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Update on tuberous sclerosis complex

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Abstract
Tuberous sclerosis complex (TSC) is a multisystemic disorder that presents an autosomal dominant inheritance pattern and is characterized by the presence of growth of hamartomas (tumors) in the brain, eyes, skin, kidneys, heart and lung.
Objective: To analyze the literature on TSC, its etiology, prevalence, clinical manifestations, diagnosis and treatment.
Methodology: Articles published at MEDLINE/PubMed and ScienceDirect were analyzed, with an emphasis on the last 5 years. Articles were evaluated with the PRISMA and AMSTAR guidelines. The search was carried out using the words "tuberous sclerosis complex", "etiology", "treatment", "diagnosis" and "clinical manifestations".
Results: TSC is a genetically inherited disorder, with a high but incomplete penetrance, this disorder with multisystem involvement is usually due to mutations in the TSC1 or TSC2 genes. The diagnosis is established with the identification of a mutation of these genes, the treatment for this condition consists of drugs to control the symptoms and sometimes in surgical procedures. The clinical manifestations are heterogeneous, usually manifesting with neurological alterations such as epilepsy, autism, intellectual disability. Dermatological alterations include facial angiofibromas, hypomelanotic macules and nail fibromas. The prevalence is estimated at 1 in 6,000 people, it has been found that it does not have a preference for any sex, and it has a great phenotypic variability, which can make its diagnosis difficult.
Conclusion: TSC is a condition with low incidence, however, dental care is necessary to define therapeutic and preventive management guidelines, which avoid diseases associated with the normal course of the disease and the deterioration of patients.

Keywords: tuberous sclerosis, ethiopathogenesis, diagnosis, treatment, clinical manifestations and prevalence

1. Introduction
Tuberous sclerosis complex (TSC) is a genetically inherited disorder of autosomal dominant form, with high but incomplete penetrance, which can affect organs such as the brain, skin, eyes, heart, lungs, liver and kidneys [1, 2]. This tuberous sclerosis complex was first described in part by Von Recklinghausen in 1862, who at that time found cardiac lesions (cardiac rhabdomyoma and cortical tubercles) in a newborn patient who died in his first days [3]. The first detailed descriptions of the clinical and neuropathological features of tuberous sclerosis were made and described by the French neurologist Désiré-Magloire Bourneville in 1880, therefore, the disease at that time was named "Bourneville's disease" in his honor [4, 5]. In the year 1908, Heinrich Vogt described the classic triad or "Vogt's triad", which was characterized by a clinical picture of clinical manifestations such as: epilepsy, intellectual disability and angiofibromas usually located in the mid-facial third commonly around the nose, cheek, and chin [5, 6]. This condition is known to affect approximately 1 in 10,000 people and has been found to have no gender preference, it has a great phenotypic variability, which can sometimes make it difficult to diagnose and can be confused with other neurological diseases. Many cases may remain undiagnosed for several years due to mild symptoms in some patients [7]. Although it is considered a rare disease, it is listed among the genetic conditions that most affect the population worldwide [8].

This multisystemic disorder is associated with hematomas or benign tumor growths in different organs, but it can also manifest in the oral cavity, gums, as well as disabling neurological conditions which are especially frequent in the form of intellectual disability, autism, and epilepsy among others [3, 9, 10].

Currently there are no or very few studies related to this condition and dentistry, therefore, the aim of the study is to analyze the literature on tuberous sclerosis, its etiopathogenesis, diagnosis, treatment, clinical manifestations, and its prevalence for patients suffering from this condition. As well as to identify the most common oral manifestations, with the aim of making dentists aware of the importance of diagnosis through the oral cavity of these patients to offer an ideal treatment and quality care.

2. Materials and methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2) [11]. The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words “Tuberous sclerosis complex”, "etiopathology", "diagnosis", "treatment" and "clinical manifestations". The keywords were used individually, as well as each of them related to each other.

3. Results and Discussion

3.1 Etiopathogeny

Tuberous sclerosis complex is an autosomal dominant disorder with multisystem involvement that is usually due to mutations in the tuberous sclerosis genes TSC1 or TSC2 [12]. The etiology of this condition is associated with germline mutations in TSC1 and TSC2, including exonic, intronic, or mosaic mutations [13].

Such mutations in the TSC1 germline, specifically on chromosome 9q34 and in the TSC2 germline on chromosome 16p13, are identified as responsible for the origin of this condition. The TSC1 gene encodes a protein called Hamartin, while another protein called tuberin is obtained from the TSC2 gene [14].

