

Coexistence of Autism Spectrum Disorders Among Three Children with Tuberous Sclerosis Complex

Case reports and review of literature

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حدوث اضطراب طيف التوحد واضطراب التصلب الدرني في وقت واحد في ثلاثة أطفال تقارير حالات ومراجعة الأدبيات

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ABSTRACT: Tuberous sclerosis complex (TSC) is a multisystem neurocutaneous disorder inherited in an autosomal dominant manner and characterised by benign tumours in the brain and other vital organs such as the heart, eyes, kidneys, skin and lungs. Links between autism spectrum disorder (ASD) and TSC have been postulated for many decades, with TSC considered to be one of the main syndromic causes of ASD; however, precise confirmation of a relationship between these two disorders required validated diagnostic tools. Fortunately, accurate evaluation of this relationship is now possible with standardised criteria for ASD diagnosis. We report three children who presented to the Sultan Qaboos University Hospital, Muscat, Oman, between 2014 and 2015 with ASD and TSC. These cases demonstrate the spectrum of neuropsychiatric involvement in TSC and highlight the importance of screening children with TSC for ASD features in order to encourage the early enrolment of these children in educational and rehabilitation programmes.

Keywords: Autism Spectrum Disorder; Tuberous Sclerosis; Case Report; Oman.

الملخص: التصلب الدرني هو اضطراب عصبي جلدي متعدد يتسم بصفة وراثية سائدة ويتميز بوجود أورام حميدة في عدة أعضاء حيوية كالدمغ والقلب والعين والكلية والجلد والرئتين. وبحسب احتمال وجود اضطراب طيف التوحد واضطراب التصلب الدرني منذ عقود طويلة، إذ يعتبر اضطراب التصلب الدرني أحد أهم المتلازمات المسببة لطيف التوحد. وعلى الرغم من ذلك فإن التأكيد الدقيق بين هذين الاضطرابين يتطلب ويحتاج إلى التحقق من صحة أدوات التشخيص. ولحسن الحظ فإن التقييم والتشخيص الدقيق لمعرفة العلاقة بين هذين الاضطرابين أصبح ممكناً بسبب وجود معايير دقيقة للتشخيص لطيف التوحد. ويتناول هذا التقرير ثلاث حالات تم علاجها في مستشفى جامعة السلطان قابوس، مسقط، عمان ما بين عامي 2014 و2015 مصابة بهذين الاضطرابين. تبرز هذه الحالات طيف الاعراض العصبية والنفسية المرتبطة بالتصلب الدرني وتؤكد على أهمية وضرورة الفحص المبكر للأطفال الذين يعانون من هذه الاضطرابات لإلحاقهم مبكراً في البرامج التعليمية والتأهيلية الخاصة.

الكلمات المفتاحية: اضطراب طيف التوحد؛ التصلب الدرني؛ تقرير حالة؛ عمان.

TUBEROUS SCLEROSIS COMPLEX (TSC) IS AN autosomally inherited multisystem neurocutaneous disorder with variable expression. It is characterised by various features, including benign tumours in the brain and other vital organs—such as the heart, eyes, kidneys, skin and lungs—and dermatological features such as hypomelanotic macules and shagreen patches.¹ According to the 2012 International Tuberous Sclerosis Complex Consensus Statements, a diagnosis of TSC is either clinical, based on the presence of a specific combination of major and minor features, or genetic, determined by mutations in the *tuberous sclerosis (TSC) 1* or *TSC2* genes.²

While a relationship between autism spectrum disorder (ASD) and TSC has been hypothesised previously, confirmation of a link between these conditions required more validated diagnostic tools for ASD. An accurate assessment of the relationship between these two disorders is now possible with the availability of standardised criteria for ASD diagnosis, such as those published in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the revised Autism Diagnostic Interview™ (WPS, Torrance, California, USA) and the Autism Diagnostic Observation Schedule™ (WPS).³ The estimated prevalence rate of autism in TSC patients is

