Objective. The objective of this study was to describe the pattern of inheritance and the clinical features in a large family with tuberous sclerosis (TS), and to focus on the general diagnosis after the initial oral examination.

Study design. To characterize the pattern of inheritance and the clinical features, 61 familial members were systematically evaluated, including dermatologic, ophthalmologic, and orofacial examination. Imaging exams, such as abdomen ultrasonography, echocardiogram, fundoscopy, cranial cone-beam computerized tomography, and brain magnetic resonance, were performed. Hematoxylin and eosin stain and scanning electronic microscopy were performed to characterize TS-associated alterations in the teeth, nails, and hair.

Results. The pedigree of the family was constructed including the 4 last generations and revealed nonconsanguineous marriages and an autosomal dominant mode of TS transmission. We identified 13 family members affected by TS, with 6 of them completely fulfilling the diagnostic criteria of this disorder. Hypomelanotic macules in the skin, facial angiofibromas, and dental enamel pits were the most common features of affected patients. Central nervous system alterations were identified in 5 family members, whereas cardiac and renal alterations were found in 1 member each.

Conclusion. We emphasize, in this study, the importance of oral findings such as dental enamel pits and gingival angiofibromas in the early diagnosis of familial TS which led to complete familial profile and pattern of inheritance establishment. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:87-94)

Tuberous sclerosis (TS; MIM 191100) is a dominantly inherited disease characterized by skin lesions, central and peripheral nervous system tumors, and brain malformations, with mental and psychiatric symptoms. Neurologic manifestations range from slight or even nonexistent to extremely severe symptoms. The most common neurologic findings are seizures, though other manifestations, such as mental retardation in different degrees, epilepsy, learning difficulties, behavioral problems, autism, and obstructive hydrocephaly (secondary), are frequently seen.

The other main TS clinical manifestations include possible alterations of the heart, kidneys, eyes, face, bones, lungs, stomach, and dentition. The reported incidence of tuberous sclerosis varies greatly, depending on the authors, ranging from 1 in 1,000,000 to 1 in 10,000. These differences may be explained by diagnostic criteria and presentation of partial forms of the disease. The phenotypic expression of TSC is highly variable and in some cases it can be difficult to establish a definitive clinical diagnosis. In this sense, the criteria proposed by Roach et al., which categorized the clinical TS-associated alterations into minor and major features, is useful in the establishment of appropriate diagnosis. Most studies suggest that the prevalence is 1 in 6,000-10,000 live births, with no ethnic clustering, and de novo mutations have been implicated in two-thirds of all cases.

Familial cases were first reported in 1910, and an autosomal dominant pattern of inheritance was recognized in 1935. Male and female individuals are equally affected, and the chance to transmit it to the offspring is of 50%. In some cases, intrafamilial phenotype variation may be explained by genetic mosaicism. It is therefore important to consider the familial background of patients who have been diagnosed with TS. Although many reports have dealt with diagnosis and
genetic and systemic characteristics of TS, there are few studies evaluating the importance of oral features in the TS familial pattern. Given this, the aim of the present study was to describe the pattern of inheritance and the clinical features of 1 large family affected by this disorder, spanning 4 generations, diagnosed initially from oral findings.

PATIENTS AND METHODS

The proband (family member IV-5), a 9-year-old boy, was identified during routine clinical examination at the Stomatology Clinic of the Dental School, State University of Montes Claros, Brazil. He complained of gingival enlargement and lobular growths in the vestibular face of anterior teeth. He presented facial, ungual, and gingival angiofibromas, enamel pits in deciduous teeth, and hypomelanotic spots on back, leading to diagnosis of TS. During the initial examination, the familial trait of the disease was referred. To characterize the pattern of inheritance and the TS features, 61 members of his family were examined clinically, representing 4 generations. Only those patients screened to exhibit a predefined set of clinical TS conditions were submitted to a full battery of tests as described subsequently.

The evaluation and management used in this study, with few adaptations, were developed at the Tuberous Sclerosis Consensus Conference in July 1998 and later revised. Subjects were examined between December 2007 and July 2009. The affected patients were aged from 9 to 90 years (mean 48.6 years). Initial protocol of evaluation included identification data and detailed medical history, which were collected at the time of the physical examination. Clinical assessment included dermatologic evaluation under Wood light, ophthalmologic and orofacial examination, and photography. Imaging analysis, including abdomen ultrasonography, echocardiograms, fundoscopy, cranial cone-beam computerized tomography, and brain magnetic resonance imaging in a 1.5-T scanner including T1, T2, and Fluid Attenuated Inversion Recovery (FLAIR), were performed. Oral biopsies were taken from supposed angiofibromas for histopathologic examination. We evaluated 7 lesions from 4 affected family members. Tissues were fixed in 10% formalin and embedded in paraffin, and sections were subjected to hematoxylin and eosin stain. Scanning electronic microscopy at 14 kV (in a Jeol JSM 5600) was performed to characterize the ultrastructural alterations on teeth, nails, and hair of TS patients.

