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ORIGINAL ARTICLE

Tooth abnormalities and soft tissue alterations in patients with G/BBB syndrome

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OBJECTIVE: The G/BBB syndrome is an X-linked recessive disorder characterized by eye anomalies, laryngotracheoesophageal cleft, congenital heart disease, genitourinary anomalies and gastrointestinal disorders. Patients may also present cleft lip and palate, high-arched palate and thin upper lip. This study aimed to investigate the occurrence of tooth abnormalities and soft tissue changes in patients with G/BBB syndrome.
DESIGN: Cross-sectional.
SUBJECTS AND METHODS: Twenty-one patients with G/BBB syndrome were analyzed as to the presence of tooth abnormalities and soft tissue alterations.
MAIN OUTCOME MEASURES: The prevalence of tooth agenesis and supernumerary teeth was compared to patients without morphofunctional alterations, matched for gender and age.
RESULTS: All patients had complete cleft lip and palate; 95.23% of patients presented tooth abnormalities, mainly hypoplastic alterations, with predominance of alterations of number, followed by alterations of structure, shape and position. The frequency of tooth agenesis and supernumerary teeth was significantly higher compared with the control group; 11 patients presented incisiform supernumerary teeth in the mandibular anterior region. Ankyloglossia was observed in 11 of 21 patients.
CONCLUSION: The presence of mandibular anterior supernumerary teeth and ankyloglossia should be investigated in the clinical evaluation of patients with suspected diagnosis of the G/BBB syndrome.
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Keywords: Opitz syndrome; tooth abnormalities; tooth agenesis; ankyloglossia

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Introduction

John Opitz first described the syndromes G (Opitz *et al*, 1969a) and BBB (Opitz *et al*, 1969b) as separate clinical disturbances. Posteriorly, reports on families in which the G and BBB syndromes segregated suggested that they represented a single disorder (Cappa *et al*, 1987; Online Mendelian Inheritance in Man, 2006).

The syndrome presents X-linked recessive inheritance associated to the chromosomal region Xp22. However, it is currently accepted that the disorder is heterogeneous and that there is also an autosomal dominant inheritance with male preference, because of the observation of deletion of the chromosomal region 22q11 in patients and families with signs of the G/BBB syndrome, with or without superimposition of signs of the velocardiofacial syndrome (Lacassie and Arriaza, 1996; McDonald-McGinn *et al*, 1996). The families often present monozygotic twinning (Online Mendelian Inheritance in Man, 2006).

Patients with the G/BBB syndrome present eye anomalies (hyperteleorbitism and telecanthus), laryngotracheoesophageal cleft (especially in patients with initial diagnosis of the G syndrome), congenital heart disease, genitourinary anomalies (hypospadia and cryptorchidism) and gastrointestinal disorders (dysphagia, gastroesophageal reflux, imperforate anus). The facial aspect is typical with prominent forehead, flat philtrum, broad nasal bridge, anteverted nares and grooved nasal tip (Opitz, 1987; So *et al*, 2005; Online Mendelian Inheritance in Man, 2006). There may be agenesis or hypoplasia of corpus callosum, besides other anomalies of the central nervous system in the midline (Guion-Almeida and Richieri-Costa, 1992). The patients may also present cleft lip and palate, high-arched palate and thin upper lip (So *et al*, 2005; Online Mendelian Inheritance in Man, 2006).

Few reports are available on the dental characteristics of individuals with G/BBB syndrome; there are reports of ankyloglossia (Gorlin *et al*, 1990; Brooks *et al*, 1992; Shaw *et al*, 2006), geographic tongue (Brooks *et al*, 1992), bifid tongue (Gorlin *et al*, 1990), tooth agenesis

(Brooks *et al*, 1992), supernumerary teeth (Gorlin *et al*, 1990), different tooth abnormalities (Gorlin *et al*, 1990; Brooks *et al*, 1992; Parashar *et al*, 2005) and micrognathia (Gorlin *et al*, 1990).

