



Newly Diagnosed and Growing Subependymal Giant Cell Astrocytoma in Adults With Tuberous Sclerosis Complex: Results From the International TOSCA Study

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The onset and growth of subependymal giant cell astrocytoma (SEGA) in tuberous sclerosis complex (TSC) typically occurs in childhood. There is minimal information on SEGA evolution in adults with TSC. Of 2,211 patients enrolled in TOSCA, 220 of the 803 adults (27.4%) ever had a SEGA. Of 186 patients with SEGA still ongoing in adulthood, 153 (82.3%) remained asymptomatic, and 33 (17.7%) were reported to ever have developed symptoms related to SEGA growth. SEGA growth since the previous scan was reported in 39 of the 186 adults (21%) with ongoing SEGA. All but one patient with

growing SEGA had mutations in *TSC2*. Fourteen adults (2.4%) were newly diagnosed with SEGA during follow-up, and majority had mutations in *TSC2*. Our findings suggest that surveillance for new or growing SEGA is warranted also in adulthood, particularly in patients with mutations in *TSC2*.

Keywords: mTOR, registry, SEGA, TOSCA, tuberous sclerosis complex

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterised by hamartomas in multiple organs, with the brain being the most commonly affected organ (1, 2). Subependymal giant cell astrocytoma (SEGA) occurs at the foramen of Monro, with a reported lifetime prevalence between 5 and 24% (3, 4). Although SEGAs are generally benign and non-infiltrative, these may grow, and obstruct cerebrospinal fluid (CSF) flow, thereby increasing intracranial pressure. Typical symptoms of growing SEGA include headaches, blurred vision, nausea, vomiting, worsening of seizure control or new-onset seizures, and sudden death from acute hydrocephalus (3, 5).

Diagnosis of SEGA has changed from pathology-based to imaging-based (6, 7), but formal diagnostic criteria have only been available since 2012, when an expert panel at the International Tuberous Sclerosis Complex Consensus Conference defined SEGA as a lesion at the caudothalamic groove with a size of >1 cm in any direction or a subependymal lesion at any location which has shown serial growth on consecutive imaging regardless of size (7). All SEGA-related studies performed before 2012 have been based on variable criteria, thus limiting the value of comparison (8).

Onset and growth of SEGA has been reported most commonly in the first two decades of life (9). In two of the largest series of operated SEGAs, the mean age of surgical intervention was 9.7 years (10), and 11.6 years, (11) suggesting that growth is most common at this age. SEGA have been reported in neonates (9). Data on SEGA prevalence and growth in adults are scarce. A retrospective case series of 16 patients with TSC who required SEGA surgery, highlighted that SEGA can still become symptomatic later in life (12).

Present guidelines recommend that patients with asymptomatic SEGA diagnosed during childhood should continue to be imaged periodically as adults to ensure that there is no growth (13). Patients with large or growing SEGA or with SEGA causing ventricular enlargement that are still asymptomatic, should undergo MRI (magnetic resonance imaging) scans more frequently, and such patients and their families should be educated regarding the symptoms of raised intracranial pressure (7).

Surgical resection (occasionally VP shunt alone) is the recommended intervention for acutely symptomatic individuals, while either surgical resection or medical therapy with mammalian/mechanistic target of rapamycin (mTOR) inhibitors can be effective for individuals with growing asymptomatic SEGA (13). Treatment decisions should be based on multiple factors such as the patient's clinical condition, anatomic considerations

specific to SEGA, surgeon's experience, experience of the centre regarding use of mTOR inhibitors, prior history of SEGA resection, other TSC-related comorbidities, and patient/parental preference (7).

This is the first study evaluating prevalence, growth, symptoms, and treatment patterns in a large prospective cohort of adults with TSC-associated SEGA.

METHODS

TOSCA, a large-scale non-interventional study in patients with TSC, was conducted at 170 sites in 31 countries. The study design and methodology of TOSCA has been published previously (14). The study enrolled patients of any age with TSC between August 2012 and November 2014 and followed for up to 5 years. Patient data, including demographics, and information related to clinical features of TSC across all organ systems, comorbidities and rare manifestations, were collected at baseline and at regular visits scheduled at a maximum interval of 1 year.

