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Oral health management implications in patients with tuberous sclerosis

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We report 6 cases of patients with tuberous sclerosis and concomitant dental pathosis. The multiple manifestations in tuberous sclerosis determine its impact on dental therapy. A lack of awareness of this condition may compound the possible side effects of dental treatment. Possible preventive measures by dentists are highlighted in this presentation. Medical evaluation and the control of risk factors in relation to general anesthesia and sedation are key considerations for the management of patients with tuberous sclerosis. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:430-5)**

The concept of tuberous sclerosis (TS) has evolved for over 160 years from clinical observations and anatomicopathological studies to the introduction of molecular biology.[1] TS (also known as Bourneville-Pringle syndrome) is a rare disorder, usually linked to a triad of conditions comprising epilepsy, mental retardation, and angiofibromas, as well as to oral and skin manifestations.[2] The disease develops as an abnormal growth of ectodermic and mesodermic cells producing benign tumors that extend to areas of the head, heart, brain, and kidneys. The term *epiloia* (epilepsy, low intelligence, and adenoma sebaceum) was proposed by Campbell and Sherlock.[3] This designation may be of some use in describing the disease, though all 3 signs are rarely present. A partial form of the condition is usually observed.

The reported incidence of tuberous sclerosis varies greatly, depending on the authors, ranging from 1 in 100,000 to 1 in 1,000,000. These differences may be explained in terms of diagnostic errors, the adoption of excessively rigid diagnostic criteria, and the presentation of partial forms of the disease. Recent studies suggest that the prevalence may exceed 1 in 6000.[4] Mutations are so frequent that almost two thirds of all cases are sporadic. In some cases, intrafamilial phenotype variation may be explained by genetic mosaicism.[5] It is thus important to consider the familial background of patients who have been diagnosed with TS. In this sense, the criteria proposed by Gómez[1] may be of use in establishing an appropriate diagnosis (Table I).

Table I. Diagnostic criteria for tuberous sclerosis[1]

Main criteria*
Facial angiofibroma
Oral fibrous papules
Cortical tuberosity (after autopsy and magnetic resonance imaging)
Subependymal hamartomas (autopsy, CAT)
Multiple retinal hamartomas
Minor criteria†
Infantile spasms
Hypopigmented macules
Shagreen patches
Retinal hamartomas
Angiomyolipomas or perirenal cysts
Cardiac rhabdomyomas
First-degree relative with a primary diagnosis of tuberous sclerosis

*Only 1 needed for diagnosis.
†Two needed for diagnosis.

Often patients will be referred for dental services with a diagnosis of TS. However, it is important to continue the diagnostic process after initial evaluations and referral.[6] The knowledge gained from a thorough diagnostic process is invaluable to the well-being of dental patients with TS. In this context, the anesthetics and sedatives used in dentistry may affect patients with TS, and as such, these interactions are reviewed. The dental clinician treating patients with TS should consider the genetic aspects of the disease, as well as possible alter-

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Table II. Description of clinical signs and conditions, and dental treatment

Patients	*1*	*2*	*3*	*4*	*5*	*6*
Age (y)	9	14	12	12	11	16
Sex	Male	Male	Male	Female	Female	Male
Mental handicap*	Severe	Severe	Severe	Slight	Severe	Slight
Dental treatment†	GA	GA	Sedation	GA	GA	Sedation
Cardiac rhabdomyomas	–	–	–	–	–	?
CNS lesions						
Autism	–	–	–	–	–	–
Epilepsy	+	–	+	+	+	+
Angiomyolipomas– perirenal cysts	–	–	–	–	–	+
Oral lesions						
Oral fibrous papules	–	–	–	–	–	–
Facial angiofibromas	+	+	+	+	+	+
Enamel lesions	–	+	–	–	–	–
Impacted teeth	–	–	+	+	–	+
Hypopigmented macules	+	+	–	–	–	+

+, Presence of clinical findings; –, no clinical findings; *?*, information not available.
*Mental handicap: severe, slight, none.
†Dental treatment with patient under general anesthesia (GA) or sedation.

ations of the heart, kidneys, skin, eyes, face, bones, lungs, stomach, and central nervous system (ie, epilepsy or autism). This study describes 6 dental patients with TS.

CASE REPORT

A total of 6 patients with TS were treated and are reported in this article. In view of the mental handicaps involved (4 severe and 2 moderate), deep sedation and general anesthetic techniques were needed in each case (Table II). No genetic studies were available. One patient was seen with a possible cardiac disorder, and all had a history of epileptic crises in the past 2 years. Two patients were on antiepileptic medication during treatment. Only 1 patient had a history of kidney pathosis. All patients had facial angiofibromas, though none had oral fibromas. The presence of enamel pitting was detected by direct visualization in 1 case, and 3 patients had impacted teeth. Three patients had skin lesions (Table II).