With regard to the craniofacial morphology, there is increased length of posterior cranial fossa, lower anterior facial height and ANB angle (Brooks *et al*, 1992), mandibular hypoplasia (Opitz, 1987; Brooks *et al*, 1992; Parashar *et al*, 2005) and increase in the y-axis (Brooks *et al*, 1992). The nose is broad and flat (Opitz, 1987; Parashar *et al*, 2005).

Additional observations on the dental aspects might be useful in the evaluation of patients with suspected diagnosis of the G/BBB syndromes, as well as for the establishment of adequate treatment protocols to their needs. Thus, this study analysed the prevalence of tooth abnormalities and soft tissue alterations in individuals with G/BBB syndrome.

Subjects and methods

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. The study was revised and approved by the Institutional Review Board of the Hospital for Rehabilitation of Craniofacial Anomalies – University of São Paulo (HRAC/USP). All patients or caretakers received oral and written information on the study and signed an informed consent term.

Patients with clinical diagnosis of the syndrome were initially identified by search in the database of HRAC/USP, from records since the hospital was established in June 1967 until October 2006. The inclusion criteria comprised Caucasoid patients, aged more than 6 years, with at least one panoramic radiograph available in the files of the Oral Radiology Sector of HRAC/USP. Until study onset, 61 patients had been registered with clinical diagnosis of G/BBB syndrome, based on observation of three or more of the following clinical features: prominent forehead, widow's peak, anomalies of the corpus callosum, telecanthus, flat philtrum, broad nasal bridge, anteverted nares, grooved nasal tip, dysphagia, gastroesophageal reflux, imperforate anus, cryptorchidism, and especially hyperteleorbitism and hypospadia. As the study was conducted in a cleft centre, the presence of unilateral or bilateral cleft lip and palate was also an important feature.

Some patients were excluded because of poor oral health with insufficient information in the records to allow conclusions on tooth agenesis (one), non-Caucasoid ethnicity (one), definitive hospital discharge (four), death (five), treatment abandonment (eight) and age below 6 years (13); eight further patients did not attend the hospital during the study period. This led to a final sample of 21 patients.

The presence of tooth abnormalities and soft tissue changes was investigated by clinical examination with the aid of a dental mirror and dental probe, under artificial light, by a single examiner. Soft tissue changes were analyzed by clinical examination of all regions of the mouth (lips, cheeks, tongue – dorsal and ventral, hard and soft palate, and gingiva). Tooth abnormalities were classified as alterations of shape, number, position and structure (enamel defects) (Cawson and Odell, 2002), and as hyperplastic, hypoplastic and heterotopic alterations (Álvares and Tavano, 1990). Enamel opacities were classified by the DDE index (FDI, 1982). Patients submitted to orthodontic intervention (10 patients) were only evaluated as to abnormalities of shape and number, as abnormalities of position and structure may be altered by the use of orthodontic appliances.

The number of present teeth, clinically and radiographically, was recorded. The presence of tooth agenesis was clinically evaluated and radiographically confirmed. All teeth were considered, except for the third molars. The history of tooth extractions was investigated by analysis of patient records and discussion with the caretakers and/or patients.

The prevalence of tooth agenesis and supernumerary teeth was compared with a control group of patients without morphofunctional alterations, paired for gender and age, obtained from analysis of pretreatment panoramic radiographs and dental history from the files of a private orthodontic clinic.

Method error

Intraexaminer agreement as to the presence of tooth agenesis and supernumerary teeth was analyzed by re-evaluation of 30 randomly selected panoramic radiographs of both groups, after a minimum period of 2 weeks. There was agreement in 100% of cases, thus the kappa coefficient was not calculated.

Analysis of results

The prevalence of tooth abnormalities was analyzed by descriptive statistics. The prevalence of tooth agenesis and supernumerary teeth in the study and control groups was compared by the chi-square test. The mean number of congenitally missing teeth and supernumerary teeth in the study and control groups was compared by the Mann–Whitney *U*-test. All statistical tests were applied at a significance level of $P < 0.05$.

