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Oro-Dental Features of Pallister–Killian Syndrome: Evaluation of 21 European Probands

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Pallister–Killian syndrome (PKS) is a rare sporadic multisystemic developmental disorder caused by a mosaic tetrasomy of the short arm of chromosome 12. A wide range of clinical characteristics including intellectual disability, seizures, and congenital malformations has previously been described. Individuals with PKS show a characteristic facial phenotype with frontal bossing, alopecia, sparse eyebrows, depressed nasal bridge, long philtrum, telecanthus, and posteriorly rotated ears. Oro-dental features, such as "Pallister lip," macroglossia, delayed eruption of primary teeth, high arched-palate, prognathism, and cleft palate have been occasionally reported in the medical literature. The aim of the study was to assess the oro-dental phenotype of PKS and to describe the oral health status in a cohort participating in the First European Workshop on PKS. A clinical dental examination was performed in 21 Caucasian probands and data regarding medical and dental history collected. Twelve probands (57%) showed an atypical dental pattern, with multiple missing teeth (primarily the first permanent molars) and 2 (10%) a double teeth. The severity of gingivitis and dental caries increased with age and gingival overgrowth was a common finding. A characteristic occlusive phenotype was found: a high-arched palate with mandibular prognathism associated with an anterior openbite and crossbite and with posterior crossbite (unilateral or bilateral). The prevalence of oral habits (non-nutritive sucking, mouth breathing, bruxism) was high, even in older probands. This study suggests that individuals affected by PKS should be observed closely for oro-dental diseases and a multidisciplinary approach is needed to implement the right preventive measures.

Key words: Pallister–Killian syndrome; oral health; dental anomalies; malocclusion

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INTRODUCTION

Pallister–Killian syndrome (PKS) is a rare genetic disorder, first described in 1977 by Dr. Philip Pallister [Pallister et al., 1977], caused by the presence of a supernumerary isochromosome composed of two short arms of chromosome 12, identified as an isochromosome 12p. The isochromosome is present in a tissue limited mosaic pattern with variable levels of mosaicism in different tissues with no evidence of a genotype–phenotype correlation [Blyth et al., 2015]. The prevalence has been estimated to be 1/20,000, based on an analysis of liveborn infants with prenatally diagnosed marker chromosomes [Izumi and Krantz, 2014], and to date more than 150 sporadic cases have been reported.

The clinical manifestations include characteristic craniofacial dysmorphism, intellectual disability, epilepsy, hypotonia, spasticity, pigmentary skin anomalies, visual and hearing impairment, and many congenital defects (diaphragmatic hernia, congenital heart defects, anal atresia, cleft palate, sacral appendage) [Pallister et al., 1977; McLeod et al., 1991; Chaouachi et al., 2010; Wilkens et al., 2012; Tilton et al., 2014; Blyth et al., 2015]. In the literature, data regarding PKS oro-dental features are very limited and include

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"Pallister lip," a typical feature of the upper lip with an extension of the philtral skin into the vermilion border [Wilkens et al., 2012], delayed eruption of primary teeth, high arched-palate, cleft palate, macroglossia, prognathism [Kostanecka et al., 2012; Blyth et al., 2015]. Only one case report describes the oral health conditions of a 4 year-old PKS child with a prominent upper lip, complete primary dentition, generalized enamel hypoplasia, cavities of the central incisors, supernumerary labial frenulae, hypotonia of tongue and labial muscles, macrostomia, high-arched palate, prognathism, anterior openbite, and abundant bacterial plaque [de Oliveira et al., 2006].

The aim of the present study was to describe the oro-dental features and the oral health status of 21 Caucasian patients with PKS.

