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Palate abnormalities in Chilean patients with chromosome 22q11 microdeletion syndrome

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ABSTRACT

Objective: Chromosome 22q11 microdeletion syndrome (del22q11) is the most frequent microdeletion syndrome in humans, with an estimated incidence of 1/4000. It is recognized as a common identifiable cause of cleft palate. We characterized palatal abnormalities in a large cohort of Chilean patients with del22q11.
Methods: Patients with the deletion were evaluated by geneticists and speech pathologists, including nasopharyngoscopy when indicated. Comparisons between groups with and without palatal abnormalities were performed using Fisher's exact test and Mann–Whitney *U* test.
Results: Two hundred and one patients were included in the study. Palate abnormalities were present in 154 patients (76.6%). The most frequent finding was submucous cleft palate (both classic and occult forms) seen in 80 patients (39.8% of the total group). Overt cleft palate or cleft lip/palate was seen in 30 patients (14.9%). Patients without palate abnormalities had significantly greater frequency of congenital heart disease and higher mortality.
Conclusions: Our data show a high frequency of palate abnormalities without significant association with congenital heart disease. The most common types of palate defects seen in this series are usually not evident on physical examination and thus require a high index of suspicion and active evaluation through nasopharyngoscopy.

1. Introduction

Chromosome microdeletion 22q11.2 (del22q11) has an estimated incidence of 1 of 4000 newborns [1], being the most common known microdeletion syndrome. It results in heterogeneous clinical manifestations known as velocardiofacial syndrome (VCFS) [2,3]. In the 1950s, Eva Sedláčková, a Czech otolaryngologist, first described patients with velar hypoplasia associated with hypernasal speech. She also recognized characteristic facial features, tapered fingers and cognitive impairment [4–6]. DiGeorge phenotype, described in 1968, with conotruncal cardiac defects, typical facial dysmorphism, hypocalcaemia, immunodeficiency and cleft palate is the most obvious presentation at birth [7]. Later, Shprintzen et al. reported several cases of overt or submucous cleft palate, congenital heart disease, typical facies and learning problems delineating the VCFS [8,9].

Newborns with the deletion are usually recognized by the presence of CHD and/or hypocalcaemia. Confirmation of the diagnosis should prompt the search for palatal anomalies with age-appropriate methods [10]. Children without CHD tend to be diagnosed later and the diagnosis is usually suspected by velopharyngeal dysfunction (VPD). Several reports of palatal anomalies have originated from cleft palate clinics [8,9,11–17], and may be biased towards inclusion of patients with palate anomalies. Few series published to date describe the palatal features of Hispanic patients with VCFS. We report the spectrum of the palatal abnormalities in a group of Chilean patients with del22q11. We included cases detected in several centers across Chile, with referral from different sources (Cleft Palate, Cardiology, Developmental Pediatrics and Genetics clinics) and with systematic palate anatomic and functional evaluation.

2. Material and methods

The cohort consisted of 201 Chilean patients diagnosed with 22q deletion detected by Fluorescence in situ Hybridization (FISH) using the Vysis DiGeorge/VCFS region probe – LSI TUPLE1 (Abbott

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Laboratories, Abbott Park, IL, USA). Clinical geneticists and speech pathologists evaluated the patients and reviewed medical records. Clinical assessment included clinical history, physical examination, speech evaluation, and nasopharyngoscopy when indicated. Local Ethics Committees at each participating institution approved the study and informed consent was obtained from all patients, their parents or legal guardians.

Patients were distributed in two groups according to the results of palatal evaluation: group 1, with palate anomalies (PA), and group 2, without palatal abnormalities. These were classified as overt cleft palate, classic submucous cleft palate, occult submucous cleft palate, and suspected occult submucous cleft palate. The latter group included patients with normal hard palate, velum, and uvula on examination with symptoms of velopharyngeal dysfunction (VPD), such as hypernasal speech, nasal emission, articulations problems and low intraoral pressure, but were younger than 4 yr and could not be evaluated by nasopharyngoscopy.

For some features, data were incomplete, and frequency of abnormalities was calculated in patients with recorded data. Fisher's exact test and Mann–Whitney *U* test were used to compare differences between groups, an alpha value of 0.05 was considered significant. The statistical software package SPSS, version 20 (SPSS Inc., Chicago, IL, USA), was used for analysis.

3. Results

The age range of the patients was 0–46 years at the time of the diagnosis of the deletion, with a median of 4.3 years. The proportion of female subjects was 52.7% (Table 1).

In our series, 154 (76.6%) patients had signs of palatal anomalies, and 47 (23.4%) had normal palates. The specific findings are shown in Table 2. The most common PA was occult submucous cleft palate (28.9%). Common nasopharyngoscopy findings in this group of patients were a small soft palatal notch, concave palate, broad wide pharynx, visible pulsation, and scarce adenoid tissue. Overt cleft palate was seen in 24 patients (11.9%), and 6 patients had cleft lip and palate (3.0%). All patients with PA had signs of VPD.