Results

The 21 patients (all males) presented a mean age of 16.48 years (range 8.00–34.94), adding up to 493 teeth.

The overall occurrence of abnormalities is presented in Table 1 and detailed in Table 2 (alterations of shape), Table 3 (alterations of number) and Table 4 (alterations of position and structure).

Among the 21 patients, two presented complete unilateral left cleft lip and palate, three complete unilateral right cleft lip and palate, and 16 exhibited complete bilateral cleft lip and palate (Table 1). With regard to the soft tissue alterations, ankyloglossia was observed in 11 of 21 patients (52.38%, Figure 1); one patient presented fissured tongue (Table 1).

Twenty patients (95.23%) presented at least one tooth abnormality, ranging from one to 10 abnormalities per

Table 1 Distribution of patients and occurrence of tooth abnormalities

Patient	Age (years)	Number of tooth abnormalities	Cleft lip and palate	Soft tissue alterations
1	28.73	3	Complete bilateral cleft lip and palate	–
2	34.94	1	Complete bilateral cleft lip and palate	–
3	21.14	0	Complete unilateral left cleft lip and palate	–
4	19.90	7	Complete bilateral cleft lip and palate	Ankyloglossia
5	17.80	5	Complete bilateral cleft lip and palate	Ankyloglossia
6	17.11	3	Complete bilateral cleft lip and palate	–
7	17.23	4	Complete unilateral right cleft lip and palate	–
8	16.47	4	Complete unilateral right cleft lip and palate	Ankyloglossia
9	17.00	7	Complete bilateral cleft lip and palate	Ankyloglossia
10	14.57	7	Complete bilateral cleft lip and palate	Fissured tongue
11	14.00	2	Complete unilateral right cleft lip and palate	–
12	19.80	4	Complete bilateral cleft lip and palate	–
13	12.43	9	Complete bilateral cleft lip and palate	Ankyloglossia
14	12.43	7	Complete bilateral cleft lip and palate	Ankyloglossia
15	19.05	3	Complete bilateral cleft lip and palate	Ankyloglossia
16	11.18	10	Complete bilateral cleft lip and palate	–
17	11.10	2	Complete bilateral cleft lip and palate	Ankyloglossia
18	13.06	6	Complete bilateral cleft lip and palate	–
19	9.87	5	Complete unilateral left cleft lip and palate	Ankyloglossia
20	9.73	4	Complete bilateral cleft lip and palate	Ankyloglossia
21	8.72	4	Complete bilateral cleft lip and palate	Ankyloglossia

Table 2 Alterations of shape per patient

	Alterations of shape					
Patient	Hypodevelopment of lingual cusp	Supernumerary cusp	Microdontia	Macrodontia	Peg-shape	Tubercle of Bolk
4	MdL1stPM, MdR1stPM	–	–	–	–	–
6	–	–	–	–	MxRLI	–
7	MdL1stPM, MdR1stPM	–	MxRLI	MxLCI	–	–
8	MdL1stPM, MdR1stPM	–	–	–	–	–
9	–	MdL1stPM, MdL2ndPM, MdR1stPM, MdR2ndPM	–	–	–	–
11	–	–	MxRLI	–	–	–
13	–	–	MxLLI	–	–	–
14	–	–	MxLLI	–	–	–
16	–	–	–	–	–	deciduous MdL1stM
18	–	–	MxR2ndPM	–	–	–
21	–	–	–	–	MxRLI	–

Mx, maxillary; Md, mandibular; R, right; L, left; 1st, first; 2nd, second; CI, central incisor; LI, lateral incisor; PM, premolar; M, molar.

patient, in a total of 98 abnormalities, being 70% hypoplastic, 25% hyperplastic and 5% heterotopic. Among the 98 abnormalities, 19.8% were alterations of shape (especially microdontia, Figure 2, and hypodevelopment of the lingual cusp of the mandibular first premolar); 53% alterations of number (agenesis of 34 teeth, especially maxillary lateral incisors, and 18 supernumerary teeth, primarily at the mandibular anterior region, Figures 3a–c); 5% alterations of position (mainly transposition between maxillary canines and first premolars, Figure 4); and 22.2% alterations of structure (enamel hypoplasia and opacity, Figure 5).

