

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,800

Open access books available

142,000

International authors and editors

180M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Demographic, Clinical, and Radiographic Characteristics of Cerebral Aneurysms in Tuberous Sclerosis Complex

Mehdi Chihi, Ulrich Sure and Ramazan Jabbarli

Abstract

To date, little is known on the prevalence, incidence, and characteristics of intracranial aneurysms (IA) in patients with tuberous sclerosis complex (TSC). Based on our recent systematic review and two cases treated in our institute, we summarize the current evidence concerning the distinct characteristics of these aneurysms. In contrast to saccular IA in healthy adults, IA in TSC present commonly with large or even giant sac size and fusiform configuration, location predilection on the internal carotid artery remote from the branching zones, remarkable higher prevalence of pediatric cases, inverted sex-ratio, and suspected rapid growth. Although the pathogenesis of IA in TSC is still unclear, all these features might point to the crucial role a congenital defect in the development of IA rather than extrinsic or environmental factors. Furthermore, we discuss the enhancement of the regular magnetic resonance (MR) imaging screening suggested by the last recommendations of the 2012 International TSC Consensus Conference with cranial time-of-flight MR angiography in order to enable timely identification and treatment of frequently complex IA in TSC.

Keywords: tuberous sclerosis complex, intracranial aneurysms, subarachnoid hemorrhage, vascular disorders

1. Introduction

Tuberous sclerosis complex (TSC) is a rare multiorgan neuroendocrine disease and belongs to the group of phacomatoses. As a multisystemic genetic disorder with an autosomal dominant inheritance, it can affect any organ in the body [1]. In fact, the damage of one of two genes, TSC1 on chromosome 9 or TSC2 on chromosome 16, that produce the tumor suppressors “hamartin” and “tuberin” [2, 3] results in the formation of benign tumors so-called hamartomas, such as subependymal giant cell tumors (SGCT) in the brain. Interestingly, more than 70% of TSC cases are new mutations, and among them, 75% are caused by TSC2 mutations [4].

The Vogt triad, a combination of epilepsy, mental retardation and adenoma sebaceum, is only present in 29% of the cases [5]. Epilepsy and mental retardation are respectively in 25 and 45% of the cases absent [5]. Because of the relatively mild disease manifestations, TSC was underdiagnosed until the 1980s [6].

Cerebral aneurysms, also known as intracranial aneurysms (IA), are usually pouch-like (saccular) or spindle-shaped (fusiform) focal dilations in the wall of major arteries in the circle of Willis [7] that grow and present a certain risk of rupture. To date, arterial wall anomalies in TSC, particularly in aneurysms, were only described in the extracranial vasculature, such as aortic aneurysms or kidney aneurysms that were considered as the result of a congenital defect [8]. The distinct features of IA in these patients have not previously been addressed in the literature. Indeed, there are sporadic cases or small case series that reported the coexistence of IA and suggested their congenital origin.

First cases of TSC and IA were reported in 1974. The first patient was a 24-year old man who died after a subarachnoid hemorrhage (SAH), and the ruptured aneurysm of the right middle cerebral artery was diagnosed at autopsy [9]. The second patient was a 12-year old girl that presented in 1965 with a sudden blurry vision, and bilateral aneurysms of both internal carotid arteries (ICAs) involving the region of the carotid siphon were diagnosed [10].

Heritable connective tissue disorders such as Marfan syndrome, Ehlers-Danlos Syndrome, Loeys-Dietz syndrome and autosomal dominant polycystic kidney disease (ADPKD) are commonly associated with small saccular aneurysms [10]. Our recent systematic review of the English literature [11] is the first to describe the characteristics of IA in TSC in comparison to the features of IA in healthy adults. Despite the eventuality of a congenital origin in TSC, there are some distinct features that characterize IA in TSC and differentiate them from common nonsyndromal IA. The purpose of this book chapter is to give an overview on the particular demographic, clinical, and radiologic features through a case illustration and discuss the possible natural history of IA in TSC patients. Patient informed consent was obtained.