Both proteins form a complex whose function is to inhibit the activation of the target of rapamycin complex 1 (mTORC1), a master serine/threonine kinase that plays a role in multiple processes, including translation, ribosome biogenesis, and autophagy. Therefore, the pathogenesis of the disease lies in the lack of function of that complex, with subsequent activation of the mTOR cascade, resulting in disorganized cell proliferation and abnormal differentiation culminating in tumor growth [15, 16, 17].

Pathogenic variants on chromosomes 9q34 and 16q13, are those that lead to hyperactivation of the mammalian target of rapamycin complex 1 (mTORC1) signaling network. Although the clinical phenotype is variable, the main neurological manifestations include autism, intellectual disability and epilepsy [18].

The etiology of tuberous sclerosis has been identified to be due to a mutation in the TSC1 or TSC2 genes, in which affecting one of the two genes may result in the disease. It has been found to include de novo or mosaic mutations and is considered an autosomal dominant disease.

3.2 Diagnosis and Treatment

The first diagnostic criteria for tuberous sclerosis were established by neurologist Manuel Rodriguez Gomez in 1979. The first update date of the diagnostic criteria dates back to 1998, these diagnostic criteria were updated in 2012, where the genetic diagnostic criterion is the pathogenic mutation of the TSC1 OR TSC2 gene [19]. Within the dermatological clinical diagnostic criteria are: hypomelanotic macules, angiofibromas and nail fibromas. In odontology, this condition presents clinical features, such as: dental enamel pits and intraoral fibromas in most patients [17]. Diagnosis can be made by documentation of clinical signs and radiographic findings or by genetic testing. Diagnostic evaluation may be initiated due to positive family history or due to clinical signs or symptoms [20].

Identification of a variant pathogenic gene in TSC1 or TSC2 is sufficient for diagnosis or the disease, this is of utmost importance, because clinical manifestations of tuberous sclerosis are known to emerge over time at various ages [21]. Accurate diagnosis is essential to implement appropriate surveillance and treatment of patients with this disorder. The International Tuberous Sclerosis Complex Consensus Group has proposed specific guidelines for diagnosis, surveillance, and treatment [22]. Studies currently indicate that patients with other neurological diseases constitute a bias in the diagnosis and treatment of tuberous sclerosis [23].

In one case of a newborn with no specific clinical manifestations, he showed evidence of tuberous sclerosis on MRI and echocardiography. Studies such as next-generation sequencing and multiplex ligation-dependent probe amplification of the exons of the TSC1 and TSC2 genes were performed to confirm the diagnosis. In this case, NGS sequencing confirmed the diagnosis of sclerosis caused by a heterozygous mutation in the TSC1 gene. This indicates the suitability of genetic testing for early diagnosis of clinically rare and difficult to diagnose diseases to guide clinical management [24].

MRI is a key way for the diagnosis and surveillance of patients with tuberous sclerosis syndrome. Ultrasound and MRI can capture TSC-associated tubercles and subependymal nodules during midgestation, allowing prenatal diagnosis and/or adequate monitoring of this disease [25].

Data from several countries show that drugs used for autism spectrum disorder are the most commonly used drugs in people with TSC followed by anxiolytic, psychoanaleptic and antipsychotic drugs. The most frequent of which were valproate, lamotrigine, carbamazepine, levetiracetam and vigabatrin, which is used much more frequently in children. Also the drug everolimus is a rapamycin inhibitor drug, which is considered a therapeutic agent [26, 27].

In addition to drugs, rehabilitation services, including occupational, speech and language therapy, physical therapy, and special education services are some of the treatments that may be indicated in this condition. Little has been said about surgical treatment, but brain surgery for epilepsy, craniotomy and brain electrodes are some of the surgical procedures for patients with tuberous sclerosis [15, 27].

The definitive diagnosis is made with an identification of a mutation in the TSC1 or TSC2 genes, however, different clinical manifestations can give a presumptive diagnosis. Treatment for this condition consists of the use of drugs to control symptoms and sometimes surgical procedures.