Tooth agenesis was observed in 76.19% of patients in the study group and 14.29% in the control group, with significant difference between groups (χ^2 16.24, $P = 0.000$). The mean number of congenitally missing teeth per patient was 1.62 in the study group and 0.19 in the control group, with statistically significant difference ($Z = -4.08$, $P = 0.000$). Supernumerary teeth were observed in 57.14% of patients in the study group and 4.76% in the control group, with statistically significant difference (χ^2 5.55, $P = 0.018$). The mean number of supernumerary teeth per patient was 0.86 in the study group and 0.04 in the control group, with statistically significant difference ($Z = -2.37$, $P = 0.009$).

Discussion

Twenty among the 21 patients presented at least one tooth abnormality, thereby indicating a high frequency, mainly hypoplastic alterations. The predominance of bilateral clefts (16 of 21 patients in the present study) agrees with previous reports in the literature (Parashar

Table 3 Alterations of number per patient

	Alterations of number		
Patients	*Agenesis*	*Maxillary supernumerary tooth*	*Mandibular supernumerary tooth*
1	MxRLI, MxLLI	–	Incisiform mandibular anterior
2	MxRLI	–	Incisiform mandibular anterior
4	MxRLI, MxLLI, MdL2ndM, MdR2ndM	–	Incisiform mandibular anterior
5	MxRCI, MxRLI, MxLCI, MxLLI	–	Incisiform mandibular anterior
6	MxLLI, MxL2ndPM	–	–
8	MxRLI	–	Incisiform mandibular anterior
9	–	Maxillary right and left incisor	Incisiform mandibular anterior
10	MxRLI, MxLLI, MdL2ndPM, MdR2ndPM	–	–
11	MxL2ndPM	–	–
12	–	Maxillary right and left incisor	Incisiform mandibular anterior
13	MxRLI, MxL2ndPM	–	Incisiform mandibular anterior
14	MxRLI	–	–
15	MxRLI, MxLLI	–	Incisiform mandibular anterior
16	MdL2ndPM, MdR2ndPM	–	–
17	MxRLI	–	Incisiform mandibular anterior
18	MxRLI, MxLLI	–	Incisiform mandibular anterior
19	MxR2ndPM, MxLLI	Maxillary left premolar (three supernumerary teeth)	–
20	MxRLI, MxL2ndPM, MdR2ndPM	–	–

Mx, maxillary; Md, mandibular; R, right; L, left; 1st, first; 2nd, second; CI, central incisor; LI, lateral incisor; PM, premolar; M, molar.

Table 4 Alterations of position and structure per patient

	Alterations				
	Position			*Structure*	
Patient	*Rotation*	*Retention*	*Transposition*	*White-cream opacity*	*Enamel hypoplasia*
10	–	–	–	MxRCI (B), MxLCI (B)	MxLCI (D)
12	MxRLI	–	–	–	–
13	–	–	–	MxLCI (B)	MxRCI (B), MxRCI (M), MxLCI (B), MxLCI (M)
14	–	–	–	MxLCI (B)	MxRCI (B), MxRCI (M), MxLCI (B), MxLCI (M)
16	–	MxLLI	between MxLC-MxL1stPM and MxRC-MxR1stPM	MxRCI (B), MxLCI (B), MxLC (M)	MxRCI (B)
18	MxRCI	–	–	MxRCI (D)	–
20	–	–	–	–	MxLLI (B)
21	–	–	–	MxRCI (B), MxLCI (B)	MxLCI (B)

Mx, maxillary; Md, mandibular; R, right; L, left; 1st, first; 2nd, second; CI, central incisor; LI, lateral incisor; PM, premolar; B, buccal; M, mesial; D, distal.

