Tuberous sclerosis complex, Serbian referral center experience

Kompleks tuberozne skleroze – kliničko iskustvo jednog referentnog centra u Srbiji

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Abstract

Background/Aim. Common features of tuberous sclerosis complex (TSC) arise from the formation of hamartomas both in the brain and multiple organ systems, mainly due to a mutation in one of two genes, TSC1 or TSC2, with well described inter- and intrafamilial different phenotypic outcomes. The aim of this work was to make a synthesis of the patients data with diagnosed tuberous sclerosis in order to better understand the disease in our environment. Methods. We reviewed retrospectively the clinical records of all patients with TSC, diagnosed and regularly followed at the Clinic of Neurology and Psychiatry for Children and Youth in Belgrade, Serbia during the period of more than two decades. Statistical analyses were performed using descriptive statistics as well as the Fisher’s exact test. Results. Cohort of 44 patients with the diagnosis of definitive TSC were included. The mean age at last follow-up was 19.4 years [age range 1–58, standard deviation (SD) 11.8]. Family history of TSC was noted in 25% of patients. Dermatological manifestations were described in 93.2%, retinal astrocytoma and cardiomyopathy was found in 36.4% each, nephrological manifestations in 34.1% and lymphangiomyomatosis was diagnosed in two female patients. All patients presented with the structural lesions of central nervous system; epilepsy was diagnosed in 88.6%, out of whom 59% of patients had seizure onset in the first year of life. The West syndrome was diagnosed in 27.3% of patients. Complete seizure control was achieved in 30.8%, in a majority with valproic acid or carbamazepine, but also with topiramate, lamotrigine and vigabatrin. At least two antiepileptic drugs were administered in 82% of patients. Mental retardation was noted in 50% of patients. Psychiatric manifestations were found in 40.9%, with attention deficit hyperactivity disorder diagnosed in 27.3%, autism spectrum disorder in 13.6 %, and psychosis and depression observed in 11.4% each. Conclusion. This kind of synthesis of the data certainly contributes to better understanding of the disease in our environment, as TSC, although well-known disease, still remains diagnostic and therapeutic challenge in daily clinical practice.

Key words: tuberous sclerosis; epilepsy; diagnosis; drug therapy; Serbia.

Apstrakt

Uvod/Cilj. Karakteristike kompleksa tuberozne skleroze uzrokovane su formiranjem hamartoma u mozgu i velikom broju organs, najčešće kao posledice mutacije u jednom od dva gena, TSC1 ili TSC2, sa veoma dobro dokumentovanim inter- i intrafamilijarnom razlikom u fenotipu. Cilj ovog rada bio je da se sintetišu podaci o bolesnicima sa dijagnostikovanom tuberoznom sklerozom radi boljeg razumевања bolesti u našem okuženju. Metode. Neka karakteristike slučajeva su proučavane u kliničkome centru u Beogradu, Srbija, tokom vremenskog perioda dužeg od dve decenije. Statistička analiza sprovedena je mera- ma deskriptivne statistike, kao i upotrebom Fisherovog testa. Rezultati. Anališena je kohort od 44 bolesnika sa dijagnostikom definitivnog kompleksa tuberozne skleroze. Srednja veličina je iznosi 19.4 godine [razvijen od 1–58, standardna devijacija (SD) 11,8 godine]. U 25% bolesnika je identifikovana dijagnostikovana tuberozna skleroza. Dermatološke manifestacije opisane su kod 93,2%, retinalni astrocitomi i kardiomyopati je kod 36,4% bolesnika, a nekrhoška manifestacije kod 34,1% bolesnika. Sve bolesnike je identifikovana s strukturnim ležirom centralnog nervnog sistema; epilepsija je identifikovana kod 88,6% bolesnika, r. 59% bolesnika je pojavila se u prvih godinama života. Westov syndrom je identifikovana kod 27,3% bolesnika. U 82% bolesnika su primenjene dugogodišnje antiepileptičke lekove. Mentalna retardacija je pronađena kod 50% bolesnika. Psihijatričke manifestacije su identifikovane kod 40,9%, sa utvrđenom deficit hyperaktivnosti kod 27,3%, autismom kod 13.6%, i psihosom kod 11.4% bolesnika. Završni zaključak. Ovaj vrsta sintezisanja podataka sigurno doprinosi boljem razumевањu bolesti u našem okuženju, jer se TSC, sa znanstveno poznatom bolesti, još uvекo zna kao dijagnostički i terapijski izazov u dnevnom praksi.