Ethical approval was obtained from the Ethics Committee of our University. Informed consent was obtained from each of the participants before inclusion in the study.

RESULTS

The physical analysis of the last 4 family generations (n = 61) revealed clinical features of TS in 13 subjects. No patients had known consanguineous weddings. The family pedigree revealed an autosomal dominant pattern of transmission (Fig. 1). The clinical and imaging features of the TS subjects are presented in Table I. Six members (2 male and 4 female, family members II-2, III-1, III-4, III-6, III-9, and IV-5) fulfilled the complete diagnostic criteria of TS, whereas 7 (2 male and 5 female; I-2, II-3, II-5, II-17, III-12, IV-8, and IV-9) presented partial forms of TS. To fulfill the complete diagnostic criteria of TS requires either 2 major features or 1 major feature with 2 minor features as depicted in Table I.

The first generation presented 1 individual (I-2) with dermatologic phenotypes of TS, who transmitted the trait to 4 family members (II-2, II-3, II-5, and II-17) out of 9 descendents. Member II-2 showed complete pen-
etrance of the disease and multiple TS-associated lesions, including facial angiofibromas, ungual and peri-ungual fibromas, hypomelanotic macules, shagreen patches, subependymal giant cell astrocytoma, renal angiomyolipoma, and dental enamel pits. Other affected members of this generation demonstrated partial forms of TS. Member II-3 presented hypomelanotic macules, member II-5 showed several facial angiofibromas, whereas member II-17 was affected by facial angiofibromas and dental enamel pits. Member II-2 transmitted TS traits to 5 descendents (III-1, III-4, III-6, III-9, and III-12), with 4 of them showing features sufficient to fulfill the complete diagnostic criteria of TS. In the third generation, 2 of the 4 affected members (III-4 and III-9) transmitted TS to their descendents, whereas the other 2 (III-1 and III-12) did not. The fourth generation presented 1 member (IV-5) that fulfilled the complete diagnostic criteria and 2 members (IV-8 and IV-9) who demonstrated features of TS.

Dermatologic features identified in the affected members were hypomelanotic macules (n = 10; 77%), facial angiofibromas (n = 9; 69.2%), “confetti” skin lesions (n = 6; 46.2%), nontraumatic ungual or peri-ungual fibromas (n = 5; 38.5%), and shagreen patches (n = 2; 15.4%; Fig. 2 and Table I). Neurologic features detected by imaging analysis were suggestive of cerebral white matter radial migration lines (n = 5; 38.5%), subependymal giant cell astrocytoma (n = 3; 23.1%), cortical tuber (n = 2; 15.4%), and subependymal nod-ule (n = 1; 7.7%; Fig. 3 and Table I). Cardiac and renal alterations were detected in 1 patient each (7.7%). Ophthalmologic examination revealed normality in all family members (Table I).

Three family members reported mental or psychiatric symptoms. Three TS-affected patients had a history of epileptic crises (II-2, III-1, and IV-5). Only 2 were receiving antiepileptic medication at the time of the study, and 1 patient had not had convulsions for the past 10 years. The 2 patients on antiepileptic medication (III-1 and IV-5) received carbamazepine and phenobarbital, respectively. Family member III-1 also presented a slight cognitive deficit.

Cone-beam computerized tomography revealed normality of oro-facial structures in all of the affected individuals. The main oral features were enamel pits (n = 7; 53.8%; family members II-2, III-1, III-4, III-6, III-9, IV-5,) and gingival angiofibroma (n = 4; 30.8%), which were confirmed by histopathological examination. Lingual (III-2), buccal (III-1), and lip fibroma/angiofibroma (II-2) were also observed. The histopathologic features of the angiofibromas were very similar among affected family members. Lesions were composed of a fibrous connective tissue containing numerous dilated capillaries surrounded by a fibroblastic proliferation and scattered large, pleomorphic, and stellate-shaped cells (Fig. 4). Ultrastructural examination revealed cuticular dysmorphology of the hair, nail dysplasia with irregular keratin plaques disposition, and irregular deep

Table I. Clinical features of the tuberous sclerosis (TS) individuals of this study and revised diagnostic criteria for TS

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<th>Clinical findings of tuberous sclerosis complex</th>
<th>IV-5</th>
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<td>Facial angiofibromas</td>
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<td>Shagreen patch</td>
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<td>Multiple retinal nodular hamartomas</td>
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<td>Cardiac rhabdomyoma, single or multiple</td>
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<td>Nonrenal hamartoma</td>
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<td>Tuberous sclerosis complex*</td>
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*To fulfill the diagnostic criteria requires either 2 major features or 1 major feature with 2 minor features.
dental enamel pits (Fig. 5). The family entered dental treatment, and the oral lesions were removed. Multiprofessional approach was requested owing to neurologic, dermatologic, and renal lesions (under consultation and follow-up at the time of writing).