2. Epidemiology

TSC is a rare condition. It has a birth incidence of 1 per 5800 and an incidence of 1 per 30,000 in the general population [6]. From all cases between 1900 and 2018 that were published in the English literature, only 33 patients with 42 IA were found [11]. But the incidence of IA in TSC might be higher as reported, as no screening trial has been performed yet. Furthermore, according to the recommendations of the 2012 TSC Consensus Conference [12], the MRI at diagnosis and every 1–3 years until the age of 25 years does not involve a special sequence for the vascular system, so-called time-of-flight MR angiography (TOF-MRA). This circumstance increases the risk of overlooking small aneurysms.

3. Characteristics of cerebral aneurysms in TSC

3.1 Case illustration

A 2.5-year-old child presented with new-onset focal seizures characterized by rightward head deviation and rhythmic movements of the right arm. Seizures were treated with Vigabatrin and were controlled. The child was born at term of 37 weeks gestation to a healthy mother who had an uncomplicated pregnancy. Further evaluation revealed multiple rhabdomyomas on echocardiography, subependymal tubers on cranial MRI leading to the diagnosis of TSC. Additionally, a left cavernous lesion was detected on MRI. A TOF-MRA showed an 8-mm-diameter left cavernous ICA aneurysm. A year later, a control MRI revealed a rapid growth of the aneurysm whose diameter reached 15.5 mm (**Figure 1**). At the age of 14 months, the child

presented with his mother to our neurosurgical department. Because of the aneurysmal rapid growth, the decision to treat the aneurysm was made and a digital subtraction angiography (DSA) was performed (**Figure 2**). The aneurysm was treated by embolization and parent vessel occlusion. After treatment, the patient tolerated the total occlusion of the ICA and no neurological deficits were noticed.

3.2 Demographic characteristics

The collected series [11] showed a specific demographic pattern. In particular, the male/female ratio was 1.9:1 and 66.7% of the patients were under the age of 18, among them 36.4% were 2 years of age or younger.

3.3 Clinical characteristics

Most IA in patients with TSC were diagnosed incidentally (36.4%) or due to a new onset of a neurological deficit (21.2%). IA were ruptured in only 7.1% of the cases [11].

3.4 Radiological characteristics

The most frequent location of IA was the anterior circulation (85.7%) in favor of the ICA (61.9%), where aneurysms originated remote from branching zones. Of the 42 IA, 57.1% were large (size: 10–24 mm) or giant (size: ≥ 25 mm) and 45.2% had a fusiform configuration. Multiple aneurysms were seen only in 21.2% of the cases and a rapid growth was described and documented only in 2 patients (6%) [11, 13].

3.5 Summary and comparison with other series

Cerebral aneurysms in TSC have distinct demographic, clinical and radiological features. Indeed, comparing TSC patients with those of the unruptured cerebral aneurysm Study of Japan (UCAS Japan) [14], significant differences are found between both series in the location on the ICA (61.9 vs. 34.1%, respectively), large/giant size (57.1 vs. 10.4%, respectively) and proportion of multiple

