Received: 12 September 2021 | Revised: 22 February 2022 | Accepted: 3 March 2022

DOI: 10.1111/odi.14187

ORIGINAL ARTICLE

ORAL DISEASES Leading in Oral, Maxillofacial, Head & Neck Medicine WILEY

Craniofacial characteristics in Van der Woude syndrome

Blanca Estévez-Arroyo[1] | Ignacio Gómez-Mendo[2] | Martín Romero-Maroto[3] | Enrique Solano-Reina[1] | Alejandro Iglesias-Linares[4]

[1]Department of Orthodontics, College of Dentistry, University of Seville, Seville, Spain

[2]Maxillofacial and Stomatology Department, Virgen Macarena University Hospital of Seville, Seville, Spain

[3]Head of the Orthodontic Department, Rey Juan Carlos University, Madrid, Spain

[4]Department of Orthodontics, Complutense University of Madrid, Madrid, Spain

Correspondence
Alejandro Iglesias-Linares, Full Professor of Orthodontics, Complutense University of Madrid, Plaza Ramón y Cajal s-n, 28001 Madrid, Spain.
Email: aleigl01@ucm.es

Abstract

Aim: To describe the particular craniofacial characteristics of Van der Woude syndrome(VWS) patients compared to patients with a non-syndromic cleft (CG1) and to a malocclusive healthy population (CG2).

Material and methods: Retrospective case-control study. A sample of 110 matched-patients was recruited (VWS ($n = 7$), CG1 ($n = 49$), CG2 ($n = 49$)). Subsequently, 37 radiometric variables were analysed and the dental-skeletal ages were determined. The intra/inter-observer method errors were quantified. Descriptive statistics were computed, and different inferential analysis tests were used depending on the normality of the data (Chi-square test, Fisher's exact test, paired Student's *T*-test, Mann–Whitney *U* test) (p-value < 0.05). Pairwise comparisons were corrected by Bonferroni's criteria.

Results: VW-patients presented specific craniofacial characteristics and morphology. A marked tendency to the vertical growth pattern was found in VW-patients compared to CG1-CG2 ($p < 0.001$); at the sagittal level, skeletal class II caused by mandibular retrognathism, with a greatly increased ANB angle compared to CG1 ($p = 0.042$). Dental analysis showed that the lower incisor was more retruded and retroclined ($p < 0.05$ in all cases) and the interincisal angulation was increased ($p < 0.001$ (CG2)). At the profile level, an open nasolabial angle ($p = 0.040$; CG1) and a more protruding lower lip with respect to the Sn-Pg plane ($p = 0.040$ (CG1); $p = 0.044$ (CG2)) were observed.

Conclusions: VW-patients present particular characteristics in the facial skeletal structures. There is a critical necessity to increase the evidence regarding specific clinical features and orofacial pathology of rare diseases such as VWS, which will help to these minorities to gain access in the future to a better quality of care with precise treatment and diagnostic necessities.

KEYWORDS
craniofacial, dental diseases, diagnostics

1 | INTRODUCTION

The Van der Woude syndrome (VWS; OMIN #119300) is a rare dysmorphic disease of genetic origin (Dissemond et al., 2004). It is characterized by the presence of lower lip pits in relation to the cleft lip and/or palate (Dissemond et al., 2004) and it is the most frequent form of syndromic clefting, accounting for 2% of all cleft lip and palate cases [prevalence 1:40000 to 1:100000 live births]. Furthermore, there are no significant differences between sexes (Cervenka et al., 1967; Rizos & Spyropoulos, 2004).

The VWS is caused by mutations in Interferon regulatory factor 6 (IRF6) in chromosome 1q32.2-q32.3 (Kondo et al., 2002; Brian C Schutte et al., 1993). IRF6 is considered a protein coding gene, a key element in oral and maxillofacial development. Therefore, alterations at this level pose a high risk of suffering cleft lip and palate (Brian C Schutte et al., 1993). This syndrome presents an autosomal dominant inheritance with high penetrance ranging from 89% to 92%. However, the expression of VWS is variable and complex; all the signs can be present, either alone or in combination, or no abnormalities can be detected clinically (Castro et al., 2012).

