Oral Findings in Children, Adolescents and Adults with Tuberous Sclerosis Complex

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Objectives: *Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the development of benign tumors. The aim of the study was to assess the prevalence of oral lesions in patients with TSC and healthy individuals.* ***Study design***: *The study included 120 patients aged 1.1 to 42.7 years: 60 patients with TSC and 60 controls. Clinical assessment of oral hygiene (Plaque Index–PLI), gingiva (Gingival Index–GI, Gingival Overgrowth Index–GOI), oral mucosa and dentition (caries, tooth wear, enamel defects) was performed. Statistical analysis was performed.* ***Results***: *40 patients with TSC received anticonvulsants. Neglected hygiene (PLI: 1.50±0.96 vs 0.92±0.72), gingival hyperplasia (50.0% vs.1.7%), gingivitis (80.7% vs. 53.4%), oral mucosal fibromas (10.0% vs. 0.0%), mucous membrane traumatic lesions (11.7% vs. 1.7%), enamel pits and hypoplasia of incisal borders (41.7% vs. 6.7%), tooth wear (35.0% vs. 11.7%) were more common in patients with TSC compared to controls; increased gingival hyperplasia was correlated with vigabatrin and levetiracetam treatment (r = 0.266 and 0.279, respectively), gingivitis was correlated with PLI (r= 0.635).* ***Conclusions***: *Although gingival fibromas in TSC are independent of patient's age, young age, anticonvulsant therapy and local factors increase their severity. Enamel defects in TSC include pits, but also enamel loss on the incisal edges and tooth wear.*

Keywords: *Oral Mucosa, Dental Enamel Hypoplasia, Tuberous Sclerosis, Tooth wear*

INTRODUCTION

Tuberous sclerosis complex (TSC) is one of the most common neurocutaneous diseases, with incidence rates of 1: 6.000–1:10.000 in the general population. It is an autosomal dominant disorder; familial rates are about 30% [1]. The main clinical manifestations include epilepsy, delayed psychomotor and mental development, multiple skin lesions and nodular lesions in the brain, heart, kidneys, liver and lungs. Although these are usually benign hyperplastic lesions, they require regular check-ups and appropriate treatment. In the last decade there was a breakthrough in the treatment of TSC due to the possible use of mTOR inhibitors, sirolimus and everolimus, which effectively block tumor growth [1].

The diagnosis of TSC is based on the presence of two from the list of major diagnostic criteria or one of the major and two of the minor criteria for TSC. Identification of pathogenic mutation confirms TSC diagnosis without the need to verify other clinical manifestations.

As opposed to other organ lesions, relatively little attention was paid to oral health in patients with TSC. The most commonly reported oral lesions include enamel pits, fibromas and gingival hypertrophy. All these lesions are included in the list of minor diagnostic criteria for TSC [2]. Gingival hyperplasia, high arched palate, bifid uvula, harelip and/or cleft palate delayed dental eruption and

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diastema are less common [3]. The vast majority of literature reports on oral lesions in TSC are case reports, hence the difficulty in estimating the actual incidence of oral symptoms [2-8]. It is believed that oral lesions typical for TSC are more common in adults than in children; however, there are few publications presenting oral health both in adult [7, 9] and pediatric patients [6,10,11].

The aim of this paper was to compare oral health in patients with TSC and healthy individuals, including an assessment of mucous membranes, gingiva, periodontium and dentition for caries, pathological tooth wear and developmental anomalies.

MATERIALS AND METHOD

Patients with TSC under the care of the Department of Paediatric Neurology of the Medical University of Warsaw were qualified to the study group. Some of the tests were performed among adults and children during their stay at a summer camp organized by the Association of Patients with Nodular Sclerosis. Children and their healthy parents reported for a check-up appointment in the Department of Paediatric Dentistry of the Medical University of Warsaw were included in the control group. Parents legal guardian's consent was obtained. Children with less than four erupted primary teeth, patients undergoing orthodontic treatment, and smokers were excluded from the study; patients with systemic diseases and those receiving chronic therapies were excluded from the control group. The study was approved by the Bioethical Commission of the Medical University of Warsaw (no. AKBE/118/2019).