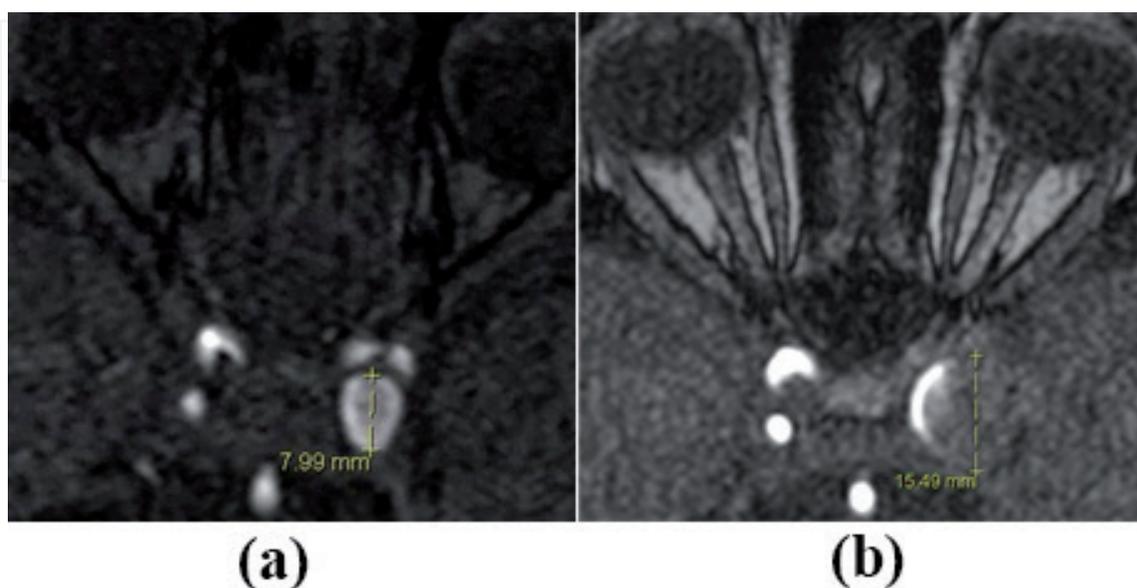


Figure 1. TOF-MRA showing an incidental fusiform left cavernous ICA aneurysm (8 mm) of a 2.5-year-old child (a) with a rapid aneurysmal growth (+7.5 mm diameter within 12 months of period). (b) ICA: internal carotid artery, TOF-MRA: time-of-flight-magnetic resonance angiography.

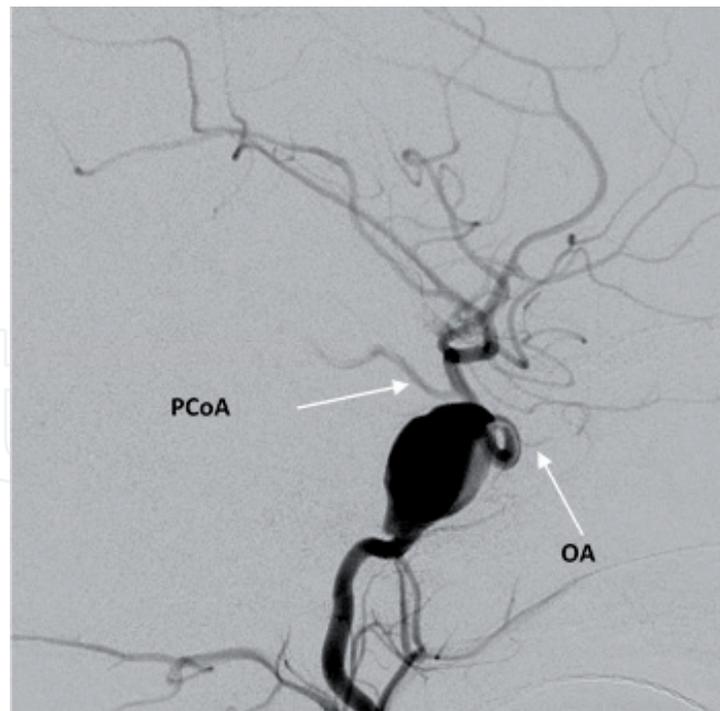


Figure 2.

DSA showing a lateral view of the fusiform left cavernous ICA aneurysm, obtained when the child was 14 months old. DSA: digital subtraction angiography, ICA: internal carotid artery, OA: ophthalmic artery, PCoA: posterior communicating artery.

IA (21.2 vs. 13.9%, respectively). Comparing TSC patients with individuals suffering from giant aneurysms, [15] a difference in the location of the IA (anterior vs. posterior circulation, respectively) and in patients' demographics are noticed, as giant IAs frequently manifest in women and during the fifth and sixth decades. Comparing TSC patients with pediatric series [16], several similarities are noticed, including the male predominance and high frequency of large/giant and fusiform aneurysms. However, the location on the ICA remote from branching zones remains the distinct characteristic of TSC.

A further comparison of IA in TSC patients with those with ADPKD [7] shows notable differences in the location on the ICA (61.9 vs. 16.8%, respectively), rupture status (7.1 vs. 37.9%, respectively), large/giant size (57.1 vs. 11.6%, respectively), fusiform configuration (57.1 vs. 2.1%, respectively), proportion of multiple IA (21.2 vs. 45.3%, respectively) and patient's median age (10.5 vs. 48.5 years, respectively).

