

Educational Article

Oral and skin manifestations of tuberous sclerosis complex

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Abstract – Tuberous sclerosis complex is a genetic disease characterized by multisystemic hamartomas with variable and non-specific clinical manifestations. The disease is associated with mutations of genes encoding the proteins hamartin and tuberin. The hamartin/tuberin complex plays an anti-tumor function by inhibiting mammalian target of rapamycin. The diagnostic criteria for the disease were reviewed at a consensus conference in 2012. Evidence of mutations of tuberous sclerosis complex 1 or 2 genes has become a clinical and independent diagnostic criterion. Among the clinical criteria used, two oral criteria include the presence of three or more enamel pits and the presence of two or more oral fibromas. Several dermatological criteria are included within these criteria and are of interest in our specialty when these are localized at the cephalic extremity.

Introduction

Tuberous sclerosis (Bourneville disease) or tuberous sclerosis of the brain is a genetic disorder characterized by multisystemic hamartomas with variable and non-specific clinical manifestations. The diagnostic criteria for the disease were updated in a consensus conference in 2012 [1]. The most significant development was the inclusion of a genetic criterion allowing the diagnostician to make diagnosis independently. Among the clinical diagnostic criteria, two oral criteria were included as minor criteria. The presence of three or more enamel pits was introduced as a diagnostic criterion during this revision, and the presence of gingival fibromas was replaced by the presence of two or more oral fibromas. Moreover, several dermatological criteria were included within the major and minor diagnostic criteria, which are of interest in our specialty, particularly when they are localized around the cephalic extremity.

The aim of this article was to emphasize the manifestations and management of oral and dermatological localizations of tuberous sclerosis.

Definition, epidemiology, and genetics

The first description of the disease was made by von Recklinghausen in 1862 [1], and in 1880 Bourneville gave it the name tuberous sclerosis. Its prevalence has been estimated at 1 case per 10,000 to 25,000 individuals [2,3]. This prevalence is probably underestimated due to undiagnosed cases [4]. Tuberous sclerosis belongs to the group of classical phacomatoses [2] with neurofibromatosis types 1 and 2, Sturge-Weber-Krabbe syndrome, Von Hippel-Lindau disease, and various neuroectodermal dysembryoplasias. It is an autosomal dominant genetic disease with almost complete penetrance; however, two-thirds of individuals develop the disease following pathogenic *de novo* variation [2,3]. The disease is associated with a pathogenic mutation of two genes. However, despite the advances in diagnostic techniques, no mutation is detected in 15%–20% of the cases, not excluding diagnosis [1,4]. In 31% of the patients, a mutation is identified in the tuberous sclerosis complex 1 gene (TSC1) located on chromosome 9 (9q34), and in 69% of the patients, a mutation is identified in the TSC2 gene located on chromosome 16 (16p13.3) [4,5]. The genes TSC1 and TSC2 respectively encode hamartin and tuberin [4] that combine to form a hamartin-tuberin complex. Mutation of either of the proteins renders the complex inactive [4]. This complex shows anti-tumor activity

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Table I. Diagnostic criteria for tuberous sclerosis (Bourneville disease) according to the 2012 consensus conference. Red: oral criteria; blue: dermatological criteria.

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| 1. Independent genetic criterion: presence of a pathogenic mutation of TSC1/TSC2 | |
| 2. Clinical Criteria | |
| 2.1 Major criteria | 2.2 Minor criteria |
| Hypomelanotic macules, at least 5 mm in diameter (n ≥ 3) | Confetti skin lesions |
| Facial angiofibromas (n ≥ 3) or cephalic fibrous plaque | Abnormalities in the dental enamel (n ≥ 3) |
| Ungual fibromas (n ≥ 2) | Intraoral or gingival fibromas (n ≥ 2) |
| Chagrin patch | Retinal achromatic patch |
| Multiple retinal hamartomas | Multiple renal cysts |
| Cortical dysplasia | Non-renal hamartomas |
| Subependymal nodules | |
| Subependymal giant-cell astrocytoma | |
| Cardiac rhabdomyoma | |
| Lymphangiomyomatosis (LAM) * | |
| Angiomyolipomas (n ≥ 2) * | |
| 3. Diagnosis | |
| 3.1 Certain diagnosis: | 3.2 Possible diagnosis: |
| <ul style="list-style-type: none"> - Independent genetic criteria OR - 2 major clinical criteria OR - 1 major clinical criterion + at least 2 minor clinical criteria | <ul style="list-style-type: none"> - 1 major clinical criterion OR - At least 2 minor clinical criteria |
| * When lymphangiomyomatosis and angiomyolipoma are present, they collectively constitute one major criterion and not two major criteria | |

by inhibiting the activity of mammalian target rapamycin target (mTOR) protein [4], which is a regulatory kinase for cell proliferation and growth [4].

Diagnosis

Tuberous sclerosis has a predominantly neurocutaneous expression characterized by multisystemic hamartomas associated with neuropsychiatric manifestations such as mental retardation and epilepsy [2]. Many symptoms associated with tuberous sclerosis are not pathognomonic, which poses

diagnostic difficulties. The Washington International Consensus Conference in 2012 [1,5] modified the diagnostic criteria for this disease.

A genetic diagnostic criterion was introduced during this revision [1,5]. The presence of pathogenic mutations of the TSC1 or TSC2 genes allows for a definitive diagnosis of tuberous sclerosis, independent of the associated clinical manifestations.

