Psychiatr. Pol. 2023; 57(4): 823–842
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/146265

Tuberous sclerosis complex-associated neuropsychiatric disorders

Anna B. Marcinkowska[1,2], Agnieszka Tarasewicz[3], Sergiusz Jóźwiak[4], Alicja Dębska-Ślizień[3], Edyta Szurowska[2]

[1] Applied Cognitive Neuroscience Lab, Department of Human Physiology, Medical University of Gdansk

[2] 2nd Department of Radiology, Medical University of Gdansk

[3] Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdansk

[4] Department of Child Neurology, Medical University of Warsaw

Summary

The aim of the study was to provide a state-of-the-art review with regard to neuropsychiatric disorders associated with tuberous sclerosis complex (TSC). TSC is a rare genetic disease classified as a phacomatosis. Due to the wide spectrum of clinical symptoms of the disease, many cases remain undiagnosed. The vast majority of people with a mutation in the *TSC1* or *TSC2* genes develop some of the neuropsychiatric symptoms during their lifetime. Diagnostic criteria, neuroanatomical pathology and pathophysiology of psychiatric, neuropsychological, developmental and psychosocial symptoms present in TSC are described. The specificity of epilepsy in TSC and its role in neuropsychiatric and neuropsychological development are presented. All levels (intellectual, developmental, behavioral, psychiatric, school, neuropsychological and psychosocial) of tuberous sclerosis complex-associated neuropsychiatric disorders (TAND) are discussed in detail. The TAND Checklist – a tool for assessing all potentially disturbed aspects of functioning – was presented. The importance of proper diagnosis of neuropsychiatric disorders and multidisciplinary patient care was emphasized.

Key words: tuberous sclerosis complex, tuberous sclerosis complex-associated neuropsychiatric disorders

Introduction

Tuberous sclerosis complex (TSC), also known as Bourneville-Pringle syndrome, is a genetic disease classified as a phacomatosis. It is associated with hamartoma-type benign tumors within the kidneys, heart, eyes, lungs, skin and brain [1]. The incidence

of TSC is approximately 1 case per 6,000 live births [2]. Tuberous sclerosis complex is inherited in an autosomal dominant manner, wherein about 66% of cases are new mutations, and only one third is inherited [3]. Due to the wide spectrum of clinical symptoms of the disease, many of the cases remain undiagnosed [4]. The clinical picture varies considerably between individuals, even within one family. This is the cause of great difficulties in the diagnosis of TSC [5]. The diagnostic criteria of TSC are presented in Table 1. Tuberous sclerosis is a chronic disease, treatment lasts many years, and many individuals require the support of other people in their daily life.

Table 1. **Diagnostic criteria for tuberous sclerosis (TSC) according to the International Tuberous Sclerosis Complex Consensus Group**

A. Genetic diagnostic criteria The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment. Note that 10% to 15% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.
B. Clinical diagnostic criteria – Major features 1. Hypomelanotic macules (≥3, at least 5-mm diameter) 2. Facial angiofibromas (≥3) or fibrous cephalic plaque 3. Ungual fibromas (≥2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias (includes tubers and cerebral white matter radial migration lines) 7. Subependymal nodules (SEN) 8. Subependymal giant cell astrocytoma (SEGA) 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM) 11. Angiomyolipomas (AMLs) (≥2, in various organs – kidneys, liver); combination of LAM and AMLs without other features of TSC does not meet the criteria of a definite diagnosis.
C. Clinical diagnostic criteria – Minor features 1. “Confetti” skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (≥2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas.
Definite diagnosis: confirmation of pathogenic mutation in the *TSC1* or *TSC*2 genes; two major features or one major feature with ≥ 2 minor features. Possible diagnosis: either one major feature or ≥2 minor features.

Tuberous sclerosis-associated neuropsychiatric disorders (TAND) are the most common and still insufficiently studied conditions. Despite the high interest in TSC research over the past two decades, there are still gaps in the full understanding of the functioning of individuals with TSC and the underlying neuropathophysiological processes. Previous studies indicate that the main risk factors for the development of neuropsychiatric disorders in TSC are the presence of infantile spasms in early childhood, drug-resistant epilepsy and mutations in the *TSC2* gene. Despite all the links discovered so far, the relationship between TAND and the neuroanatomical features of TSC is not well understood, and the disorders remain insufficiently diagnosed and treated.

Central nervous system abnormalities

TSC is a disease in which cell differentiation, proliferation and migration are disturbed in the early stages of development [6]. The lesions present in the brains of patients with TSC show typical histopathological features, including altered regional architecture, abnormal cellular morphology, and an excessive number of astrocytes. Neuronal abnormalities occur in 80-95% of individuals with TSC and include cortical and subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter radial migration lines. The constellations of neuroanatomical abnormalities may differ from one patient to another. From a minority of patients who do not have neuronal malformations, to a majority with both, cortico-subcortical dysplasias and subependymal nodules [7].

Cortical and subcortical tubers can occur throughout the brain and can be described as areas of cortical disorganization in the form of poorly myelinated hamartias. Most often they include the cerebral cortex and the adjacent white matter. These changes are often numerous, varying in size and location. The number of cortico-subcortical tumors varies in individuals from zero to more than 40, and their size ranges from millimeters to several centimeters [7]. Histologically, cortico-subcortical tubers have a neuronal and glial structure with the presence of dysplastic cells [8].

Subependymal nodules (SEN) are hamartomas that usually appear along the walls of the lateral ventricles. They are present in approximately 90% of patients, often numerous and generally small (1 cm or less) and most of them calcify. Multiple subependymal nodules with a typical location are considered by some authors to be pathognomonic for tuberous sclerosis complex. SEN usually do not cause significant clinical symptoms over a long follow-up period. There was also no significant correlation between the number of subependymal nodules and the severity of epilepsy or psychomotor delay [9].