Table 1
Clinical features of patients with or without PA.

	With PA (total = 154)	Without PA (total = 47)	*P* value
Females/males (*n* patients)	82/72	24/23	n.s.
Median age at diagnosis (years)	4.70	1.24	n.s.
Deceased	1/154 (0.6%)	3/47 (6.4%)	0.04
Congenital heart disease[a]	79/153 (51.6%)	33/47 (70.2%)	0.03
Developmental delay[a]	123/142 (86.6%)	37/41 (90.2%)	n.s.
Mental retardation[a]	38/87 (43.7%)	13/22 (59.0%)	n.s.
Height/age < p10[a]	42/82 (51.2%)	21/32 (65.6%)	n.s.
Weight/age < p10[a]	41/81 (50.6%)	19/32 (59.3%)	n.s.
Cranial circumference/age < p10[a]	19/42 (45.2%)	12/23 (52.2%)	n.s.
Chronic or recurrent otitis media[a]	57/125 (45.6%)	9/34 (26.5%)	n.s.
Hypocalcaemia[a]	26/118 (22.0%)	15/38 (39.5%)	n.s.
Hypoparathyroidism[a]	15/48 (31.3%)	7/15 (46.7%)	n.s.
Hypothyroidism[a]	15/102 (14.7%)	7/35 (20.0%)	n.s.
Facial asymmetry[a]	11/111 (9.9%)	5/34 (14.7%)	n.s.
Hernia[a]	41/144 (28.5%)	13/45 (28.9%)	n.s.
Thymic aplasia[a]	16/24 (66.7%)	13/20 (65.0%)	n.s.

[a] For each listed feature, the denominator represents the number of patients with recorded data.

Table 2
Palatal abnormalities in 201 Chilean patients.

	Patients	
	n	%
Normal palate	47	23.4
Cleft lip and palate	6	3.0
Overt cleft palate (without cleft lip)	24	11.9
Submucous cleft palate	22	10.9
Occult submucous cleft palate	58	28.9
Suspected occult submucous cleft palate[a]	44	21.9

[a] Based primarily by clinical history and physical examination, in children too young to perform a definitive evaluation by nasopharyngoscopy.

Comparisons between group 1 (with PA) and group 2 (without PA) are presented in Table 1. We observed a similar gender distribution in both groups. Patients in group 1 were older at the time of diagnosis of the deletion compared to patients from group 2, the difference was non significant (median age, 4.70 years and 1.24 years, respectively; $p = 0.76$, Mann–Whitney *U* test).

Congenital heart disease was seen in 51.6% of patients of group 1 and in 70.2% of patients of group 2 ($p = 0.03$, Fisher's exact test). Three of 47 (6.4%) patients in group 2 had died, and 1 of 154 (0.6%) patients in group 1 were deceased ($p = 0.04$, Fisher's exact test).

There were no significant differences between both groups in presence or absence of developmental delay/mental retardation, facial asymmetry, thymic aplasia, hypocalcaemia or hernias, and stature, weight or cranial circumference below the 10th percentile.

4. Discussion

This study shows the spectrum of palatal anomalies in a large group of del22q11 Chilean patients. Structural and functional palatal abnormalities are common in VCFS patients. We found palatal abnormalities in 76.6% of our patients, an intermediate value in relation to previously reported observations that range between 42% and 100% [11–22], with the maximum values reported from otolaryngology and craniofacial centers. Specific defects had similar frequencies as those reported by other published series that describe overt cleft palate in 9–18% [11,15–21].

VPD was a constant feature in our patients, associated to overt and submucous cleft palate. Velopharyngeal hypotonia and other variables that cause palatopharyngeal disproportion (platybasia, upper cervical spine abnormalities, adenoid hypoplasia, short velum, and deep cavum) could contribute to VPD [23–25].

Heart disease was less frequent in patients with abnormal palates (group 1) than in those with normal palate (group 2). This could be explained by the presence of distinct modifiers and/or developmental pathways involved in the pathogenesis of either defect [17], or due to the relative smaller sample size of group. Higher lethality in group 2 seems be related to the higher proportion of congenital heart disease [1,18,26–28].

This study is limited by its retrospective nature, and by the fact that some patients had incomplete data. Nevertheless, the results presented here are useful since we included a large number of patients, referred from several centers, ascertained by different modes, and with systematic evaluation, thus the results probably reflect the variability present in the wider clinical setting.

In summary, we observed a high proportion of palatal abnormalities in our cohort of patients with del22q11, but are not associated to the presence cardiovascular anomalies. The most common types of palate defects seen in this series are usually not

evident on physical examination and thus require a high index of suspicion and active evaluation through nasopharyngoscopy.

Our results support the recommendation for universal evaluation of 22q11 deletion patients by an experienced speech language pathologist [1]. Establishing the correct diagnosis of del22q11 has important implications for proper genetic counseling and long-term clinical management, such as the timely identification of occult palate anomalies [15,16,29].

Conflict of interest statement

All authors have no financial and personal relationships that could inappropriately influence this work.

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