The treatment of VW-patients includes all the necessary surgical and multidisciplinary procedures for the correction of all the anomalies they present; such as medicine, dermatology, maxillofacial surgery, aesthetic surgery, psychiatry, paediatric dentistry, orthodontics, speech therapy, orthopaedic care, feeding and hearing evaluation (Rizos & Spyropoulos, 2004; Tehranchi et al., 2017).

The craniofacial growth of patients with isolated cleft palate is well known. In these patients, although the relationship between the maxilla and the mandible is correct, independently both usually are short and retrusive in relation to the cranial base (Bishara & Iversen, 1974; Shibasaki & Ross, 1969). It is possible that the appearance of the cleft lip and palate is similar, but it is not clear whether their effect at craniofacial level in VW-patients is equivalent to the effect of non-syndromic cleft lip and palate. Up to date, the information of craniofacial growth in VWS is limited and there is some degree of controversy (Heliövaara et al., 2015; Kane et al., 2002; Oberoi & Vargervik, 2005). Kane and Oberoi agree that there is a poorer maxillary growth in VW-patients than in matched controls (Kane et al., 2002; Oberoi & Vargervik, 2005). However, Heliövaara concluded that 6-year-old children with VWS and non-syndromic cleft have similar craniofacial morphology (Heliövaara et al., 2015).

Due to the scarcity of studies and the lack of consensus among authors, our working hypothesis raises the following: by cephalometrically comparing patients with VWS, patients with non-syndromic cleft palate and malocclusive healthy patients, without cleft and systemic pathology, a specific pattern of craniofacial alterations at airway, skeletal, dental and aesthetic levels may be established in VWS. So, the main objective was to identify any shared pattern of craniofacial characteristics in VWS compared to a non-syndromic cleft and to a malocclusive healthy population.

2 | MATERIALS AND METHODS

2.1 | Study design and study sample

The present research was designed as a case-control study. A total population of 110 were screened from the maxillofacial units of the Hospital reference and the master of orthodontic of the University of Seville. In the case group (VWSG, $n = 7$), the total universe of patients with VWS diagnosed and treated by professionals of the Stomatology Section of public Hospitals in the south of Europe were included (Virgen Macarena University Hospital of Seville and 12 de octubre University Hospital of Madrid). We added a first control group (CG1, $n = 49$) of patients with non-syndromic cleft from the same setting as the case group, matching by chronological age, sex and type of cleft palate. In addition, a second control group (CG2, $n = 49$) of malocclusive healthy patients, without cleft and systemic pathology, treated in the Master of orthodontic of the University of Seville was added and paired with case group by age and sex. These patients were randomly selected from the corresponding database.

Inclusion and exclusion criteria were established: Regarding the age and sex of VWSG, no limits were indicated due to the very low prevalence. The control groups (CG1 and CG2) were adapted to the chronological age range and sex provided by the case group, so there were no statistically significant differences in these respects. All the subjects had to have an available, computerized and complete medical history as well as available and computerized radiographic records with good definition. They must also not have undergone orthodontic or orthopaedic treatment prior to radiographic examination. Individuals who did not meet these criteria were excluded from our study.

2.2 | Ethics statement

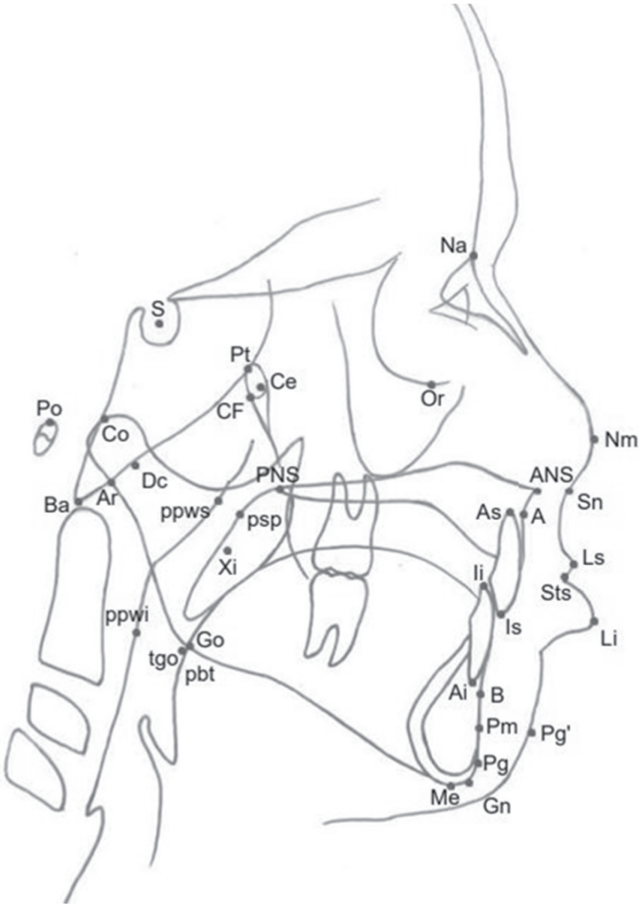
Principles outlined in the Declaration of Helsinki were followed in the conduct of this study (World Medical Association, 2013). The data was treated with absolute confidentiality. Methods of data collection and storage are subject to the Spanish Organic Law governing personal data protection. The Ethics committee for biomedical research in Andalusia independently approved the protocol on the third of May of 2021 (Internal Code: 1284-N-20).