After a first visit to our dental clinic, the patients were referred to the hospital for medical evaluation. A lack of patient cooperation because of mental impairment was the main reason for performing dental treatment with the patient under sedation and general anesthesia. All treatments necessitated 2 sessions with the patient under general anesthesia and sedation. Nitrous oxide, propofol, fentanyl, and midazolam were used for deep sedation, whereas general anesthesia was administered with isoflurane. Medical exploration before the intervention, the administration of drugs, and follow-up after general anesthesia were all carried out by the anesthetist. Informed consent was obtained from the parents before dental treatment with the patient under sedation and general anesthesia and before preparation of the present manuscript.

DISCUSSION

The possible presence of systemic pathosis associated with the TS complex (TSC) necessitates exhaustive medical evaluation of these patients, particularly when dental treatment with the patient under sedation and general anesthesia is contemplated.

TSC is a genetically heterogeneous process involving the 9q34 (TSC1) or 16p13.3 (TSC2) gene. Alterations of the latter (a tumor suppressor gene) induce the development of hamartomas and occasionally more aggressive tumors.[7,8]

In none of our patients was a genetic study available to allow TSC classification and thus provide data of use in establishing tumor prognosis and the planning of dental management. On the other hand, no hamartomas or more aggressive tumors were present at the time.

The cardiac manifestations of TSC may be among the first signs of the disease in undiagnosed patients and consist of single or multiple tumor processes called rhabdomyomas.[9] Ventricular tachycardia, paroxysmal arrhythmia, Wolff-Parkinson-White syndrome, and obstructive or reflux phenomena resulting from valve impairment are all possible consequences of intracardiac tumor development.[10-12] Patient No. 6 was seen with an aortic valve systolic murmur that had previously gone unnoticed. Complementary studies confirmed the existence of valve stenosis of uncertain origin. After consulting the cardiologist, we decided to provide prophylaxis against bacterial endocarditis.[13]

The possible remission or increase in size of the intracardiac tumor when corticoids are provided,[14] the frequent association of epilepsy, and the valve impairment and circulatory alterations caused by tumor obstruction emphasize the need for systematic evaluation of heart function in patients with TS programmed for dental treatment.

Epileptic crises, accompanied by learning disorders and abnormal behavior, are common manifestations of

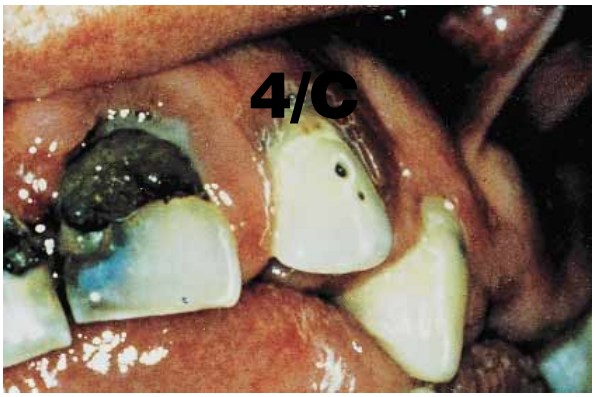

Fig 1. Enamel pitting in maxillary left second incisor.

TS.[15] Recent studies have related the presence of an increased number of cortical tuberosities in TS to brain dysfunction, measured in terms of the presence and number of convulsions, the corresponding degree of control, and the severity of mental retardation.[16] However, the causal relation between TS and epilepsy is not fully clear.[17] All our patients had a history of epileptic crises. Only 3 were receiving antiepileptic medication at the time of the study, and 1 patient had not had convulsions for the past 2 years. In this context, the risk of an epileptic episode during dental treatment and the possible adverse effects of antiepileptic drugs must be taken into consideration in the management of dental patients with TS.

Passive protection of the oral tissues is needed to prevent injury from epileptic crises, and instrumentation should be used with caution. Removable dentures are counterindicated because of the risk of fracture and possible aspiration in the event of convulsions. In this sense, fixed dentures with esthetic resin fronts are preferred. Rubber dams may also be counterindicated.[18] In any case, each patient should be evaluated according to the frequency and control of his or her epileptic attacks. No such episodes were recorded in our series either during surgery or at subsequent follow-up visits in the absence of anesthesia.