The evaluation involved a medical interview with the patient and/or their legal guardians to collect data on systemic diseases and pharmacotherapy used, as well as clinical examination. The examinations were performed by three dentists with at least two years of experience in pediatric dentistry, who underwent training and calibration (the value of the Cohen's kappa coefficient was calibrated and achieved a minimum of 0.8), in the dental office, using dental unit lamp, dental mirror, dental probe and periodontal probe.

A clinical assessment of oral hygiene, gingiva (the presence and severity of inflammation and hyperplasia), mucous membrane and dentition was performed. Gingival Index (GI) and Plaque Index (PLI) according to Silness and Löe [12] were used for the assessment of oral hygiene and gingivitis. The amount of dental plaque and gingival health were assessed in the cervical area of six indexed teeth: 16 or 55, 12 or 51, 24 or 63, 36 or 75, 32 or 71, 44 or 83. If the index tooth was missing, the adjacent tooth was assessed. The two indexes were calculated on the basis of the average measured tooth sites for a given subject.

Gingival hyperplasia was assessed using the Gingival Overgrowth Index (GOI) according to McGaw [13]. Data on the location (front/lateral teeth) and the number of teeth adjacent to the hyperplastic site, the color and condition of the surface of hyperplastic gum (smooth/popular), and the highest GOI value were recorded [13].

The assessment of oral mucosa included pathological lesions (number, type, and location), in accordance with the principles of differential diagnosis [14].

Dental assessment covered all teeth . Data on the presence of decayed (d/D), missing (m/M), and filled (f/F) teeth according to the WHO criteria (Basic), as well as hypoplastic enamel (pits, groves, areas) and tooth wear were recorded. The dmf and DMF indices were calculated for primary and permanent teeth, respectively [15]. The presence of tooth wear on the labial, incisal and palatal/lingual surfaces of the upper and lower anterior teeth and on the occlusal surfaces of all four permanent first molars (mixed and permanent dentition) or second primary molars was assessed. Tooth wear was assessed using the *Tooth Wear Index* according to Smith and Knight and modified by Bardsley *et al* [16]. The highest score was recorded for each patient. Surfaces destroyed by dental caries or with fillings were not included [16]. The chi-square test, Mann–Whitney U test, and Spearman's rank correlation were used for statistical analysis. The level of significance was set to 0.05.

RESULTS

A total of 60 patients aged between 1.1 and 42.7 years and diagnosed with TSC (mean age 12.67± 10.28 years), including 32 males, were included in the study group. The control group included 60 generally healthy patients aged between 1.1 and 41.0 years (mean age 12.12 ± 8.84 years), including 30 males (Table 1). Among TSC patients, 52 patients from different families, three pairs of siblings and their two parents were examined. Two pairs of siblings and two parents were examined in the control group. Primary dentition was reported for 17 children in the TSC group and 20 children in the control group, mixed dentition in 15 and 16 children, and permanent dentition in 26 and 25 children, respectively.

Epilepsy was the most common general medical problem in the TSC group (n = 40; 66.7%). Polycystic kidney disease (n=3), mental disorders (schizophrenia and depression n=3), asthma (n=2), hypertension (n=2), heart defects (n=1), and hypothyroidism (n=1) were less common. The most frequently used anticonvulsants included valproic acid (n=19) and vigabatrin (n=29), while levetiracetam (n=5), topiramate (n=4) and carbamazepine (n=3) were less common. Four patients additionally received an immunosuppressant–sirolimus, and two patients received everolimus. A total of 19 patients received multidrug therapy. Two patients were treated with calcium channel inhibitor due to hypertension.