Most of the SENs calcify, but some of them can develop into subependymal giant cell astrocytoma (SEGA) [9]. SEGA occurs in a minority (6-25%) of individuals with TSC, but represents an important risk of worsening a patient's condition and potential cause of death. Histologically, SEGA and SEN are identical [10], distinguished by their

location (SEGA – in the head of the caudate nucleus, in the vicinity of the interventricular foramen of Monro) and a tendency to rapid growth. In magnetic resonance imaging (MRI), SEGA can capture gadolinium contrast [7]. The greatest risk of SEGA emerging is in the first two decades of life. This type of tumor, invading into the lateral ventricles of the brain near the foramen of Monro and obstructing the flow of cerebrospinal fluid, may lead to gradual development of hydrocephalus and symptoms of increased intracranial pressure. As a consequence, patients may develop clinical symptoms in the form of altered mental and behavioral state, severe headache and loss of vision, stasis at the ocular fundus, vomiting, and coma, leading to the patient's death. These tumors are statistically more common in patients with *TSC2* gene mutations [11].

White matter abnormalities, which appear as sporadic radial migration lines (RML), extend from the lateral ventricles towards the cortex. They are present in approximately 80% of patients and reflect heterotropic neuronal and glial elements that have been arrested during migration. In MRI images, they have signal similar to cortical tubers (low signal on T1-weighted images and elevated signal on T2-weighted images). As in the case of cortico-subcortical tubers, RMLs are best visualized by the FLAIR sequence and are rarely enhanced by contrast agents [12]. There is also clear evidence that abnormal myelination in the subcortical white matter occurs in patients with TSC [13]. Studies about brain white matter have shown that the tumors and the surrounding white matter show cortical lamination disruption, the presence of dysplastic neurons and giant cells, as well as hypomyelination [14].

Epilepsy and infantile spasms

Clinical manifestations of epilepsy, psychomotor delay, behavioral disorders and autism spectrum disorders (ASD) are the result of structural changes in the brain. The most common neurological symptom in patients with TSC is epilepsy. It occurs in about 70-90% of patients [15, 16]. Seizures can be focal, multifocal, infantile spasms, or a combination of these or other types of seizures. Because of these early neurological manifestations, tuberous sclerosis complex is sometimes classified as a genetic neurodevelopmental disorder [17]. The incidence of infantile spasms in TSC is extremely high (up to 30%) [15]. In approximately 5% of children with tuberous sclerosis complex, seizures persist or develop after 2 years of age [18]. Seizures in individuals with tuberous sclerosis complex are very often numerous and respond poorly to treatment. The epileptic focus in people with TSC may change its localization. Different areas of the brain can be epileptogenic foci at different times, which significantly complicates the attempts of surgical treatment of epilepsy. In longitudinal studies, the morphology of seizures changed in more than half of the patients. The deficiency of GABA-ergic interneurons explains the early onset and severe course of TSC-related seizures. Consequently, the GABA transaminase inhibitor – vigabatrin in the treatment of epilepsy in patients with tuberous sclerosis complex is effective in approximately 95% of patients [19]. Other anti-epileptic drugs (AEDs) are less effective in TSC. Successful therapy of

epilepsy remains the most important aspect in preventing the development of epileptic encephalopathy. In some cases, non-pharmacological methods such as neurosurgery or a vagus nerve stimulator are used.

A number of factors correlating with the results of intelligence quotient (IQ) tests in TSC were investigated. The following are associated with a greater risk of developing more severe forms of intellectual disability: early onset and drug resistance of epilepsy, mutation of the *TSC2* gene, and greater number and specific location of cortical tubers [2]. Other factors associated with a higher risk of intellectual disability include poor seizure control and the need to use more AEDs [28, 29]. Epilepsy in TSC is also associated with autism spectrum disorders and attention-deficit hyperactivity disorder (ADHD), but not with anxiety and depression [21, 22]. Słowińska and colleagues [23] have shown that early diagnosis of TSC, before the onset of infantile spasms and the introduction of treatment, has fundamental importance for the prevention of delays in mental and cognitive development. This way of therapy is currently used in many health centers around the world. The authors considered MRI of the head, skin examination and echocardiography to be the most useful clinical tests for the early diagnosis of TSC, which in the first months of a child's life should be based mainly on clinical symptoms [23]. The literature also describes cases of patients with TSC who had a history of infantile spasms, yet developed a normal level of intelligence [24].

Jóźwiak et al. [25] showed that videoEEG testing from the neonatal period to the age of two allows for the identification of patients at high risk of developing epilepsy. The introduction of preventive antiepileptic treatment in these children makes it possible to limit psychomotor delay [23]. These studies have been confirmed by the results of the EPISTOP project under the 7th Framework Program of the European Union [16]. Currently, this method of treatment is used in over 50% of TSC centers worldwide [23].

Etiology of TSC-associated neuropsychiatric disorders

The above-described changes in the central nervous system of individuals with tuberous sclerosis complex may cause seizures, intellectual disability, cognitive deficits and psychiatric disorders [26]. The most common psychiatric conditions include: autism spectrum disorders, intellectual disability, depression and anxiety disorders, and neuropsychological disorders [27]. According to the literature, the greatest importance in the pathogenesis of neuropsychiatric symptoms is attributed to epileptic seizures, as well as the volume and location of the cortical and subcortical tubers [27]. Some studies also emphasize the significant influence of white matter changes (hypomyelination, reduced integrity) in the development of neuropsychological symptoms and other neuropsychiatric symptoms [28]. It is known for certain that the presence of infantile spasms, drug-resistant epilepsy and *TSC2* gene mutations are factors of increased risk of developing cognitive disorders and autism spectrum disorders in TSC [26-28].

The largest, multidisciplinary study of tuberous sclerosis complex to date, the TuberOus SClerosis registry to increase disease Awareness (TOSCA), noted that

TSC2 mutations were associated with a significantly higher incidence of behavioral disturbances than *TSC1* mutations. On a psychiatric level, autism spectrum disorders were seen much more frequently in participants with *TSC2* mutations than with *TSC1* mutations. The prevalence of ADHD, anxiety and depression did not differ significantly between genotypes, but observation showed that all three were more frequently present in the *TSC1* group than in the *TSC2* group. There was a significant difference between *TSC1* and *TSC2* groups for IQ levels (lower for *TSC2*). Academic / school difficulties were more common in people with the *TSC2* mutation than in *TSC1*. More people with the *TSC2* mutation had neuropsychological test scores below the 5th percentile compared to those with the *TSC1* mutation. In contrast, the results of IQ, academic abilities, and behavioral, mental and neuropsychological disorders of people with no mutation identified (NMI) were between those of the groups with *TSC1* and *TSC2* mutations. It should also be noted that the NMI group includes individuals with mosaicism, who may have fewer symptoms than people with the *TSC1* mutation [29].