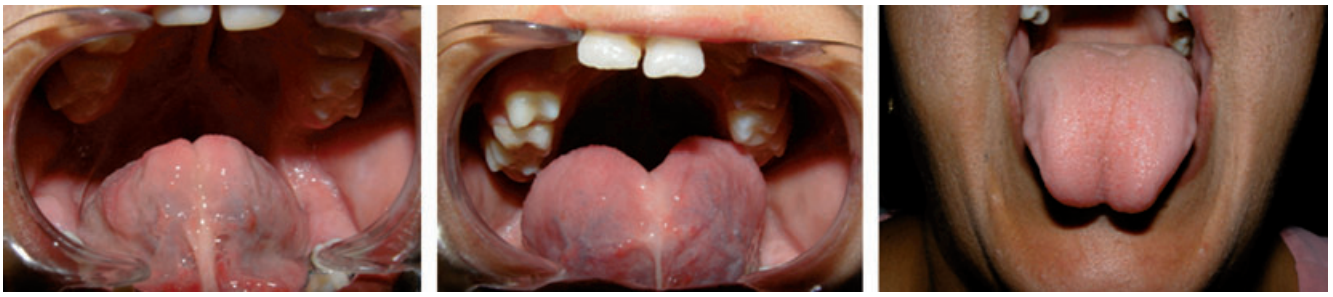

Figure 1 Ankyloglossia in twin brothers with G/BBB syndrome and their mother

et al, 2005). The observation of unilateral or bilateral complete cleft lip and palate in the patients explains the high frequency of microdontia and agenesis of maxillary lateral incisors.

As previously reported by Brooks *et al* (1992) and Parashar *et al* (2005), anomalies of number were significantly more frequent in patients with G/BBB syndrome compared with the control group, suggesting a possible

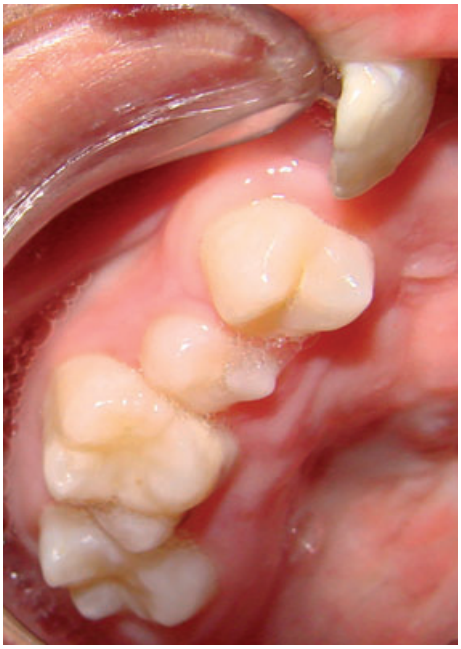

Figure 2 Microdontia of maxillary second premolar in patient with G/BBB syndrome

association with the syndrome. The prevalence of these alterations was also higher than reported in the general population (76.19% compared with 2.7–6.9%) (Davis, 1987; Nordgarden *et al*, 2002; Silva Meza, 2003). Tooth agenesis affected mainly the maxillary lateral incisors, followed by maxillary and mandibular second premolars; these findings are explained by the presence of complete cleft lip and palate in all patients, as aforementioned reported, and corroborates previous reports (Brooks *et al*, 1992).

A noticeable frequency of supernumerary teeth was observed, affecting 57.14% of patients, adding up to 18 supernumerary teeth, among which 11 were incisiform supernumerary teeth in the mandibular anterior region. This observation was highly consistent and would hardly be a casual finding. As mentioned by Thesleff (2006), supernumerary teeth are much less common than tooth agenesis. The overexpression of ectodysplasin in the dental epithelium of transgenic mice (K14-Eda) leads to formation of an extra tooth in front of the first molar (Thesleff, 2006). In patients with G/BBB syndrome, the overexpression of some factor in the dental epithelium seems to occur consistently in the mandibular midline, giving rise to supernumerary teeth in this region. It is agreed that the syndrome is originated from a developmental defect of the midline field (Cappa *et al*, 1987) and virtually all anomalies in this syndrome represent midline defects (Opitz, 1987). Interestingly, the presence of a supernumerary mandibular incisor was reported in a patient with frontonasal dysplasia, which also constitutes a midline defect (Haro Montero *et al*, 2005). Thus, the frequent observation of incisiform supernumerary teeth in the mandibular anterior region may also constitute a midline defect and, based on these findings, might be included among the characteristics of the syndrome.