3.3 Clinical Manifestations

3.3.1 Skin

Cutaneous manifestations develop in almost all those affected by this condition, these include facial angiofibromas (skin eruptions on the nose and cheeks that are present in 75% of patients), nail fibromas (fibrous growths around the nails present in 20-80% of patients), fibrous cephalic plaques, shagreen patches (areas of thickened and raised skin usually found on the lower back and present in 50% of patients) and focal hypopigmented changes (present in 90% of patients). Facial angiofibromas are benign skin tumors seen in 80% of patients with tuberous sclerosis complex [28]. The pathognomonic dermatologic clinical features are more than three hypomelanotic macules, more than three angiofibromas or cephalic fibrotic plaque of face or scalp, more than two nail fibromas, shagreen plaque, multiple retinal hamartomas, and so on, therefore, the dermatologist has a fundamental role in the history and evolution of the disease despite being a multisystem disorder [29].

3.3.2 Neurological

Among the most frequent neurological manifestations are neuropathological disorders such as epilepsy, which is the most common symptom and affects 80-90% of patients with this syndrome. Neuropsychiatric disorders and behavioral problems are considered the most important because they establish diagnostic criteria [30]. However, several authors point out that in addition to epileptic seizures in 80% of patients with tuberous sclerosis, the level of intelligence is also affected from a normal intellectual disability to a more profound level. Intellectual disability is present in more than half of the patients and autism spectrum disorder in about half of those with this condition [31]. Neurological and psychiatric manifestations include epilepsy (70-85%), intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, and depression and anxiety [32]. Approximately 10% of patients have subependymal giant cell astrocytoma (SEGA), a benign tumor in the wall of the lateral ventricle that can cause hydrocephalus [33].

3.3.3 Orals

Oral manifestations of the disease have been reported to include abnormal enamel dysplasia (enamel dimpling) in 100% of patients with tuberous sclerosis, oral fibromas in gingiva in 69%, lips and buccal mucosa [34]. The presence of gingival hypertrophy has also been identified. All these lesions are included in the list of minor diagnostic criteria for tuberous sclerosis: gingival hyperplasia, high arched palate, bifid uvula, cleft lip and/or palate, late tooth eruption and diastema, supernumerary teeth are less frequent [20, 35]. Approximately 70% of adults develop nodular growths on their gums known as gingival fibroma, which can cause irritation and affect tooth alignment. Oral hygiene is of utmost importance in these patients and it is known that typical oral lesions are more frequent in adults than in children) [20].

3.3.3 Others

There are other clinical manifestations of this condition that affect organs such as the heart, causing cardiac rhabdomyomas, kidneys in the form of renal angiomyolipomas, renal cell carcinoma, polycystic disease and other conditions in the lung, liver and pancreas [16, 20, 25, 28, 31].

This condition is characterized as a multisystemic disease, where it can cause manifestations in many organs of the body such as heart, lungs, liver, skin, pancreas and brain, the neurological and dermatological manifestations are the most evident, however, in the oral cavity we can find clinical manifestations that serve for the diagnosis of the disease.

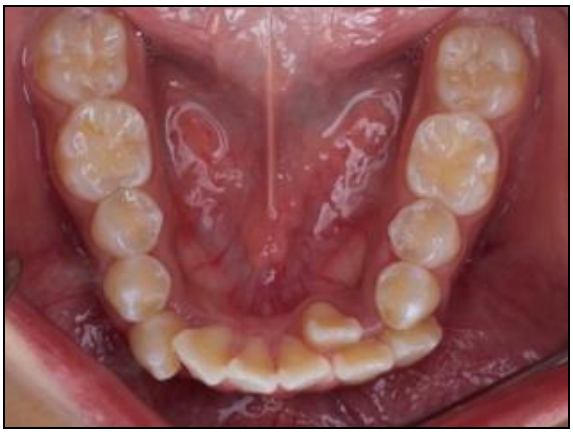

Fig 1: Oral manifestations of tuberous sclerosis (Supernumerary teeth)

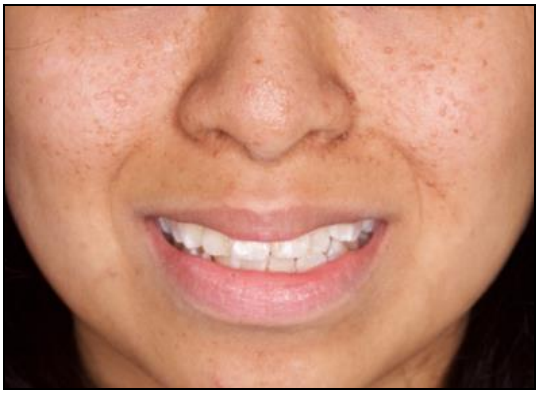

Fig 2: Dermatological manifestations, facial angiofibromas in the nose and cheekbone area.