The presence of cortical tubers has been suggested as a possible variable explaining the occurrence of autism spectrum disorders and specific cognitive deficits in TSC [30]. However, further studies showed that even in patients with a normal IQ, there are common structural abnormalities in the brain, especially in the gray and white matter [31]. There are also cases of patients in whom, despite numerous cortical tubers, no symptoms of autism spectrum disorders are found. This suggests that cortical tubers or seizures do not explain all neuropsychiatric symptoms in TSC.

Researchers emphasize the presence of epilepsy or the history of seizures, not just the number of tubers, as a risk factor for the development of cognitive disorders [26]. However, it seems that the scope and individual variability of neuropsychological features are so unique and varied due to the influence of many factors (including epilepsy history, seizure onset, and age). Arulrajah and colleagues [31] in a study of 23 TSC patients (children, adolescents, and young adults) performed a white matter integrity assessment using diffusion-weighted MRI. Higher rates of the apparent diffusion coefficient (ADC) in the normal appearing white matter (without tuber changes) suggest delayed or disturbed myelination. According to the authors, it could explain the global cognitive deficits in this group of patients. Although the results of cognitive tests may be partially related to the presence of cortico-subcortical tubers, many patients without a significant burden of brain tumors have neuropsychological disorders, while patients with a large number of tubers may have only mild cognitive decline [26, 33].

Some researchers suggest that TSC should be considered as a disorder of neuronal migration, not simply as a complex of isolated lesions in the central nervous system [33]. Such thinking is justified because the results of histological examinations in TSC show features characteristic of disorders of neuronal migration. Disruptions in the processes of cell differentiation and migration, already present in the embryonic period, are responsible for the occurrence of neuropathology in TSC [3]. These disturbed processes, including incorrect migration and organization of nerve cells, lead to anomalies in the structural and functional connections between individual brain structures [34].

Although the relationship between organic lesions (i.e., cortical and subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter radiant lines), neurological abnormalities and the neuropsychiatric phenotype remains unclear, there is some evidence suggesting that the severity of white matter abnormalities may be associated with a more severe phenotype of TAND symptoms [28].

Clearly, TSC has complex and multifactorial pathophysiology of neuropsychiatric disorders, and it is important to remember that none of the factors, i.e., the type of mutation, structural abnormalities or seizures, is necessary or sufficient to predict individual symptoms of TAND [35–37].

Tuberous sclerosis complex-associated neuropsychiatric disorders

People with TSC have a much greater risk of developing some forms of psychopathology. The most common neuropsychiatric symptoms include: autism spectrum disorders, intellectual disability, depression and anxiety disorders, as well as cognitive dysfunction [27]. Together, these aspects can be described as TSC-related neuropsychiatric disorders. The vast majority of people with a mutation in the *TSC1* or *TSC2* genes develop some of these neuropsychiatric symptoms during their lifetime [38].

The symptoms of TAND can be divided into six subgroups / levels that can occur independently and should therefore be assessed accordingly. Individual symptoms that may appear have been divided into subgroups, i.e., developmental, behavioral and affective disorders, neuropsychological deficits, psychiatric disorders, social functioning problems, as well as intellectual disability and school difficulties [38]. The symptoms occurring in individual TAND subgroups are presented in Table 2.

(1) Intellectual disability

Approximately 40-60% of TSC patients are affected by various degrees of intellectual disability. Studies have shown a higher percentage (50-64%) of intellectual disability (IQ <70) in people with *TSC2* mutation [20, 39, 40]. In the TOSCA cohort study, 44.4% of participants were within the normal range of intellectual abilities, while mild, moderate, severe and profound disabilities were reported in 28.1%, 15.1%, 9.3% and 3.1% of patients, respectively. Other studies confirm the great variability of intellectual abilities in TSC. In an epidemiological trial of 108 TSC patients, Joinson et al. [40] used standardized intelligence tests to compare people diagnosed with tuberous sclerosis with their healthy siblings. Approximately 40-50% of patients have an IQ similar to the general population and within the normal range, but the mean IQ of individuals with tuberous sclerosis complex appears to be slightly shifted downwards [40].

Consistent observations in the TSC literature indicate that the range of intellectual abilities related to TSC is very wide – from profound intellectual disability to high intelligence quotient. This is an important observation that is useful in clinical practice. People with an IQ score in the range of severe or profound intellectual disability are

often unable to proceed with IQ testing with "formal" standardized tests that allow for an accurate assessment of intellectual abilities. In this group of patients with TSC, IQ scores are usually estimated by characterizing the functional abilities based on a structured interview with the parent or guardian and observation of the patient. By comparison, more intellectually capable individuals are able to participate in a series of standardized tests to assess their intellectual abilities to extract their strengths and weaknesses. Furthermore, children with the most severe intellectual disabilities are often characterized by an early developmental stoppage. This means that they do not show an increase in intellectual abilities with age. In contrast, most children with tuberous sclerosis complex will progress through their intellectual development, reaching milestones and progressing through their developmental stages over time. In individual with TSC often intellectual development will be slower, less harmonious, and at a lower level than that of their healthy siblings [39, 40].

(2) Neurodevelopmental disorders

Children with tuberous sclerosis complex are at high risk of developing neurodevelopmental disorders. The prevalence of autism spectrum disorders in TSC varies greatly depending on the studies, but on average it is estimated to be from 40% to 50% [35, 38]. From a phenomenological point of view, children with TSC-related autism spectrum disorders do not seem to differ from children with idiopathic autism [26, 41]. Recognizing symptoms early and undertaking prompt and appropriate, evidence-based interventions are crucial. However, it is recommended for physicians to use comprehensive assessments and interventions for autism spectrum disorders for children with TSC in the same way as for children without TSC. The prevalence of autism spectrum disorders varies significantly within the patient population depending on the IQ, and the 6% prevalence of ASD among children with TSC with an IQ within the normal range is still a 10-fold overrepresentation compared to the general population [42].