MATERIALS AND METHODS

A cohort of 21 Caucasian probands (9 males and 12 females; mean age 9.2 ± 7.1 years old, range 2–33) with a documented cytogenetic diagnosis of PKS were examined during the First European Workshop on PKS (September 6–8, 2013, Loup Palace, Loiano, Bologna, Italy), organized by PKS Kids Italy Onlus, Italian Association of PKS. The participation was voluntary: 21 of the 27 present families accepted the invitation to take part in the study. Fifteen probands (71%) were from Italy, three (14%) from the Netherlands, one (5%) from Denmark, one (5%) from Britain, and one (5%) from Sweden. Demographic data are listed in Table I (probands are identified in the text by numbers from 1 to 21). The local Ethics Committee of the Bologna University Hospital Authority St. Orsola-Malpighi Polyclinic (Bologna, Italy) approved this research protocol. In full accordance with the ethical principles of the Helsinki Declaration, written informed consent for participation and publication was obtained from the adults responsible for each patient before enrolment.

Data Collection

Medical and dental history. For each proband, a parent filled in a medical anamnestic form (pregnancy, birth, general medical history, pharmacologic therapies), a dental anamnestic form (history of pain, swelling, dental trauma, previous dental treatments), and the "WHO Oral Health Questionnaire" regarding oral hygiene, fluoride intake, diet, oral habits, dental recalls [World Health Organization, 2013].

Oral examination. Two of the authors (GP, SB), specialists in special needs dentistry, examined each patient with gloves, surgical masks, sterile dental mirrors and WHO periodontal probes. Oral and orthodontic diagnoses were based on clinical findings due to the lack of appropriate radiographic facilities. The Silness and Loe Plaque Index (PI) was used for oral hygiene [Silness and Loe, 1964], the Gingival Index (GI) for gingival conditions [Loe and Silness, 1963], the decay, missing, filled teeth Index for dental caries in the primary dentition (dmft), and in the permanent dentition (DMFT) [World Health Organization, 2013]. Dental history was taken to identify teeth extracted for caries or missing for other reasons (agenesis, dental trauma). The modified index of developmental defects of enamel (mDDE) was used to assess dental enamel defects [Federation Dentaire Internationale, 1992].

Regarding occlusion, the following clinical variables were evaluated: the relationship between the maxillary and mandibular first permanent molars (Angle's classification system) and the relationship between the upper and lower dental arch in the three planes of space (sagittal, vertical, transverse).

Training and calibration. One month before the patients' examination, the two investigators were trained and calibrated in the application of the PI, GI, and dmft/DMFT Index on a group of 20 patients with special health care needs seen at the Unit of Dental Care for Special Needs Patients (Department of Biomedical and Neuromotor Sciences, Bologna University, Italy). Using Cohen's kappa statistics, the inter-examiner agreement was reported as good (0.75 PI; 0.65 GI) and very good (0.85 dmft/DMFT). Intra-examiner reliability of the method, tested by one investigator repeating the assessment in 10 patients after 2 hr, was reported as good (0.78 PI; 0.68 GI) and very good (0.86 dmft/DMFT).

Statistical Analysis

The statistical analysis was performed using the Software Package for the Social Sciences (SPSS for Windows, version 21.0, SPSS Inc., Chicago, IL). Continuous variables were expressed as mean ± standard deviation and categorical variables by count and percentage. Simple linear regression analysis was performed to assess the association of PI, GI, and dmft/DMFT indexes with the age, considering age as independent variable. The level of statistical significance was set at $P < 0.05$.

RESULTS

Medical History

Data regarding medical history of the cohort are listed in Table II.

Dental History

Teething began before the 10th month in 9 probands (43%), at 11–18 months in 5 (24%); 7 (33%) did not remember. Regarding oral hygiene, none of the probands were able to brush their teeth autonomously and oral hygiene was carried out by the parents and caregivers. In 10 probands (48%), parents reported difficulty to perform an effective daily tooth brushing. In 13 probands (62%), teeth were brushed at least once a day; in 3 (14%), several times per week; in 2 (6%), several per month; in 3 (14%), never. In 10 (48%), a manual toothbrush was used; in 8 (38%), an electric device. In 11 probands (57%), a fluoride toothpaste was used; in 2 (10%), dietary fluoride supplements were used; in 1 (5%), both; 7 (33%), never took fluoride. A low intake of cariogenic foods (soft drinks, honey, candy, and sugars) was reported; the consumption of fresh fruit was high (68% at least once a day). All the parents reported an open mouth posture during day and night with excessive drooling, 13 (62%) a non-nutritive sucking, 10 (48%) mouth breathing, and 9 (43%) bruxism. Fourteen patients (67%) visited a dental office during the previous year: 8 (38%) for a dental recall, 6 (29%) for pain experience. A history of pain and swelling due to dental caries was reported in 6 probands (29%); none of the probands had a history of dental trauma.

TABLE I. Demographic Data and Dentition Patterns in a Cohort of 21 Probands With Pallister–Killian Syndrome

N.	Natonality	Gender	Age	Dentition	Missing teeth in relation to age
1	Italy	M	2	X° 54 53 52 51 | 61 62 63 64 X° X° 84 83 82 81 | 71 72 73 74 X°	
2	Denmark	M	2	X° 54 53 52 51 | 61 62 63 64 X° X° 84 83 82 81 | 71 72 73 74 X°	
3	British	F	3	55 54 53 52 51 | 61 62 63 64 65 85 84 83 82 81 | 71 (72-73)[d] 74 75	
4	Netherlands	F	4	X 54 53 52 51 | 61 62 63 64 X 85 84 83 82 81 | 71 72 73 74 75	55 65
5	Netherlands	F	4	55 54 53 52 51 | 61 62 63 64 65 85 84 (83-82)[d] 81 | 71 72 73 74 75	
6	Italy	F	5	55 54 53 52 51 | 61 62 63 64 65 85 84 83 82 81 | 71 72 73 74 75	
7	Italy	F	5	55 54 53 52 51 | 61 62 63 64 65 85 84 83 82 81 | 71 72 73 74 75	
8	Italy	F	6	55 54 53 52 51 | 61 62 63 64 65 85 84 83 82 41 | 31 72 73 74 75	
9	Italy	M	6	55 54 53 52 51 | 61 62 63 64 X 85 84 83 82 81 | 71 72 73 74 75	65
10	Italy	M	7	X 55 54 53 12 11 | 21 22 63 64 65 X X X 84 83 42 41 | 31 32 73 74 X X	16 26 75 36 85 46
11	Netherlands	F	8	16 55 54 53 52 11 | 21 62 63 64 65 26 46 85 84 83 42 41 | 31 32 73 74 75 36	
12	Italy	F	8	X 55 54 53 12 11 | 21 22 63 64 65 X X 85 84 83 42 41 | 31 32 73 74 75 X	16 26 36 46
13	Italy	M	8	X 55 54 53 12 11 | 21 22 63 64 65 X X 85 84 83 42 41 | 31 32 73 74 75 36	16 26 46
14	Italy	M	8	X 55 54 53 12 11 | 21 22 63 64 65 X 46 85 84 83 42 41 | 31 32 73 74 75 36	16 26
15	Italy	M	10	X X° 54 53 12 11 | 21 22 63 X° X° 26 46 85 X° 83 42 41 | 31 32 73 74 75 36	16
16	Italy	F	11	X 55 54 13 12 11 | 21 22 63 64 65 X X 85 84 X° 42 41 | 31 32 33 34 75 X	16 26 36 46
17	Italy	M	12	16 15 14 13 12 11 | 21 22 23 24 25 X 46 45 44 43 42 41 | 31 32 33 34 35 36	26
18	Italy	M	16	X X 55 54 13 12 11 | 21 22 23 64 65 X X X 46 85 84 43 42 41 | 31 32 33 74 75 36 X	14 15 16 17 24 25 26 27 34 35 37 44 45 47
19	Italy	F	17	X* X 15 14 13 12 11 | 21 22 23 24 65 X X* X* X 45 44 43 42 41 | 31 32 33 34 75 X X*	16 25 26 35 36 46
20	Italy	M	19	17 16 15 14 13 12 11 | 21 22 23 24 25 26 X* 47 46 X* X* 43 42 41 | 31 32 33 34 35 36 37	
21	Sweden	F	33	X* 16 15 14 13 12 11 | 21 22 23 24 X* X* X* 47 46 85 44 43 42 41 | 31 32 33 X* 35 X* 37	45

M, male; F, female; d, double tooth; X, absent tooth; *, extracted; °absent according to the age.
The International Standards Organization Designation System (ISO System) by the World Health Organization was used for dental notation.

TABLE II. Medical History in a Cohort of 21 Probands With Pallister–Killian Syndrome

	N (%)
Pregnancy	
Physiological	17 (81)
At risk	4 (19)
Polyhydramnios	2 (10)
Gestational diabetes	1 (5)
ns	1 (5)
Medication during pregnancy	
Insulin	1 (5)
Vasosuprina	1 (5)
Folic acid	1 (5)
Smoking during pregnancy	2 (10)
Born	
At term	14 (62)
Prematurely	7 (33)
Congenital anomalies	13 (62)
Cardiac defects	5 (24)
Interatrial defects	3 (5)
Patent foramen ovale	1 (5)
ns	1 (5)
Cleft palate	4 (19)
Inguinal hernia	3 (14)
Anal atresia	1 (5)
Intellectual disability	21 (100)
Hypotonia	(90)
Epilepsy	13 (62)
Respiratory diseases	9 (43)
Visual anomalies	7 (33)
Hearing impairment	6 (29)
Gastroesophageal reflux	4 (19)
Dysphagia	2 (10)
Hypothyroidism	2 (10)
Growth hormone deficiency	1 (5)
Drugs regularly (daily)	13 (62)
Anti-epileptics	11 (52)
Melatonin	5 (24)
Levothyroxine	2 (10)
Lorazepam	2 (10)

ns, not specified.

Oral Examination

The dentition. Twelve probands (57%) showed an atypical dental pattern due to the absence of primary and/or permanent teeth in relation to the age (excluding third permanent molars, teeth extracted for dental caries, and unerupted teeth according to the age). Two probands (10%) had a double tooth (two teeth joined together by the enamel or by dentin) in primary dentition in the anterior region of the mandible. For each proband, dentition stages, extracted teeth, and missing teeth are shown in detail in Table I.

Oral hygiene, periodontal diseases, dental caries, and dental enamel defects. The main features are shown in Table III.

The mean PI of the cohort was 1.6 ± 0.9; oral hygiene was rated as poor (PI 2–3) in 10 probands (48%), good (PI 0–1) in 6 (28%), fair (PI 1–2) in 5 (24%). Linear regression analysis showed no statistically significant association between age and PI. The mean GI of the cohort was 1.5 ± 0.8; gingivitis varied from mild to severe in 18 probands (86%) and was absent in 3 young (2–3 years old) patients (14%). A statistically significant linear regression was seen between age and GI score ($r = 0.5715$, $P = 0.006806$).

Seven probands (33%) showed an alveolar ridge overgrowth (increased width of the alveolar ridges) in the posterior regions of the jaws. Five probands (24%) showed gingival overgrowth (thickening of the soft tissue overlying the alveolar ridge) associated with alveolar ridge overgrowth. Five probands (24%) a low attachment of the upper buccal frenulum.

The mean dmft of the cohort was 0.2 ± 0.6 ($d = 0.2$; $m = 0$; $f = 0$) (range 0–2), the mean DMFT was 3.5 ± 6.3 ($D = 2.1$; $M = 1.1$; $F = 0.3$) (range 0–22). A statistically significant linear regression was seen between age and dmft/DMFT ($r = 0.434$, $P = 0.04932$) and the number of caries-free probands decreased with age: 7 of 9 probands (78%) in primary dentition, 5 of 10 (50%) in mixed dentition and 0 of 2 in permanent dentition. In both primary and permanent dentition, the decay component was predominant. Three probands (14%) had affected primary teeth (mean per patient: 1.3) and 6 (29%) permanent teeth (mean per patient: 7). Three probands (n. 19, 20, 21) (14%) had missing permanent teeth extracted due to caries and 1 (n. 20) (5%) had 4 filled permanent molars. Parents reported that all the dental treatments were done under general anesthesia. One proband (n. 17) (5%) showed 22 severely compromised carious teeth. None of the probands showed pit or fissure sealants.

Developmental defects of enamel were not found.

Occlusion. A complete orthodontic evaluation was made in 16 probands (76%); it was not possible for probands n. 1–5 due to the young age (2–4 years old). The Angle's classification system, based on the relationship between the maxillary and mandibular first molars, was not applicable due to the atypical dental formula found in most of the cohort and to the absence of the first permanent molars (Table I). The main occlusal features are shown in Table IV. Fourteen probands (88%) showed a high-arched palate (palatal height at the level of the first permanent molar more than twice the height of the teeth), 12 (75%) a mandibular prognathism (anterior protrusion of the mandibular alveolar ridge beyond the vertical plane of the maxillary alveolar ridge, best appreciated in profile), 11 (69%) an anterior crossbite (inversion of the sagittal relation between maxillary incisors and mandibular incisors: maxillary incisors locked lingual to mandibular incisors), 10 (63%) a posterior crossbite (inversion of the transversal relation between maxillary posterior teeth and mandibular posterior teeth: posterior mandibular teeth buccally positioned in relation to the posterior maxillary teeth), and 10 (63%) an anterior openbite (absence of vertical overlap of anterior teeth). Eight probands (50%) showed a characteristic phenotype consisting in high-arched palate, posterior crossbite (unilateral or bilateral), mandibular prognathism associated with anterior crossbite, and anterior openbite. Ten probands (48%) showed a large protuberant tongue. Dental crowding (overlapping teeth within an alveolar ridge) was not found.

TABLE III. Dental Features in a Cohort of 21 Probands With Pallister–Killian Syndrome

	DMFT dmft	Oral hygiene[a]	Gingivitis[b]	Gingival overgrowth
1	0	Good	None	−
2	0	Good	None	−
3	0	Fair	None	−
4	0	Fair	Mild	−
5	1 (d:1)	Poor	Mild	−
6	0	Good	Mild	−
7	0	Poor	Mild	+
8	0	Fair	Moderate	−
9	0	Poor	Moderate	−
10	1 (d:1)	Poor	Mild	+
11	0	Good	Mild	−
12	0	Fair	Mild	−
13	0	Good	Mild	−
14	0	Fair	Mild	−
15	2 (d:2)	Poor	Moderate	+
16	1 (D:1)	Poor	Moderate	+
17	22 (D:22)	Poor	Severe	−
18	2 (D:2)	Good	Mild	+
19	4 (M:4)	Poor	Mild	−
20	7 (M:3; F:4)	Poor	Severe	−
21	6 (M6)	Poor	Moderate	−

M, missing; F, filled; +, Present; −, absent.
[a]Oral hygiene assessment corresponds to Plaque Index (PI) scores as follows: Good, PI 0–1; Fair, PI 1–2; Poor, PI 2–3.
[b]Gingivitis assessment corresponds to Gingival Index (GI) scores as follows: none Gingivitis, GI 0–1; mild Gingivitis, GI ≥1–2; moderate Gingivitis, $2 \leq GI < 3$; severe Gingivitis, $GI = 3$.

DISCUSSION

Data regarding medical history of the cohort confirmed the clinical manifestation of PKS previously described: intellectual disability, hypotonia, epilepsy, respiratory diseases, visual anomalies, hearing impairment, and congenital birth defects [Pallister et al., 1977; Reynolds et al., 1987; Candee et al., 2012; Wilkens et al., 2012; Blyth et al., 2015].

This study represents the first systematic data collection on the oro-dental features of PKS.

The dental anamnesis showed a delayed eruption of the first primary tooth in five probands (24%): this finding could represent an underestimate, since seven (33%) families did not answer the question and Blyth et al. [2015] reported a delayed eruption of the first primary teeth in 57.1% of the cohort. However, these data were obtained from parents' report, which makes it subject to memory bias.

No history of dental trauma was reported. The reduced physical activity of individuals with PKS caused by hypotonia may explain the low prevalence of dental trauma, as previously described for patients affected by cerebral palsy [Costa et al., 2008].

An atypical dental pattern was a common finding: 12 probands (57%) showed the absence of primary and/or permanent teeth. When there is a clinical absence of some teeth and the dental anamnesis excluded previous extractions, hypodontia (single or multiple teeth agenesis), tooth impaction, or eruption delay are suspected. Hypodontia is often associated with chromosomal and genetic disorders such as Down syndrome, Ellis–van Creveld syndrome, ectodermal dysplasia syndromes, and other conditions such as cleft lip and palate [Klein et al., 2013]. However, because tooth agenesis of both primary and first permanent molars is rare [Tavajohi-Kermani et al., 2002] and the alveolar ridges in the posterior region were thickened in seven probands (33%), the hypothesis of multiple impacted teeth seems more likely. Multiple impacted teeth were previously described in association with other syndromes such as Cleidocranial dysplasia [Cooper et al., 2001], Gardner syndrome [Bradley and Orlowski, 1977], Yunis–Varon syndrome [Lapeer and Fransman, 1992], Noonan syndrome [Uloopi et al., 2015], and mucopolysaccharidosis [Nakamura et al., 1992]. The absence of the second primary molars in probands n. 4, of the first permanent molars in probands n. 10, 12, 13, 14, and of the premolars and of the second permanent molars in proband n. 18 could be due to a delay in the eruption process. To establish an accurate diagnosis radiographic examination would be necessary. In the analysis of dentition pattern, it must be taken in consideration that data regarding previously extracted teeth was obtained from parents' report, which makes such data subject to memory bias.

Similarly, alveolar ridge overgrowth associated with gingival hyperplasia were previously described in Costello syndrome [Goodwin et al., 2014]: tissue hyperplasia was not correlated with medications and the authors suggested a possible correlation to an upstream activation of Ras signalling, also implicated in hereditary gingival fibromatosis type 1 [Hart et al., 2002].

Two probands (10%) showed a double primary tooth, a rare dental anomaly in the healthy population, which generally occurs

TABLE IV. Oral Habits and Occlusal Features in a Cohort of 16 Out of 21 Probands With Pallister–Killian Syndrome

Proband n.	Sucking	Mouth breathing	Open mouth posture	High-arched palate	Crossbite	Openbite	Mandubular prognathism	Anterior crossbite
6	+	+	+	+	+	+	+	+
7	+	−	+	+	+	−	+	+
8	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+
10	+	+	+	−	−	−	+	−
11	−	+	+	+	+	+	+	+
12	+	−	+	+	−	+	+	+
13	+	+	+	+	+	+	+	+
14	+	−	+	−	−	+	+	+
15	+	+	+	+	−	−	−	−
16	+	−	+	+	−	−	−	−
17	+	−	+	+	−	−	−	−
18	+ till 6 yo	−	+	+	+	+	+	+
19	+ till 7 yo	−	+	+	+	−	−	−
20	−	+	+	+	+	+	+	+
21	+	+	+	+	+	+	+	+
	13/16 81%	9/16 56%	16/16 100%	14/16 88%	10/16 63%	10/16 63%	12/16 75%	11/16 69%

yo, years old.

in primary dentition and is often associated with aplasia of the corresponding permanent tooth [Zengin et al., 2014].

The intellectual disability and the hypotonia severely impair the self-care skills in most individuals with PKS, leading to a complete reliance on parents and caregivers for daily personal and oral hygiene procedures. In the anamnestic forms parents reported difficulties in performing these activities and oral hygiene was rated as poor or fair in most of the cohort (71%). In five patients (24%) the gingival overgrowth, previously associated with the daily use of anti-epileptics [Uzel et al., 2001; Kim et al., 2013], presented major problems for the maintenance of low PI and GI. Carrying out oral hygiene procedures is easier during the childhood period, while the higher number of teeth and the greater difficulty in managing behaviour and poor cooperation in adolescence and adulthood make oral hygiene management more complicated. As a result, gingivitis was a common finding (86%) and its severity increased with age. The prevalence of dental caries demonstrated the same trend: seven of nine probands (78%) in primary dentition were caries free, while a high mean DMFT score was reported in permanent dentition. Data indicate that most of the carious teeth remained untreated or were extracted: the decayed and missing components were predominant and only one proband (n. 20) had filled teeth. The low level of cooperation may make it difficult to provide dental care in the conventional dental setting and in our cohort all treatments required general anesthesia.

The results of the present study showed a high prevalence of malocclusion. The evaluation was exclusively clinical due to the impossibility to take radiographs and dental impressions. The craniofacial dysmorphism was characterized by the clinical features of the skeletal class III malocclusion with an increased lower facial height, a high-arched palate, anterior, and posterior crossbite. These phenotypic characteristics may be the result of the interaction among intrinsic factors such as the underlying genetic cause of PKS or secondary to the resultant muscular hypotonia and large protuberant tongue with an open mouth posture. Extrinsic factors likely also play a role, in particular oral habits, such as non-nutritive sucking, open mouth posture, and mouth breathing. Previous studies stressed the multifactorial etiopathogenesis of malocclusion in children and adolescents with a normal development or with disability, in particular in Down syndrome [Warren et al., 2001; Gòis et al., 2008, Oliveira et al., 2010]. X-rays are needed to clarify the feature of the mandibular prognathism and support the clinical diagnosis of class III malocclusion.

The difficulty in maintaining good oral health status suggests the need for more information, provided by pediatricians and dentists, regarding the importance of oral health and for more dental prevention: in a context of systemic diseases, such as congenital heart diseases, parents of PKS patients should be aware of the primary role of the oral health in the prevention of infective endocarditis [Wilson et al., 2008] and in the promotion of overall body health [Sheiham and Watt, 2000]. In particular, pediatricians should inform parents regarding delayed tooth eruption and encourage parents to seek dental care for periodic dental recalls early after the eruption of the first primary tooth. The early establishment of a dental home is necessary to prevent oral diseases or to diagnose them, including malocclusion, at an early stage, leading to minimal interventions provided in the traditional dental setting without requiring general anesthesia. A daily use of fluoride

toothpaste and additional fluoride treatments, as in office fluoride varnish, are recommended for all the individuals with PKS: topical fluoride exposure is to date considered the most protective factor from dental caries [Weyant et al., 2013]. Since in our cohort poor oral hygiene was the major risk factor for dental caries and gingivitis, frequent dental hygiene recalls are needed; additionally, the placement of pit and fissure sealants is an easy procedure strongly encouraged to prevent dental caries of permanent molars and premolars. Early preventive care leads to decreased treatment needs and fewer opportunities for negative experiences, promoting a positive relationship between the pediatric dentist and patient. Cooperation is necessary to perform radiographs for early pick up of a developing malocclusion due to a high-arched palate with posterior crossbite and class III malocclusion. The orthopedic–orthodontic treatment in some individuals with PKS is a challenge: the absence of primary and permanent molars prevents the possibility to bond orthodontic appliances; the intellectual disability, often severe, may preclude the treatment; protracted oral habits associated with an unfavorable genetic influence on skeletal growth make the stability of the treatment questionable. However, disability is not a limitation for the orthodontic therapy [Taddei et al., 2016], and when the patient's cooperation is sufficient, an early treatment of class III malocclusion is strongly encouraged [Westwood et al., 2003]; furthermore a high-arched palate in a mouth breathing patient with a low tongue posture requires a comprehensive evaluation with a multidisciplinary approach (otolaryngologist, orthodontist, speech therapist, physiotherapist).

The establishment of specialized structures in treating children with disabilities is a strong community need in order to ensure a continuous healthcare service of PKS individuals with a smooth transition from childhood to adultlife.

The results of this study add clinical data regarding occlusion to the cranio-facial phenotype and increase the knowledge of PKS with the oro-dental features and the oral health status. The most interesting finding in PKS is the disturbance in the dentition pattern. Future PKS studies, that include radiographic investigations, are strongly encouraged to enable an elucidation of further aspects regarding this rare syndrome.

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