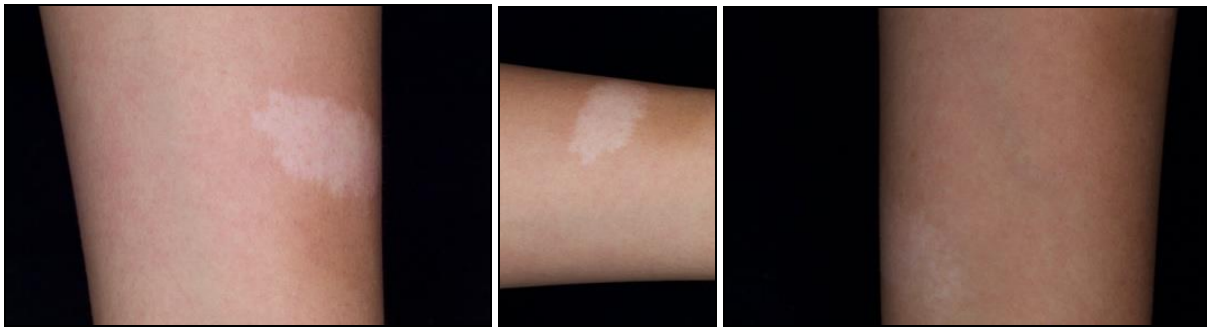

Fig 3: Dermatological manifestations, hypomelanotic spots on the forearms.

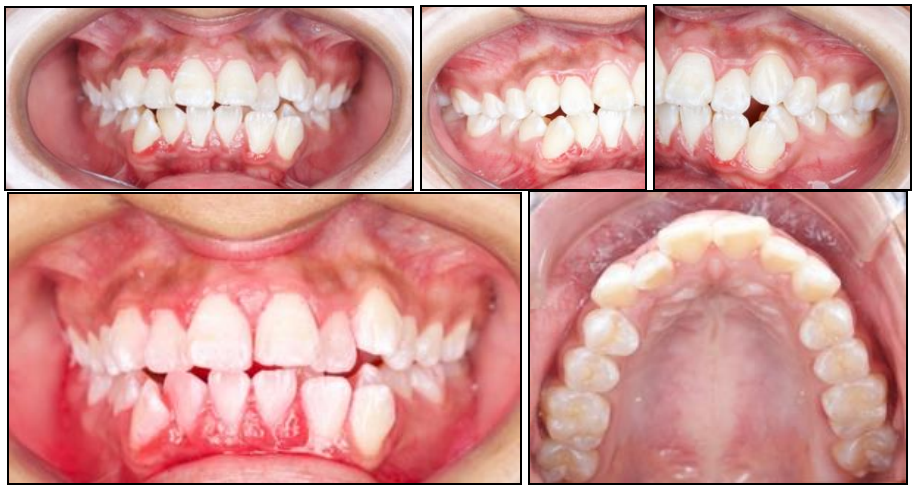

Fig 4: Dental manifestations of tuberous sclerosis, gingival hyperplasia, gingival fibromas in the anteroinferior zone, enamel pits in the upper central zone.

3.4 Prevalence

Incidence rates of tuberous sclerosis are increasing; in the 1980s, incidence rates of TSC were estimated to be between 1/100 000 and 1/200 000 [36]. Because it is an autosomal dominant neurocutaneous disorder, it has an estimated incidence of 1/6000 to 1/10 000 live births [37, 38, 39] and its prevalence approximately 1/20,000 to 1/100,000. It is known to have no preference to any gender [23, 40]. In 2016, it was estimated that nearly 2 million people worldwide suffered from this tuberous sclerosis complex, with approximately 50,000 people affected in the United States alone [20]. While in Europe the prevalence in the general population is estimated at 8.8/100,000 [41, 42]. Sclerosis is considered a rare hereditary disease, where the prevalence is estimated at an average of 1 in 6000 births. In Latin America there is not much data on the prevalence of this condition, however, individual cases have been reported.