2.3 | Craniofacial measurements, dental age and maturation stage

We recorded and analysed the medical history and the radiographies (orthopantomography and lateral cephalogram) of all the patients.

For the metric study of the craniofacial skeletal base, it is very important to know not only if the patients of the different groups have the same chronological age, but also if they are in the same maturing moment. For this reason, on the orthopantomography, the dental age was estimated using Demirjian's Method (Demirjian et al., 1973) and on the lateral cephalogram, the cervical vertebral maturation was analysed, using the method modified by Baccetti et al. (Baccetti et al., 2002).

Craniofacial skeletal proportions and measurements were assessed and calculated after being classified into four groups: dental problems, airway analysis, aesthetic analysis and skeletal problems. This classification provides useful information for determining which, if any, developmental field is affected in VWS. Anatomical landmarks were recorded on each cephalogram to obtain 37 radiometric variables (Figure 1) (Table S1,S2), which correspond to the most representative and widely used methods according to orthodontic and craniofacial researchers (Björk, 1955; Jarabak et al., 1975; McNamara, 1984; Ricketts, 1961; Steiner, 1953, 1959). The study was carried out using specific software Nemoceph (Madrid, Spain,



Anatomical landmarks	*Cephalometric variables*
Ppws-psp	Width of the upper pharynx
Ppwi-pbt	Width of the lower pharynx
Ans-sts	Upper lip length
Perp (sn-pg)-Ls	Protrusion of the upper lip relative to the sn-pg line
Perp (sn-pg)-Li	Protrusion of the lower lip relative to the sn-pg line
Nm-sn-Ls	Nasolabial angle
Cf-go	Lower posterior face height
ANS-Me	Lower anterior face height
Ar-Go	Ramus length
Ce-Na	Cranial length
Si-Ar	Posterior cranial base length
Si-Na	Anterior cranial base length
Perp (na-pg)-A	Facial convexity
Co-A	Maxillary length
Co-Gn	Mandibular length
Go-Me	Length of the mandibular corpus
Ba-Na-Pt	Facial axis
ANS-Xi-Pm	Inferior face height
Si-Na-Go-Gn	Angulation of the mandible to the anterior cranial base
De-Xi-Pm	Angulation of the mandibular corpus relative to the mandibular ramus
Ar-Go-Me	Total gonial angle
Ar-Go-Na	Upper gonial angle
Na-Go-Me	Lower gonial angle
Na-Cf-A	Nasomaxillary height
Po-Or-PNS-ANS	Maxillary inclination relative Po-Or plane
Po-Or-Ba-Na	Cranial base angulation relative to Po-Or plane
Si-Na-Ba	Angulation between anterior and posterior cranial base
Si-Na-A	SNA angle
Si-Na-B	SNB angle
(Na-Me)-(Si-Go)	Anterior facial height takes away posterior facial height
(Si-Na-A)-(Si-Na-B)	ANB angle
(Co-A)-(Co-Gn)	Maxillomandibular relationship index
A-Pg-As-Is	Inclination of the maxillary incisor
A-Pg-Ni-Ii	Inclination of the mandibular incisor
A-Pg-Is	Position of the maxillary incisor
A-Pg-Ii	Position of the mandibular incisor
As-Is-Ai-ii	Angulation between maxillary and mandibular incisors