In this study, designed prior to the 2012 imaging-based consensus, prevalence, and growth of SEGA were defined as per clinical practice of the participating centres. We evaluated SEGA manifestations among adult patients (>18 years) enrolled into the TOSCA study. SEGA-related questions included in the case report form (CRF) were presence of single or multiple SEGA, newly diagnosed SEGA, SEGA growth, clinical signs, and symptoms associated with SEGA and information regarding SEGA treatment. In addition, possible associations of SEGA prevalence with genotype were analysed using a Chi-square test. Statistical significance was set at p -value < 0.05.

Statistics were descriptive considering the exploratory nature of this study. Categorical data were reported as frequencies and percentages, and continuous variables were expressed as mean (\pm standard deviation) or as median (range), unless stated otherwise.

The study was designed and conducted in accordance with the Good Clinical Practice principles, the Declaration of Helsinki and all local regulations. The institutional review board or ethics committee at each participating site approved required TOSCA-related documents. Written informed consent was obtained from all patients, parents or guardians before enrolment.

RESULTS

A total of 2,214 patients with TSC were enrolled in TOSCA study, and data were analysed for 2,211 patients. In the

TABLE 1 | Demographics of adult patients with SEGA.

Characteristics	Patients with SEGA			
	All adults (n = 220)	>18 to ≤25 years (n = 91)	>25 to ≤40 years (n = 96)	>40 years (n = 33)
Age at diagnosis of TSC, years; median (range)	4.0 (<1–48)	1.0 (<1–24)	4.0 (<1–37)	15.0 (<1–48)
Gender, n (%)				
Male	98 (44.5)	35 (38.5)	46 (47.9)	17 (51.5)
Female	122 (55.5)	56 (61.5)	50 (52.1)	16 (48.5)
Patients with molecular testing, n (%)	96 (43.6)	40 (44.0)	41 (42.7)	15 (45.5)
Genetic Testing, n (%)				
No mutation identified	12 (12.5)	6 (15.0)	3 (7.3)	3 (20.0)
TSC1 mutation	12 (12.5)	2 (5.0)	5 (12.2)	5 (33.3)
TSC2 mutation	69 (71.9)	31 (77.5)	31 (75.6)	7 (46.7)
Results not available*	5 (5.2)	1 (2.5)	1 (2.4)	0
Variation Type, n (%)				
Pathogenic mutation	59 (61.5)	22 (55.0)	27 (65.9)	10 (66.7)
Variant of unknown significance	5 (5.2)	4 (10.0)	1 (2.4)	0
Both pathogenic mutation and variant of unknown significance	2 (2.1)	0	2 (4.9)	0
Results not available*	30 (31.3)	14 (35)	11 (26.8)	5 (33.3)
Patients with prenatal diagnosis, n (%)	1 (0.5)	1 (1.1)	0	0

Values are expressed as n (%), unless otherwise specified. *Include missing data and those results not made available due to legal/medical confidentiality statements. SEGA, subependymal giant cell astrocytoma. TSC, tuberous sclerosis complex.

final analysis performed on data collected until August 2017, a history of SEGA was reported in 30.3% (671/2,211; 332 males and 339 females) of patients. Other neuroimaging features reported included cerebral white matter radial migration lines in 25.5, cortical tubers in 87.2, and subependymal nodules 82.9%.

Of the 803 adult patients included in the final analysis, a history of SEGA was reported in 220 patients (27.4%). The demographic of the adult patients with SEGA are shown in **Table 1**. SEGA were ongoing during study in 186 (84.5%) patients. Of these, multiple and bilateral SEGA were reported in 66 (35.5%), and 61 (32.8%) patients, respectively. SEGA growth since previous scan was reported in 39 (21%). The median age at SEGA diagnosis in this adult cohort was 20 years (range, <1–57 years), as compared to 7 years (range, <1–57 years) in the entire TOSCA cohort.