Oral and gingival hygiene, as well as the prevalence of oral mucosal lesions in both groups are shown in Table 2. GI and PLI were not calculated for three TSC children and two controls due to the lack of cooperation or an insufficient number of teeth in the youngest patients. Gingival hyperplasia was observed in 30 TSC patients and 1 patient in the control group (Fig. 1). The highest GOI equaled 3 in TSC patients' group, and 1 in control group.

Among the 28 TSC patients, gingival hyperplasia was found in 1 to 12 teeth. Extensive hyperplastic lesions (diameter >1 cm) similar to epulis were found in 5 of these patients, including 4 located near an erupting primary (n=2) or permanent (n=2) tooth (Fig. 1 A, B and C). Generalized gingival hyperplasia involving all teeth was observed in 2 patients (Fig. 1D). Both of these patients used antiepileptic drugs (e.g. vigabatrin, levetiracetam). Bright red hyperplastic gingiva was observed in only one girl aged 12 years (Fig. 1D). The other participants had a normal gingival color. Gingival hyperplasia was observed in one patient in the control group – an inflammatory granuloma.

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Table. 1. Age structure and the type of dentition in patients with TSC and controls

	TSC		Controls	
Age	**N/%**	**Mean ± SD (years)**	**N/%**	**Mean ± SD (years)**
up to 6 years	18/30.0%	3.77±1.50	20/33.3%	4.21±1.51
>6-12 years	17/28.3%	8.40 ±1.95	15/25.0%	8.75 ±1.71
>12-18 years	13/21.7%	15.44± 2.05	13/21.7%	15.31± 1.66
>18 years	12/20.0%	29.08 ± 9.61	12/20.0%	26.09 ± 7.40
Dentition				
primary	34/56.7%	6.17±3.37	35/58.3%	6.15±2.77
permanent	43/71.7%	16.17± 10.16	42/66.7%	16.08±8.31

Table 2. Oral, gingival and oral mucosal hygiene in patients with TSC vs. control group.

Parameters	TSC	Controls	P
	mean ± SD		
Plaque Index (PLI)			
total	1.50±0.96	0.92±0.72	<0.001y
primary dentition	1.30±1.12	1.09±0.63	0.510y
mixed dentition	1.64±0.93	1.04±0.88	0.075y
permanent dentition	1.54±0.89	0.71±0.64	<0.001y
Gingival Index (GI)			
total	0.71±0. 69	0.38±0.56	0.005y
primary dentition	0.59±0.54	0.35±0.50	0.194y
mixed dentition	0.60±0.63	0.73±0.78	0.614y
permanent dentition	0.87±0.79	0.19±0.29	<0.001y
	n (%)		
Gingivitis (GI > 0.1)			
Total	46/57 (80.7%)	31/58(53.4%)	0.002z
primary dentition	11/15 (73.3%)	10/18 (55.6%)	0.291z
mixed dentition	14/17 (82.4%)	9/15 (60.0%)	0.161z
permanent dentition	21/25 (84.0%)	12/26 (46.2%)	0.005z
Gingival hyperplasia (GOI >0)			
total	30/60 (50.0%)	1/60 (1.7%)	<0.001z
primary dentition	10/17 (58.8%)	0/20 (0.0%)	<0.001z
mixed dentition	9/17 (52.9%)	1/15 (6.6%)	<0.001z
permanent dentition	10/26 (38.5%)	0/25 (0.0%)	<0.001z
Oral mucosal hyperplastic lesions	6/60 (10.0%)	0/60 (0.0%)	0.042 z
Buccal mucosal bites	7/60 (11.7%)	1/60 (1.7%)	0.028 z
Angular cheilitis	2/60 (3.3%)	2/60 (3.3%)	1.000 z
Erosions/ ulcerations	3/60 (5.0%)	1/60 (1.7%)	0.309 z
Geographic tongue	0/60 (0.0%)	3/60 (5.0%)	0.079 z