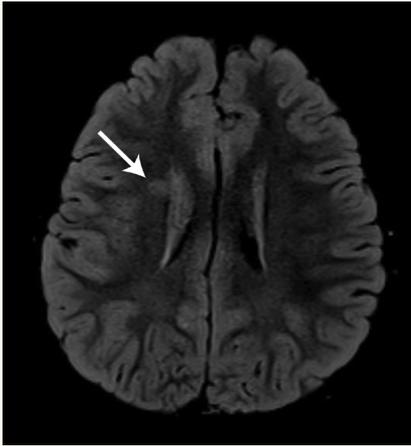


Figure 1: T2-weighted magnetic resonance fluid-attenuated inversion recovery sequence transverse image showing an isointense nodular lesion in the right periventricular region (arrow) of a 5-year-old boy with autism spectrum disorder and tuberous sclerosis complex.

approximately 50%, a similar rate to that of other neurological comorbidities, such as epilepsy (84.5%) and intellectual disability (44%).⁴⁻⁶ However, despite this high prevalence rate, few studies have assessed the severity of autism among patients with TSC. This report describes three children with both ASD and TSC, illustrating the coexistence of these disorders.

Case One

A 5-year-old girl presented to the Developmental Paediatrics Clinic of the Sultan Qaboos University Hospital (SQUH), Muscat, Oman, in 2014 with major speech and language delays. She demonstrated challenging behaviours typical of ASD, including impulsiveness and hyperactivity. She was described by her parents as a very quiet infant who rarely cried, even during vaccinations. When she was approximately one year old, the patient was noted to show poor response to her name and rarely make eye contact. By 18 months of age, there were reported delays in sitting, walking, speech and language. She could crawl by 18 months and walk without support by 20 months of age. When she was four years old, the patient experienced one febrile seizure but had since had no further seizures. Her father had a seizure disorder along with adenoma sebaceum. He was evaluated by brain computed tomography (CT); however, the findings were reportedly normal.

A clinical examination revealed a hyperactive child who could not speak clearly and who demonstrated a poor response to verbal commands. Her head circumference was below the third centile for her age. She had a shagreen patch on her lower back

extending to the left side which measured 8 x 5 cm and three hypopigmented macules (two on her lower limbs and one on her back). Her neurological and systemic examinations were normal. A comprehensive developmental assessment indicated that she fulfilled the DSM-V diagnostic criteria for ASD.⁷ Genetic testing showed that there was a deletion of exon 37 of the *TSC2* gene, confirming the diagnosis of TSC. The patient was enrolled in a rehabilitation centre for children with special needs and several of her challenging behaviours improved without the need for medical therapy.

Case Two

A 5-year-old boy presented to the Developmental Paediatrics Clinic at SQUH in 2014 due to concerns related to his language, communication and social milestones. At 19 months old, he was noted to have delayed speech, poor eye contact, poor response to his name, many repetitive play behaviours and restricted interests. He had attention problems and could not remain focused on specific tasks. There were no other reported health issues. A skin examination revealed three hyperpigmented spots and three hypomelanotic macules, with the rest of examination being otherwise normal. A developmental evaluation showed significant deficits in social interaction and communication in addition to significant behaviours and interests typical of ASD. He also fulfilled the DSM-V diagnostic criteria for ASD.⁷

Magnetic resonance imaging (MRI) of the brain showed nodular heterotopias and tubers adjacent to the right lateral ventricle [Figure 1]. The clinical and MRI findings confirmed the diagnosis of TSC. However, genetic testing revealed no mutations, deletions or duplications in the *TSC1* and *TSC2* genes. His mother was noted to have one major and one minor feature of TSC—angiofibromata and dental pits, respectively—which suggested that she also had TSC. Furthermore, two maternal cousins had had learning problems, with one also having a psychiatric disorder. The patient received treatment at a specialised rehabilitation centre for children with special needs, with notable improvement in his development and behaviours.

Case Three

A 1-year-old female infant presented to the Developmental Paediatrics Clinic at SQUH in 2015 for a seizure disorder which had initially manifested at three months of age. On examination, she was found to have five hypomelanotic macules measuring 0.5 x 1.5 cm.