4. Conclusions

Tuberous sclerosis is a neurocutaneous syndrome, the most accepted etiology of this condition is a mutation in the tuberous sclerosis genes identified as TSC1 or TCS2, which generate two proteins that cause this neuronal disorder. The identification of a genetic mutation in these genes is required to establish the diagnosis, within the treatment different therapies and medications are proposed to control the neuropathologies present as medications used in autism spectrum disorders. Within the clinical manifestations, dermatological and neuronal manifestations can be observed as the most common, but different organs such as the heart, lung, liver, and pancreas can also be affected. Dental consultation is essential for the diagnosis and treatment of tuberous sclerosis as oral manifestations such as enamel pits and oral fibromas and gingival hyperplasia can be observed during consultations. This genetic disorder is uncommon where the prevalence is estimated at an average of 1 in 6000 births, so it is currently considered within the list of rare diseases according to WHO.

References

1 Salussolia CL, Klonowska K, Kwiatkowski DJ, Sahin M. Genetic Etiologies, Diagnosis, and Treatment of Tuberous Sclerosis Complex. Annu Rev Genomics Hum Genet. 2019;31;20:217-240.

2 Kaneda M. [Tuberous Sclerosis Complex]. Brain Nerve. 2019;71(4):374-379

3 Hasbani DM, Crino PB. Tuberous sclerosis complex. Handb Clin Neurol. 2018;148:813-822.

4 Uysal SP, Şahin M. Tuberous sclerosis: a review of the past, present, and future. Turk J Med Sci. 2020;50(SI-2):1665-1676.

5 Brigo F, Lattanzi S, Trinka E, Nardone R, Bragazzi NL, Ruggieri M, *et al*. First descriptions of tuberous sclerosis by Désiré-Magloire Bourneville (1840-1909). Neuropathology. 2018;38(6):577-582

6 Sánchez-Meza E, Ancer-Arellano J, Villarreal-Villarreal CD, Cárdenas-de la Garza JA, *et al*. Características clínicas y epidemiológicas de esclerosis tuberosa en un centro de referencia dermatológico del noreste de México. Dermatol Rev Mex. 2018;62(6):475-485.

7 Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018;93(3):323-331.

8 Peron A, Northrup H. Tuberous sclerosis complex. Am J Med Genet C Semin Med Genet. 2018;178(3):274-277.

9 Nair N, Chakraborty R, Mahajan Z, Sharma A, Sethi SK, Raina R. Renal Manifestations of Tuberous Sclerosis Complex. J Kidney Cancer VHL. 2020;27;7(3):5-19.

10 Giannikou K, Lasseter KD, Grevelink JM, Tyburczy ME, Dies KA, Zhu Z, *et al*. Low-level mosaicism in tuberous sclerosis complex: prevalence, clinical features, and risk of disease transmission. Genet Med. 2019;21(11):2639-2643.

11 Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, *et al*. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

12 Arbune AA, Toron BR, Lupescu IC, Lupescu IG, Tatu AL, Dulamea AO. Tuberous sclerosis with negative genetic testing and multiple cerebral cavernomas: A new association (Case report). Exp Ther Med. 2021;22(4):1183.

13 Han B, Lee J, Kwak YJ, Kim HY, Lee KH, Shim Y, Lee H, et l. A second hit somatic (p.R905W) and a novel germline intron-mutation of TSC2 gene is found in intestinal lymphangioleiomyomatosis: A case report with literature review. Diagn Pathol. 2021;16(1):83.