[Y] – Mann Whitney U test

[Z] – Chi squared test

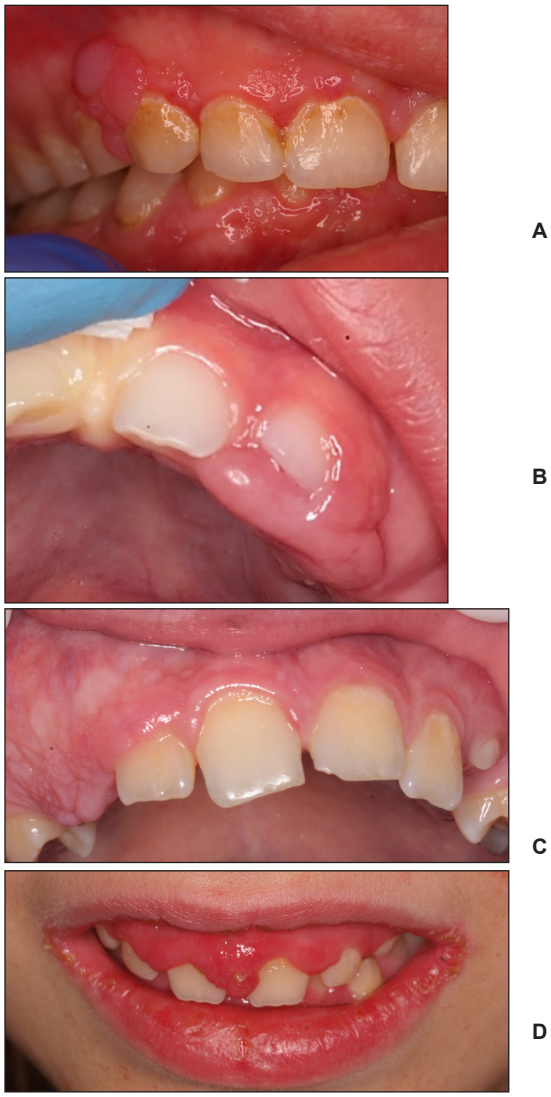

Fig. 1. Gingival hyperplasia in children with TSC: A–marginal gingival inflammation and hyperplasia in the vicinity of permanent mandibular and maxillary front teeth with extensive hyperplastic lesion around the left maxillary canine (GOI 2); B–extensive gingival hyperplasia in the vicinity of an erupting primary lateral maxillary incisor (GOI – 3) and hypoplastic enamel of the incisal edge of the primary central incisor; C- gingival hyperplasia in the vicinity of right maxillary dentition, more severe around the erupting canine; hypoplasia of the incisal edges of incisors, and fractured enamel of the left central incisor (11 years); D – generalised gingival hyperplasia in permanent dentition (GOI– 3).

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In 6 patients with TSC, gingival hyperplasia was accompanied by fibromas in other regions of the oral cavity, including palatal (n=2), glossal (n=2), lower lip (n=1) and buccal mucosa (n=2). One of these patients presented with multiple fibromas on the tongue and palate (Fig. 2). In other cases, these were single lesions. All lesions were of the same color as mucosa, had a papular structure and produced no clinical symptoms.

Spearman's correlation analysis in the TSC group showed statistically significant correlations between GI and PLI (r=0.635), the presence of epulis-like hyperplasia and patient's age (r= -0.260), increased gingival hyperplasia and the use of vigabatrin and levetiracetam (r=0.266 and 0.279, respectively), as well as between vigabatrin therapy and buccal mucosal bites (r=-0.352).

Dental caries was a common problem among the study participants (Table 3). Enamel hypoplasia was observed 6.2 times more often in the TSC group vs. control group and affected 3.7 times more teeth (Table 3). Enamel hypoplasia on the labial tooth surfaces was observed in 18 patients and was accompanied by enamel defects on incisal edges in 5 patients; enamel defects on incisal edges alone were reported in 2 patients (Fig. 1BC, Fig. 3). Enamel hypoplasia affected the incisal edges of primary upper incisors in four patients, (mean age 2.94 ± 1.76 years), and permanent upper incisors in three patients (mean age 7.88 ± 2.76 years). In the control group, pits were observed in 3 and grooves in 1 patient.