The prevalence of IA in patients with TSC was retrospectively estimated to be 0.74% during a 10-year period in a cohort of 404 patients [17]. This is definitely lower than the prevalence of IA in the general population (3.2%) [18], but slightly higher than that of the incidental findings of IA on brain MRI after screening of "asymptomatic individuals" in the general population (0.35%) [19]. In a large series of patients with heritable connective disorders, the prevalence of IA during a 10-year period was estimated to be 14% by Marfan syndrome, 12% by Ehlers-Danlos syndrome and 28% by Loeys-Dietz syndrome [20]. Patients were adult individuals (mean age: 49.4 vs. 41.7 vs. 36.5, respectively) with a male/female equidistribution or female predominance (49 vs. 82 vs. 52%). IA were small (mean size: 4.4 vs. 6.9 vs. 4.8 mm), mostly saccular (75 vs. 64.3 vs. 87.5%), located on the ICA (75 vs. 85.7 vs. 62.5%) and unruptured (0 vs. 14.3 vs. 12.5%) [20].

In contrast, TSC patients are mostly young male individuals that present with asymptomatic, unruptured, large/giant, fusiform aneurysms that are located on the ICA, remote from the branching zones, with an eventual rapid growth. These

characteristics may support the idea that IA in patients with TSC are characteristically different from other syndromal and nonsyndromal aneurysms.

4. Diagnostic modalities, treatment strategies, and outcome

4.1 Diagnostic modalities

In our systematic review [11], digital subtraction angiography (DSA) was the most common diagnostic modality (57.6%) for the identification of IA followed by MRI (30.3%). DSA remains the gold-standard in the diagnosis of IA. However, because of the crucial technological advances, MR angiography at 3 Tesla was found to have a high positive predictive value (mean: 93.4%) and high sensitivity for the detection of unruptured IA (74.1% for aneurysms <3 mm and 100% for aneurysms ≥3 mm) [21]. Furthermore, contrast-free 3D-TOF-MRA at 3 Tesla accurately identifies the presence of IA and may replace DSA as a contrast-free, noninvasive, and nonradiation-based modality for the diagnosis and screening of IA [22].

4.2 Treatment strategies

Several treatment strategies were performed including aneurysm clipping and endovascular coiling. However, because of the complex morphology of IA with often-times fusiform and/or giant aneurysm sac, many other techniques as surgical ICA occlusion after superficial temporal artery-MCA bypass or stent-assisted coiling or endovascular ICA occlusion were also performed [11]. In the last two decades, an increase in endovascular treatment of IA was noticed. Nevertheless, the proportion of microsurgical vs. endovascular treatment was almost the same in the pooled TSC cohort. This circumstance might be related to high prevalence of above-mentioned complex IA, which are less eligible for conventional endovascular treatment. However, recent improvements in neuro-interventional radiology such as flow-diverters might enhance the indications to endovascular treatment.

4.3 Outcome

Among 16 patients that were operated, neurological outcome was reported in only 12 patients. Six patients had postoperatively no neurological deficits, three patients met an improvement of their focal neurological deficits (Oculomotor paresis/palsy, visual loss) and four patients experienced focal deficits (Oculomotor paresis, facial palsy and hemiparesis) [11].

5. Pathogenesis

The natural history of saccular aneurysms is to date well established, as higher hemodynamic shear stress and consequently stronger flow acceleration frequently promote aneurysm formation in cerebral vessel bifurcations [23]. In contrast, natural history of cerebral aneurysms remote from the branching zones as fusiform aneurysms still remains unclear. Some authors found a correlation between fusiform aneurysms and larger aortic root dimension, suggesting a shared pathophysiological mechanism with aortopathy [24, 25]. However, the lack of histological findings of IA in TSC patients represents a considerable drawback in understanding aneurysm pathogenesis in this disease. The sole histological analysis was performed in 1980 at autopsy on the cerebral aneurysm wall of a 26-year-old woman.

It revealed a “relatively hypocellular hyaline fibrous tissue.” There were neither elastic fibers nor evidence of inflammation or necrosis [26].