The median interval between consecutive scans was 1 year (range <1–34 years). During the study period (up to 5 years), 14 new diagnoses of SEGA were made (2.4% of total adults minus those with history of SEGA). The oldest patient with a newly reported SEGA was 57 years. Of the 186 adults with ongoing SEGA, 153 (82.3%) remained asymptomatic, and 33 (17.7%) were reported to ever have developed symptoms related to SEGA growth in the past, including primarily increase in seizure frequency (15.6%), behavioural disturbance (13.4%), and headache (10.8%), either alone or in combination with other symptoms (**Table 2**). Over time, SEGA had been treated with surgery in 55 out of 117 patients (47.0%) and with mTOR-inhibitors in 46 out of 117 patients (39.3%). Nine patients (7.7%) required a shunt for the management of hydrocephalus.

SEGA were significantly more frequent in adults with a TSC2 mutation compared to those with a TSC1 mutation (35.2 vs. 15.6%, $p < 0.0004$). However, there was no significant difference in multiple ($p = 0.1158$), bilateral ($p = 0.1062$), or growing SEGA ($p = 1.0000$), and presence of SEGA-related symptoms ($p = 0.2598$) between those with TSC1 and TSC2 mutation. The median age at SEGA diagnosis was higher in patients with TSC1 mutations (29 years, range 9–51) compared to patients with TSC2 mutations (21 years, range <1–49), but this difference was non-significant (**Table 3**). Furthermore, 12 of 14 adults with newly diagnosed SEGA had mutations in TSC2 gene, while two had no mutation identified.

DISCUSSION

To our knowledge, this is the first study to evaluate SEGA prevalence, growth, symptoms, and current treatment modalities in adults with TSC-associated SEGA. The international TOSCA study allowed us to evaluate data from 803 adults (age > 18 years), 220 of whom had SEGA (27.4%). During the 5 years follow-up period of the study, 23.2% of adults reported that the SEGA was still ongoing.

The occurrence of new SEGA after the age of 18 years was relatively low (2.4%) but more common than previously thought (7). In this cohort, age at SEGA diagnosis was as late as 57 years. Newly diagnosed SEGA were associated with mutations in TSC2 in the large majority of cases (85.7%). Other risk factors such as contrast enhancement of SEN in the caudo-thalamic groove were beyond the scope of this study.

Another key finding was that SEGA growth since previous scan (mean time of 1.5–2.3 years between previous scan

TABLE 2 | Clinical characteristics of SEGA.

	Overall TOSCA population (<i>n</i> = 2211)	Adult patients			
		All adults (<i>n</i> = 803)	>18 to ≤25 years (<i>n</i> = 235)	>25 to ≤40 years (<i>n</i> = 344)	>40 years (<i>n</i> = 224)
Patients with history of SEGA	671 (30.3)	220 (27.4)	91 (38.7)	96 (27.9)	33 (14.7)
No. of patients with ongoing SEGA during the study, <i>n</i>	579	186	71	87	28
Multiple	240 (41.5)	66 (35.5)	24 (33.8)	33 (37.9)	9 (32.1)
Bilateral	236 (40.8)	61 (32.8)	21 (29.6)	30 (34.5)	10 (35.7)
Growing SEGA since previous scan* [#]	208 (35.9)	39 (21.0)	19 (26.8)	17 (19.5)	3 (10.7)
Signs and symptoms					
None	476 (82.2)	153 (82.3)	57 (80.3)	72 (82.8)	24 (85.7)
Increase in seizure frequency	98 (16.9)	29 (15.6)	14 (19.7)	13 (14.9)	2 (7.1)
Behavioural disturbance	77 (13.3)	25 (13.4)	8 (11.3)	16 (18.4)	1 (3.6)
Regression/loss of cognitive skills	51 (8.8)	16 (8.6)	5 (7.0)	10 (11.5)	1 (3.6)
Headache	47 (8.1)	20 (10.8)	7 (9.9)	10 (11.5)	3 (10.7)
Ventriculomegaly	32 (5.5)	8 (4.3)	5 (7.0)	3 (3.4)	0
Increased intracranial pressure	24 (4.1)	10 (5.4)	6 (8.5)	2 (2.3)	2 (7.1)
Sleep disorder	22 (3.8)	7 (3.8)	1 (1.4)	6 (6.9)	0
Eye movement abnormalities	16 (2.8)	6 (3.2)	4 (5.6)	2 (2.3)	0
Visual impairment	10 (1.7)	4 (2.2)	3 (4.2)	1 (1.1)	0
Papilloedema	8 (1.4)	4 (2.2)	2 (2.8)	1 (1.1)	1 (3.6)
Neuroendocrine dysfunction	8 (1.4)	4 (2.2)	0	3 (3.4)	1 (3.6)
Other	28 (4.8)	7 (3.8)	4 (5.6)	3 (3.4)	0