Tooth wear was 3 times more common in the TSC group vs. controls. Tooth wear with dentin exposure >1/3 was reported for only 2 patients with TSC. Other patients in both groups presented with less severe tooth wear, i.e. barely exposed dentin or dentin exposure < 1/3. Spearman's correlation analysis for both groups confirmed the statistically significant relationship between dmft/DMFT and PLI (r=0.184). A similar analysis in the TSC group demonstrated statistically significant relationships between GI and dmft/DMFT (r=0.407), as well as GI and enamel hypoplasia (r=-0.273

Table 3. Dental status in TSC patients vs. controls

Parameters	TSC	Controls	P
	n (%)		
dmft/DMFT>0	50 (83.3%)	55 (91.7%)	0.168
	mean ± SD		
dmft	4.35±5.16	6.40±4.36	0.041
DMFT	7.86±6.83	6.83±5.24	0.469
	n (%)		
Enamel hypoplasia			
total	25 (41.7%)	4 (6.7%)	<0.001
primary dentition	14/34 (41.2%)	2/35 (5.7%)	<0.001
permanent dentition	19/43 (44.2%)	2/42 (4.8%)	<0.001
	mean ±SD		
Number of teeth with enamel hypoplasia	2.32±4.21	0.62±3.27	
	n (%)		
Tooth wear	21(35.0%)	7 (11.7%)	0.003
	mean ±SD		
Number of teeth with wear lesions	2.60 ± 4.80	0.63 ± 2.16	0.017

Chi-squared test

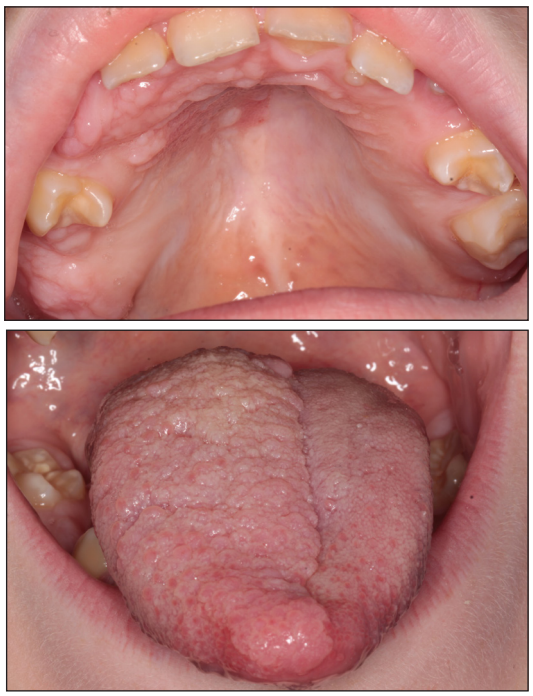

Fig. 2. Hyperplastic lesions of gums and palate (A), and dorsal tongue (B) in an 11-year-old boy with TSC