The question of aneurysm formation always focused on their acquired vs. congenital nature. Many arguments plead in favor of a congenital defect of the arterial wall. First, the higher frequency of pediatric cases (66.7%) and the distinct location of IA unrelated to branching zones [11] might indicate the inferiority of extrinsic/environmental factors, which are considered to play a crucial role in the genesis of nonsyndromal IA in healthy adults [27]. Furthermore, the suspected rapid growth [11, 13] of these aneurysms could also support the presence of a genetic predisposition to IA development. Moreover, there is evidence of the pathogenesis of extracranial aneurysms in TSC that are likely caused by disorders of the connective tissue [28–31]. In fact, the postoperative pathologic examination of a large thoracoabdominal aneurysm wall of a 3-year-old child with a TSC2 mutation revealed a subintimal proliferation of smooth muscle cells (SMC) [32]. Further, it was demonstrated that the de-differentiation of aortic SMC through the activation of mammalian target of rapamycin complex 1 (mTORC1) signaling, characterized by increased proliferation of SMC and decreased expression of contractile proteins, contributed to the formation of the aneurysm [32]. Indeed, *in vitro* and *in vivo* evidence that the effect of TSC2 deficiency on vascular SMC is primarily driven by increased mTORC1 signaling was provided [32]. And these findings plead in favor of a coexistence of both diseases rather than a coincidence.

Therefore, genetic and histopathological studies must further investigate the anomalies of the vascular connective tissue in TSC, especially in the wall of intracranial aneurysms to better understand IA formation.

6. Recommendations

Morbidity and quality of life during adulthood in patients with TSC are determined by the neurological manifestations [33]. Life expectancy can be reduced by uncontrolled seizures and tuber burden that significantly affect the cognitive impairment of patients [34]. Indeed, 13 cases of “unclear death circumstances” preceded by seizures were retrospectively reported among 639 patients with TSC in two different investigations at the Mayo Clinic [35] and the Bath TSC Clinic [36]. Status epilepticus was listed in 9 cases and sudden unexplained death in epilepsy in 4 cases. Because of advances in diagnostic procedures and medical management, life expectancy of patients with TSC has drastically improved during the last 2 decades and the number of patients who survive to middle age and beyond is increasing [37].

The relatively young age of the individuals with TSC, the disproportionately high number of large/giant IA and the well-described rapid aneurysm growth in two children are sufficient arguments to prompt aneurysm treatment. Additionally, three cases of SAH were described. As long as the real incidence of IA in TSC remains unknown, the risk of aneurysm rupture in this population cannot be estimated. Therefore, the enhancement of the 2012 International TSC Consensus Conference with a cranial TOF-MRA at diagnosis and at the control examinations every 1–3 years might be reasonable for young individuals [11]. Prospective IA screening studies on a national and even international scale are urgently needed.

7. Conclusion

The epidemiology and pathogenesis of intracranial aneurysm formation in patients with TSC remains unclear. IA in TSC seem to have distinct characteristics

that differentiate them from other individuals with IA. Several demographic, clinical and radiological arguments plead in favor of a coexistence of both entities rather than a coincidence, due to a congenital defect of the arterial wall. Therefore, large population-based patient registers, prospective screening studies as well as genetic and histopathological studies are required to improve the understanding of IA formation in TSC. In this way, regular MRI screening with TOF-MRA seems to be appropriate in TSC young individuals.

8. Conclusions

Aneurysms were well described in the extracranial vasculature of patients with tuberous sclerosis complex (TSC) such as aortic and kidney aneurysms, where anomalies of the vascular connective tissue have been histopathologically and genetically investigated. In contrast, cerebral aneurysms remain uncommon and their incidence totally unknown. A recent systematic review of the literature found 33 patients with 42 intracranial aneurysms (IA) that seem to have distinct characteristics compared to other syndromal and nonsyndromal IA. Indeed, TSC patients with cerebral aneurysms were found to be young male individuals that present with large/giant, fusiform, mostly asymptomatic, and unruptured aneurysms, located on the internal carotid artery unrelated to branching zones, with an eventual rapid growth. Although the pathogenesis of IA in TSC is still unclear, several demographic, clinical, and radiological arguments plead in favor of the coexistence of both entities, due to a congenital defect of the cerebral arterial wall. As long as the real incidence of IA in TSC remains unknown, the risk of aneurysm rupture in this population cannot be estimated, especially that three cases of subarachnoid hemorrhage were reported. Therefore, prospective screening, genetic and histopathological studies are urgently needed to improve the understanding of the pathogenesis and epidemiology of IA formation in TSC. This cannot be achieved without enhancing the recommendations of the 2012 International TSC Consensus Conference with a cranial TOF-MRA at diagnosis and all regular screening consultations.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this chapter.