**DISCUSSION**

Tuberous sclerosis is one of a group of related disorders known as neurocutaneous syndromes. Besides TS, the other major disorders of this group include types 1 and 2 neurofibromatosis, Sturge-Weber syndrome, ataxia-telangiectasia, and von Hippel–Lindau disease. The term TS refers to multiple sclerotic masses scattered throughout the cerebrum. TS was described first by von Recklinghausen in 1862 and in more recent reports by Bourneville, Pringle, and Vogt.

Mutations in TSC1 (9q34) and TSC2 (16p13.3) genes, which encode the proteins hamartin and tuberin...
respectively, are associated with TS. Both proteins have been reported to interact as a complex negatively regulating cell growth and proliferation. The products of the TSC1 and TSC2 genes, hamartin and tuberin, form a dimer, which mediates a key step in the phosphoinositide 3-kinase (PI3K) signaling pathway. Binding of extracellular growth factors, including insulin, to their cell membrane receptors leads through a series of steps to phosphorylation of tuberin. This reduces the inhibitory action that the hamartin-tuberin complex exerts via the small guanosine triphosphatase Rheb (Ras homologue enriched in brain) on the mammalian target of rapamycin (mTOR). Activation of mTOR results in increased phosphorylation of 2 of its downstream targets, ribosomal S6 kinase (S6K) and eukaryotic initiation factor 4E binding protein 1 (4EBP1), both of which lead to increased protein translation. Other signaling pathways influence the activity of the hamartin-tuberin complex, which appears to have a key role in integrating information on growth stimuli, cellular energy levels, nutrient availability, and hypoxia and, through mTOR, in regulating protein synthesis and cell growth. Functions for hamartin and tuberin independent of the complex have been suggested by evidence of their binding to a variety of other proteins, but it is uncertain whether these interactions have any physiologic significance. Mutations in TSC1 or TSC2 that impair the inhibitory function of the hamartin-tuberin complex lead to greatly increased activity of mTOR. As the name implies, mTOR is inhibited by the immuno-suppressant drug rapamycin, which opens up exciting prospects for therapy. In TSC1 and TSC2 null cell lines, rapamycin restores phosphorylation downstream of mTOR to normal levels, and in rodent models of TS, rapamycin and its analogues can inhibit the growth of hamartomas.

The presence of 2 major features or 1 major and 2 minor features is necessary to fulfill the complete diagnostic criteria of TS. There are cases in which the patient does not completely fulfill the diagnostic criteria and is considered to have the partial, incomplete form of the disease. The most common features of TS include facial angiofibromas, hypomelanotic cutaneous macule, shagreen patches in the lumbar area, cerebral cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, cardiac rhabdomyomas, and

Fig. 4. The main tuberous sclerosis oral features were (A) enamel pits in the permanent tooth (II-2), (B) gingival angiofibromas and enamel pits in the deciduous tooth (IV-3), and (C) lingual fibromas (III-4). D. Histopathology reveals a dome-shaped gingival lesion (IV-3) was composed of a fibrous connective tissue containing numerous dilated capillaries surrounded by a fibroblastic proliferation and scattered large, pleomorphic, and stellate-shaped cells underlying thickened epithelium. The lesion analyzed did not contain calcifications or areas of ulceration and presented significant collagenization (HE, ×100, low magnification).
renal angiomyolipomas. Minor features may include hamartomatous rectal polyps, nonrenal hamartomas, and multiple renal and bone cysts. Nevin and Pearce, in a classical study with TS patients, described angiofibromas in the nasolabial folds and lumbar shagreen patches in 83% of patients. Areas of skin

Fig. 5. Ultrastructural examination in a Jeol JSM 5600 scanning electronic microscopy at 14 kV revealed (A) cuticular alterations of the hair, nail dystrophy with irregular keratin plaques disposition on (B) foot and (C) hand respectively, and (D) irregular deep dental enamel pit with an increase in the striations around the cavity affect the labial surfaces of the central incisor. E-G, Ultrastructural images of comparative control hair and nails from unaffected family individuals.
discoloration were found in 61% of the patients, whereas periungual and subungual fibromas were observed in few TS patients. In agreement, the present report found hypomelanotic spots, facial angiofibromas, periungual and subungual fibromas, and shagreen patches to be the most prevalent dermatologic lesions.