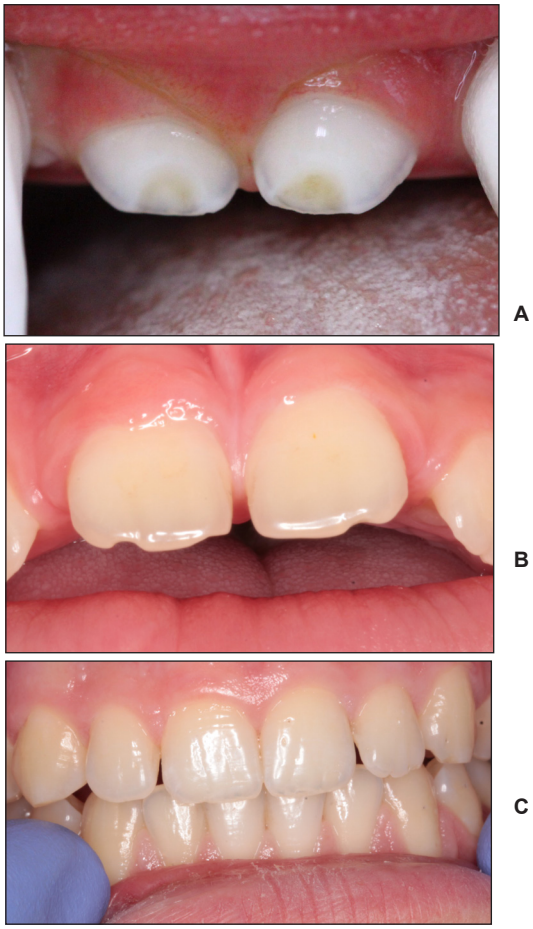

Fig. 3. Enamel defects in TSC patients: A – enamel hypoplasia on the incisal edges of primary central maxillary incisors; B – enamel hypoplasia on the incisal edges of permanent central maxillary incisors; C–pits on the labial surfaces of the left maxillary incisor.

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DISCUSSION

Oral fibromas and enamel pits are considered typical oral manifestations of tuberous sclerosis. The incidence of oral fibromas in TSC patients can even reach 69% [2]. However, such lesions were not observed in any of the patients in a series of 6 cases reported by Cutando [8]. Fibroma/angiofibroma-like lesions may be located in gums or other oral regions. It seems that buccal and labial mucosa is a predisposed extragingival site [2,5,17]. Frenular, upper lip, palatal and glossal lesions were less common [2, 17].

Gingival involvement alone was observed in 33.3%, while lesions involving gums and other oral regions were found in 10.0% of our TSC patients. In a group of 58 adult patients with TSC, the rates of gingival fibromas were similar (52.0%); however, fibrous lesions in other oral regions were 4 times more common compared to our group (40.0%) [2].

According to most authors, fibrous papule typical of TSC is described as domed papule, same color as the gingiva or slightly whitish, which may form separately or in clusters similar to papillomatous [2].

Diffuse gingival overgrowth [2,18], which was diagnosed as drug-induced gingival enlargement [18] was also reported in TSC patients. However, Sparling *et al* showed diffuse gingival overgrowth in 7 TSC patients, none of whom received antiepileptic therapy [2]. One of the patients received nifedipine, and the other patient presented with mouth breathing. Two of the patients with diffuse gingival overgrowth used antiepileptic drugs–vigabatrin and levetiracetam. One of these patients additionally was a mouth breather . There is a known relationship between gingival enlargement and the use of drugs such as phenytoin [19], valproic acid [20] and vigabatrin [21], as well as calcium antagonists, e.g. dihydropyridines, verapamil and diltiazem [22]. Vigabatrin and valproic acid were the most commonly used drugs in our study. We observed no effects of valproic acid on the gingival tissue. However, we noted the importance of vigabatrin therapy, with corresponds to literature reports [21].