IntechOpen

IntechOpen

Author details

Mehdi Chihi*, Ulrich Sure and Ramazan Jabbarli
Department of Neurosurgery and Spine Surgery, University Hospital Essen,
University Duisburg-Essen, Essen, Germany

*Address all correspondence to: mehdi.chihi@uk-essen.de

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, et al. Tuberos sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberos Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013;**49**:243-254
- [2] Green AJ, Johnson PH, Yates JR. The tuberous sclerosis gene on chromosome 9q34 acts as a growth suppressor. *Human Molecular Genetics*. 1994;**3**:1833-1834
- [3] Green AJ, Smith M, Yates JR. Loss of heterozygosity on chromosome 16p13. 3 in hamartomas from tuberous sclerosis patients. *Nature Genetics*. 1994;**6**:193
- [4] Hyman MH, Whittemore VH. National Institutes of Health consensus conference: Tuberous sclerosis complex. *Archives of Neurology*. 2000;**57**:662-665
- [5] Gomez MR. *Criteria for Diagnosis. Tuberous Sclerosis*. 2nd ed. New York: Raven Press; 1988. pp. 9-19
- [6] Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Annals of the New York Academy of Sciences*. 1991;**615**:125-127
- [7] Nurmonen HJ, Huttunen T, Huttunen J, Kurki MI, Helin K, Koivisto T, et al. Polycystic kidney disease among 4,436 intracranial aneurysm patients from a defined population. *Neurology*. 2017;**89**(18):1852-1859. DOI: 10.1212/WNL.0000000000004597
- [8] Beltramello A, Puppini G, Bricolo A, Andreis IAB, El-Dalati G, Longa L, et al. Does the tuberous sclerosis complex include intracranial aneurysms? *Pediatric Radiology*. 1999;**29**:206-211
- [9] Snowdon J. Cerebral aneurysm, renal cysts and hamartomas in a case of tuberous sclerosis. *British Journal of Urology*. 1974;**46**:583-583
- [10] Davidson S. Tuberous sclerosis with fusiform aneurysms of both internal carotid arteries manifested by unilateral visual loss and papilledema. *Bulletin of the Los Angeles Neurological Societies*. 1974;**39**:128-132
- [11] Chihi M, Gembruch O, Oppong MD, Chen B, Dinger TF, Barthel L, et al. Intracranial aneurysms in patients with tuberous sclerosis complex: A systematic review. *Journal of Neurosurgery: Pediatrics*. 2019;**24**:174-183
- [12] Krueger DA, Northrup H, Roberds S, Smith K, Sampson J, Korf B, et al. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberos Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013;**49**:255-265
- [13] Yi J, Galgano M, Tovar-Spinoza Z, Deshaies E. Coil embolization of an intracranial aneurysm in an infant with tuberous sclerosis complex: A case report and literature review. *Surgical Neurology International*. 2012;**3**:129-129
- [14] Investigators UJ. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *New England Journal of Medicine*. 2012;**366**:2474-2482
- [15] dos Santos MLT, Spotti AR, dos Santos RMT, Borges MA, Ferrari AF, Colli BO, et al. Giant intracranial aneurysms: Morphology and clinical presentation. *Neurosurgical Review*. 2013;**36**:117-122
- [16] Beez T, Steiger H-J, Hänggi D. Evolution of management of intracranial aneurysms in children: A systematic review of the modern literature. *Journal of Child Neurology*. 2016;**31**:773-783