14 Kumar P, Zadjali F, Yao Y, Bissler JJ. Renal cystic

disease in tuberous sclerosis complex. Exp Biol Med (Maywood). 2021:15353702211038378.
15 Lin S, Zeng JB, Zhao GX, Yang ZZ, Huang HP, Lin MT, *et al*. Tuberous Sclerosis Complex in Chinese patients: Phenotypic analysis and mutational screening of TSC1/TSC2 genes. Seizure. 2019;71:322-327.
16 Cammarata-Scalisi F, Stock F, Velazco N, Silva GD, Lacruz-Rengel MA, Avendaño A. Hallazgos clínicos y epidemiológicos en la neurofibromatosis tipo 1 y el complejo esclerosis tuberosa en una serie de pacientes pediátricos. Bol Med Hosp Infant Mex. 2018;75(5):287-294.
17 Daphna Marom. Genetics of tuberous sclerosis complex: an update. Childs Nerv Syst. 2020;36(10):2489-2496.
18 Moschopoulos C, Peters JM, Takeoka M, Stredny CM. Infantile Hemiconvulsion-Hemiplegia and Epilepsy (IHHE) in a boy with tuberous sclerosis complex. Epilepsy Behav Rep. 2021;16:100473.
19 Pfirmann P, Combe C, Rigothier C. [Tuberous sclerosis system: A review]. Rev Med Interne. 2021:S0248-8663(21)00061-8.
20 Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:16035.
21 Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, *et al*. International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021;123:50-66.
22 Randle SC. Tuberous Sclerosis Complex: A Review. Pediatr Ann. 2017;46(4):e166-e171.
23 Volpi A, Sala G, Lesma E, Labriola F, Righetti M, Alfano RM, *et al*. Tuberous sclerosis complex: new insights into clinical and therapeutic approach. J Nephrol. 2019;32(3):355-363.
24 Qiao L, Yang Y, Yue D. Early diagnosis of a newborn with tuberous sclerosis caused by a genetic mutation. J Int Med Res. 2021;49(8):3000605211035895.
25 Cotter JA. An update on the central nervous system manifestations of tuberous sclerosis complex. Acta Neuropathol. 2020;139(4):613-624.
26 Uliel-Sibony S, Chernuha V, Meirson H, Fattal-Valevski A. Medical treatment of tuberous sclerosis-related epilepsy. Childs Nerv Syst. 2020;36(10):2511-2517.
27 Zöllner JP, Franz DN, Hertzberg C, Nabbout R, Rosenow F, Sauter M, *et al*. A systematic review on the burden of illness in individuals with tuberous sclerosis complex (TSC). Orphanet J Rare Dis. 2020;21;15(1):23.
28 Jindal R, Sethi S, Chauhan P. Dermoscopy of Facial Angiofibromas in Four Patients of Skin of Color with Tuberous Sclerosis Complex: A Case-Series. Dermatol Pract Concept. 2021;11(3):e2021036.
29 Amorim BDB, Azulay D, Ramos-E-Silva M. Tuberous Sclerosis. Skinmed. 2021;19(3):179-185.
30 Carmona JM, Moyano EG, de Castro Almeida AR, Pilar LM. Tuberous sclerosis complex. Cleve Clin J Med. 2021;88(7):367-368.
31 Samanta D. An Updated Review of Tuberous Sclerosis Complex-Associated Autism Spectrum Disorder. Pediatr Neurol. 2020;109:4-11.
32 Parthasarathy S, Mahalingam R, Melchiorre J, Harowitz J, Devinsky O. Mortality in tuberous sclerosis complex, Epilepsy Behav. 2021;121(Pt A):108032.
33 Mizuguchi M, Ohsawa M, Kashii H, Sato A. Brain Symptoms of Tuberous Sclerosis Complex: Pathogenesis and Treatment. Int J Mol Sci. 2021;22(13):6677.
34 Taga H, Yonenaga K, Eno Y, Yasumitsu T, Hatano T, Matsuo A, *et al*. Significant cases of central cusps, enamel pits, and oral fibromas in tuberous sclerosis complex. Odontology. 2021;109(1):279-283.
35 Korporowicz E, Olczak-Kowalczyk D, Lipiec M, Słowińska M, Gozdowski D, Jóźwiak S. Oral Findings in Children, Adolescents and Adults with Tuberous Sclerosis Complex. J Clin Pediatr Dent. 2020;44(3):190-195.
36 Wataya-Kaneda M, Uemura M, Fujita K, Hirata H, Osuga K, Kagitani-Shimono K, *et al*. Tuberous Sclerosis Complex Board of Osaka University Hospital. Tuberous sclerosis complex: Recent advances in manifestations and therapy. Int J Urol. 2017;24(9):681-691.
37 Dragoumi P, O'Callaghan F, Zafeiriou DI. Diagnosis of tuberous sclerosis complex in the fetus. Eur J Paediatr Neurol. 2018;22(6):1027-1034.
38 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 Mar 28;29(3):295-301.
39 Islam MP. Tuberous Sclerosis Complex. Semin Pediatr Neurol. 2021;37:100875.
40 Pfirmann P, Aupy J, Jambon E, Idier L, Prezelin-Reydit M, Fermis M, *et al*. Description of a multidisciplinary model of care in a French cohort of adult patients with tuberous sclerosis complex. J Med Genet. 2021;58(1):25-31.
41 Rosset C, Netto CBO, Ashton-Prolla P. *TSC1* and *TSC2* gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. Genet Mol Biol. 2017;40(1):69-79.
42 Amin S, Lux A, Calder N, Laugharne M, Osborne J, O'callaghan F. Causes of mortality in individuals with tuberous sclerosis complex. Dev Med Child Neurol. 2017;59(6):612-617.