Oral fibromas are believed to be more common in adults than in children [9]. However, our Spearman's correlation analysis demonstrated a negative correlation between extensive epulis-like local hyperplastic gingival lesions and patient's age. We also observed an increased incidence of gingival hyperplasia in children with primary versus permanent dentition. We confirmed that bacterial plaque is the main cause of gingivitis. We showed no relationship between PLI and GI and the presence/severity of gingival hyperplasia, which may be associated with reduced gingival response to bacterial plaque in developmental age patients compared to adults. It is also worth noting that four of the five sites of extensive gingival hyperplasia were found in the area of erupting teeth. This may indicate the importance of changes occurring in the gingival tissue during tooth eruption in the pathogenesis of epulis in patients with tuberous sclerosis. It is known that during the process of eruption the dental follicle releases multiple factors, such as interleukins, parathyroid hormone-dependent protein (PTHrP), growth factor (EGF), and transforming growth factor β 1 (TGF-β1), to form an eruption pathway. The release of inflammatory cytokines leads to *gingivitis eruptiva* [23]. It is also known that cytokines, prostaglandins and growth factors play an indirect role in the pathogenesis of gingival overgrowth by promoting fibroblast formation and gingival fibrosis [24]. However, this hypothesis should be confirmed with observations in a larger group of patients during tooth eruption. Harutunian *et al* pointed to the role of increased local inflammation in the development of epulis in a 35-year-old woman with TSC. A large (2.5 cm in diameter) and rapidly growing fibroma occurred in the vicinity of the right mandibular third molar, tender to percussion, which indicated inflammation. A similar, smaller lesion (1 cm) was located in the region of root fragments of the left lower third molar [25]. It seems that the aggressivity of the lesions depends on the severity of the local factors. Fibromas are also known to sporadically develop in the general population and are causally associated with local irritation, e.g. repeated mucosal injury [26].

In addition to oral fibromas, buccal mucosal damage due to bites (which is commonly reported in children with neurological disorders, epilepsy in particular) was observed more frequently in TSC patients vs. controls in our study population. Among 150 children (age between 12 and 17 years), buccal and glossal bites were observed in up to 74.0% and 56.0% of patients, respectively. According to some studies, dental fractures were also a common problem among children with epilepsy (12%) [27]. In our study population, two patients presented with crown fractures. Although we did not confirm a direct relationship between epilepsy and traumatic damage, the negative correlation between their occurrence and vigabatrin therapy suggests that decreased rates of seizures reduce the risk of dental and mucosal damage.

Enamel pits, which are usually located on the labial surfaces of the central and lateral teeth and canines, are an oral manifestation of tuberous sclerosis classified as a minor diagnostic criterion. Their incidence for permanent dentition is estimated at 48-100% [11,28]. Only few researchers described enamel defects in primary teeth. Araújo *et al* presented a single case of enamel pits in a child with primary dentition [29]. Ho *et al* assessed dentition in 13 patients aged between 2.5 and 18 years with varying stages of TSC [28]. Enamel pits were observed in 10 patients, with the youngest one aged 5 years. In contrast, Sampson *et al* showed no such lesions in any of his 6 patients with primary dentition [10].

Those studies showed enamel hypoplasia in TSC only in the form of dental enamel pitting. In our group of children, we also observed visible enamel defects in the incisal edges. Tooth wear, which is an often-occurring manifestation in patients with neurological disorders, was also common. Thus, a higher incidence of hypoplasia of the incisal edges, which can only be seen for a short time after tooth eruption, is likely.

Despite statistically significantly worse oral hygiene and increased rates of enamel defects, the incidence of caries was slightly lower in TSC patients vs. controls. The severity of caries in primary teeth was also statistically significantly lower. This is in contrast with literature reports pointing to enamel hypoplasia as a risk factor of caries in this group of patients [25]. It is believed that enamel hypoplasia promotes dental plaque retention. Although our analysis did not confirm the relationship between PLI and enamel hypoplasia, it showed statistically significant correlations between plaque-related GI and enamel hypoplasia and dental caries. Vigabatrin therapy was negatively correlated with the presence and severity of dental caries. Many factors, including the amount and properties of saliva, are known to play an important role in caries etiology. Some anticonvulsants, such as valproic acid and carbamazepine, reduce salivary production. In turn, hypersalivation, which improves oral self-cleaning, may be a side effect of vigabatrin therapy [30].

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CONCLUSIONS

Results indicate that the incidence of oral fibromas and enamel defects is higher among TSC patients than healthy individuals and independent of age and type of dentition. Local factors, such as tooth eruption, may promote the development of gingival fibromas, the severity of which may be increased by anticonvulsants. Enamel defects may take the form of pits or enamel defects on the incisal edges of the teeth, often masked with tooth wear, which is a common problem in TSC patients.

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