Oral manifestations of TS are quite frequent and are characterized mainly by fibrous hyperplasia, angiofibroma, and dental enamel pitting. Fibrous hyperplasias and angiofibromas are frequently localized in the anterior portions of the gingiva, but they are not rare on the lips, tongue, and palate. These lesions may be normal-colored or red and typically appear in late childhood. Although a prevalence of 11% has been reported, the true frequency of these lesions may be significantly greater. Lygidakis and Lindenbaum found oral fibromas in 56% of TS patients. In the present report, angiofibromas were observed in 5 patients and affected the anterior region of the gingiva, dorsal tongue, buccal mucosa, and lip. Besides TS, other syndromes may have facial and oral papules/nodules in their clinical spectrum of alterations, including Cowden syndrome, Birt-Hogg-Dubé syndrome, and multiple endocrine neoplasia type 1. These disorders can be distinguished from TS by absence of dental enamel pits, dermatologic lesions other than fibroma/angiofibroma, and abdominal alterations, including those of the heart and kidneys. Oral manifestations of Cowden syndrome are typically more extensive than in TS, but they can be clinically and histologically similar. Histopathology reveals a dome-shaped papule with elongated rete, fibrosis, prominent fibroblasts, increased vascularity, and scattered large, pleomorphic, and stellate-shaped cells underlying thickened epithelium. Usually, the lesions analyzed did not contain calcifications or areas of ulceration and presented significant collagenization.

Dental enamel pitting is observed in up to 100% of patients with TS. Dental pits can also be observed in the general population, but at lower frequency and with fewer lesions than in TS. Enamel pits are also observed in pitted hypoplastic amelogenesis imperfecta, vitamin D–dependent rickets, pseudohypoparathyroidism, and junctional epidermolysis bullosa. The occurrence of pits in healthy individuals and other diseases puts this sign in the minor feature level of the TS diagnosis. All TS affected members of this study showed enamel pits. The presence of enamel pitting was detected by direct visualization after 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. These findings were detected in the deciduous teeth of the proband (family member IV-5), a 9-year-old boy, and permanent dentition of 5 TS-affected adults (II-2, III-1, III-4, III-6, and III-9).

Brain alterations in TS range from increased number of cortical tuberousities and formation of white matter radial migration lines to a more complex phenotype, such as tumors. Furthermore, epilepsy accompanied by learning disorders or abnormal behavior is a common manifestation of TS. Three TS-affected patients had a history of epileptic crises. Only 2 were receiving anti-epileptic medication at the time of the study, and 1 had not had convulsions for the past 10 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. TS patients also demonstrate renal alterations, including angiomyolipomas or polycystic lesions. Approximately 30% of TS patients reveal cardiac rhabdomyomas that are associated with a high risk of death during the first year of life. Indeed, ~75% of TS patients die before they reach the age of 25 years, usually as a result of cardiac insufficiency, secondary infections, or malignant disease. In the reported family, imaging studies revealed white matter radial migration lines in 5 patients, subependymal giant cell astrocytoma in 3 patients, increased number of cortical tuber in 2 patients, and subependymal nodule in 1 patient. Interestingly, there was a lack of symptoms in all of the affected patients. However, patients are on regular medical follow-up. Approximately 50% of TS patients exhibit renal hamartomas, those were not found in this report.

Scarce familial reports are mentioned in the literature, such as one study with a nuclear family in which 3 persons in 2 generations were diagnosed as having TS with multiple hypomelanotic dermal patches and epilepsy. Computerized tomography showed subependymal calcifications and ophthalmological investigations indicated phakomas as retinal involvement in all of them. Khare et al. reported a 4-generation family with mild physical features of TS, but in which there was significant clustering of neuropsychiatric disorders, including mood disorder, anxiety disorder, and autism, among affected individuals. A second family from the same geographic region also had mild physical features of tuberous sclerosis, but no neuropsychiatric assessment had been performed. Ruggieri et al. described a family in which all 4 siblings, born to consanguineous, healthy, asymptomatic parents, had a severe form of TS. Three of these infants had a course that was rapidly fatal in the neonatal period. In a study conducted by Sampson et al. with TS familial emphasis, 35 patients were members of families with >1 affected subject. In 1 family, 4 generations were affected, in 4 families 3 generations, and in 7 families 2 generations.
families, TS was inherited as an autosomal dominant trait, and no skipped generations were seen. Great variation in expression was evident within as well as between families. Subgrouping of clinical features among these families, which might suggest heterogeneity, was not noted. In the present studied family, the wide phenotypic heterogeneity and a dominant trait were evident. In summary, we showed 1 large familial TS with neurocutaneous and oral phenotypes affecting 13 familial members with 6 diagnosed spanning 4 generations.

REFERENCES


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