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The oro-dental phenotype in Prader–Willi syndrome: a survey of 15 patients

ISABELLE BAILLEUL-FORESTIER[1,3], VERONIEK VERHAEGHE[2], JEAN-PIERRE FRYNS[3], FRANS VINCKIER[2], DOMINIQUE DECLERCK[2] & ANNICK VOGELS[3]

[1]Paediatric Dentistry, Garancière Hotel-Dieu Hospital, AP-HP France, [2]Paediatric Dentistry and Special Care and [3]Centre for Human Genetics, Catholic University Leuven, Belgium

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Background. Prader–Willi syndrome (PWS) is a rare disorder caused by genetic defects in certain regions of chromosome 15q11–13. It is characterized by severe neonatal hypotonia and feeding problems, childhood-onset hyperphagia and obesity, short stature, facial dysmorphy, hypogonadism, learning and behavioural difficulties, and dental abnormalities.
Aim. To describe the oro-dental phenotypic spectrum of patients with PWS.
Design. Fifteen PWS patients (3–35 years of age) being followed at the Centre for Human Genetics of the University Hospital of Leuven were examined at the dental clinic of the same institution. Medical information collected included age at diagnosis, body mass index (BMI) and level of cognitive functioning. Oral, clinical and radiological evaluations were performed. Caries experience (cavitation level), dental erosion and salivary flow rates were assessed.
Results. The 15 patients had dmft/DMFT scores ranging from 0 to 28, while nine were cavity-free. Those with severe caries experience also presented advanced dental erosion. BMI ranged from 16 to 42.6. There was no association between BMI and caries experience or erosive tooth wear. The PWS patients in our survey presented with a more favourable oral health status than those in previous studies. This might be due to early diet management or better oral hygiene during childhood or both.

Introduction

Prader–Willi syndrome (PWS) is a complex disorder characterized by severe neonatal hypotonia and feeding problems, childhood-onset hyperphagia and obesity, short stature, facial dysmorphy, hypogonadism, and learning and behavioural difficulties[1]. It is a rare disorder caused by genetic defects in certain regions of chromosome 15q11–13, including paternal interstitial deletion, maternal uniparental disomy and imprinting defect[2]. The prevalence of PWS is estimated to be 1 in every 26 000 live births[3]. Oro-facial manifestations reported in PWS include almond-shaped eyes with up-slanting palpebral fissures and a triangular mouth (Figs 1 and 2). Descriptions of intraoral and dental features are rare and are mostly limited to case reports (Table 1). Oral findings include the presence of hypoplastic enamel, rampant caries, low basal salivary secretion, delayed tooth eruption and excessive tooth wear[4–15].

The aim of the present survey was to describe the oro-dental phenotypic spectrum of PWS patients and to formulate suggestions for the oral management and follow-up of children with this syndrome.

Materials and methods

PWS patients benefit from multidisciplinary follow-up at the Centre of Human Genetics of the University Hospital of Leuven, including general paediatric, endocrinologic and psychiatric evaluations. An educational psychologist and a child psychiatrist evaluate the cognitive levels of the patients and manage behavioural issues. An educational therapist provides support for teachers (school visits) and other caregivers. Group sessions are organized for parents, with an emphasis on providing information on feeding problems, diet, health problems and behaviour management. A dietician experienced in the field of Prader–Willi

Correspondence to:
I Bailleul-Forestier, UFR d'Odontologie, 5 rue Garancière, 75006 Paris, France. E-mail: ibailleul@noos.fr

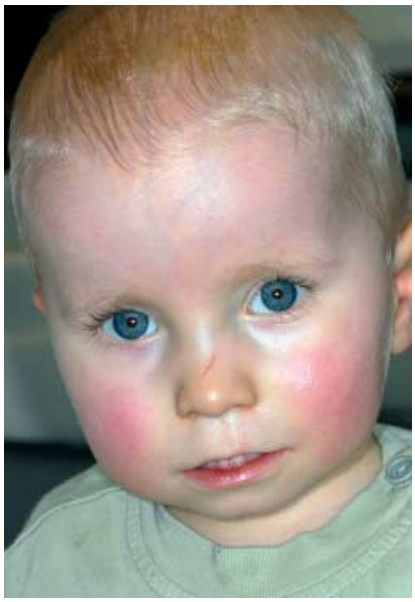

Fig. 1. Characteristic oro-facial features of Prader–Willi syndrome: small triangular mouth, thin upper lip and almond-shaped eyes (patient 1).

Fig. 2. Characteristic oro-facial features of Prader–Willi syndrome: low set ears (patient 11).

syndrome provides advice to families and caregivers, which includes maintaining a low caloric intake [70% of that of a normal person with a comparable body mass index (BMI)], maintaining low fat and sugar intakes, limiting food intake to three meals and two snacks (fruit or yoghurt) a day, avoiding additional snacks and preventing access to places where food is stored such as the kitchen.

Fifteen patients with a genetically confirmed diagnosis of PWS and a history of long-term follow-up at the multidisciplinary clinic were included in the present survey. The group was made up of 11 children and 4 adults with an age distribution of 3–35 years and a gender distribution of 10 males and 5 females. Written informed consent was obtained before they were recruited for the survey. For those under 18 years of age and adults who were incapable of making informed decisions because of a mental disability, consent was obtained from a parent or guardian.

Medical information included type of genetic defect, age at diagnosis, age at the start of the multidisciplinary follow-up, medications (e.g. growth hormone therapy) and level of cognitive functioning (intelligence quotient – IQ). BMIs [body weight/(body height)^2 in kg/m^2] were calculated based on the internationally recognized classification of BMI[16]. For children, the BMI-for-age weight status categories were underweight (less than the 5th percentile), healthy weight (5th to less than the 85th percentile), at risk of overweight (85th to less than the 95th percentile) and overweight (equal to or greater than the 95th percentile). For adults, the weight status categories were underweight (BMI < 20), normal weight (BMI 20–24.9), overweight (BMI 25–30) and obese (BMI > 30).

Oro-dental assessments completed the medical work-ups. A single dentist (V.V.) at the dental clinic of the University Hospital of Leuven performed the clinical and radiological evaluations. Caries experience was scored at the cavitation level based on World Health Organization criteria[17] and was expressed as dmft/DMFT scores[18]. The restorative index (RI) was calculated (f/d + f or F/D + F × 100%) for patients with caries experience (dmft/DMFT ≠ 0).

Since the oral screenings were performed as part of the follow-up evaluations of these PWS patients, orthopantomographic radiographs could only be obtained when clinically indicated and, even then, only from cooperative patients. No intraoral radiographs were taken.

Table 1. Prader–Willi syndrome: oro-dental findings (selected English-language reports in chronological order).

Author	Number and gender	Saliva	Delayed eruption	Hypoplastic enamel	Rampant caries	Remarks
Zellweger and Schneider[4]	1 M/1 F + Review of 12 cases	Dry oral mucosa	+ +		Yellowish teeth with defective enamel Decay 35%	
Foster[5]	1 M/1 F		1 of 2 (1 year delay)	100%	50%	
Hall and Smith[6]	32			12%		
Takano *et al.*[7]	24			8%		
Butler *et al.*[8]	37	Thick saliva		35%	46%	
Anavi and Mintz[9]	1 M adult		0	Generalized (not shown)	Extensive	Localized periodontal involvement
	1 M		1 year delay	Yellowish hypoplasia		Pitting and brownish tooth surface
Greenwood and Small[10]	1 F		Normal except delay in eruption of canines	0	Low caries rate	Periodontal disease (diabetes) Bimaxillary proclination Increased overjet and anterior open bite
Bazopoulou and Papagianoulis[11]	1 M	Thick, sticky saliva		+ +	Generalized	
Salako and Ghafouri[12]	1 M	Dryness of oral cavity (Xerostomia??)	No	?	+ + + + and abscess	Geographic tongue
Banks *et al.*[13]	1 M		No	0	0	Angle Class III malocclusion Short clinical crown heights of upper incisors
Young *et al.*[14]	1 M	Frothy, glutinous saliva		0	0	Grinding, erosion

M, male; F, female.

Enamel defects were recorded using the developmental defects of enamel index (DDEI)[19]. Loss of tooth substance as a result of a chemical process induced by acids of nonbacterial origin (dental erosion) was scored (excluding other forms of tooth wear) using the O'Sullivan index[20]. This index scores tooth surfaces affected, severity of erosive damage and area of the surface affected, and has proved to be a reproducible and reliable way of measuring dental erosion in children[21]. In the two oldest patients, the presence and extent of erosion could not be scored because they had received extensive dental treatments.

The dental age of patients 18 years and under was determined if an orthopantomogram was available (seven children). Dental age was calculated using the technique described by Demirjian[22], which uses the radiological appearance of seven permanent teeth of the left side of the mandible. The addition of the scores of the seven teeth results in a dental maturity score, which can be converted directly into dental age using reference tables.

Unstimulated saliva samples were collected using a standard method. The patients were placed in a calm environment from approximately 11 AM to noon. They were instructed to refrain from eating and drinking for at least 1 h before the sampling procedure. After the waiting period, they were asked not to swallow saliva for exactly 5 min and then to spit

Table 2. Summary of medical and oro-dental findings.

	Age (years)	Age at diagnosis	Age at start of multidisciplinary follow-up	IQ	BMI	GH therapy	DA-CA	dmft	DMFT	RI	Saliva (ml/min)	Tooth erosion	Sweet beverages	Acidic beverages
1 (1)	3	Neonatal	Neonatal		16	/	/	0	/	/	/	0	0	0
2	4	Neonatal	Neonatal	/	16.6	/	/	0	/	/	/	0	DU	DU
3	5	Neonatal	Neonatal	/	24.9†	/	/	0	/	/	/	0	+	+
4	6	Neonatal	Neonatal	/	16	X	/	2	5	33	/	0	+	0
5	6	Neonatal	Neonatal	81	17	X	+ 1.5	0	0	/	/	0	+	+
6	7	/	/	/	25 †	/	+ 0.0	0	0	/	0	0	0	+
7	9	Neonatal	Neonatal	60	27.3†	X	+ 0.0	0	0	/	0	+	+	+
8 (3)	9	6 months	6 months	83	20.8	X	+ 2.5	4	0	75	0.14	+	+	+
9	11	1 year	1 year	89	16.3	X	+ 1.9	0	2	100	0*	0	+	+
10	11	1 year	1 year	56	20.5	X	+ 2.5	0	0	/	0.18	0	0	+
11 (2,5)	12	Neonatal	Neonatal	55	16.9	X	+ 2.0	0	5	0	0	+	0	+ +
12	18	6 months	6 months	74	42.6†	X	/	/	0	/	0.24	0	DU	DU
13 (4)	23	Neonatal	Neonatal	78	26.2	X	/	/	0	/	0.16*	+	0	+
14	32	2 years	20 years	94	29.4	/	/	/	9	25	0.44*	/	0	+
15	35	8 months	19 years	47	34.1†	/	/	/	28	100	/	/	DU	DU

(1–5 refer to the figures); IQ, intelligence quotient; BMI, body mass index; GH, growth hormone; DA, dental age; CA, chronological age; RI, restorative index; DU, data unknown.*Drugs taken that might reduce salivary output. †Overweight for children, obesity for adults. Sweet beverages: sweetened milk, syrup; acidic beverages: diet coke, fruit juice.

the saliva that had collected in their mouths into individual graduated tubes. Flow rates were calculated as millilitres of saliva secreted per minute.

Results

Table 2 summarizes the medical and oro-dental findings. For all patients but one, PWS was diagnosed before the age of 1 year. PWS was caused by a deletion in 12 of the 15 patients (80%), and by maternal uniparental disomy in three (20%) (data not shown). For patients 1 through 13, the multidisciplinary follow-up started before the age of 1 year while for patients 14 and 15, the follow-up started around the age of 20. IQ levels ranged from 47 to 94 (mean = 72 ± 16). Based on their BMI, 3 of the 11 children were overweight, 1 was at risk of overweight and the remaining 7 had healthy weights. Two adults were overweight and two were obese. Patients 4 through 13 (except 6) had received growth hormone therapy for at least 6 months prior to the survey. The dental examinations revealed minor enamel opacities limited to the primary incisors in two children. There were no cases of hypoplastic enamel. Nine of the patients were cavity-free. dmft/DMFT scores ranged from 0 to 28. The RI ranged from 0 to 100%.

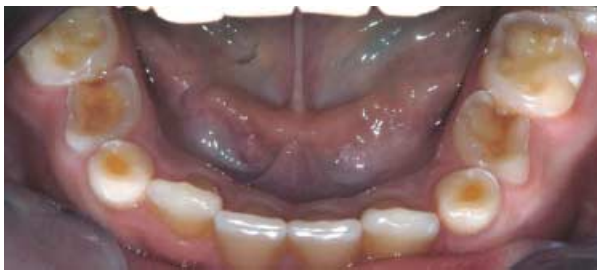

Fig. 3. Loss of tooth substance in primary canines and molars due to erosion (patient 8).

Dental erosion was observed in 4 of 13 patients. Patient 8 had severe erosion in the mixed dentition that was limited to the primary teeth (Fig. 3) while patient 13 had early signs of erosion on the permanent teeth (Fig. 4). Table 3 presents more details of the patients with dental erosion.

Saliva sampling was attempted in all patients. However, it was unsuccessful in 10 due to their age (five children), limited cooperation (one adult) and/or a combination of low salivary output and high viscosity (four patients) (Fig. 5). Unstimulated flow rates ranged from 0.14 to 0.44 mL/min. Patients 9, 13 and 14 used medication that might have had an effect on salivary output (fluoxetine, methylphenidate and risperidone).

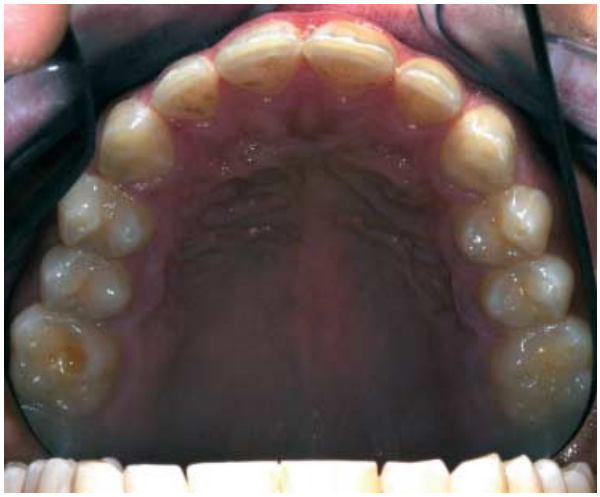

Fig. 4. Fissures in maxillary permanent molars showing erosion (patient 13).

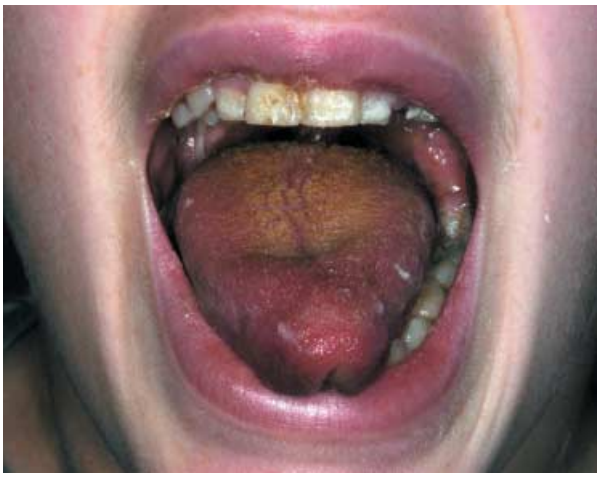

Fig. 5. Frothy and glutinous saliva covering the tongue and incisors (patient 11).

The dental age of five of the six patients who had received growth hormone therapy was accelerated by between 1.5 and 2.5 years.

Discussion

The present survey examined the oro-dental phenotypes of 15 PWS patients. It should, however, be kept in mind that our survey had some inherent limitations. One was the age distribution of the patients. Since PWS is a rare disorder, it is difficult to collect data from large groups or groups with a tight age distribution. To obtain more reliable and relevant results, multicentre studies would be needed. Another limitation was the potential underestimation of caries experience due to the lack of intraoral radiographs.

Unlike earlier reports on dental findings in PWS[5–9,11,12,15], none of our patients had hypoplastic enamel. Unbalanced neonatal feeding is one of the possible causal factors of enamel hypoplasia. In the past, most PWS patients were diagnosed at an older age, and severe feeding difficulties with unbalanced feeding and failure to thrive during the first months of life were frequent[3,13]. All but one of our patients were diagnosed during the neonatal period and gavage feeding with a balanced diet was started during the first days of life, possibly explaining the lack of enamel hypoplasia in this group.

The low prevalence of caries experience in our study cohort might be due to the early multidisciplinary follow-up provided. Instructions included information on a suitable

Table 3. Extent and distribution of erosive tooth damage in PWS patients.

	Patient 7		Patient 8		Patient 11		Patient 13	
	Number of teeth affected	Surface affected/ extent	Number of teeth affected	Surface affected/ extent	Number of teeth affected	Surface affected/ extent	Number of teeth affected	Surface affected/ extent
Normal enamel	21	None	14	None	22	None	11	None
Loss of surface contour of enamel	1	C –	1	C –	5	C –	10	7 × D –
								3 × C –
Loss of dentin	1	E –	3	C –	2	C –	0	
Loss of dentin with pulp exposure	1	E +	6	F +	0		0	

Surface affected: A, labial; B, lingual; C, occlusal; D, labial and incisal; E, lingual and occlusal; F, multisurface. Area of surface affected: –, less than half; +, more than half.

diet, regular feeding habits, low carbohydrate intake, regular oral hygiene measures and the use of a fluoridated toothpaste. Recent studies have reported that healthy obese children have a higher caries prevalence than normal weight controls, possibly due to their unhealthy and irregular feeding habits[23,24]. The low caries prevalence in obese PWS patients (with regular and healthy feeding habits) tends to confirm this hypothesis.