- [17] Boronat S, Shaaya EA, Auladell M, Thiele EA, Caruso P. Intracranial arteriopathy in tuberous sclerosis complex. *Journal of Child Neurology*. 2014;**29**:912-919
- [18] Vlaskovits MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: A systematic review and meta-analysis. *The Lancet Neurology*. 2011;**10**:626-636
- [19] Morris Z, Whiteley WN, Longstreth W, Weber F, Lee Y-C, Tsushima Y, et al. Incidental findings on brain magnetic resonance imaging: Systematic review and meta-analysis. *The BMJ*. 2009;**339**:b3016
- [20] Kim S, Brinjikji W, Kallmes DF. Prevalence of intracranial aneurysms in patients with connective tissue diseases: A retrospective study. *American Journal of Neuroradiology*. 2016;**37**:1422-1426
- [21] Mine B, Pezzullo M, Roque G, David P, Metens T, Lubicz B. Detection and characterization of unruptured intracranial aneurysms: Comparison of 3 T MRA and DSA. *Journal of Neuroradiology*. 2015;**42**:162-168
- [22] Li M-H, Li Y-D, Tan H-Q, Gu B-X, Chen Y-C, Wang W, et al. Contrast-free MRA at 3.0 T for the detection of intracranial aneurysms. *Neurology*. 2011;**77**:667-676
- [23] Alfano JM, Kolega J, Natarajan SK, Xiang J, Paluch RA, Levy EI, et al. Intracranial aneurysms occur more frequently at bifurcation sites that typically experience higher hemodynamic stresses. *Neurosurgery*. 2013;**73**:497-505
- [24] Can A, Xu J, Volovici V, Dammers R, Dirven CM, MacRae CA, et al. Fusiform aneurysms are associated with aortic root dilatation in patients with subarachnoid hemorrhage. *World Neurosurgery*. 2015;**84**:1681-1685
- [25] Yu Y, Huang Q, Liu J. Intracranial saccular aneurysm formation is different from similar extracranial lesions: A hint from the correlation between intracranial fusiform aneurysms and arterial root dilatation. *World Neurosurgery*. 2015;**84**:1558
- [26] Ho K-L. Intraventricular aneurysm associated with tuberous sclerosis. *Archives of Neurology*. 1980;**37**:385-386
- [27] Brown RD Jr, Broderick JP. Unruptured intracranial aneurysms: Epidemiology, natural history, management options, and familial screening. *The Lancet Neurology*. 2014;**13**:393-404
- [28] Millar A, Gilbert R, Brown R, Immelman E, Burkimsher D, Cywes S. Abdominal aortic aneurysms in children. *Journal of Pediatric Surgery*. 1996;**31**:1624-1628
- [29] Tamisier D, Goutière F, Sidi D, Vaksman G, Bruneval P, Vouhé P, et al. Abdominal aortic aneurysm in a child with tuberous sclerosis. *Annals of Vascular Surgery*. 1997;**11**:637-639
- [30] Tsukui A, Noguchi R, Honda T, Tobita T, Fukuda S, Shimoji K. Aortic aneurysm in a four-year-old child with tuberous sclerosis. *Pediatric Anesthesia*. 1995;**5**:67-70
- [31] van Reedt D, Dortland RW, Bax NM, Huber J. Aortic aneurysm in a 5-year-old boy with tuberous sclerosis. *Journal of Pediatric Surgery*. 1991;**26**:1420-1422
- [32] Cao J, Gong L, Guo D-C, Mietzsch U, Kuang S-Q, Kwartler CS, et al. Thoracic aortic disease in tuberous sclerosis complex: Molecular pathogenesis and potential therapies in *Tsc2*^{+/-} mice. *Human Molecular Genetics*. 2010;**19**:1908-1920

[33] Leung AK, Robson WLM. Tuberos scleros complex: A review. *Journal of Pediatric Health Care*. 2007;**21**:108-114

[34] Winterkorn EB, Pulsifer MB, Thiele EA. Cognitive prognosis of patients with tuberous sclerosis complex. *Neurology*. 2007;**68**:62-64

[35] Shepherd CW, GOMEZ MR, Lie J, CROWSON CS. Causes of death in patients with tuberous sclerosis. In: *Mayo Clinic Proceedings*. USA: Elsevier; 1991. pp. 792-796

[36] Amin S, Lux A, Calder N, Laugharne M, Osborne J, O'callaghan F. Causes of mortality in individuals with tuberous sclerosis complex. *Developmental Medicine and Child Neurology*. 2017;**59**:612-617

[37] Coppus A. People with intellectual disability: What do we know about adulthood and life expectancy? *Developmental Disabilities Research Reviews*. 2013;**18**:6-16