Key words: tuberous sclerosis; epilepsy; diagnosis; drug therapy; Serbia.

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As a multisystem genetic disease with variable expression, tuberous sclerosis complex (TSC) represents a challenge for both diagnosing and management of different aspects of the disease. The estimated frequency of TSC ranges from 1:6,000 to 1:10,000 live births and population prevalence is around 1 in 20,000. Approximately 85% of patients with TSC have a mutation in one of two genes TSC1 or TSC2, with described inter- and intrafamilial different phenotypic outcomes. Common features of TSC arise from the formation of hamartomas in multiple organ systems. The central nervous system (CNS) implies specific brain lesions, such as cortical tubers, subependymal nodules (SEN), subependymal giant cell astrocytomas (SEGA) and heterotopic bands in the white matter, clinically often manifested as intractable epilepsy, mental retardation, autistic spectrum disorder, psychosis and behavioral disorders. Cortical tubers are seen as the primary site of epileptogenesis, even though non-tuber regions of cortex may be capable of generating seizures, that present a challenge in surgical treatment of epilepsy in TSC. Early onset of seizures, during the first year of life, carries a high risk of neurodevelopmental and cognitive impairments. The seizure control must be accomplished as early as possible in the course of the disease in order to achieve more favorable outcome of condition. Recommendations for the treatment of epilepsy in the patients with TSC are given at an international TSC consensus conference in Rome 2012. The latest clinical controlled study reflects the favorable effect of adjunctive everolimus therapy for pharmacoresistant focal epilepsy associated with TSC. Characteristic multisystem involvement in TSC includes the skin lesions, kidney and lung lesions, retinal hamartomas and heart rhabdomyomas, that all contribute significantly to the severity of clinical presentation of disease. The individuals with TSC also have a range of behavioral, psychiatric, intellectual, academic, neuropsychologic and psychosocial difficulties. Their importance has become more visible by introducing a new term – TSC associated neuropsychiatric disorders (TAND), which can be assessed using a specific checklist.

Methods

We reviewed retrospectively the clinical records of all patients with TSC, diagnosed and regularly followed at the Clinic of Neurology and Psychiatry for Children and Youth in Belgrade, Serbia, during the period of more than two decades (1993–2015). The patients were included if they met the International tuberous sclerosis diagnostic clinical criteria for definite TSC. Charts were reviewed for the history of multisystem visceral involvement, morphological CNS manifestations and epilepsy, including age of onset, occurrence and frequency of multiple seizure types, level of the seizure control, response to antiepileptic non-pharmacological therapy and/or antiepileptic drugs (AEDs). Intellectual impairment was seen through the intelligence quotient (IQ), and where IQ was not obtained (in 7 patients), a developmental quotient (DQ) was considered equal parameter of intellectual capacity. Patients with an IQ or DQ lower than 70 were considered to be the subjects with mental insufficiency. Psychiatric pathologies, such as, behavior and mood disorders, autism spectrum disorder (ASD) and psychosis, were evaluated and diagnosed by psychiatrist. We also assessed the relationship between the neurological and psychiatric manifestations of TSC, such as seizure control in certain psychiatric disorders.

Statistical analyses were performed using descriptive statistics (absolute and percentage values with the determination of the arithmetic mean and standard deviation) as well as the Fisher’s exact test.

Results

A cohort of 44 patients with the diagnosis of definitive TSC were included, among them 26 were females, and 18 males. The mean age at last follow-up was 19.4 years (age range 1–58, standard deviation – SD 11.8). The family history for TSC was noted in 11 (25%) patients. The mutational analysis was available for 10 (6 females, 4 males) patients only. The results of study disclosed the TSC1 mutation in 3, the TSC2 mutation in 5 and no mutation in 2 patients. The testing using the multiplex ligation-dependent probe amplification (MLPA), or other method was advised to exclude the presence of possibly pathogenic deletions of single or multiple exons.