Another possible explanation for the low caries prevalence in our patients could be the composition of the saliva. Harta studied the saliva in PWS patients and reported that the levels of salivary ions (F, Ca, P, Cl, Na) and proteins were higher than in control subjects[25]. Calcium levels were twice as high and fluoride almost twice as high. This could also explain the limited enamel demineralization and enhanced remineralization observed in PWS, which would result in a low caries experience. However, an evaluation of patients with healthy dietary habits would be needed to confirm this association. Differences in the dietary habits of study cohorts might thus explain the contradictory reports in literature.

The salivary flow rates measured in the present survey were low and were in agreement with those reported by Friedlander[26]. Saliva samples could not be collected from very young patients because of a lack of cooperation due to their age. In some cases, samples could not be collected because of extremely low salivary flow rates. The thick, ropey consistency of the saliva of some patients, which is common in PWS, also made sampling difficult.

Dental erosion can be caused by extrinsic (acidic drinks) or intrinsic (gastro-oesophageal reflux) factors[14,27]. While 25% of the patients in the present survey showed signs of dental erosion, none complained of frequent vomiting or a sour taste in the mouth, which are indicative of gastro-oesophageal reflux. The dental erosion observed in our PWS patients might thus be caused by a low salivary flow rate combined with a high acidic diet cola intake, which was part of the carbohydrate-reduced diet of our patients. Further research is needed to explore this question in greater detail.

Deficient secretion of growth hormone and low or low-normal levels of insulin growth factor-1 are frequent findings in children with PWS, and growth hormone treatment is often indicated[28]. In the present survey, patients who received growth hormone substitution therapy exhibited accelerated dental maturity, which is in agreement with the findings of Krekmanova *et al*.[29].

Enamel hypoplasia was not a common finding and caries experience was low in our PWS patients, who had benefited from early multidisciplinary follow-up. We observed an acceleration of the dental age of the children treated with growth hormone. The prevalence of enamel erosion was high and salivary flow rates were low. Further long-term follow-up of these patients will be needed to confirm the results. A multicentre survey will be needed to ensure a larger patient cohort and to compare the impact of different approaches on the oral health outcome of the patients. The findings reported here clearly indicate that a paediatric dentist should be part of any multidisciplinary medical team managing PWS children.

Suggestions for the oral health follow-up of PWS patients

- Parents/guardians should *inform the dentist* of the child's diagnosis, developmental level, any additional medical problems and any adverse drug effects.
- General dentists treating Prader–Willi syndrome patients should contact the *paediatric dentist on the medical team managing these patients* to exchange up-to-date, personalized information.
- The review by Friedlander[26] should be consulted to determine the potential *adverse effects of drugs* prescribed for these patients.
- *The first oral examination* should be scheduled around the time of the emergence of the first primary teeth[30].
- *Dietary guidelines* need to be developed that respond to both medical and dental concerns.
- A comprehensive *oral preventive programme* should be initiated, including optimal topical fluoride treatments and daily oral hygiene by the parent and/or the patient.
- Patients able to cooperate with dentists can have *dental procedures* performed using local

anaesthesia, including *orthodontic treatments*. Management of uncooperative patients is more complex. The levels of sedation, respiratory depression and possible adverse drug effects of oral sedative medication are difficult to control in these vulnerable patients. When other behaviour management techniques fail, long and invasive treatment procedures can be performed using general anaesthesia, except when patients are experiencing a psychotic episode[31].

- For cases of *dental erosion*, additional daily fluoride rinses should be prescribed to limit demineralization[32].
- *Regular follow-ups* adapted to the individual needs of the patient should be instituted and should be scheduled at least semi-annually.

What this paper adds

- This is the first paper describing the oro-dental phenotype of patients with Prader–Willi syndrome.
- The presence of previously reported enamel hypoplasia and high caries experience could not be confirmed in patients with early multidisciplinary follow-up.
- The low salivary flow rates and high prevalence of erosive tooth damage need to be investigated in greater detail.

Why this paper is important to paediatric dentists

- It contains useful information for paediatric dentists on multidisciplinary medical teams managing PWS patients.
- It shows the need for the long-term follow-up of the oral health of Prader–Willi syndrome patients.

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