Another neurodevelopmental disorder is ADHD, which occurs in approximately 30-50% of children with TSC [43, 44]. As in the case of autism, the diagnosis of ADHD is 10 times overrepresented among children with normal IQ, over 30%. However, in the general population of peers matched in terms of sex, age and IQ without TSC, it is approximately 3-5% [45]. To date, no studies have been conducted on the treatment of ADHD in TSC. Therefore, also in this case, clinicians are advised to use the same evidence-based treatment and ADHD therapy as in people without TSC [46]. There is a theoretical risk that stimulant drugs (such as methylphenidate) may lower the seizure threshold, but there is no evidence in patients with TSC to support this hypothesis. Stimulants are recommended to be used when clinically indicated, according to the same guidelines, but bearing in mind the possible consequences and with caution in relation to any potential risks.

(3) Behavioral problems

Behavioral difficulties are defined as symptoms or problems identified in everyday life by parents, caregivers, teachers, or others from the social environment. The most frequently observed in TSC are outbreaks of aggression, severe and persistent tantrums, hyperactivity, restlessness, impulsiveness and poor concentration, self-harm, anxiety and depressed mood [4, 47-49]. Over 50% of children with TSC may show some behavioral difficulties during development. Up to 60-70% of children with TSC and intellectual disability may develop one or more behavioral problems, while only about 20-30% of children with TSC and normal intellectual abilities will have such difficulties [50-52].

The TOSCA study results indicate that 36% of individuals with TSC reported at least one behavioral problem. At the same time in this study: hyperactivity, impulsiveness and difficulties with sleep are the most common, typical behavioral problems, affecting about 20% of people with TSC [29]. Anxiety, mood swings and severe aggression were also relatively common, followed by depressed mood, self-harm and obsessive behavior [29, 47]. In previous studies, the incidence of individual behavioral symptoms was much more frequent than in the TOSCA registry, but it has a significantly larger number of participants, with greater variation in intellectual abilities and wider range of age of subjects. This diversity may reflect the actual TSC patient population. It may also result from the increased awareness of the disease, as well as the percentage of patients who received help [29, 53].

Unlike most behavioral problems in TSC, those related to low mood and anxiety do not appear to differ between people with and without intellectual disabilities [51]. Therefore, all caregivers and specialists should be cautious to the possibility of such difficulties and implement proactive therapeutic strategies when they occur. In less capable and more dependent individuals, communication difficulties may preclude self-reporting of specific symptoms, which is why appropriate awareness and diagnosis of behavioral problems related to mood is extremely important.

Patient reports of sleep problems in TSC vary widely and are likely to depend on individual factors. Caregiver reports of problems with awaking at night [54] are supported by polysomnographic findings in children with TSC, which showed shorter sleep durations. Other types of sleep problems include daytime sleepiness, parasomnias, and longer sleep times [54].

The identification and recognition of behavioral problems should lead to the determination of the need for a psychiatric intervention to diagnose behavioral disorders and to identify possible causes of behavioral difficulties, and to implement appropriate therapeutic strategies.

(4) Psychiatric disorders

There has been a significant increase in research into psychiatric disorders in people with TSC over the past two decades. Depressive and anxiety disorders occur most frequently in adults with TSC (30-60% of all patients). Mowrey et al. [55], in their research on TAND, indicate that among the studied group of TSC patients, the results of the depression and anxiety questionnaires are statistically significantly higher in people with a greater self-reported subjective level of disease severity, as well as in individuals with intellectual disability. Other psychiatric disorders include bipolar disorder, schizophrenia, panic attacks, agoraphobia, specific phobias, social phobia, and obsessive-compulsive disorder [38, 47]. The survey documented a high percentage of anxiety symptoms (40%), depressed mood (23%) and aggressive behavior (58%) also in children and adolescents with TSC [40]. In a study of adults with TSC who used structured diagnostic interviews (42 people with epilepsy; 25 with IQ <70), less than half (40%) had at least one mental disorder [4]. The most common psychiatric diagnoses in this group of patients are depression, alcoholism and anxiety disorders [2].

In the TOSCA registry, anxiety disorders were observed in 9.7% of patients, depressive disorders in 6.1% and "other" mental disorders in 8.4% of participants. The median age at diagnosis of mental disorders was 13.5 years for anxiety disorders, 21 years for depressive disorders and 11 years for "other" mental disorders. Importantly, the TOSCA registry identified infants and children with anxiety disorders, emphasizing the need for a comprehensive assessment at all key stages of development [47]. Psychotic disorders (including schizophrenia) are very rarely observed in patients, largely consistent with the incidence in the general population where the schizophrenia rate is ~ 1%. In the TOSCA study, hallucinations (1.5%) and psychoses (2.3%) were observed to a small extent [29]. So far, no systematic research has been conducted on obsessive-compulsive disorder in TSC. However, obsessive and repetitive behavior is very common in connection with autism spectrum disorder in TSC. Therefore, clinicians should always consider an appropriate diagnosis whenever dealing with children, adolescents or adults with TSC who display obsessive traits.

Despite the high rate of anxiety and depressive symptoms, as indicated by behavioral problems, relatively little research has been conducted to date on anxiety and depressive disorders in TSC. Lewis et al. [56] emphasized the high percentage of anxiety symptoms in adults with intellectual disabilities with TSC (56%) and indicated that none of them received a comprehensive assessment or treatment.

(5) Scholastic problems

Learning disorders are often referred to as learning difficulties, school difficulties, academic difficulties, or concern a specific diagnosis, such as dyslexia or dyscalculia. Data on patients with TSC show that school difficulties affect approximately 30% of school-age patients with a level of intellectual development within the normal range

[57]. Jambaqué and colleagues [58] reported a high rate of dyscalculia (a learning disorder in mathematics), while de Vries and Prather [52] noted that 36% of school-age children with normal intellectual capacity with TSC were at high risk of developing reading, writing and math difficulties. Moreover, it was found that disturbances in math skills were common, especially in children with individuals with TSC who were also diagnosed with ADHD [26]. In addition to specific learning disabilities, Prather and de Vries [4] noted that children with TSC are also at high risk for secondary school difficulties; this includes issues such as refusal to leave school, fear of going to school, social skills deficits and low self-esteem. In the TOSCA study [29], participants were asked if they had ever had difficulties with their academic performance and how many of them had been diagnosed with a learning disability. School difficulties in terms of mathematics, reading, writing, or spelling were reported in 58.6% of participants [47]. It is striking that only 48.9% of them have ever received a formal assessment of these difficulties. This clearly highlights the great need for further research at this important TAND level.