All patients presented with the structural lesions of central nervous system, among them 93.2% had subependymal nodules and 81.8% had cortical tubers. The subependymal giant cell astrocytoma (SEGA) was diagnosed in 15 (34.1%) patients and it was successfully operated in 10 patients, but one female patient who was reoperated at the age of 4 years due to tumor rest recurrence. Dermatological manifestations were described in 41 (93.2%) patients; hypomelanotic macules were present in 81.8%, facial angiofibromas in 68.2%, shagreen patch was observed in 31.8%, hyperpigmentations in 22.7% and other types of skin lesions in 25% of patients. Retinal astrocytoma and cardiac rhabdomyomas was found in 36.4% each. Nephrological manifestations were present in

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34.1%, among them 27.3% had renal cysts and 53.3% renal angiomyolipoma (AML). Two patients with multiple AML were nephrectomised. Lymphangioleiomyomatosis (LAM) was diagnosed in 2 female patients, after the age of 20 and 40 years.

Focal neurological deficit was described in 36.4% and slowed early psychomotor development was seen in 22.7%. Mental retardation was present in 50% of patients, with the following distribution of 27.2% having mild, 22.7% moderate, 9.1% severe, 13.6% profound mental retardation and remaining 27.2% of patient were without accurate level of mental retardation.

Epilepsy was diagnosed in 39 (88.6%) patients with TSC. The epileptic seizures were revealing clinical manifestation of the TSC in almost all patients with the TSC and epilepsy, but 2 in whom the first manifestation was congenital rhabdomyoma. In the remaining 5 patients without epilepsy, the first manifestations of the disease were: in a 3-year old girl a headache and double vision as a sign of increased intracranial pressure, indicating SEGA; in a 13-years old girl ungual fibroma; in a 15-years old boy weight loss and leg pain, when the skin lesions were noticed; in a 15-years old girl an acute psychosis with productive symptoms and in the fifth female patient skin lesions in adulthood, after the diagnosis of TSC was established in her daughter. The mean age of the first seizure onset was 2.8 years (range from 1 month to 16 years, SD 4.1), with 59% of patients with seizure onset in the first year of life. The West syndrome was diagnosed in 27.3% of patients. In 16.7% of patients with the West syndrome, the focal seizure preceded the occurrence of infantile spasms. Of 12 patients with a history of West syndrome, 11 (91.7%) were cognitively impaired, compared with 11 of 27 (40.7%) patients without a history of West syndrome (p = 0.003). The focal seizures were present in 84.6% of patients with epilepsy, of which secondary generalized seizures were recorded in 39.3% of cases. Coexistence of focal seizures and infantile spasms were described in 23.1% of patient with the TSC and epilepsy. Other seizure types were tonic, atonic and absences. The complete seizure control was achieved in 30.8%, in a majority with valproic acid or carbamazepine, but also with topiramate, lamotrigine and vigabatrin. At least two antiepileptic drugs were administered in 82% of patients.

Psychiatric manifestations of TSC in our group of patients were present in 40.9%, with attention deficit hyperactivity disorder (ADHD) diagnosed in 27.3%, ASD in 13.6%, and psychosis and depression present in 11.4% each. All patients with TSC and ADHD had epilepsy, and one third maintained the complete seizure control while on medication. One-quarter of patients with ADHD and TSC had ASD, and 75% of patients with ADHD and TSC had mental retardation. Of 6 patients with TSC and ASD, 5 had epilepsy diagnosed, of whom 3 with the complete seizure control and one with more than 75% reduction in the seizure frequency. The opposite was seen in the group of patients with TSC and psychosis, where unfavorable seizure control was present in 3 out of 4 patients.

We compared two subgroups of patients with TSC and with/without SEGA and we found slight differences in some clinical characteristics, but not reaching statistical significance (Table 1). Of 15 patients with SEGA, 5 had a positive family history for TSC compared with 6 of 29 patients without SEGA. The West syndrome was diagnosed in 5 patients with SEGA and in 7 without SEGA, neurological deficits were seen in 8 patients with SEGA compared with 8 patients without SEGA. Intellectual impairment was present in 8 patients with SEGA compared with 14 patients without SEGA. We did not find a higher incidence of neuropsychiatric disorders (ASD, ADHD, psychosis, depressive disorder) in the group of patients with SEGA compared with the patients without SEGA.

**Table 1**

| Clinical parameter                  | Patients with SEGA n (%) | Patients without SEGA n (%) |
|------------------------------------|--------------------------|-----------------------------|
| Family history                     | 5 (33.3)                 | 6 (20.7)                    |
| West syndrome                      | 5 (33.3)                 | 7 (21.4)                    |
| Neurological deficits              | 8 (53.3)                 | 8 (27.6)                    |
| Intellectual impairment            | 8 (53.3)                 | 14 (48.3)                   |
| Neuropsychiatric disorders         | 5 (33.3)                 | 11 (37.9)                   |

**Discussion**

A series of 44 patients with the diagnosis of definitive TSC was retrospectively assessed. Positive family history for TSC was seen in 25% of patients indicating a high level of *de novo* mutations, which is in concordance with data from the relevant literature. The molecular genetic studies were conducted only in a limited number of patients by sending samples abroad, due to the lack of this analysis in the country. The frequency of mutations in TSC2 is higher than in TSC1. Our limited experience confirms this observation (5/10 of our patients have mutation in TSC2 gene). There is some evidence from case series that mutations in TSC2 tend to result in more severe disease. No mutation is identifiable in 15%–20% of TS patients and these patients generally have milder clinical manifestations. Both of our patients (15 and 21 month old children) with no mutation identified had favorable seizure control and normal early psychomotor development, but the long-term clinical follow-up will be necessary.

SEGA, as a characteristic brain tumor, was present in 34.1% of our cohort, that is higher than usually described frequency of 10%–20% of patients with TSC. The probable reason is partly related to the selection bias. Our institution is the regional neuropaediatric reference center and often receives referrals of operated children with SEGA as early manifestation of the disease for further clinical monitoring. In our group, the dermatological manifestations were described in 93.2%, compared to up to 96% in a published series of patients. Retinal astroctyma were present in 36.4%, lower than usually described (around 50%). These benign retinal tumors tend to regress during the course of the disease and it is possible that this process occurred in our pa-
tients who were referred and diagnosed at later age. According to the data from the literature, cardiac rhabdomyomas was present in 20% to 60% of patients, depending on the age, and in our group it was seen, with cardiac ultrasound, in 36.4%. In the study of Jóźwiak et al. 13, of 154 patients, 48% of them had cardiac rhabdomyomas, the majority of which was asymptomatic. In 2 of our patients, the congenital cardiac rhabdomyoma was clinical TSC manifestation. In one of them, it was removed during the first year of life. Similar results were found in Osaka where percentage of registered cardiac rhabdomyomas was 49% 14. The nephropathological manifestations were present in 34.1% of our patients, among them 53.3% had AML. This is lower than expected (up to 80%) and one of the reasons may be the incomplete medical reports done in other institutions during the outpatient follow-up. LAM was diagnosed in 2 female patient only, although this manifestation is present in 40% of patients with TSC. LAM is related to older age and our patient mainly belonged to the population of children, youth and young adults. Only two of our patients with LAM were females and diagnosed at the age of 20 and 41 years. Johnson et al. 15, describing the characteristics of the disease and its progression in 57 female patients, stated 33.6 years as the mean age of onset of the first symptoms of LAM.

Intellectual impairment was present in 50% of our patients. Early studies described more frequent occurrence of intellectual impairment (60% and above), but the new studies state the frequency of 42% to 44%, noting the association of early seizure onset, presence of mixed seizure type and lower intellectual capacity 16,17.

The most common neurological manifestations of TSC was epilepsy, diagnosed in 88.6% of our patients which is a little higher than usually specified (85%) and the one of the reasons may be found in the most common indication (epilepsy) under which the patients were sent to our institution, making the sample highly selected on referral. The epileptic seizures are certainly most common first manifestation of the disease, however the first symptoms highly depend on the age at which the diagnosis is made (e.g., prenatal period - heart rhabdomyomas; adulthood - known family history) 18. Other characteristics of our patients were similar to the large retrospective study conducted by Chu-Shore et al. 19, that included 291 patients with TSC. They described 63.2% of patients with the seizure onset in the first year of life; 37% with the history of infantile spasms (IS) and epilepsy in remission in 33.5% of patients with TSC. The patients with the West syndrome showed a greater degree of cognitive impairment compared with the patients without history of IS, as it was seen in our group of patients. Mental retardation was observed in 76% of patients with IS and TSC 4, and early recognition and aggressive treatment of IS (especially with early given vigabatrin, in the first week after the IS appearance) may be of a great importance for a favorable outcome. The focal seizures may precede, coexist or emerge after the occurrence of IS in the patients with TSC. Some authors recommended the preventive use of vigabatrin in children with TS (e.g., cardiac rhabdomyoma) without spasms, but with the EEG abnormalities. They stated that such approach could be beneficial 13. We have not such clinical experience.

The most common psychiatric manifestation of the disease in our cohort was ADHD, diagnosed in 27.3% of patients, reaching the lower limit of indicated frequency of 30%–60% in the literature 20. Described association between ADHD and ASD in the patients with TSC in the literature, was also seen in our group (25%), as well as considerably high number of patients with ADHD and TSC that had developed mental retardation (75%). It was demonstrated that 60% of patients with mental retardation and TSC had ADHD diagnosed 20. Proportion of ASD in the general population is about 1%, while in the patients with TSC, this disorder is diagnosed more often, in 25%–50%. ASD in our cohort was described in 6 patients (13.6%), that is considerably higher than in the general population. Some children in our TSC group with soft and rare autistic traits were not diagnosed as ASD. In a review article, written by Curatolo et al. 21, a large number of studies on autism and related disorders in TSC was specified, stating a wide range of incidence of autism from 5% to 61%, but still emphasizing the personal experiences in their series of patients, estimating the percentage of autism at 26% in the patients with TSC. The different diagnostic tools for ASD were used with influence on the incidence of this condition. The risk factors for the development of ASD in TSC are localization of cortical tubers, malformation of cortical development, EEG localization related abnormality, epilepsy and “abnormal gene program”. Although it is stated that ASD in TSC is often associated with the occurrence of pharmaco-resistant epilepsy and epileptic encephalopathies, in our series of patients, this association was not observed. Of 5 patients with epilepsy and ASD, 3 had the stable, long-term, complete seizure control and one more than 75% reduction in the seizure frequency. Our patients with the seizure freedom mainly showed EEG low-amplitude, irregular, slow background activity. Occasional spike-wave discharges were noted in only one girl with ASD, TSC and diabetes mellitus as comorbid condition. However, in conclusion, we should remain restrained due to a small number of patients that had been analyzed. Disabling association of intractable seizures and ASD was mainly found in the TSC2 patients 22. Without molecular genetic study of all our patients we are not able to comment that finding in the literature.

Some authors present the data showing the association between SEGAs and ASD in the patients with TSC, that was not the case in our study group, but not reporting any significant common occurrence of SEGAs and ADHD, or depressive disorder, the same observation as it was seen in our cohort 21.

Since 2016, we prospectively started with administration of the tuberous sclerosis associated neuropsychiatric disorders (TAND) checklist 9 in all our patients with TSC. Standardized questionnaire in Serbian language will be used to better assess to the long-term mental development of patients.

Potential limitations of the study include the retrospective model disabling verification of longitudinal data that could be helpful to allow more precise prognostic indicators.

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and a relatively small size of cohort which could be insufficient to achieve results with greater power.

However this kind of synthesis of the data certainly contributes to better understanding of the disease in our environment, as tuberous sclerosis complex, although well-known disease, still remains diagnostic and therapeutic challenge in daily clinical practice.

Conclusion

The characteristics and frequencies of manifestations of the disease are shown in a series of 44 patients with the diagnosis of tuberous sclerosis complex.

Family history for TSC was noted in 25% of patients. Dermatological manifestations were described in 93.2%, rectal astrocytoma and cardiac rhabdomyomas was found in 36.4% each, nephrolithiasis manifestations in 34.1% and LAM was diagnosed in two female patients. All patients presented with the structural lesions of central nervous system; epilepsy was diagnosed in 88.6%, out of whom 59 % of patients had seizure onset in the first year of life. Psychiatric manifestations of TSC were present in 40.9%, with ADHD diagnosed in 27.3%, ASD in 13.6 %, and psychosis and depression present in 11.4% each.

Presented data will help to better understanding of TSC in our environment.

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REFERENCES

1. Northrup H, Krueger D A. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49(4): 243–54.
2. Jentzsch GM, Rix SG, Ojers S, Saffen D, Narayanan V. Evidence for population variation in TSC1 and TSC2 gene expression. BMC Med Genet 2011; 12: 29.
3. Wongs M. Mechanisms of epileptogenesis in tuberous sclerosis complex and related malformations of cortical development with abnormal glioneuronal proliferation. Epilepsia 2008; 49(1): 8–21.
4. Maczynski DA, Castello DJ, Halpern EF, Thiele EA. Infantile spasms in tuberous sclerosis complex: Prognostic utility of EEG. Epilepsia 2009; 50(2): 290–6.
5. Bombardieri R, Pinci M, Maureen R, Cerminara C, Curatolo P. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. Eur J Paediatr Neurol 2010; 14(2): 146–9.
6. Carmai R, Maureen R, Bombardieri R, Vigozzo F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy Behav 2011; 22(4): 735–9.
7. Krueger D A. Management of CNS-related Disease Manifestations in Patients With Tuberous Sclerosis Complex. Curr Treat Options Neurol 2013; 15(5): 618–33.
8. French JA, Lawson JA, Yapici Z, Ikeda H, Pinski M, Nabbout R, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): A phase 3, randomised, double-blind, placebo-controlled study. Lancet 2016; 388(10056): 2153–63.
9. Vries PJ, Whittemore VH, Leveugle 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.
10. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13): 1345–56.
11. Ruth J, Roach SE, Bartels U, Jezierski 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(6): 439–44.
12. Thiele E, Korf B. Phakomatosis and allied conditions. In: Swaiman K, Ashwal S, Ferriero D, Schor N, editors. Swaiman’s pediatric neurology: Principles and Practice. 5th ed. New York, NY: Elsevier Inc; 2012. p. 497–517.
13. Jezierski S, Kowalska K, Kacprzyk-Obara J, Domanska-Pakielka D, Tomyn-Drabik M, Roberti P, et al. Clinical and genotype studies of cardiac tumors in 154 patients with tuberous sclerosis complex. Pediatrics 2006; 118(4): 1146–51.
14. Wataya-Kameda M, Tanaka M, Hamaizumi T, Katayama I. Trends in the prevalence of tuberous sclerosis complex manifestations: An epidemiological study of 166 Japanese patients. PLoS ONE 2013; 8(5): e63910.
15. Johnson SR, Whedon CJ, Hubbertt BB, Lewis S, A, Tattersfield AE. Survival and disease progression in UK patients with lymphangioleiomyomatosis. Thorax 2004; 59(9): 800–3.
16. Joinson C, O’Callaghan FJ, Osborn J, Martin C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med 2003; 33(2): 335–44.
17. Winterkorn EB, Pulsifer MB, Thiele EA. Cognitive prognosis of patients with tuberous sclerosis complex. Neurology 2007; 68(1): 62–4.
18. Stalwy B, Vail EA, Thiele EA. Tuberous sclerosis complex: Diagnostic challenges, presenting symptoms, and commonly missed signs. Pediatrics 2011; 127(1): 117–25.
19. Chu-Shore CJ, Major P, Camposano S, Mczynski D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010; 51(7): 1236–41.
20. D’Agati ED, Cerminara C, Curatolo P, Chalifoux JR, Staley BA, Weiner HL, et al. Tuberous sclerosis associated neuropsychiatric disorders: An epidemiological study of 166 Japanese patients. PLoS ONE 2013; 8(5): e63910.
21. Stalwy B, Vail EA, Thiele EA. Tuberous sclerosis complex: Diagnostic challenges, presenting symptoms, and commonly missed signs. Pediatrics 2011; 127(1): 117–25.
22. Chu-Shore CJ, Major P, Camposano S, Maczynski D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010; 51(7): 1236–41.
23. D’Agati ED, Maureen R, Cerminara C, Curatolo P. Attention-deficit hyperactivity disorder (ADHD) and tuberous sclerosis complex. J Child Neurol 2009; 24(10): 1282–7.
24. Curatolo P, Porfirio MC, Muniz B, Sari S. Autism in tuberous sclerosis. Eur J Paediatr Neurol 2004; 8(6): 327–32.
25. Curatolo P, Bombardieri R, Jezierski S. Tuberous sclerosis. Lancet 2008; 372(9639): 657–68.
26. Kolb DE, Sing K, Holsman T, Chalifoux JR, Stalwy B, Weiner HL, et al. Genotype/phenotype in tuberous sclerosis complex: Associations with clinical and radiologic manifestations. Epilepsia 2014; 55(7): 1020–4.

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