's Hospital, and the PLA General Hospital are among the top hospitals in China for managing TSC. The PLA General Hospital, in particular, sees approximately 1000 TSC patients annually, making it one of the busiest in the country for this condition. These centers typically house multidisciplinary teams comprising neurologists, pediatricians, dermatologists, nephrologists, respiratory physicians, psychologists, and imaging physicians. For diagnostic purposes, a combination

of clinical presentation, family history assessment, physical examination, and imaging modalities are commonly employed to ascertain the presence of TSC. Genetic testing is increasingly utilized to confirm diagnoses and provide genetic counseling. In terms of treatment, personalized plans are meticulously designed to address the specific symptoms and organ involvement associated with TSC. Common therapeutic approaches encompass the use of anti-seizure medications, mammalian targets of rapamycin inhibitors, surgical interventions, and interventional therapies.[29] Additionally, comprehensive treatment measures, including rehabilitation and psychological support, are offered to enhance the overall well-being of patients. This approach reflects a holistic strategy aimed at providing optimal care to individuals with TSC in China.

ENHANCING THE UTILITY OF TAND CHECKLIST

Since the introduction of the term "TAND" in 2012, research in this domain has made notable progress. The updated international TSC diagnostic criteria in 2012, along with surveillance and management recommendations, underscored the significance of addressing TAND in individuals, particularly children. The guidelines recommended the implementation of behavioral, intellectual, and neuropsychiatric assessments at crucial developmental stages, with the provision of comprehensive evaluations in adulthood when deemed necessary.[2] Chinese scholars have advocated for the use of objective assessment tools, such as scales, specifically tailored for patients with intellectual developmental disabilities. This proposal is grounded in an analysis of TSC literature published in China over the past 13 years.[30]

For Chinese individuals with TSC, the implementation of the TAND Checklist provides a comprehensive approach to evaluating potential manifestations across various domains. Following the assessment of TAND symptoms, engagement with relevant specialists is essential to initiate evidence-based interventions as necessary. Additionally, it is crucial for parents and caregivers to undergo education and training on TAND, ensuring their ability to recognize symptoms promptly and seek timely interventions. Throughout the diagnostic process, extending psychological and social support to families is paramount. This facilitates the acceptance of both the TSC and TAND diagnoses, fostering the development of coping strategies that contribute to the well-being of caregivers. Furthermore, the adoption of a standardized TAND Checklist has the potential to alleviate significant disparities in healthcare access and quality between urban and rural areas in China. This standardized approach not only enhances the consistency of care but also ensures that individuals with TSC, regardless of geographical location, receive equitable and timely interventions based on their TAND profiles.

Chinese pediatric researchers are encouraged to pursue the comprehensive collection of clinical data, encompassing information on seizures, intelligence, ASD, and genotypes. Large-scale cohort studies across multiple centers can significantly contribute to advancing our understanding of TSC in the Chinese pediatric population. Once translated and validated, the Checklist must be actively utilized in the research conducted among the Chinese TSC cohort. Additionally, qualitative research is deemed necessary to address existing gaps in TAND research. Given the global impact of the COVID-19 pandemic, there is an urgent need for digital solutions. It is recommended to integrate the TAND Checklist into smartphone applications, facilitating broader accessibility and efficient data collection. In 2022, Heunis et al.[31] introduced the new TAND Toolkit App. Once launched in China, it is poised to offer significant convenience to TSC patients, greatly aiding in the early identification and treatment of TAND. Establishing a global TAND alliance through networking is also advised, promoting collaboration and knowledge sharing among researchers, clinicians, and patients worldwide. This collaborative approach can potentially accelerate advancements in TAND research and improve outcomes for individuals affected by TSC on a global scale.[31]

CONCLUSIONS

In conclusion, the TAND Checklist, a user-friendly and cost-free screening questionnaire intended for completion by patients or their caregivers, stands as a valid screening tool for TAND in clinical settings. Its widespread use has been observed across various regions globally. The introduction of the TAND-SQ Checklist, further enhances its utility, as the questions within the TAND Checklist have been quantified.[31] This adaptation anticipates a more prominent role in both the screening and continuous monitoring of TAND-related disorders. With the translation of the TAND Checklist into Chinese, our aim is to extend its applicability in China. This initiative seeks to unveil previously undetected psychological, psychiatric, and behavioral issues associated with TSC patients in China. Ultimately, this endeavor is poised to contribute to the delivery of a more comprehensive medical service for individuals affected by TSC in the Chinese population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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