Values are expressed as *n* (%), unless otherwise specified. *Median time from previous scan to last assessment was 1 year. [#]Growing of SEGA since previous scan was measured among those with ongoing SEGA during the study. SEGA, subependymal giant cell astrocytoma.

and last assessment) was observed in 21% of our adult patients. Although not negligible, this is less frequent compared with children. In a cohort of 58 patients (33 children, 25 adults), Tsai et al. reported similar results, with SEGA growth in children being significantly higher than in adults (75.6 vs. 16.5%) (15).

The fact that SEGA may still grow during adulthood emphasises the need for continuous surveillance even after the age of 25 years. This was highlighted in the current guidelines that recommend that patients with asymptomatic SEGA diagnosed in childhood should continue to undergo periodical imaging as adults to ensure that there is no growth. This highlights the need for continued multidisciplinary follow-up, also at adult age. Although newly occurring SEGA during adulthood seem relatively rare and do not warrant systematic screening, physicians should keep this possibility in mind when symptoms potentially related to SEGA growth occur. Special attention should be paid to adults with mutations in *TSC2* since they seem to be at a higher risk for newly occurring SEGA and SEGA growth in adulthood as well as to individuals with intellectual disability who might not be able to verbally express SEGA-related symptoms. Importantly, certain SEGA-related symptoms (especially early symptoms) are not limited to signs of increased intracranial pressure, and therefore, parents and patients should be informed about all relevant symptoms which require referral for medical evaluation, particularly sudden behavioural

changes such as acute-onset and unexplained aggression, academic difficulties or any other acute and unexplained manifestations of TSC-associated neuropsychiatric disorders (TAND) (16–18).

We acknowledge the limitations intrinsic to a large-scale, international, non-interventional/observational study. These included the fact that participants were recruited from expert TSC centres around the world and the fact that data on SEGA diagnosis, growth and SEGA-related symptoms were collected as reported per clinical practice. However, these limitations are, at least in part, offset by the large-scale and “real-world” nature of the cohort across multiple centres and countries. Being an observational study, detailed information on the treatment initiated for SEGA at adult age were not collected. The very low number of missing data for SEGA reflects good quality of data collection for this specific manifestation.

CONCLUSION

Findings from this large international study highlight the need for continued monitoring for SEGA growth in adults with ongoing SEGA. Clinicians and adults with TSC should be aware of the potential new onset SEGA in adults with SEGA-related symptoms, especially in the presence of mutations in *TSC2*.

TABLE 3 | Clinical characteristics of SEGA in adults with mutations in TSC1 vs. TSC2.

	Adults with TSC1 mutation (n = 77)	Adults with TSC2 mutation (n = 196)	p-value
Patients with history of SEGA	12 (15.6)	69 (35.2)	0.0004
Median (range) age at SEGA diagnosis, years	29 (9–51)	21 (<1–49)	0.0599
No. of patients with ongoing SEGA during the study	8 (66.7)	61 (88.4)	0.1317
Multiple	5 (62.5)	19 (31.1)	0.1158
Bilateral	5 (62.5)	18 (29.5)	0.1062
Growing SEGA since previous scan	1 (12.5)	13 (21.3)	1.0000
Signs and Symptoms			
None	5 (62.5)	49 (87.5)	0.3580
Increase in seizure frequency	3 (37.5)	15 (28.3)	0.6243
Behavioural disturbance	1 (12.5)	14 (26.4)	1.0000
Headache	1 (12.5)	10 (18.9)	0.5753
Regression/loss of cognitive skills	0	5 (9.4)	1.0000
Ventriculomegaly	0	4 (7.5)	1.0000
Increased intracranial pressure	1 (12.5)	3 (5.7)	1.0000
Papilloedema	1 (12.5)	3 (5.7)	1.0000
Sleep disorder	0	2 (3.8)	1.0000
Eye movement abnormalities	0	2 (3.8)	1.0000
Visual impairment	0	2 (3.8)	1.0000
Neuroendocrine dysfunction	1 (12.5)	2 (3.8)	0.2408
Other	1 (12.5)	3 (5.7)	0.3098
Patients received treatment	8 (66.7)	37 (53.6)	0.0716

Values are expressed as n (%), unless otherwise specified.
SEGA, subependymal giant cell astrocytoma.

DATA AVAILABILITY

Novartis supports publication of scientifically rigorous analysis which is relevant to patient care, regardless of a positive or negative outcome. Qualified external researchers can request access to anonymised patient-level data, respecting patient informed consent, by contacting study sponsor authors. The protocol can be accessed through the EnCePP portal <http://www.encepp.eu/> (EU PAS Register Number EUPAS3247).

ETHICS STATEMENT

The study protocol and all amendments were reviewed and approved (if applicable) by independent ethics committee/institutional review board for each centre: National Hospital Organization Central Ethics Committee; Gazi University Clinical Research Ethics Committee; Independent Multidisciplinary Committee on Ethical Review of Clinical

Trials; Peking Union Medical College Hospital; Commissie Medische Ethiek UZ Brussel; CNIL (Commission National de l'Informatique et des Libertés); CCTIRS (Comité Consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé); CEIC-E (Comité Etico Investigación Clínica de Euskadi; Consejería de Salud y Bienestar Social, Dirección General de Calidad, Investigación, Desarrollo e Innovación, Comité Coordinador de Ética de la Investigación Biomédica de Andalucía; UT REC (Research Ethics Committee of the University of Tartu); Ethikkommission der Medizinischen Universität Graz; North Wales REC–West; Regionala Etikprövningsnämnden i Göteborg; REK–Regionale komiteer for medisinsk og helsefaglig forskningsetikk; Komisja Bioetyczna przy Instytucie Pomnik Centrum Zdrowia Dziecka; Ethikkommission bei der Ludwig-Maximilians-Universität München; Hokkaido University Hospital Independent clinical research Institutional Ethics Committee; Medical Juntendo University Institutional Ethics Committee; National Center for Chile Health and Development of IRB; Osaka University Hospital of IRB; Ethics Committee at Moscow Institute of Pediatrics and Pediatric Surgery; Peking University First Hospital; Sanbo Brain Hospital Capital Medical University; Tianjin Children's Hospital; Childrens Hospital Of Fudan University; Zhongshan Hospital Fudan University; Fudan University Shanghai Cancer Center; The Second Affiliated Hospital of Guangzhou Medical University; The First Affiliated Hospital, Sun Yan-Sen University; The First Affiliated Hospital of Guangzhou Medical University; Shenzhen Children's Hospital; West China Hospital, Sichuan University; Xijing Hospital; Children's Hospital of Chongqing Medical University; Wuhan Children's Hospital; The second affiliated hospital of Xi'an jiaotong university; Guangdong 999 brain hospital; Seoul National University Hospital Institutional Review Board; National Taiwan University Hospital (NTUH) Research Ethics Committee (REC); Institutional Review Board of the Taichung Veterans General Hospital; Institutional Review Board of Chung Shan Medical University Hospital; Institutional Review Board, Tungs' Taichung MetroHarbor Hospital; Institutional Review Board of National Cheng Kung University Hospital; Metro South Human Research Ethics Committee; Sydney Children's Hospital Network Human Research Ethics Committee; St Vincents Hospital Human Research Ethics Committee; Royal Melbourne Hospital Human Research Ethics Committee; Siriraj Institutional Review Board; The Institutional Review board, Faculty of Medicine, Chulalongkorn University, 3rd Floor, Ananthamahidol Building, King Chulalongkorn Memorial Hospital; The committee on Human Rights Related to Research Involving Human Subjects; Institutional Review board, Royal Thai Army Medical Department IRB RTA, 5th Floor, Phramongkutklaowevjitya Building, Phramongkutklao College of Medicine; Research Ethics Committee, Faculty of Medicine, Chiang Mai University; Research and Development, Queen Sirikit National Institute of Child Health; Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town; Shaare Zedek Medical center Helsinki committee; Sheba Medical center Helsinki committee; Tel Aviv Sourasly Medical center Helsinki committee; General University Hospital

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REFERENCES

- Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet*. (2008) 372:657–68. doi: 10.1016/S0140-6736(08)61279-9
- Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol*. (2015) 14:733–45. doi: 10.1016/S1474-4422(15)00069-1
- Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. *Neurology*. (2004) 63:1457–61. doi: 10.1212/01.WNL.0000142039.14522.1A
- Kingswood JC, d'Augeres GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. Tuberous Sclerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. *Orphanet J Rare Dis*. (2017) 12:2. doi: 10.1186/s13023-016-0553-5
- Adriaensen ME, Schaefer-Prokop CM, Stijnen T, Duyndam DA, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. *Eur J Neurol*. (2009) 16:691–6. doi: 10.1111/j.1468-1331.2009.02567.x
- Roach ES, Smith M, Huttenlocher P, Bhat M, Alcorn D, Hawley L. Diagnostic criteria: tuberous sclerosis complex. report of the diagnostic criteria committee of the national tuberous sclerosis association. *J Child Neurol*. (1992) 7:221–4. doi: 10.1177/088307389200700219
- Roth J, Roach ES, Bartels U, Jozwiak S, Koenig MK, Weiner HL, et al. Subependymal giant cell astrocytoma: diagnosis, screening, and treatment. Recommendations from the International tuberous sclerosis complex consensus conference 2012. *Pediatr Neurol*. (2013) 49:439–44. doi: 10.1016/j.pediatrneurol.2013.08.017
- Chan DL, Calder T, Lawson JA, Mowat D, Kennedy SE. The natural history of subependymal giant cell astrocytomas in tuberous sclerosis complex: a review. *Rev Neurosci*. (2018) 29:295–301. doi: 10.1515/revneuro-2017-0027
- Kotulska K, Borkowska J, Mandera M, Roszkowski M, Jurkiewicz E, Grajkowska W, et al. Congenital subependymal giant cell astrocytomas in patients with tuberous sclerosis complex. *Childs Nerv Syst*. (2014) 30:2037–42. doi: 10.1007/s00381-014-2555-8
- Kotulska K, Borkowska J, Roszkowski M, Mandera M, Daszkiewicz P, Drabik K, et al. Surgical treatment of subependymal giant cell astrocytoma in tuberous sclerosis complex patients. *Pediatr Neurol*. (2014) 50:307–12. doi: 10.1016/j.pediatrneurol.2013.12.004
- Sun P, Kohrman M, Liu J, Guo A, Rogerio J, Krueger D. Outcomes of resecting subependymal giant cell astrocytoma (SEGA) among patients with SEGA-related tuberous sclerosis complex: a national claims database analysis. *Curr Med Res Opin*. (2012) 28:657–63. doi: 10.1185/03007995.2012.658907
- Amin S, Carter M, Edwards RJ, Pople I, Aquilina K, Merrifield J, et al. The outcome of surgical management of subependymal giant cell astrocytoma in tuberous sclerosis complex. *Eur J Paediatr Neurol*. (2013) 17:36–44. doi: 10.1016/j.ejpn.2012.10.005
- Krueger DA, Northrup H. 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
- 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
- Tsai JD, Wei CC, Tsao TF, Hsiao YP, Tsai HJ, Yang SH, et al. Association between the growth rate of subependymal giant cell astrocytoma and age in patients with tuberous sclerosis complex. *Childs Nerv Syst*. (2016) 32:89–95. doi: 10.1007/s00381-015-2947-4
- de Vries 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) 13:157. doi: 10.1186/s13023-018-0901-8
- Wilde L, Eden K, de Vries P, Moss J, Welham A, Oliver C. Self-injury and aggression in adults with tuberous sclerosis complex: frequency, associated person characteristics, and implications for assessment. *Res Dev Disabil*. (2017) 64:119–30. doi: 10.1016/j.ridd.2017.03.007
- de Vries PJ, Wilde L, de Vries MC, Moavero R, Pearson DA, Curatolo P. A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). *Am J Med Genet Part C*. (2018) 178:309–20. doi: 10.1002/ajmg.c.31637

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