The 3 patients on antiepileptic medication received carbamazepine, valproic acid, or both. Blood dyscrasia, exfoliative dermatitis, and jaundice are some of the side effects of carbamazepines. Erythromycin should not be administered to these patients because blood levels may rise to toxic levels. In turn, valproic acid can qualitatively and quantitatively alter platelet function. Bleeding time should be determined before invasive procedures are performed, and drugs such as aspirin or ibuprofen should be avoided.[18]

An important advance in the treatment of epileptic crises in patients with TSC has been the introduction of vigabatrin, a γ-aminobutyric acid transaminase enzyme inhibitor. According to recent research, vigabatrin has been found to be effective in treating infantile spasms and has fewer undesirable effects in dental treatment.[19,20]

Autism is frequently associated with TSC,[21] though none of our patients were autistic. Bolton et al[22] related mental retardation and autism to the number and distribution of cerebral hamartomatous processes and cortical tuberosities in children with TSC. These studies suggest that alterations in temporal lobe development are an important risk factor in the appearance of autism. The presence of important behavioral disorders makes dental treatment of these patients difficult, and deep sedation and general anesthetic measures are sometimes needed.[23]

Kidney alterations are frequent in TSC. Angiomyolipomas and renal cysts are present in approximately 50% and 30% of affected patients, respectively, though renal carcinoma is less common. Kidney disease is a major cause of morbidity and mortality in these patients.[24,25] In clinical terms, the main problem is persistent bleeding caused by the intense vascularization of the angiomyolipomas, which may even produce kidney failure. These complications are typically treated by selective embolization or highly conservative surgery. In this context, embolization removes the necessity of a nephrectomy, with the resulting loss of kidney function.[26,27] Only 1 of our patients had renal angiomyolipomas and was referred for the evaluation of possible kidney functional disorders and anemia resulting from excessive blood loss. In our case, no additional measures proved necessary. Nevertheless, care is needed with sedation and general anesthesia because of possible oxygen transport deficiencies in cases of severe anemia. The hematocrit, hemoglobin concentration, and kidney functional parameters need special attention in dental patients with TS.[28]

Fibromas, enamel pitting, and an important lack of oral hygiene attributable to the mental handicaps of these patients are the most frequent findings in dental patients with TS. None of our patients had oral fibromas.

The prevalence of enamel pitting in TS has been studied by a number of authors. These enamel lesions mainly affect the labial surfaces of the central and lateral teeth and canines. It is generally accepted that enamel pitting is more frequent in TS than in healthy controls or even in patients with cerebral paralysis, Down syndrome, and phenylketonuria.[29] A first diagnosis of these lesions can be established by applying 1 or 2 drops of dental plaque-disclosing stain on the facial surfaces of the suspect teeth; this generates intense staining that allows us to identify even very small cavities.[30] The definitive diagnosis is established

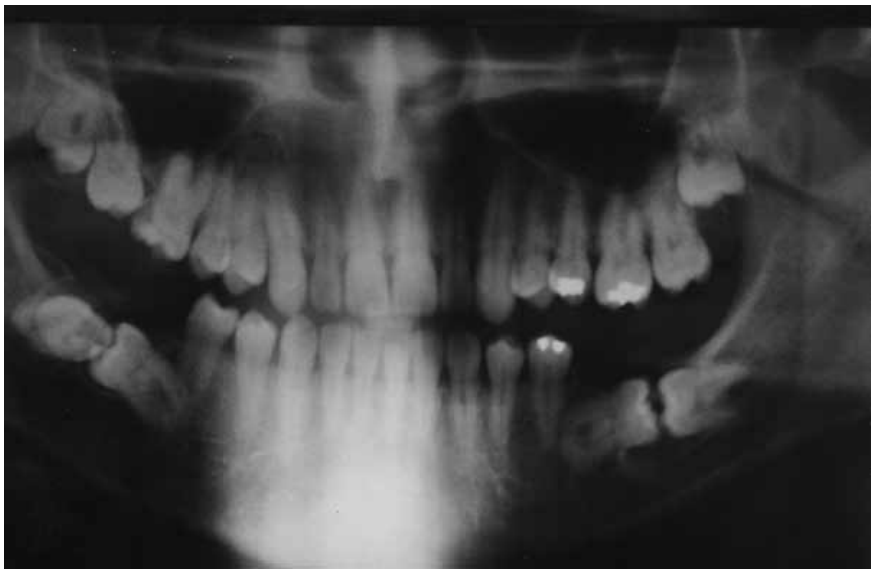

Fig 2. Impacted mandibular left second molar, mandibular left first molar, mandibular right first molar, and mandibular right second molar.

by electron microscopic identification of an increase in the Rezius striations around the cavities once the tooth has been removed.[31]

The low incidence of TS in the general population makes it difficult to establish a series sufficiently large to allow correlation between the number of enamel pits and other typical disorders of TSC. However, the presence of these lesions in patients suspected of having the disease may expedite the diagnosis and allow for genetic screening of the rest of the patient's family members.[32] The literature reports the prevalence of enamel pitting in patients with TS to range from 48% in permanent teeth to 100%. In our series of 6 cases, a lesion compatible with pitting of the labial enamel of the upper left canine was directly visualized in 1 patient (Fig 1). Dental plaque-disclosing stain or microscopic examination would probably uncover more lesions of this type. It seems reasonable to suppose that the development of caries over these lesions is more likely, though plaque accumulation is not as important as in the case of pitting of the molars. Periodic preventive measures are thus indicated, along with instructions on appropriate oral hygiene and lesion restorative management.