FIGURE 1 Anatomical tracing with identification of the landmarks used to obtain variables of cephalometric analysis methods by Steiner, Ricketts, Jaraback and Fizzel, McNamara and Björk (Björk, 1955; Jarabak et al., 1975; McNamara, 1984; Ricketts, 1961; Steiner, 1953, 1959), on the profile x-ray of a patient with Van der Woude syndrome with vertical component in the growth, skeletal class II malocclusion caused by mandibular retrognathism, marked dental biretrusion, open nasolabial angle and protruded lower lip. Perp, perpendicular

v2018). Measurements obtained from VW subjects were compared with the measurements of the control samples. To make the interpretation, we used standard measurements provided by cephalometric studies, and standard deviations calculated on the bases of standardized age, sex, and race norms (Table S2).

2.4 | Statistical analysis

2.4.1 | Accuracy and method error assessment

Methodological cephalometric tracing errors were assessed using previously described methods (Baumrind & Frantz, 1971), where *d* is the difference between measured pairs, *N* is the number of cephalograms, and *K* represent the tracing per cephalogram. Each measurement was repeated twice at 4-week intervals by one examiner blinded to the patient data.

Intra- and inter-observer errors were calculated for the methods, using paired Student's *T*-test and ICC, which were tested twice by the same professional and once by another professional with 4 weeks between the measurements.

2.4.2 | Descriptive and comparative analysis

A univariate analysis of the results consisted of descriptive statistics of the quantitative and qualitative variables. Kolmogorov–Smirnov, Shapiro–Wilk's tests and Q-Q plots were conducted to check the normality of the data. Depending on results, a bivariate analysis was tested using the two-sample or paired Student's *T*-test or Mann–Whitney *U* test for quantitative variables and the Chi-square test or Fisher's exact test in qualitative variables, establishing a value *p* less than 0.05. Pairwise comparisons between groups were corrected by Bonferroni's criteria.

The data obtained were analysed using SPSS 17.0 software for Windows (LEAD Technologies, Charlotte, NC, USA).

3 | RESULTS

3.1 | Intra/inter-observer error

The reproducibility of the methods used to detect the vertebral maturation stage and dental age was adequate and presented good coefficients for both intra- and inter-observer error determination

($p = 0.9$). As for the indices of intraclass correlation, both errors were above 0.9 in all methods. The accuracy of cephalometric error was 0.51 mm for linear measurements and 0.64° for angular measurements. There were no statistically significant differences between original and repeat measurements ($p < 0.05$).

3.2 | Characteristics of the VWS

The presence of the clinical variables that according to the literature belong to VWS was analysed, such as family history of VWS, cleft lip, cleft palate, labial pit, labial pit with salivary drainage, speech disorder, syndactyly, congenital heart disease, limb disorder, musculoskeletal diseases, rheumatologic diseases, hearing loss, dental agenesis, dental transposition, supernumerary tooth, taurodontism, narrow palatal arch, posterior crossbite, anterior crossbite, ankyloglossia, oral synechiae and temporomandibular disorders. Of the 12 patients found in the mentioned area, ten patients, two females and eight males, with a mean age of 11.85 years and a standard deviation of 2.72 years, had a complete medical history, and the presence of these clinical signs was studied (Table S3).

Of the twelve individuals with VWS found, seven patients had the full set of radiographic records meeting the inclusion and exclusion criteria and were included in the case-control study design. Particularly, one female and six males, with a mean age of 11.98 years and a standard deviation of 2.51 years (Table 1). All the subjects presented cleft palate. The distribution of the sample according to the type of cleft palate was as follows: 42.9% presented complete bilateral cleft palate, 14.3% incomplete bilateral cleft palate, 28.6% complete right unilateral cleft palate and 14.3% submucous cleft palate. The first cohort of control subjects affected by non-syndromic cleft palate were matched with the case-group subjects. With respect to age, we established a range of 2 years to expand, within what is reasonable and clinically possible, the number of pairings with case group individuals. A 1:7 ratio was established between individuals from these groups, as seven was the lowest number of pairings found with respect to one of the individuals of the case group. The seven similar patients included in this group of the remaining six individuals who presented a major number of pairings of non-syndromic cleft were selected randomly. Therefore, the CG1 was made up of 49 patients: Seven females and 42 males, with a mean age of 12.73 years and a standard deviation of 1.95 years. Furthermore, the distribution according to the cleft palate was the same as in VWSG (Table 1). The CG2 of malocclusive patients without clefts or systemic pathology were paired with the case-group subjects according to sex and age. Following the same protocol as with the CG1, a 1:7 ratio was established between individuals from VWSG and CG2. Therefore, CG2 is made up of 49 patients: Seven females and 42 males, with a mean age of 12.02 years and a standard deviation of 2.25 years (Table 1). None of the patients included in this study had temporomandibular disorders. No statistically significant differences were found in any of the characteristics of the compared groups ($p > 0.05$).