(6) Neuropsychological disorders

The group of neuropsychological disorders includes problems with shifting attention, maintaining attention, memory recall, spatial memory, and performing several activities simultaneously. In the TOSCA study, neuropsychological abilities were formally assessed in 41.6% of participants, and neuropsychological deficits (performance <5th percentile) were identified in 55.7% of the assessed [29]. Jambaqué et al. [58] examined the intellectual and neuropsychological skills of 23 children with tuberous sclerosis complex. Among the children (aged 3-16 years) with normal intellectual abilities, the authors found neuropsychological deficits such as dyspraxia, speech delay, visual-spatial disorders, memory impairment and dyscalculia. In a group of 42 children, Hunt [59] observed the same deficits. Among 10 children with intellectual disabilities without autism, the authors observed linguistic and visual-spatial problems [59]. Prather and de Vries [4] assessed 43 children and adolescents. In the study group with normal IQ, 19% had spatial skills deficits, 24% language-related deficits, 38% impaired memory, 54% complex visual-spatial deficits, and 66% difficulties in processing and executive control (disturbances of planning, verbal fluency, sequencing, monitoring and error correction) [4]. De Vries and colleagues [42] studied the attention functions of children with TSC and their healthy siblings. The results showed that children and adolescents with tuberous sclerosis complex performed significantly worse than their siblings in tests of selectivity and shifting of attention, as well as in tests requiring performing two tasks simultaneously.

In 1999, Harrison and colleagues [60] described specific deficits in executive function in a group of seven adults with TSC without intellectual disabilities. A significant number of specific neuropsychological deficits, such as long-term memory and working memory disorders or impaired executive functioning have been noted. Ridler

and colleagues [61] measured various aspects of verbal and visual-spatial memory in patients with TSC and compared their results with a healthy control group. The most significant differences between groups concerned the functions of verbal working memory, visual-spatial working memory and short-term memory related to linguistic material. Tierney and colleagues [62] conducted a systematic study of 22 adults with TSC without intellectual disabilities. The results showed disturbances in spatial working memory and deficits in the planning process in people with TSC.

(7) Psychosocial problems

Psychosocial difficulties encompass self-esteem and self-effectiveness, the level of parental stress, and problems in relationships. For people with TSC, lowered self-esteem and self-efficacy, as well as dependence are often a concern [26].

In a qualitative study in the Italian population of TSC patients' caregiver experiences, in detailed interviews and online conversations with the parents of 48 TSC patients (1-22 years old), the authors identified three main problems. The most often mentioned problems included: (1) the "lack of control" associated with TSC, described by caregivers as incomprehensible and unpredictable, making it very difficult to plan for the future, (2) "coping with the disease", its acceptance, anger and fear, (3) "unmet needs" including support towards social inclusion, psychological support for parents / caregivers, and awareness-raising in the community [63].

Rentz et al.'s [64] published results of an online survey of 294 parents / guardians and 82 people with TSC, mostly from the United States of America, clearly showed high importance of neuropsychiatric symptoms for family systems. The survey covered all aspects of TSC, including epilepsy and changes of the skin and kidneys, yet parents / caregivers and subjects with TSC rated TAND as the second largest problem and the second highest priority for future research after epilepsy in children and kidney problems in adults.

All TSC patients, due to various challenges posed by the disease, have a reduced quality of life (QoL). The QoL of children with TSC is lower than that of children suffering from asthma, diabetes, cancer or inflammatory bowel disease [65]. In adult patients with TSC, the severity of epilepsy is one of the main factors that significantly reduces the quality of life [66]. The psychosocial problems of patients and their relatives are one area that still requires a lot of research, which translates into the help they need.

Table 2. **TAND symptoms across all domains [47]**

Level	Symptom	Description
Behavioral	aggression tantrums anxiety self-harm attention disorders hyperactivity impulsiveness delay in speech development insufficient eye contact stereotypical behavior sleep disturbance	The level includes all observed behaviors. It is usually assessed by direct observation.
Psychiatric	autism spectrum disorders ADHD depression anxiety disorders schizophrenia	The level determines the psychiatric diagnosis according to current classification systems such as DSM-5 or ICD-11. At this level, the clinician determines whether the observed behaviors meet the criteria specific to a mental disorder.
Intellectual	intellectual disability inharmonious intellectual profile	This level determines the intellectual abilities according to the measures of standardized IQ tests.
Scholastic problems	writing reading spelling mathematics	This level refers to specific learning disabilities (as defined in DSM-5) related to school achievement.
Neuropsychological	long-term memory impairment working memory impairment attention deficits executive function impairment	This level explores specific cognitive functions through the use of standardized neuropsychological methods.
Psychosocial	low self-esteem, independence and self-sufficiency parental stress relationship difficulties high family stress stigma and social isolation	Level explores the psychological and social impact of TSC in terms of self, family, and social relationships.

DSM-5 – *Diagnostic and Statistical Manual of Mental Disorders* 5th edition; ICD-11 – International Classification of Diseases 11th Revision

TAND Checklist

The tool that enables the assessment of all neuropsychiatric symptoms in TSC and allows for the standardization of the assessment system is the TAND Checklist developed by Petrus de Vries et al. [67]. The Polish adaptation was made by Sergiusz Jóźwiak and Agnieszka Maryniak [68]. The structure of the questionnaire allows the examiner by marking items in a logical order to notice the existing problem and possibly deepen it through additional specialist diagnostics. The detailed structure of the TAND Checklist is presented in Table 3. The questionnaire consists of 12 groups of questions divided into individual levels / subgroups of neuropsychiatric disorders; it can be completed with the person with TSC or their parent / guardian. A validation study found that 93% of participants reported four or more life difficulties in the TAND Checklist [67]. Toldo and colleagues [49] in a study using the TAND Checklist, which enrolled 32 patients with TSC (age range 1-19 years), found that 88% of the subjects had at least one symptom of TAND, and 78% of patients had more than four. However, the authors were not able to define a constant and specific neuropsychiatric profile in individual groups of patients. Higher severity of TAND symptoms prevailed in patients with de novo *TSC2* mutations, large volume of brain tubers and more severe clinical features in terms of neurological symptoms and epilepsy. The authors emphasized that the Tuberous Sclerosis-Related Neuropsychiatric Disorders Questionnaire is an effective screening tool and is helpful in identifying psychopathology and neuropsychiatric aspects in children and adolescents with TSC.

Table 3. **Structure of the TAND Checklist**

TANDChecklist	Neuropsychiatric domain
1. (a-g)	Development – milestones
2. (a-c)	Current functioning level
3. (a-s)	Behavioral and affective symptoms
4. (a-f)	Diagnosed psychiatric and neurodevelopmental disorders
5. (a-d)	Intellectual abilities
6. (a-d)	School difficulties
7. (a-f)	Cognitive functioning
8. (a-c)	Psychosocial functioning
9.	Subjective rating of the impact of TAND symptoms on life
10.	Priority issues
11.	Additional issues
12.	Rating of the severity of TAND symptoms according to the examiner

Conclusions

Tuberous sclerosis complex has been the subject of more intensive research for about three decades. Nevertheless, the knowledge of neuropsychiatric disorders is still insufficient to define the functioning profile of patients. Given the variety of symptoms and variability over time, systematic evaluation and a tailored action plan are essential. Different constellations of neuropsychiatric symptoms from seven groups are noticeable in almost all patients: intellectual disability, neurodevelopmental disorders, behavioral problems, psychiatric disorders, school difficulties and neuropsychological impairments. Many of these issues are overlooked during the diagnostic process. Correct diagnosis is particularly difficult due to the multiplicity of psychopathologies influencing each other. It is necessary to systematically diagnose all risk areas and provide patients with the necessary psychological and psychiatric care, as well as introduce effective therapies for individual disorders. Although TAND disorders concern the vast majority of patients, only less than 20% of patients with TSC are properly diagnosed and receive the necessary help [27, 69].

During a neuropsychiatric panel at the 2012 Tuberous Sclerosis Complex International Consensus Conference recommendations were made regarding the diagnosis and treatment of TSC, indicating that each patient with tuberous sclerosis complex should be assessed at least annually for the presence and severity of TAND symptoms [70, 71]. Due to the complex, multi-system nature of the disease, a multidisciplinary approach to TSC treatment is advisable [6, 19–21], which should include specialists such as a neurologist, nephrologist, geneticist, psychiatrist, psychologist, urologist, pulmonologist, ophthalmologist, cardiologist, dermatologist and neurosurgeon. A multidisciplinary therapeutic plan should be established for each patient based on his individual needs and in consultation with his family [71-73].

References

1. Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. *Tuberous sclerosis complex.* Nat. Rev. Dis. Prim. 2016; 2: 16035.
2. Raznahan A, Joinson C, O'Callaghan F, Osborne JP, Bolton PF. *Psychopathology in tuberous sclerosis: An overview and findings in a population-based sample of adults with tuberous sclerosis.* J. Intellect. Disabil. Res. 2006; 50(8): 561–569.
3. Zaroff CM, Isaacs K. *Neurocutaneous syndromes: Behavioral features.* Epilepsy Behav. 2005; 7(2): 133–142.
4. Prather P, Vries de PJ. *Behavioral and cognitive aspects of tuberous sclerosis complex.* J. Child Neurol. 2004; 19(9): 666–674.
5. Lyczkowski DA, Conant KD, Pulsifer MB, Jarrett DY, Grant PE, Kwiatkowski DJ et al. *Intrafamilial phenotypic variability in tuberous sclerosis complex.* J. Child Neurol. 2007; 22(12): 1348–1355.

6. Bade-White PA, Obrzut JE, Randall PP. *Neuropsychological aspects of pervasive developmental and autism spectrum disorders.* In: Handbook of clinical child neuropsychology. Boston: Springer US; 2009. pp. 765–781.
7. Gupta P, Mukund A, Chandrashekhara SH, Gupta AK. *Tuberous sclerosis complex: Imaging findings.* Indian J. Pediatr. 2012; 79(1): 127–129.
8. Scholl T, Mühlebner A, Ricken G, Gruber V, Fabing A, Samueli S et al. *Impaired oligodendroglial turnover is associated with myelin pathology in focal cortical dysplasia and tuberous sclerosis complex.* Brain Pathol. 2017; 27(6): 770–780.
9. Firat AK, Karakaş HM, Erdem G, Yakinci C, Biçak U. *Diffusion weighted MR findings of brain involvement in tuberous sclerosis.* Diagnostic Interv. Radiol. 2006; 12(2): 57–60.
10. Cotter JA. *An update on the central nervous system manifestations of tuberous sclerosis complex.* Acta Neuropathol. 2020; 139(4): 613–624.
11. Jansen AC, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P et al. *Clinical characteristics of subependymal giant cell astrocytoma in tuberous sclerosis complex.* Front. Neurol. 2019; 10: 705.
12. Braffman BH, Bilaniuk LT, Naidich TP, Altman NR, Post MJD, Quencer RM et al. *MR imaging of tuberous sclerosis: Pathogenesis of this phakomatosis, use of gadopentetate dimeglumine, and literature review.* Radiology. 1992; 183(1): 227–238.
13. Luat A, Makki M, Chugani H. *Neuroimaging in tuberous sclerosis complex.* Curr. Opin. Neurol. 2007; 20(2): 142–150.
14. Mühlebner A, Iyer AM, Van Scheppingen J, Anink JJ, Jansen FE, Veersema TJ et al. *Specific pattern of maturation and differentiation in the formation of cortical tubers in tuberous sclerosis complex (TSC): Evidence from layer-specific marker expression.* J. Neurodev. Disord. 2016; 8(1): 1–14.
15. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. *The natural history of epilepsy in tuberous sclerosis complex.* Epilepsia. 2010; 51(7): 1236–1241.
16. Karnebeek van CDM, Bowden K, Berry-Kravis E. *Treatment of neurogenetic developmental conditions: From 2016 into the future.* Pediatr. Neurol. 2016; 65: 1–13.
17. Hsieh DT, Jennesson MM, Thiele EA. *Epileptic spasms in tuberous sclerosis complex.* Epilepsy Res. 2013; 106(1–2): 200–210.
18. Curatolo P, Verdecchia M, Bombardieri R. *Vigabatrin for tuberous sclerosis complex.* Brain Dev. 2001; 23(7): 649–653.
19. Vries de PJ. *Neurodevelopmental, psychiatric and cognitive aspects of tuberous sclerosis complex.* In: *Tuberous sclerosis complex.* Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2010. pp. 229–267.
20. Jansen FE, Vincken KL, Algra A, Anbeek P, Braams O, Nellist M et al. *Cognitive impairment in tuberous sclerosis complex is a multifactorial condition.* Neurology 2008; 70(12): 916–923.
21. Eeghen van 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): 510–515.
22. Overwater IE, Verhaar BJH, Lingsma HF, Bindels-de Heus GCB, Ouweland van den AMW, Nellist M et al. *Interdependence of clinical factors predicting cognition in children with tuberous sclerosis complex.* J. Neurol. 2017; 264(1): 161–167.