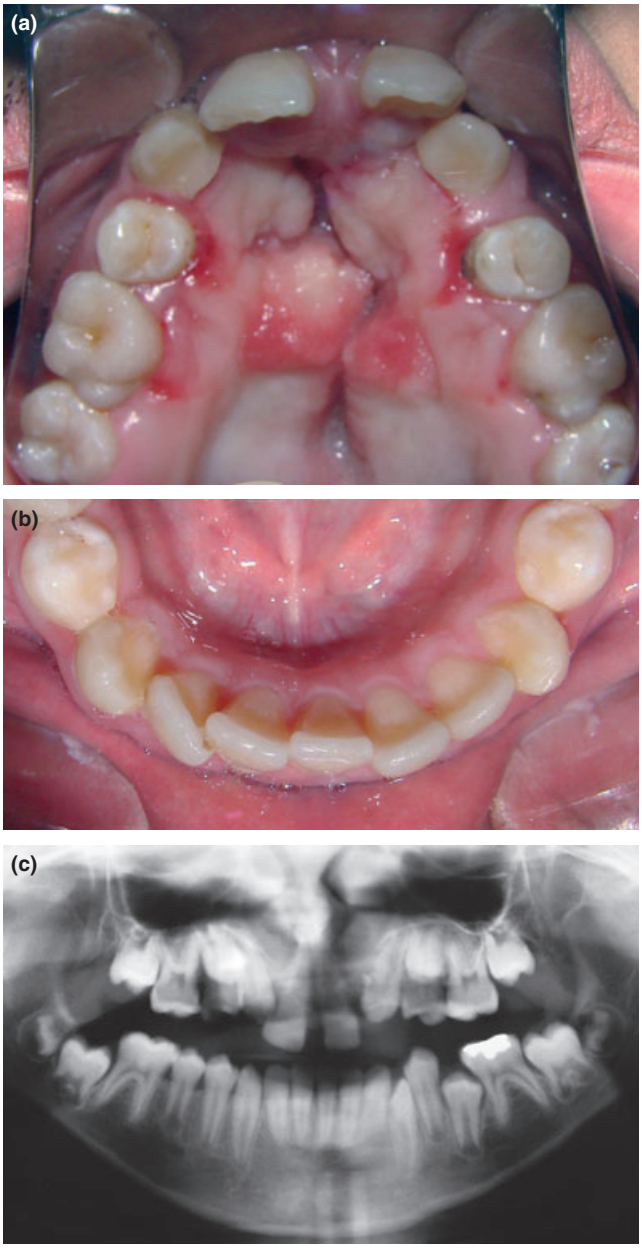

Figure 3 Clinical (**a** and **b**) and radiographic (**c**) aspect of bilateral agenesis of maxillary lateral incisors and second premolars and incisiform mandibular anterior supernumerary tooth in patient with G/BBB syndrome

For statistical purposes, the prevalence of tooth agenesis and supernumerary teeth was investigated in a group paired for gender and age, thus composed of only 21 individuals without morphofunctional alterations. Studies investigating the prevalence of these alterations in larger samples of patients with G/BBB syndrome and especially on a larger group of patients without morphofunctional alterations might provide more definitive conclusions on these features.