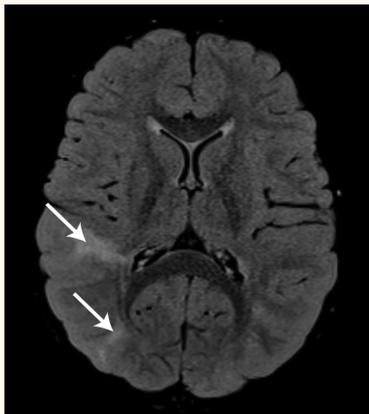


Figure 2: T2-weighted magnetic resonance fluid-attenuated inversion recovery sequence transverse image showing ill-defined hyperintense lesions in the cortical-subcortical right parietal region (arrows) of a 1-year-old female infant with autism spectrum disorder and tuberous sclerosis complex.

An MRI brain scan demonstrated multiple cortical and subcortical tubers and subependymal nodules [Figure 2], confirming a clinical diagnosis of TSC. Her family history was significant for seizure disorders, ASD, intellectual disabilities and similar skin findings.

Both the developmental history interview and clinical observations of the patient revealed significant deficits in social interaction and communication in addition to typical ASD behaviours and interests. She fulfilled the DSM-V diagnostic criteria for ASD.⁷ The

patient was prescribed levetiracetam and clonazepam for her seizures, which resulted in reasonable control.

A summary of the clinical features, radiological findings and family history of each case is shown in Table 1. Unfortunately, it was difficult to ascertain a correlation between MRI findings and the severity of autistic features in each patient due to limited resources.

Discussion

The clinical presentation of TSC can be variable and challenging. The three patients in the current report highlight the importance of thoroughly evaluating patients with features of ASD in order not to miss other potential causes of these disorders, such as TSC. Patients may present to different specialties which can delay diagnosis; for example, two of the patients in the present report were diagnosed with TSC after being evaluated at a paediatric developmental centre. All three patients in the current report fulfilled the clinical diagnostic criteria for both TSC and ASD; two patients had tubers and subependymal brain nodules along with major dermatological features of TSC, while the third patient was found to have a mutation in the *TSC2* gene. Although the genetic testing of one patient did not show any mutations, deletions or duplications in the *TSC1* and *TSC2* genes, a lack of genetic confirmation has been reported

Table 1: Clinical features and radiological findings of three patients with autism spectrum disorder and tuberous sclerosis complex

| | Case 1 | Case 2 | Case 3 |
|------------------------------|---|---|---|
| Age in years at presentation | 5 | 5 | 1 |
| Gender | Female | Male | Female |
| Clinical features | <ul style="list-style-type: none"> • ASD • History of one febrile seizure • Three hypomelanotic macules on the back and lower limbs • Shagreen patch on the back | <ul style="list-style-type: none"> • ASD • Three hyperpigmented spots • Three hypomelanotic macules | <ul style="list-style-type: none"> • ASD • Seizure disorder • Five hypomelanotic macules on the back and lower limbs |
| Radiological findings | <ul style="list-style-type: none"> • Normal echocardiograph | <ul style="list-style-type: none"> • Brain MRI showed nodular heterotopias and tubers in the right lateral ventricle | <ul style="list-style-type: none"> • Echocardiograph showed two rhabdomyomas in the heart • Brain MRI showed multiple small cortical, subcortical and subependymal hamartomas |
| Family history | <ul style="list-style-type: none"> • Seizure disorder in the father • Angiofibromata, multiple hypomelanotic macules and shagreen patches in the father and one of his sisters • Multiple family members affected with seizure disorders, skin findings and intellectual disability on the father's side | <ul style="list-style-type: none"> • Dental pits and angiofibromata in the mother • Two maternal cousins had learning problems and one had a psychiatric disorder | <ul style="list-style-type: none"> • Multiple hypopigmented lesions in the mother • History of epilepsy, mental retardation and hypopigmented lesions in four maternal uncles and aunts |

ASD = autism spectrum disorder; MRI = magnetic resonance imaging.

in approximately 10% of patients with a confirmed clinical diagnosis of TSC.² All three patients fulfilled the DSM-V diagnostic criteria for ASD.⁷