The second diagnostic criterion is clinical [1]. Clinical manifestations are grouped into 11 major and 6 minor criteria (Tab. I). Diagnosis is considered definitive in the presence of two major clinical criteria or one major clinical criterion and



Fig. 1. Gingival fibromas of the mandible.

two minor clinical criteria. Diagnosis is considered possible in the presence of a major clinical criterion or at least two minor clinical criteria. Lymphangiomyomatosis and angiomyolipoma constitute, when concomitant, a single major criterion and not two major criteria. Among the minor clinical criteria, two are oral diagnostic criteria: The presence of at least two intraoral fibromas and at least three enamel pits.

Oral manifestations

Oral manifestations of tuberous sclerosis are noted in 11%–56% of the patients [6]. These are sometimes barely perceptible or at other times remarkable. Oral lesions are usually diagnosed between the age of 4 to 10 years or during puberty [6,7].

Enamel pits are the most common oral manifestation of the disease and are present in almost all patients [1,10,14]. These correspond to enamel hypoplasia [6,10] without associated dentinal involvement [6,7]. Their diameter varies from 4 to 100 μm . These are detected clinically or by retroalveolar radiography when radiolucent [12]. These increase the risk of cavities [10]. Treatment is necessary when enamel pits are symptomatic, decayed, or unsightly [5].

Oral fibromas are the second most common manifestation of tuberous sclerosis (Fig. 1). They are localized most often on the maxillary anterior gingiva but can be observed on the cheeks, lips, edge of the lip, tongue, or palate [7–11]. According to the studies, their prevalence is 11%–69% [6,9,10,12–15] and average diameter is 5 mm [6,10]. These fibromas can achieve gingival growth [14], which can be confused with a drug-related etiology when anticonvulsant therapy, particularly phenytoin, is concomitantly prescribed [5,7,10,12,13]. According to Curi *et al.* [16], the differential diagnosis is based on the purely gingival involvement in cases



Fig. 2. Hypomelanotic macula of the right leg.

of increased drug dose without lesions affecting any other mucous membranes contrary to the tuberous sclerosis. Removal of these fibromas is indicated in case of an increase in size or aesthetic or functional discomfort with associated bleeding [5]. This excision can be achieved via surgery, CO₂ laser vaporization, or electrocauterization [5,6].

Other oral manifestations have been described in tuberous sclerosis cases. According to Gavren *et al.* [3], tuberous sclerosis can be associated with cleft lip and palate, high-arched palate, bifid uvula, and macroglossia. Cases of bony desmoid fibroids [6,13,17], odontogenic fibroids [10], and myxomas [10] have been reported, with sporadic cases of oral angiomyolipoma [12]. According to Barron *et al.* [12], the treatment of intraosseous fibroblastic lesions is performed by curettage and enucleation. Oral monitoring every 6 months is recommended [5,6,10].

Dermatological manifestations

Dermatological manifestations are lesions of interest for an oral surgeon. These contribute to the diagnosis of the disease as four manifestations are part of the major clinical criteria (hypomelanotic macules at least 5 mm in diameter ($n \geq 3$), facial angiofibromas ($n \geq 3$) or fibrous cephalic plaques, nongelial fibroids ($n \geq 2$), and shagreen patch) and one is a part of the minor clinical criteria (“confetti-like” skin lesions) [5].

Hypomelanotic macules (Fig. 2) are found in 90% of the patients [5]. These may be present from birth or may appear during childhood [1,5]. These do not generally require treatment unless they affect a patient’s appearance. Topical mTOR inhibitors have been successfully used for management [4,6]. Facial angiofibromas (Fig. 3) are reported in more than



Fig. 3. Facial angiofibromas.

70% of the patients. These appear in the form of reddish fibrovascular papules. These angiofibromas usually appear before the age of 10 years and are usually a pathognomonic sign [5]. They are localized around the nose, cheeks, and chin, with a classically symmetrical arrangement. Their numbers increase at puberty [3]. Their management is based on topical mTOR inhibitors, vascular or surgical lasers, and resection [4,6]. A cephalic fibrous plate, usually unilateral, is found in 25% of the patients [5]. Its histology is similar to that of angiofibromas [1]. Surgery is proposed when it increases in size and/or is unsightly [6]. Ungular fibromas are found in 20% of the children, but this percentage can increase over time to become 80% of the adults [1]. Laser or surgical excision is indicated when their size is >3 mm [6]. A “shagreen patch” appears in more than 50% of the patients, usually before the age of 10 years. It is in the form of a large bumpy lesion with a so-called orange peel surface, usually located on the lower back [1]. “Confetti-like” skin lesions occur as millimetric hypomelanotic macules [5]. They differ from hypomelanotic macules in their smaller diameter and greater number [1]. These lesions, quite common in adults, are useful for diagnosis when they are congenital or appear before the age of 10 years [5].

Annual skin monitoring is recommended in children and should be individually adapted according to the clinical course [6].

Conclusion

Tuberous sclerosis (Bourneville disease) is a rare pathology with potentially severe consequences. Because of its rarity, oral clinical manifestations are often overlooked by different oral specialists. Although non-specific, two oral signs form part of the clinical diagnostic criteria for the disease, as determined at the last consensus conference (2012). The presence of enamel pits or multiple oral fibromas should evoke the diagnosis of tuberous sclerosis. Oral specialists should therefore adopt a

multidisciplinary approach both in terms of diagnosis and management.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to the publication of this article.

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