We have found no clear reference in the literature to the presence of impacted teeth. In our series, 3 patients had impacted teeth (Fig 2). The reason for this is uncertain, however, and studies involving larger series are needed to establish whether patients with TS have an increased incidence of dental impaction.

Leaf-shaped macules on the skin and facial angiofibromas[33] are constant findings in patients with TSC that allow us to suspect the diagnosis in very early stages of the process. Electron microscopic studies of the hypomelanotic lesions point to a decrease in the presence of epidermal melanocytes, though cell density remains normal.[33] Three of our patients had skin lesions with these characteristics (Fig 3), and all presented facial angiofibromas (Fig 4). These lesions need no treatment.

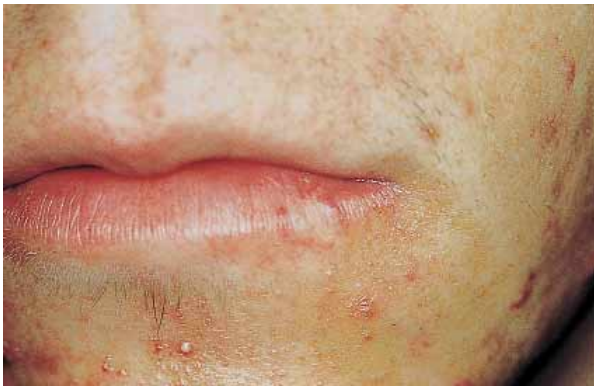

Fig 3. White leaf-shaped macules on lower lip.

Another complication of dental management in patients with TSC—particularly when deep sedation or general anesthesia is contemplated—may be the presence of pulmonary fibrous degeneration or cysts, causing dyspnea and even spontaneous pneumothorax.[34] Dental treatment should be postponed until the process

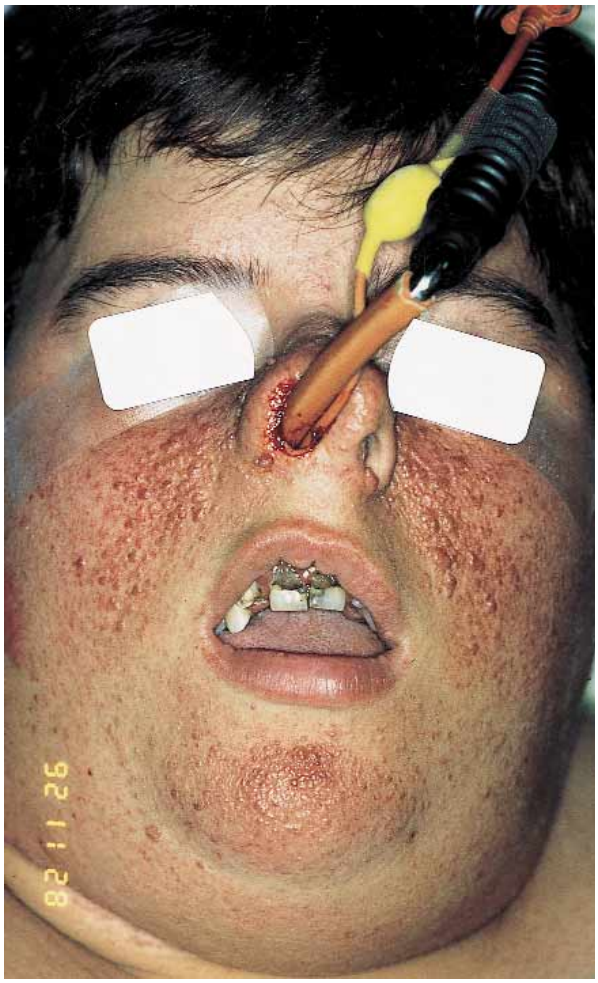

Fig 4. Oral angiofibromas in patient No. 2.

has stabilized.[35] The development of retinal astrocytomas and hamartomas,[36] nasal angiofibromas,[37] and bone involvement (facial bones)[38] producing recurrent sinusitis and lacrimal duct obstruction,[39] together with intestinal polyposis,[40] is an additional complication associated with TSC.

Mental retardation in patients with TSC often necessitates dental treatment being completed with the patient under deep sedation or general anesthesia. A complete multiorgan exploration before anesthesia is very important because of the risk of cardiac, kidney, and pulmonary problems, as well as frequent epileptic crises. Likewise, the dentist should implement effective preventive measures from the start to secure a good posttreatment prognosis. In this context, recent studies promote the combination of anesthetic agents such as thiopentone, vecuronium, and nitrous oxide with isoflurane when using general anesthesia on dental patients.[41]

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