3.3 | Association between skeletal, dental and chronological age in the VWS

The relationship between chronological age and dental age according to Demirjian's method is shown in Table 2 (Demirjian et al., 1973). Within each study group, the difference between the ages does not exceed 1 year, being the VWSG the group in which there is the smallest difference, just 0.36 years between dental age and chronological age. In all groups, the dental age is slightly higher than the chronological age, being able to establish that according to

TABLE 1 Comparability of the groups of children with VWS (VWSG), with non-syndromic cleft palate (CG1) and malocclusive healthy patients (CG2)

Variable		VWSG ($n = 7$)	CG1 ($n = 49$)	GC2 ($n = 49$)	p-Value
Sex, n (%)	Males	6 (85.7)	42 (85.7)	42 (85.7)	1†
	Females	1 (14.3)	7 (14.3)	7 (14.3)	
Chronological mean age (SD)		11.98 (±2.51)	12.73 (±1.95)	12.02 (±2.25)	0.714‡ (VWSG-CG1) 1.000‡ (VWSG-CG2)
Dental mean age (SD)		12.34 (±2.71)	13.25 (±2.21)	12.98 (±2.66)	0.454‡ (VWSG-CG1) 1.000‡ (VWSG-GC2)
Cleft palate n (%)	Bilateral complete cleft palate	3 (42.9)	21 (42.9)		1†
	Bilateral incomplete cleft palate	1 (14.3)	7 (14.3)		1†
	Unilateral right complete cleft palate	2 (28.6)	14 (28.6)		1†
	Submucous cleft palate	1 (14.3)	7 (14.3)		1†

VWSG, case group; CG1, control group 1; CG2, control group 2; SD, standard deviation; †, Exact Fisher Test; ‡, Student's *T*-test; Bonferroni's correction applied; not statistically significant ($p > 0.05$).

TABLE 2 Relationship between chronological age and dental age according to Demirjian's method, years (SD)

Group	Chronological mean age	Dental mean age	Difference between dental age - chronological age	*p*-Value
VWSG	11.98 (±2.51)	12.34 (±2.71)	0.36	1.000†
CG1	12.73 (±1.95)	13.25 (±2.21)	0.52	0.444†
CG2	12.02 (±2.25)	12.98 (±2.66)	0.96	0.110†

SD: Standard deviation; VWSG, case group; CG1, control group 1; GC2, control group 2; †, Student's *T*-test; Bonferroni's correction applied; not statistically significant ($p > 0.05$).

TABLE 3 Comparison of the frequency of occurrence of each Vertebral Maturation Stage according to the Method modified by Baccetti et al., %

Vertebral maturation stage	VWSG (n:7)	CG1 (n:49)	GC2 (*n* = 49)	*p*-Value
Stage 1	28.6	14.3	32.7	0.620† (VWSG-CG1)
Stage 2	28.6	34.7	26.5	
Stage 3	28.6	20.4	18.4	1.000† (VWSG-GC2)
Stage 4	14.3	18.4	12.2	
Stage 5	0.0	12.2	10.2	

VWSG, case group; CG1, control group 1; GC2, control group 2; †, Chi-square test; Bonferroni's correction applied; not statistically significant ($p > 0.05$).

