SSBP Syndrome Sheets

Tuberous Sclerosis Complex (TSC)

First description and alternative names
Even though earlier cases exist, the first detailed description of the disorder was by Désiré-Magloire Bourneville, a French Physician, in 1880 when he described the case of a young girl with severe intractable epilepsy, intellectual disability and a 'confluent vesiculo-papular eruption on her nose, cheeks and forehead'. Neuropathology showed white, potato-like growths in the brain, referred to by Bourneville as 'tuberous sclerosis of the cerebral convolutions'. The term tuberous sclerosis *complex* was introduced by Moolten in 1942 to describe the multi-system nature of the disorder. The abbreviation 'TSC' is used (Curatolo, Moavero & de Vries, 2015).

Genetics and Molecular Biology
Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The TSC1 and TSC2 proteins form an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1-2 complex functions upstream of mTOR (mammalian/mechanistic Target Of Rapamycin). TSC mutations cause mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes. mTOR inhibitors have been approved by the FDA and EMA for the treatment of brain SEGA (subependymal giant cell astrocytoma), renal angiomyolipoma, and treatment-resistant epilepsy associated with TSC. Topical preparations of mTOR inhibitors are frequently used for facial angiofibromas and other skin manifestations of TSC. Clinical trials of mTOR inhibitors are underway for neuropsychiatric features of TSC, but have so far shown mixed results, at least in part due to the highly heterogeneous nature of the behavioural phenotype of TSC (see Curatolo, Moavero & de Vries, 2015 for primary references).

Incidence/prevalence
Birth incidence of about 1 in 5,800 (Osborne et al., 1991, see Curatolo, Moavero & de Vries, 2015 for primary references).

Physical features and natural history
Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 70-80% of people with TSC have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder or having a pathogenic mutation in one of the TSC genes (Northrup et al., 2021). Mutations are identified in >90% of individuals with clinically confirmed TSC and mosaic mutations in a further proportion.

TSC is not an inevitably declining condition, and any deterioration in physical or neuropsychiatric profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, SEGA and renal failure secondary to angiomyolipomas may be causes of death. However, molecularly-targeted treatments with mTOR inhibitors are now available for many of these manifestations (see Curatolo, Moavero & de Vries; de Vries, Wilde et al., 2018 for primary references).

Behavioural and psychiatric characteristics
Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term 'TAND' (TSC-Associated Neuropsychiatric Disorders) was coined in 2012 as an umbrella term for all the bio-psycho-social aspects of the disorder (de Vries et al., 2015) and a TAND Checklist has been

developed to aid clinical teams to screen for TAND (de Vries et al., 2015; Leclezio et al., 2015). In 2023 a self-report, quantified TAND Checklist (TAND-SQ) was published (Heunis et al., 2023). At the behavioural level, TSC is associated with high rates of mood/anxiety, overactive/impulsive, sleep/eating, dysregulated behaviours (aggression and tantrums), and many autism-related behaviours. At the psychiatric level, neurodevelopmental disorders are common, with autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries et al., 2015).

Neuropsychological characteristics

At the intellectual level, more than 50% of individuals with TSC will have global intellectual abilities in the normal range, but often with an uneven profile of strengths and weaknesses. Intellectual abilities tended to show a bimodal distribution in TSC where 30% of individuals with TSC had profound global intellectual disability (IQ equivalent <20) and the remaining 70% fell on a normal distribution curve, shifted to the left. Interestingly, the bimodal distribution of IQ has become less pronounced in TSC research studies over the last decade. At the scholastic/academic level, almost 60% of people with TSC will have a history of reading, writing, spelling or mathematics difficulties (de Vries et al., 2018; de Vries, Wilde et al., 2018). At the neuropsychological level, there are high rates of specific neuropsychological deficits, even in those with normal or high global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These neuropsychological deficits may be associated with significant impairment of functional abilities in daily life (de Vries, Wilde et al., 2018; Curatolo, Moavero & de Vries, 2015; de Vries et al., 2015).

Available guidelines for behavioural assessment/treatment/management

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries et al., 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup et al., 2013) and by the TAND Checklist (de Vries et al., 2015; Leclezio et al., 2015). The most recent update of diagnostic criteria and treatment guidelines were published in 2021 (Northrup et al., 2021).
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population. International consensus recommendations for the identification and treatment of TAND is expected in 2023.
- Targeted treatments using mTOR inhibitors are currently in clinical trials for TSC-associated neuropsychiatric disorders (TAND) (Curatolo, Moavero & de Vries, 2015; de Vries, Wilde, et al., 2018), but these are not at present recommended outside clinical trials.

Useful websites/associations for more information

- www.tuberous-sclerosis.org [UK user/carer organization]
- www.tsalliance.org [USA user/carer organization]
- www.tscinternational.org [International user/carer organization]
- www.tandconsortium.org [International TAND research consortium]

References

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Updated July 2023

The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation