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Original Research

The Effect of the Age at Seizure Onset on Seizure Resistance in Tuberosclerosis Patients

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ABSTRACT

Objective: To evaluate the clinical status of epilepsy, which is extremely widespread in tuberosclerosis patients and the findings and characteristics of a pediatric case series.

Methods: The study included pediatric patients diagnosed with tuberosclerosis from clinical or genetic examination who were followed up between 2015 and 2022 in the Pediatric Neurology and Pediatric Genetics Clinics of Necmettin Erbakan University Meram Medical Faculty Hospital. A retrospective examination was made of the clinical characteristics of the patients, the electroencepahalography (EEG) reports, and radiological findings (magnetic resonance imaging [MRI], ultrasonography, echocardiography). The patients were separated into two groups of monotherapy and polytherapy according to the number of drugs used, and the groups were compared in respect of the time of onset of epilepsy. The patients were also categorised according to the presence of cortical tuber and subependymal nodule and these groups were compared in respect of the presence of epilepsy.

Results: The 27 patients comprised 18 (66.6%) males and 9 (33.4%) females. Complaints on presentation were seizure and skin patches in 25 (92.5%) cases and only skin patches in 2 (7.5%). The most common finding determined on MRI was the combination of subependymal nodule and cortical tuber (51.8%). Autism spectrum disorder was present in 5 (18.5%) patients and mental retardation in 16 (59%). The age at onset of epilepsy was earlier in the polytherapy group [5±4.75 (1-18) months] than in the monotherapy group [8.0±16 (4-36) months] ($p=0.032$). The rates of presence of cortical tuber and subependymal nodule were similar in respect of the time of onset of epilepsy ($p>0.05$).

Conclusion: The early onset of epilepsy in tubersclerosis patients indicates that it may have a resistant course and there may be a need for polytherapy. There may also be accompanying neuropsychiatric retardation in these patients. The clinical status of epilepsy in tuberosclerosis was found to be similar in the cortical tuber and subependymal nodule groups.

Keywords: Tuberosclerosis, epilepsy, polytherapy, cortical tuber

INTRODUCTION

Tuberosclerosis complex (TSC), which was first described by Bourneville in 1880, is a multi-systemic disease that is seen in 1 in 6000 live births [1]. The organs most affected are the skin, brain, kidneys, heart, eyes, and lungs. A broad spectrum of manifestations of the disease can be seen such as skin, heart,

brain and kidney-origin tumours, seizures and autism spectrum disorder. There are two genetic mechanisms for tuberosclerosis; TSC1 gene on chromosome 9q34 and TSC2 gene on chromosome 16p33. The protein named hamartin encodes TSC1 gene, and tuberin encodes TSC2 gene. In the physiology of a normal healthy individual, hamartin and tuberin function together, and any dysfunction in either of these causes the formation of hamartoma in tuberosclerosis [2]. Findings of the disease can show variability even within the same family. Familial cases are inherited as autosomal dominant, but the vast majority of cases occur as a result of de novo mutation [3].

Epilepsy is the most frequently seen neurological disorder in tubersclerosis patients. All seizure types may be seen in patients with epilepsy and the majority of seizures are resistant to anti-epileptic treatment [4]. The glial neurons in the cortical tubers are thought to play a role in the epileptogenesis of tuberosclerosis [5]. That regions corresponding to cortical tubers are encountered as epileptic focus on electroencephalography (EEG) supports this view. In a previous study that examined the EEGs of tuberosclerosis patients, the EEG was disrupted in approximately three-quarters of the case series, a smaller proportion was normal, and there was seen to be slowing down on the EEG of a few [6]. In the treatment of epilepsy in tuberosclerosis, many anti-epileptic treatments and non-pharmacological treatments such as ketogenic diet can be used. The International Tubersclerosis Consensus decision made in 2012 recommended vigabatrin as the first option for infants, and anti-epileptic drugs that are effective on gamma aminobutyric acid (GABA) for older patients [7]. The aim of this study was to evaluate the clinical characteristics of epilepsy, in tuberosclerosis patients followed up in our clinic and to examine the relationship between these characteristics and other clinical findings.

Main Points;

- Epilepsy clinic is frequent in tuberosclerosis patients and the present study is focusing on this clinic in our paediatric case series.
- This study reveales that early onset of epilepsy in tubersclerosis patients may have a more resistant course and there may be a need for polytherapy
- The clinical status of epilepsy in tuberosclerosis is similar in patients with cortical tuber and subependymal nodüle.

MATERIALS AND METHODS

Approval for the study was granted by the Local Ethics Committee (Aprovval no:2022/490) and all procedures were performed in compliance with the Helsinki Declaration.

A total of 45 patients were identified who were diagnosed with tuberosclerosis between 2015 and 2022 in the Pediatric Neurology and Pediatric Genetics Clinics of Necmettin Erbakan University Meram Medical Faculty Hospital. All the patients included were aged 2-18 years with at least 2 years of follow-up. Patients were excluded from the study if they were diagnosed and followed up at another centre. The study included 27 patients who met the study criteria.

The e-medical records system of the hospital were scanned retrospectively for the demographic data of the patients (age, gender, family history, etc.) clinical data (the presence of seizures, anti-epileptic drugs used, age at onset of seizures, physical examination findings, etc.), and the findings of electroencepahalography (EEG), abdominal ultrasonography (USG), echocardiography (ECHO) and brain magnetic resonance imaging (MRI).

The diagnosis of tuberosclerosis in all the patients was made based on the International Tuberosclerosis Consensus criteria published in 2012 [8]. In 17 patients, there was also a genetic confirmation test. Seizures which could not be controlled with two well tolerated and appropriately selected drugs (monotherapy or combination) for an appropriate treatment were evaluated as resistant epilepsy [9]. The patients in this study receiving anti-epileptic treatment were separated into two groups as those receiving polytherapy (2 or more drugs) or monotherapy (a single drug). The seizure types were classified as focal, generalised [10].

Pathologies such as the presence of renal cortical cyst and the presence of renal angiomyolipoma in the abdomen were evaluated radiologically with USG. On brain MRI, the presence of conditions such as cortical tuber (hamartoma) and/or subependymal nodule, and hydrocephaly in the brain were evaluated.

The data of the present study were analyzed statistically using SPSS version 22 software (SPSS, Chicago, IL, USA). In the descriptive analysis of the data, continuous variables were presented as median and interquartile range (IQR), minimum

and maximum values, and categorical variables as frequency (n) and percentage (%). The tuberosclerosis patients were classified according to seizure treatment with monotherapy (Group 1) or polytherapy (Group 2) and the groups were compared in respect of age at onset of seizures.The study population was also divided according to the presence of cortical tuber and subependymal nodule, and these two groups were compared in respect of the clinical status of seizures. Conformity of the data to normal distribution was evaluated using the Kolmogorov–Smirnov test and according to the results, non-parametric tests were used. The Mann Whitney U-test was used for the comparisons of the numerical data of the age of onset of seizures and the Pearson Chi square test was used for the comparison of the categorical data of the clinical presence of epilepsy. A value of $p<0.05$ was considered statistically significant throughout the study.

RESULTS

The 27 patients comprised 18 (66.6%) males and 9 (33.4%) females, with a mean age of 10.0±8.5 years (range, 3-17 years). The mean age at presentation was 6.0±7.0 months and the mean age at onset of seizures was 5.0±6.0 months (1-36 months). The most common complaint on presentation was seizure (n: 25, 92.5%). Epilepsy started within the first 6 months of life in 15 (55.5%) patients (Figure 1). The seizures were in the form of focal seizure in 17 (68%) patients, and generalised seizures in 8 (32%). Of the patients receiving anti-epileptic treatment, resistant seizures were present in 11 (44%) patients, and the seizures were kept under control with a single drug in 14 (56%) patients.

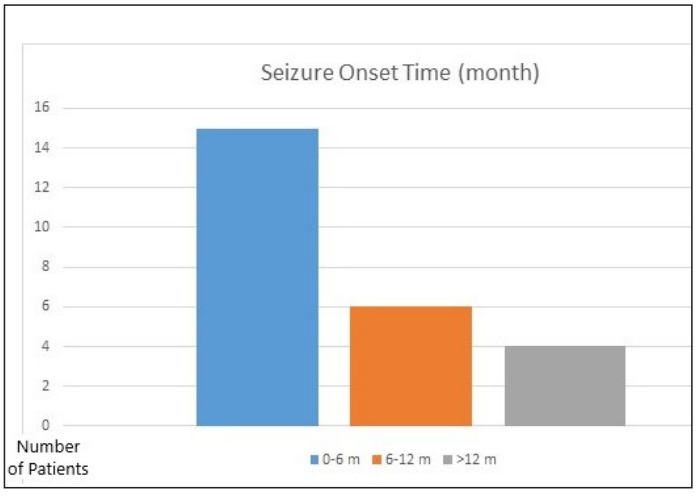

Figure 1. The number of patients with epilepsy onset time within 0-6 months, 6-12 months, and over 12 months is shown.

The most common EEG disorder was multifocal and generalised epileptiform abnormalities. The EEG results were seen as normal in 8% of the patients, hypsarrhythmia in 8%, multifocal epileptiform changes in 20%, focal epileptiform and focal slowing in 20%, and generalised epileptiform discharges in 44%. The most frequently used anti-epileptic drugs were valproic acid, carbamazepine, vigabatrin, oxcarbazepine, lamotrigine, clobazam, and levetiracetamide. The age at onset of seizures was determined to be statistically significantly younger in the polytherapy group (5±4.75 months [range, 1-18 months]) than in the monotherapy group (8.0±16 months [range, 4-36 months]) (p=0.032) (Figure 2).

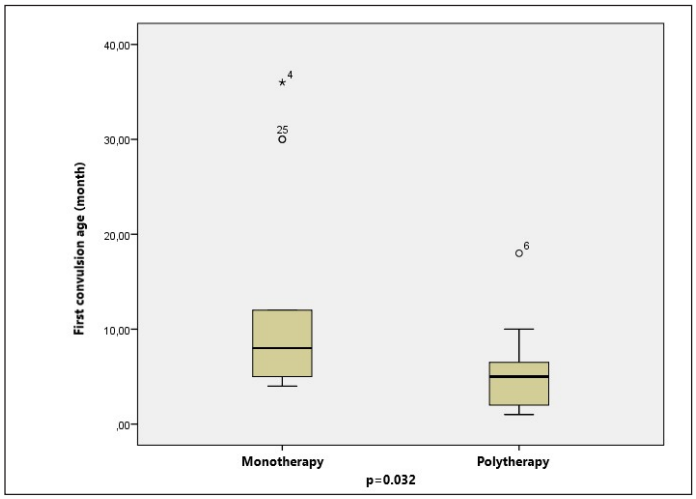

Figure 2. The epilepsy onset time was 8.0±16 (4-36) months in the monotherapy group and 5±4.75 (1-18) months in the polytherapy group. It was found that the onset time was statistically smaller in the polytherapy group compared to the monotherapy group (*p=0.032; Mann Whitney U-test).

The brain MRI findings were seen to be cortical tuber in 6 (22.2%) patients, subependymal nodule in 6 (22.2%), and the combination of subependymal nodule and cortical tuber in 15 (55.6%) (Figure 3). Hydrocephaly was present in 1 patient but there was no requirement for shunt during follow up. The groups (isolated cortical tuber, subependymal nodule and concurrent of subependymal nodule and cortical tuber) were found to be similar in respect of the presence of epilepsy ($p>0.05$).

Mental retardation was present in 16 (59%) patients and autism spectrum disorder in 5 (18.5%). When the skin examination findings were examined, there were seen to be hypopigmented patches in all the patients, facial angiofibroma in 6 and shagreen plaque in 1. Other system involvements were seen to be renal

involvement in 12 (44.4%) patients (10 renal angiomyolipoma, 2 renal cortical cyst), cardiac rhabdomyoma in 15 (55.5%), and eye involvement (retinal hamartoma) in 2. Of the total 27 patients, there were genetic results for 17. Of these, mutation in the TSC2 gene was determined in 14 (82.3%) and mutation in the TSC1 gene in 3 (17.7%). A family history of tuberosclerosis was present in 8 cases. The demographic data of the patients are shown in Table 1.

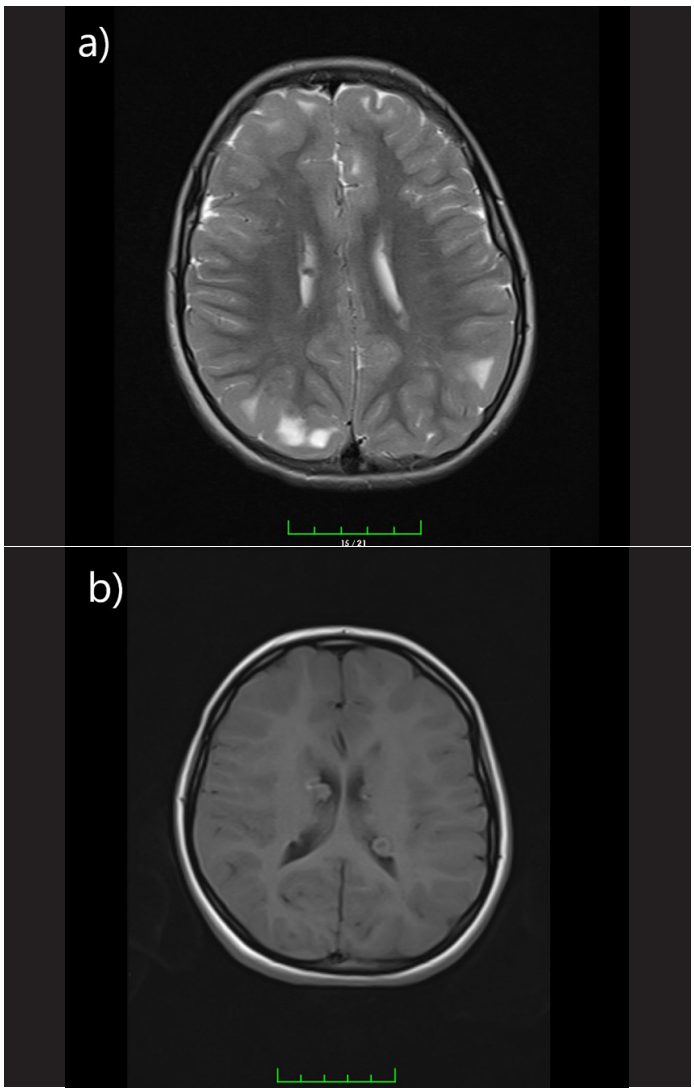

Figure 3. a) 8-year-old girl patient with tuberous sclerosis. Magnetic resonance imaging, T2 sequence examination, axial section. Subependymal nodules adjacent to the lateral ventricle and cortical tubers in the posterior regions are observed.

b) 15-year-old girl patient with tuberous sclerosis. Magnetic resonance imaging, T1 sequence examination, axial section. Subependymal nodules located adjacent to the lateral ventricle are observed.

Table 1. Demographic results of the study patients

Gender
Male (n:18)
Female (n:9)
First Presentation
Seizure (n:25)
Focal seizures (n:17)
Generalized seizures (n:8)
Other (n:2)
Antiepileptic Treatment
Monotherapy (n:14)
Polytherapy (n:11)
EEG Findings
Generalized epileptiform discharges (n:11)
Focal epileptiform and focal slowings (n:5)
Multifocal epileptiform changes (n:5)
Hypsarrhythmia (n:2)
Normal (n:2)
MRI Results
Cortical tubers (n:6)
Subependymal nodules (n:6)
Coexistence of subependymal nodules and cortical tubers (n:15)
Level of Cognitive Development
Mental retardation (n:16)
Autism spectrum disorder (n:5)
Normal (n:6)
Skin Examination
Hypopigmented spots (n:27)
Facial angiofibromas (n:6)
Shagreen patches (n:1)
Extracutaneous System Involvement
Renal angiomyolipoma (n:10)
Renal cortical cyst (n:2)
Cardiac rhabdomyoma (n:15)
Retinal hamartoma (n:2)
Genetic Results (n:17)
Mutation in TSC2 gene (n:14)
Mutation in TSC1 gene (n:3)
Familial History
History of familial tuberous sclerosis (n:8)

DISCUSSION

Tuberosclerosis complex is a neurocutaneous, multi-systemic disease, which has different manifestations by affectng several organs. The central nervous system is one of the most commonly affected body parts in tuberosclerosis. Epilepsy is extremely common in tuberosclerosis patients and neurocognitive functions are negatively affected as a result of recurrent seizures

[11]. In the current study of a group of tuberosclerosis patients, the majority of whom had epilepsy, the age at onset of seizures, seizure type, the drugs used, the seizure course, and the effect on cognitive functions were evaluated. The study results demonstrated that early onset of seizures resulted in greater resistance to anti-epileptic drugs.

Epilepsy is the most frequently seen neurological finding, at the rate of 80-90%, in tuberosclerosis patients [4]. In a study by Incecik et al., 89.4% of the patients presented because of seizure, and in the current study the reason for first presentation was seizure in 92.5% of the patients [11]. Seizures starting in the first 6 months of life have been shown to lead to neurocognitive delay and increased frequency of autism coexistence are seen in epilepsy patients [12]. There has been reported to be mental or cognitive retardation in 75% of tubersclerosis patients with resistant epilepsy [13]. Consistent with the lierature, it was seen in the current study that epilepsy started within the first 6 months of life in 55.5% of patients, and mental retardation was present in 75% of these patients.

In patients with tuberosclerosis and epilepsy, the seizures are known to generally have an early onset and are more often in the form of focal seizures and infantile spasm [14]. Most of the seizures in the current study had early onset and 68 % of patients experienced focal seizures and infantile spasms. The patients with earlier onset of epilepsy were also seen to need polytherapy because of clinical resistance.

The most specific test for imaging of central nervous system (CNS) involvement in tuberosclerosis is MRI. Lesions showing involvement are seen as hyperintense on T2-weighted slices in adult patients, whereas in young children, this hyperintensity may not be seen in which case T1-weighted sequences should be examined. Cortical tubers which are malformations of cortical development may be involved anywhere from the cortex up to the white matter [15]. Epilepsy, autism, or other symptoms can be seen associated with the site of involvement of tubers. Cortical tubers and subependymal nodules, which have a more benign course, are observed in the vast majority of patients with tuberosclerosis [8]. In the current study, cortical tuber and subependymal nodule were present in 55.6% of the patients. In addition cortical tuber only was present in 22.2% of patients and subependymal nodule only in the other 22.2%. A previous study reported that cortical tubers could be seen at the rate of 90% and subependymal nodules at 80%, but in that study, the rate of combination seen was not stated [16]. Giant cell astrocytoma and white matter abnormalities are more rarely seen CNS abnormalities. No giant cell astrocytoma was observed in any of the current study patients. The association between cortical tuber and epilepsy and the epileptogenesis mechanism are matters of debate in literature and there are conflicting views [17, 18]. In the current study, the cortical tuber and subependymal nodule groups were seen to be similar in respect of the presence of epilepsy. These pathological structures were not seen to be different in respect of epileptogenesis.

There has been reported to be accompanying mental retardation in 50-55% and autism spectrum disorder in 20-50% of tuberosclerosis patients [18, 19]. In the current study, mental retardation was present in 59% of the patients and autism spectrum disorder in 18.5%.

Renal involvement is the second most frequently involved system in tuberosclerosis after the CNS, with renal angiomyolipoma constituting 80% of renal involvement and renal cysts 20% [20]. In the current study, renal involvement was determined in 44.4% of the patients. Consistent with the literature, angiomyolipoma was present in 83% of the current study patients, and cortical cyst in 17%.

Cardiac rhabdomyoma constitutes 45% of primary heart tumours in children, and this is the most common form of heart tumour in childhood [21]. Moreover, 70-90% of children diagnosed with cardiac rhabdomyoma are diagnosed with tuberosclerosis over time [22]. Although cardiac rhabdomyoma are histologically benign tumours, depending on the localisation and diagnosis in the neonatal period, they can occasionally lead to arrhythmia, ventriculomegaly and heart failure [23]. Cardiac rhabdomyoma was present in 55.5% of the current study patients, but no cardiac dysfunction was observed in any patient during follow-up.

Although this study is of value in respect of presenting the long-term follow-up of a series of cases with tuberosclerosis, which is an uncommon disease, there were also some limitations. In addition to the inherent limitation of the retrospective design of the study, as the majority of the patient group had epilepsy, the relationship with other findings (the presence of cortical tuber, mental retardation) could not be evaluated in the absence of epilepsy. A further limitation was that the effect of tuberosclerosis genetics on other parameters could not be evaluated as only 17 patients had genetic analysis results and there were very few

patients (n:3) with TSC1 gene mutation.

CONCLUSION

The results of this study demonstrated that epilepsy with early onset in tuberosclerosis patients could have a resistant course and there may be a need for polytherapy. There may also be neuropsychiatric retardation in these patients. However, the clinical status of epilepsy in tuberosclerosis was similar in both the cortical tuber and subependymal nodule groups.

Conflict of Interests: The authors declare that they have no conflict of interests to disclose

Financial Support: The authors declare that they had no financial support to disclose.

Declarations of interest: None.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee (Approval number: 2022/490) and was conducted in accordance with the principles of the Declaration of Helsinki.

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REFERENCES

[1] Raznahan A, Joinson C, O'Callaghan F, Osborne J, Bolton P (2006) Psychopathology in tuberous sclerosis: an overview and findings in a population-based sample of adults with tuberous sclerosis. Journal of Intellectual Disability Research. 50(8):561-569. https://doi.org/10.1111/j.1365-2788.2006.00828.x

[2] Cohen AL, Kroeck MR, Wall J, McManus P, Ovchinnikova A, Sahin M, et al. (2022) Tubers affecting the fusiform face area are associated with autism diagnosis. Annals of Neurology. https://doi.org/10.1002/ana.26551

[3] Schwartz RA, Fernández G, Kotulska K, Jóźwiak S (2007)Tuberous sclerosis complex: advances in diagnosis, genetics, and management. Journal of the American Academy of Dermatology. 57(2):189-202. https://doi.org/10.1016/j.jaad.2007.05.004

[4] Holmes GL, Stafstrom CE, Group TSS (2007) Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia. 48(4):617-630. https://doi.org/10.1111/j.1528-1167.2007.01035.x

[5] Thiele EA. Managing epilepsy in tuberous sclerosis complex (2004) Journal of child neurology. 19(9):680-686. https://doi.org/10.1177/08830738040190090801

[6] Westmoreland B. The electroencephalogram in tuberous sclerosis (1999) Tubrous Sclerosis Complex: Developmental Perspectives in Psychiatry, ed.3:63-74.

[7] Curatolo P, Jóźwiak S, Nabbout R (2012) Management of epilepsy associated with tuberous sclerosis complex (TSC): clinical recommendations. european journal of pediatric neurology. 16(6):582-586. https://doi.org/10.1016/j.ejpn.2012.05.004

[8] Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, et al. (2013) Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric neurology. 49(4):243-254. https://doi.org/10.1016/j.pediatrneurol.2013.08.001

[9] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Wiley Online Library. https://doi.org/10.1111/j.1528-1167.2009.02397.x

[10] Fisher RS. The new classification of seizures by the International League Against Epilepsy (2017) Current neurology and neuroscience reports. 17(6):1-6. https://doi.org/10.1007/s11910-017-0758-6

[11] Overwater I. Bindels--de Heus K, Rietman AB, Ten Hoopen LW, Vergouwe Y, Moll HA, et al. (2015) Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs. Epilepsia. 56(8):1239-1245. https://doi.org/10.1111/epi.13050

[12] Jóźwiak S, Migone N, Ruggieri M (2008) The Tuberous Sclerosis Complex. Neurocutaneous Disorders Phakomatoses and Hamartoneoplastic Syndromes: Springer; p. 181-227. https://doi.org/10.1007/978-3-211-69500-5_5

[13] Samir H, Ghaffar HA, Nasr M (2011) Seizures and intellectual outcome: clinico-radiological study of 30 Egyptian cases of tuberous sclerosis complex. european journal of pediatric neurology. 15(2):131-137. https://doi.org/10.1016/j.ejpn.2010.07.010

[14] Józwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J (2000) Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. Journal of child neurology. 15(10):652-659. https://doi.org/10.1177/088307380001501003

[15] Baron Y, Barkovich AJ (1999) MR imaging of tuberous sclerosis in neonates and young infants. American Journal of Neuroradiology. 20(5):907-916.

[16] Saltık S, Karatoprak EY, Taşel B (2013) Characteristics and the clinical prognosis of epilepsy in patients with a diagnosis of tuberous sclerosis complex. Turk Arch Pediatr. 48:123-130. https://doi.org/10.4274/tpa.116

[17] Park SM, Lee YJ, Son YJ, Kim YO, Woo YJ (2011) Clinical progress of epilepsy in children with tuberous sclerosis: prognostic factors for seizure outcome. Chonnam Medical Journal. 47(3):150-154. https://doi.org/10.4068/cmj.2011.47.3.150

[18] Kassiri J, Snyder TJ, Bhargava R, Wheatley BM, Sinclair DB (2011) Cortical tubers, cognition, and epilepsy in tuberous sclerosis. Pediatric neurology. 44(5):328-332. https://doi.org/10.1016/j.pediatrneurol.2011.01.001

[19] Wiznitzer M (2004) Autism and tuberous sclerosis. Journal of child neurology. 19(9):675-679. https://doi.org/10.1177/08830738040190090701

[20] Kingswood JC, Bissler JJ, Budde K, Hulbert J, Guay-Woodford L, Sampson JR, et al. (2016) Review of the tuberous sclerosis renal guidelines from the 2012 consensus conference: current data and future study. Nephron. 134(2):51-58. https://doi.org/10.1159/000448293

[21] Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK (2014) Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. Journal of the American Heart Association. 3(6):e001493. https://doi.org/10.1161/JAHA.114.001493

[22] Davis PE, Filip-Dhima R, Sideridis G, Peters JM, Au KS, Northrup H, et al. (2017) Presentation and diagnosis of tuberous sclerosis complex in infants. Pediatrics. 140(6). https://doi.org/10.1542/peds.2016-4040

[23] Schlaegel F, Takacs Z, Solomayer EF, Abdul-Kaliq H, Meyberg-Solomayer G (2013) Prenatal diagnosis of giant cardiac rhabdomyoma with fetal hydrops in tuberous sclerosis. Journal of prenatal medicine. 7(3):39.

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