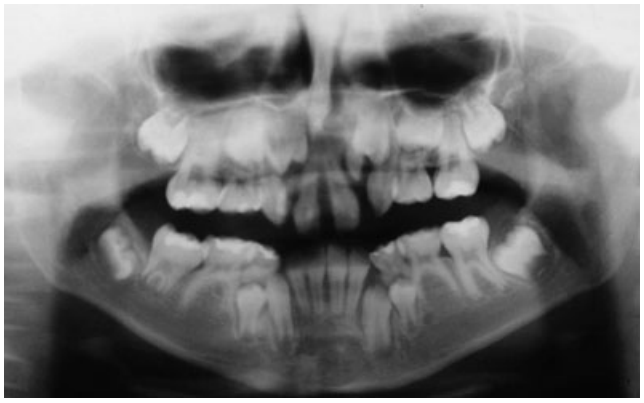

Figure 4 Transposition between maxillary right and left canines and first premolars, retention of maxillary left lateral incisor and agenesis of mandibular right and left second premolars in patient with G/BBB syndrome

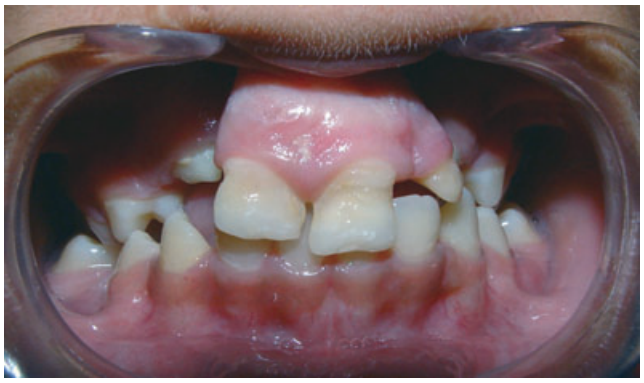

Figure 5 Enamel opacities and hypoplasia on maxillary central incisors and microdontia of maxillary lateral incisor in patient with G/BBB syndrome

Abnormalities of position and structure were also observed in some patients, yet with lower frequency and apparently without any etiological relationship with the syndrome.

Ankyloglossia was consistently observed in 11 of 21 patients, revealing a higher frequency than observed in populations without morphofunctional alterations, in which the prevalence of this alteration ranges from 0.88% to 20% (Ballard *et al*, 2002; Sanchez, 2000; Vörös-Balog *et al*, 2003; Ekenze *et al*, 2006). Opitz (1987) and Brooks *et al* (1992) had previously reported the occurrence of ankyloglossia or short lingual frenum in patients with G/BBB syndrome. Shaw *et al* (2006) reported the presence of ankyloglossia in patients with G/BBB syndrome and their mothers; even though this was not under the scope of the present study, during clinical examination, some mothers reported to have ankyloglossia. The presence of ankyloglossia may also represent a midline defect and might be included among the characteristics of the syndrome. Future studies might investigate the frequency of ankyloglossia in female individuals in affected families, in order to determine if the presence of ankyloglossia, similar to the hyperteleorbitism (Online Mendelian Inheritance in Man, 2006), might represent a sign of a milder phenotype of the syndrome in female MID1 mutation carriers.

In conclusion, 95.23% of individuals with G/BBB syndrome in the present study presented at least one tooth abnormality, with predominance of hypoplastic alterations; the frequency of tooth agenesis and supernumerary teeth was significantly higher compared with the control group. Ankyloglossia was observed in 52.38% of patients.

As a suggestion, the presence of mandibular anterior supernumerary teeth and ankyloglossia might be included among the features commonly observed in patients with G/BBB syndrome.

Author contributions

This study was part of a thesis, conducted as part of the requirements for the postgraduate degree, PhD in Oral Pathology. Dr. da Silva Dalben was the PhD candidate and is the main investigator. Dr. Richieri-Costa was co-supervisor and supervised the study in the aspects related to Genetics.

Dr. Taveira was the supervisor and supervised the study in the aspects related to Oral Pathology. The study was designed by Dr. da Silva Dalben, who also examined the patients and performed statistical analysis of results. Drs. da Silva Dalben, Richieri-Costa and Taveira discussed the results and approved the final version of the thesis and the manuscript.

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