Demirjian's method, there is no eruptive delay in the VWS or in the two control groups. The comparison of the frequency of occurrence of each Vertebral Maturation Stage according to the Method modified by Baccetti is shown in Table 3 (Baccetti et al., 2002). In all the groups, most patients are between stage I and III, which corresponds to before or around the pubertal peak of growth, meaning that there is still room for growth in most of the patients in our sample. Results showed that chronological and skeletal ages did not present statistically significant differences within the individuals of each group and in the comparison between groups (Tables 1-3) (Baccetti et al., 2002; Demirjian et al., 1973). The patients with VWS and the control samples not only had the same chronological age, but they were also at the same maturing moment, a favourable point for the cephalometric comparison.

3.4 | Craniofacial characterization of the VWS patients

The results of the cephalometric study and the comparison between groups are shown in Table 4.

Regarding the skeletal problem, in the VWSG, all the means / medians of the linear measurements of the anatomically studied structures were hyperplastic with respect to those of matched controls. The following variables obtained statistically significant differences: lower posterior face height ($p = 0.048$ (CG1)), lower anterior face height ($p = 0.016$ (CG2)), cranial length ($p = 0.026$ (CG2)), posterior cranial base length ($p = 0.006$ (CG1) and $p = 0.020$ (CG2)), anterior cranial base length ($p = 0.004$ (CG2)), maxillary length ($p < 0.001$ (CG1) and $p = 0.002$ (CG2)) and mandibular length ($p = 0.016$ (CG1) and $p = 0.014$ (CG2)). However, this situation does not mean generalized hyperplasia in the cranial structures of the patient with Van der Woude syndrome, since in all cases these measures are close to or in line with established age, sex and racial norms (Table S2). At the vertical level, in contrast with both cohorts of control patients, there were parameters that demonstrate a vertical component in the growth in VWS indicated by the following values: the proportion between the anterior and posterior facial height was more decreased to a greater extent, although not significantly with respect control groups ($p > 0.05$ (CG1 and CG2)), the total, upper and lower gonial angles were larger ($p < 0.001$, $p = 0.002$ and $p > 0.05$ (CG2)), and the facial axis was around two grades decreased with respect to the control groups, a situation clinically significant but not statistically significant ($p > 0.05$ (CG1 and CG2)). At the sagittal level, patients with VWS in contrast with patients with non-syndromic cleft, presented skeletal class II caused by mandibular retrognathism, indicated by a facial convexity significantly greater than in patients of CG1 ($p = 0.032$), a lower SNB angle (although not significantly with respect to CG1 and CG2 ($p > 0.05$)) and ANB angle greatly increased from a clinical point of view ($p > 0.05$ (CG1 and GC2)). As for the maxillary length, in both control groups, the mean value was decreased from the cephalometric standard and the mean value of the VWSG ($p < 0.001$ (CG1) and $p = 0.002$ (CG2)), much more in CG1 by the effect of the cleft palate. However, in the SVWG, the mean value is 85.34 mm, almost at the lower limit set by the cephalometric norm (90.5 mm ±4). The mandibular length was significantly more decreased in control groups than in the VWSG ($p = 0.016$ (CG1) and $p = 0.014$ (CG2)), but in all cases it was lower than the cephalometric norm.

With regards to cephalometric data at dentoalveolar level, retrusion and lingual inclination of the mandibular incisor was found ($p < 0.05$ in all cases). A retruded upper incisor with a lingual inclination was also observed in the VWSG, although only significantly compared to CG2 ($p = 0.002$ and $p = 0.006$). In addition, the angulation between maxillary and mandibular incisors was found to be increased, although only significantly with respect to CG2 ($p > 0.05$ (CG1) and $p < 0.001$ (CG2)).

Lastly, at the profile level an open nasolabial angle ($p = 0.040$ (CG1)) was found, although not significantly with respect to CG2 ($p > 0.05$), and a more protruding lower lip respect to the Sn-Pg ($p = 0.040$ (GC1), $p = 0.044$ (GC2)).