23. Słowińska M, Jóźwiak S, Peron A, Borkowska J, Chmielewski D, Sadowski K et al. *Early diagnosis of tuberous sclerosis complex: A race against time. How to make the diagnosis before seizures?* Orphanet J. Rare Dis. 2018; 13(1): 1–10.

24. Gupta A, Bruyn de G, Tousseyn S, Krishnan B, Lagae L, Agarwal N et al. *Epilepsy and neurodevelopmental comorbidities in tuberous sclerosis complex: A natural history study.* Pediatr. Neurol. 2020; 106: 10–16.

25. Jóźwiak S, Kotulska K, Domańska-Pakieła D, Lojszczyk B, Syczewska M, Chmielewski D et al. *Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex.* Eur. J. Paediatr. Neurol. 2011; 15(5): 424-31.

26. Zaroff CM, Barr WB, Carlson C, LaJoie J, Madhavan D, Miles DK et al. *Mental retardation and relation to seizure and tuber burden in tuberous sclerosis complex.* Seizure. 2006; 15(7): 558–562.

27. Kingswood JC, D'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R et al.; TOSCA consortium and TOSCA investigators. *TuberOus SClerosis registry to increase disease Awareness (TOSCA) – Baseline data on 2093 patients.* Orphanet J. Rare Dis. 2017; 12(1): 2.

28. Shepherd CW, Houser OW, Gomez MR. *MR findings in tuberous sclerosis complex and correlation with seizure development and mental impairment.* AJNR Am. J. Neuroradiol. 1995; 16(1): 149–155.

29. Curatolo P, Bombardieri R, Jozwiak S. *Tuberous sclerosis.* Lancet 2008; 372(9639): 657–668.

30. Kaczorowska M, Jurkiewicz E, Domańska-Pakieła D, Syczewska M, Lojszczyk B, Chmielewski D et al. *Cerebral tuber count and its impact on mental outcome of patients with tuberous sclerosis complex.* Epilepsia 2011; 52(1): 22–27.

31. Arulrajah S, Ertan G, Jordan L, Tekes A, Khaykin E, Izbudak I et al. *Magnetic resonance imaging and diffusion-weighted imaging of normal-appearing white matter in children and young adults with tuberous sclerosis complex.* Neuroradiology 2009; 51(11): 781–786.

32. DiMario Jr FJ. *Brain abnormalities in tuberous sclerosis complex.* J. Child Neurol. 2004; 19(9): 650–657.

33. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. *A developmental and genetic classification for malformations of cortical development.* Neurology 2005; 65(12): 1873–1887.

34. Curatolo P, Napolioni V, Moavero R. *Autism spectrum disorders in tuberous sclerosis: Pathogenetic pathways and implications for treatment.* J. Child Neurol. 2010; 25(7): 873–880.

35. Vries de PJ, Howe CJ. *The tuberous sclerosis complex proteins – A GRIPP on cognition and neurodevelopment.* Trends Mol. Med. 2007; 13(8): 319–326.

36. Schneider M, Vries de PJ, Schönig K, Rößner V, Waltereit R. *mTOR inhibitor reverses autistic-like social deficit behaviours in adult rats with both Tsc2 haploinsufficiency and developmental status epilepticus.* Eur. Arch. Psychiatry Clin. Neurosci. 2017; 267(5): 455–463.

37. Curatolo P, Moavero R, Vries de PJ. *Neurological and neuropsychiatric aspects of tuberous sclerosis complex.* Lancet Neurol. 2015; 14(7): 733–745.

38. Bolton PF, Clifford M, Tye C, Maclean C, Humphrey A, Le Maréchal K et al. *Intellectual abilities in tuberous sclerosis complex: Risk factors and correlates from the Tuberous Sclerosis 2000 Study.* Psychol. Med. 2015; 45(11): 2321–2331.

39. Vries de 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(1): 16–24.

40. 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): 335–344.

41. Jeste SS, Varcin KJ, Hellemann GS, Gulsrud AC, Bhatt R, Kasari C et al. *Symptom profiles of autism spectrum disorder in tuberous sclerosis complex.* Neurology 2016; 87(8): 766–772.

42. Vries de PJ, Gardiner J, Bolton PF. *Neuropsychological attention deficits in tuberous sclerosis complex (TSC).* Am. J. Med. Genet. Part A. 2009; 149(3): 387–395.

43. D'Agati E, Moavero R, Cerminara C, Curatolo P. *Attention-deficit hyperactivity disorder (ADHD) and tuberous sclerosis complex.* J. Child Neurol. 2009; 24(10): 1282–1287.

44. Fombonne E. *Epidemiological surveys of autism and other pervasive developmental disorders: An update.* J. Autism Dev. Disord. 2003; 33(4): 365–382.