A wide range of neuropsychiatric disorders have been observed in patients with TSC, with an estimated lifetime prevalence of approximately 90%.^{8,9} The association of TSC with ASD has been documented in various studies; one study reported that 1–4% of autistic patients may have TSC while another indicated that the rate of autism among TSC patients could be as high as 36%.^{10,11} The coexistence of TSC and ASD seems to be underestimated worldwide, mostly due to the under-reporting of both of these conditions. There is currently a worldwide initiative to introduce a TSC-associated neuropsychiatric disorders (TAND) checklist to help evaluate TSC patients.⁸ The findings of an international tuberous sclerosis registry shows that, even in expert TSC centres, patients are often inadequately examined for ASD and TAND features.¹² Hopefully, the exponentially increasing amount of research being conducted on neuropsychiatric comorbidities associated with TSC will lead to an improvement in TAND detection rates and, eventually, individualised treatment and rehabilitation plans for affected patients.¹³

The pathophysiological mechanisms leading to neurological manifestations in TSC patients include disorganised cell growth and motility, altered axon outgrowth, abnormal synapse formation and impaired myelination, leading to disorganisation of the central nervous system architecture and neuronal connectivity.^{14–16} Three proteins (TSC1, TSC2 and Tre2-Bub2-Cdc16 domain family member 7) form a complex which acts as a guanosine triphosphate phosphohydrolase (GTP)-activating protein. Mutations in the *TSC1* or *TSC2* genes result in accumulation of the GTP-bound protein which stimulates mammalian target of rapamycin (mTOR).¹⁷ Designed transgenic models of TSC have been used to enhance understanding of ASD; homozygous knock-out mice with *TSC1* and *TSC2* mutations displayed an autistic-like phenotype with social impairment, restrictive behaviours and abnormal vocalisations.^{18,19} Heterozygous *TSC1* or *TSC2* knock-out mice have also shown cognitive and social deficits, even in the absence of gross neuropathological changes.^{18,19}

Neuropsychiatric manifestations of TSC are among the most difficult to manage for patients, parents and caregivers, as management is often multidisciplinary and requires multiple interventions directed towards rehabilitation.^{20,21} Recent research has changed the outlook for patients with TSC and associated manifestations. Molecular-targeted

treatments using mTOR inhibitors such as rapamycin and everolimus are promising interventions, aimed at relieving cognitive and neurodevelopmental features of TSC.²² In addition to its antiproliferative and immunosuppressive properties, rapamycin inhibits mTOR, reversing the process that occurs due to *TSC1* and *TSC2* mutations. Three clinical trials are currently exploring the use of everolimus for patients with neurocognitive manifestations of TSC.²²

Vigilant assessment of ASD in patients with TSC is essential. Additionally, new advances in diagnostic and screening tools available for assessing TAND in ASD patients with TSC should lead to the mandatory screening of TSC patients for associated features.⁸ It is imperative that paediatricians carry out detailed examinations of children with ASD in order to identify any associated disorders and provide an accurate recurrence risk assessment for other family members.²³ Moreover, children with TSC should undergo screening for features of ASD; early interventions in the form of rehabilitation or therapy are recommended to improve the outcomes for and the quality of life of ASD patients with TSC and reduce the burden of this disease on affected families and society as a whole.

Conclusion

The current report highlights the spectrum of neuro-psychiatric involvement in TSC by describing three children with both ASD and TSC. It is of vital importance that children with TSC be screened for coexisting ASD features in order to encourage the rapid implementation of educational and rehabilitation measures.

References

1. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008; 372:657–68. doi: 10.1016/S0140-6736(08)61279-9.
2. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013; 49:243–54. doi: 10.1016/j.pediatrneurol.2013.08.001.
3. de Bildt A, Sytema S, Ketelaars C, Kraijer D, Mulder E, Volkmar F, et al. Interrelationship between Autism Diagnostic Observation Schedule-Generic (ADOS-G), Autism Diagnostic Interview-Revised (ADI-R), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) classification in children and adolescents with mental retardation. *J Autism Dev Disord* 2004; 34:129–37. doi: 10.1023/B:JADD.0000022604.22374.5f.
4. Kong SW, Sahin M, Collins CD, Wertz MH, Campbell MG, Leech JD, et al. Divergent dysregulation of gene expression in murine models of fragile X syndrome and tuberous sclerosis. *Mol Autism* 2014; 5:16. doi: 10.1186/2040-2392-5-16.