45. Szatmari P, Offord DR, Boyle MH. *Ontario child health study: Prevalence of attention deficit disorder with hyperactivity.* J. Child Psychol. Psychiatry 1989; 30(2): 219–223.

46. Pliszka S. *Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder.* J. Am. Acad. Child Adolesc. Psychiatry 2007; 46(7): 894–921.

47. Vries de 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.

48. Liu AJ, Staffaroni AM, Rojas-Martinez JC, Olney NT, Alquezar-Burillo C, Ljubenkov PA et al. *Association of cognitive and behavioral features between adults with tuberous sclerosis and frontotemporal dementia.* JAMA Neurol. 2020; 77(3): 358–366.

49. Toldo I, Brasson V, Miscioscia M, Pelizza MF, Manara R, Sartori S et al. *Tuberous sclerosis-associated neuropsychiatric disorders: A paediatric cohort study.* Dev. Med. Child Neurol. 2019; 61(2): 168–173.

50. Vries de P, Humphrey A, McCartney D, Prather P, Bolton P, Hunt A. *Consensus clinical guidelines for the assessment of cognitive and behavioural problems in tuberous sclerosis.* Eur. Child Adolesc. Psychiatry 2005; 14(4): 183–190.

51. Jambaqué I, Chiron C, Dumas C, Mumford J, Dulac O. *Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients.* Epilepsy Res. 2000; 38(2–3): 151–160.

52. Vries de PJ, Prather PA. *The tuberous sclerosis complex.* N. Engl. J. Med. 2007; 356(1): 92.

53. Annear NMP, Appleton RE, Bassi Z, Bhatt R, Bolton PF, Crawford P et al. *Tuberous sclerosis complex (TSC): Expert recommendations for provision of coordinated care.* Front. Neurol. 2019; 10: 1116.

54. Trickett J, Heald M, Oliver C, Richards C. *A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex.* J. Neurodev. Disord. 2018; 10(1): 9.

55. Mowrey KE, Ashfaq M, Pearson DA, Hashmi SS, Roberds SL, Farach LS et al. *The impact of psychiatric symptoms on tuberous sclerosis complex and utilization of mental health treatment.* Pediatr. Neurol. 2019; 91: 41–49.

56. Lewis JC, Thomas HV, Murphy KC, Sampson JR. *Genotype and psychological phenotype in tuberous sclerosis.* J. Med. Genet. 2004; 41(158): 203–207.

57. Curatolo P, Maria BL. *Tuberous sclerosis.* In: Handbook of Clinical Neurology, 1st ed. Vol. 111. Elsevier B.V.; 2013. pp. 323–331.

58. Jambaqué I, Cusmai R, Curatolo P, Cortesi F, Perrot C, Dulac O. *Neuropsychological aspects of tuberous sclerosis in relation to epilepsy and MRI findings.* Dev. Med. Child Neurol. 1991; 33(8): 698–705.

59. Hunt A. *Development, behaviour and seizures in 300 cases of tuberous sclerosis.* J. Intellect. Disabil. Res. 1993; 37(1): 41–51.

60. Harrison JE, O'Callaghan FJ, Hancock E, Osborne JP, Bolton PF. *Cognitive deficits in normally intelligent patients with tuberous sclerosis.* Am. J. Med. Genet. 1999; 88(6): 642–646.

61. Ridler K, Suckling J, Higgins N, de Vries P, Stephenson C, Bolton P et al. *Neuroanatomical correlates of memory deficits in tuberous sclerosis complex.* Cereb. Cortex 2007; 17(2): 261–271.

62. Tierney KM, McCartney DL, Serfontein JR, De Vries PJ. *Neuropsychological attention skills and related behaviours in adults with tuberous sclerosis complex.* Behav. Genet. 2011; 41(3): 437–444.

63. Graffigna G, Bosio C, Cecchini I. *Assisting a child with tuberous sclerosis complex (TSC): A qualitative deep analysis of parents' experience and caring needs.* BMJ Open 2013; 3(12): e003707.

64. Rentz AM, Skalicky AM, Liu Z, Wheless JW, Dunn DW, Frost MD et al. *Tuberous sclerosis complex: A survey of health care resource use and health burden.* Pediatr. Neurol. 2015; 52(4): 435–441.

65. Amin S, Mallick AA, Lux A, O'Callaghan F. *Quality of life in patients with tuberous sclerosis complex (TSC).* Eur. J. Paediatr. Neurol. 2019; 23(6): 801–807.

66. Tritton T, Bennett B, Brohan E, Grant L, Cooper A, Fladrowski C et al. *Health utilities and quality of life in individuals with tuberous sclerosis complex (TSC) who experience epileptic seizures: A web-based survey.* Epilepsy Behav. 2019; 92: 213–220.

67. Leclezio L, Jansen A, Whittemore VH, Vries de PJ. *Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist.* Pediatr. Neurol. 2015; 52(1): 16–24.

68. Siłuszyk A, Maryniak A, Jóźwiak S. *TAND Checklist – A new tool for assessment of neuropsychiatric disorders in tuberous sclerosis patients.* Child Neurol. 2018; 27(54): 59–63.

69. Vries de 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(1): 25–35.

70. Northrup H, Krueger DA. *Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.* Pediatr. Neurol. 2013; 49(4): 243-254.

71. Krueger DA, Northrup H, Krueger DA, Roberds S, Smith K, Sampson J et al. *Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference.* Pediatr. Neurol. 2013; 49(4): 255–265.

72. Auvin S, Bissler JJ, Cottin V, Fujimoto A, Hofbauer GFL, Jansen AC et al. *A step-wise approach for establishing a multidisciplinary team for the management of tuberous sclerosis complex: A Delphi consensus report.* Orphanet J. Rare Dis. 2019; 14(1): 91.

73. Thiele EA, Granata T, Matricardi S, Chugani HT. *Transition into adulthood: Tuberous sclerosis complex, Sturge-Weber syndrome, and Rasmussen encephalitis.* Epilepsia 2014; 55(Suppl 3): 29–33.

Address: Anna Barbara Marcinkowska
Applied Cognitive Neuroscience Lab
Department of Human Physiology
Medical University of Gdansk
80-210 Gdańsk, Tuwima Street 15
e-mail: anna.marcinkowska@gumed.edu.pl