5. Jeste SS, Sahin M, Bolton P, Ploubidis GB, Humphrey A. Characterization of autism in young children with tuberous sclerosis complex. *J Child Neurol* 2008; 23:520–5. doi: 10.1177/0883073807309788.
6. 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; 33:335–44. doi: 10.1017/S0033291702007092.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, Virginia, USA: American Psychiatric Publishing, 2013. doi: 10.1176/appi.books.9780890425596.
8. de Vries PJ, Whitemore VH, Leclezio L, Byars AW, Dunn D, Ess KC, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. *Pediatr Neurol* 2015; 52:25–35. doi: 10.1016/j.pediatrneurol.2014.10.004.
9. Vignoli A, La Briola F, Peron A, Turner K, Vannicola C, Sacconi M, et al. Autism spectrum disorder in tuberous sclerosis complex: Searching for risk markers. *Orphanet J Rare Dis* 2015; 10:154. doi: 10.1186/s13023-015-0371-1.
10. Wiznitzer M. Autism and tuberous sclerosis. *J Child Neurol* 2004; 19:675–9. doi: 10.1177/08830738040190090701.
11. Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: A decade of new twin studies. *Am J Med Genet B Neuropsychiatr Genet* 2011; 156B:255–74. doi: 10.1002/ajmg.b.31159.
12. Kingswood JC, Bruzzi P, Curatolo P, de Vries PJ, Fladrowski C, Hertzberg C, et al. TOSCA: First international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. *Orphanet J Rare Dis* 2014; 9:182. doi: 10.1186/s13023-014-0182-9.
13. Leclezio L, de Vries PJ. Advances in the treatment of tuberous sclerosis complex. *Curr Opin Psychiatry* 2015; 28:113–20. doi: 10.1097/YCO.0000000000000136.
14. Crino PB. Evolving neurobiology of tuberous sclerosis complex. *Acta Neuropathol* 2013; 125:317–32. doi: 10.1007/s00401-013-1085-x.
15. Sundberg M, Sahin M. Cerebellar development and autism spectrum disorder in tuberous sclerosis complex. *J Child Neurol* 2015; 30:1954–62. doi: 10.1177/0883073815600870.
16. Hampson DR, Blatt GJ. Autism spectrum disorders and neuropathology of the cerebellum. *Front Neurosci* 2015; 9:420. doi: 10.3389/fnins.2015.00420.
17. Switon K, Kotulska K, Janusz-Kaminska A, Zmorzynska J, Jaworski J. Tuberous sclerosis complex: From molecular biology to novel therapeutic approaches. *IUBMB Life* 2016. doi: 10.1002/iub.1579.
18. Reith RM, McKenna J, Wu H, Hashmi SS, Cho SH, Dash PK, et al. Loss of Tsc2 in Purkinje cells is associated with autistic-like behavior in a mouse model of tuberous sclerosis complex. *Neurobiol Dis* 2013; 51:93–103. doi: 10.1016/j.nbd.2012.10.014.
19. Ehninger D, Han S, Shilyansky C, Zhou Y, Li W, Kwiatkowski DJ, et al. Reversal of learning deficits in a Tsc2^{+/-} mouse model of tuberous sclerosis. *Nat Med* 2008; 14:843–8. doi: 10.1038/nm1788.
20. Chung TK, Lynch ER, Fiser CJ, Nelson DA, Agricola K, Tudor C, et al. Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex. *Ann Clin Psychiatry* 2011; 23:263–9.
21. Krueger DA, Northrup H; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013; 49:255–65. doi: 10.1016/j.pediatrneurol.2013.08.002.
22. Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, et al. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature* 2012; 488:647–51. doi: 10.1038/nature11310.
23. Johnson CP, Myers SM; American Academy of Pediatrics Council on Children With Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics* 2007; 120:1183–215. doi: 10.1542/peds.2007-2361.