TABLE 4 Comparative statistics of 37 craniofacial variables between patients with SVW (VWSG), non-syndromic cleft patients (CG1) and malocclusive healthy patients (CG2)

				Equal variances assumed	
				Student's *T*-test / Mann–Whitney *U* test	
Variable	**Group (*n*)**	**Mean/ Median**	**±SD/ IQR**	***p*-Value**	**Mean difference**
Airway analysis					
Width of the upper pharynx (mm)	VWSG (7)	8.31†	±3.44	0.442§	−1.57
	CG1 (48)	9.89†	±3.10		
Width of the lower pharynx (mm)	VWSG (7)	11.00‡	3	0.118¶	
	CG1 (49)	9.00‡	5		
Aesthetic analysis					
Upper lip length (mm)	VWSG (7)	18.96†	±4.10	0.634§	−1.77
	CG1 (49)	20.72†	±4.36		
Protrusion of the upper lip relative to the Sn-Pg line (mm)	VWSG (7)	1.61†	±3.31	0.144§	2.28
	CG1 (49)	−0.66†	±3.04		
Protrusion of the lower lip relative to the Sn-Pg line (mm)	VWSG (7)	4.61†	±2.67	0.040§*	2.97
	CG1 (49)	1.64†	±3.11		
Nasolabial angle (°)	VWSG (7)	113.00†	±18.10	0.040§*	16.10
	CG1 (49)	96.90†	±16.39		
Skeletal analysis					
Lower posterior face height (mm)	VWSG (7)	53.97†	±5.71	0.048§*	6.72
	CG1 (49)	47.27†	±7.31		
Lower anterior face height (mm)	VWSG (7)	63.33†	±9.97	0.228§	7.26
	CG1 (49)	56.07†	±11.30		
Ramus length (mm)	VWSG (7)	39.56†	±3.68	0.358§	3.65
	CG1 (49)	35.91†	±6.91		
Cranial length (mm)	VWSG (7)	58.00‡	10	0.062¶	
	CG1 (49)	47.20‡	12		
Posterior cranial base length (mm)	VWSG (7)	33.23†	±2.14	0.006§*	5.28
	CG1 (49)	27.95†	±4.46		
Anterior cranial base length (mm)	VWSG (7)	66.87†	±6.62	0.104§	7.72
	CG1 (49)	59.15†	±9.93		
Facial convexity (mm)	VWSG (7)	4.91†	±4.95	0.032§*	4.54
	CG1 (49)	0.37†	±4.48		
Maxillary length (mm)	VWSG (7)	85.34†	±7.29	0.000§*	16.60
	CG1 (49)	68.74†	±10.03		
Mandibular length (mm)	VWSG (7)	106.00‡	7	0.016¶*	
	CG1 (49)	87.30‡	21.8		
Length of the mandibular corpus (mm)	VWSG (7)	62.96†	±6.87	0.196§	5.88
	CG1 (49)	57.08†	±8.85		
Facial axis (°)	VWSG (7)	85.64†	±6.24	0.894§	−1.77
	CG1 (49)	87.41†	±5.64		
Inferior face height (°)	VWSG (7)	45.57†	±6.65	1.000§	−0.96
	CG1 (47)	46.53†	±5.11		
Angulation of the mandible to the anterior cranial base (°)	VWSG (7)	34.36†	±7.87	1.000§	−1.85
	CG1 (49)	36.20†	±6.82		

					Equal variances assumed			
					Student's *T*-test / Mann–Whitney *U* test			
95% confidence interval							95% confidence interval	
Min	Max	Group (*n*)	Mean/ Median	±SD/ IQR	*p*-Value	Mean difference	Min	Max
−4.12	0.97	VWSG (7)	8.31†	±3.44	0.194§	−2.19	−4.78	0.41
		CG2 (49)	10.50†	±3.17				
		VWSG (7)	11.00‡	3	0.046¶*			
		CG2 (49)	8.70‡	4				
−5.27	1.74	VWSG (7)	18.96†	±4.10	0.212§	−2.24	−4.98	0.49
		CG2 (49)	21.20†	±3.28				
−0.21	4.77	VWSG (7)	1.61†	±3.31	1.000§	−0.01	−2.07	2.06
		CG2 (49)	1.62†	±2.44				
0.49	5.46	VWSG (7)	4.61†	±2.67	0.044§*	2.41	0.37	4.45
		CG2 (49)	2.20†	±2.40				
2.66	29.54	VWSG (7)	113.00†	±18.10	0.258§	8.03	−2.42	18.48
		CG2 (49)	104.97†	±12.09				
0.93	12.51	VWSG (7)	53.97†	±5.71	0.574§	3.49	−2.35	9.33
		CG2 (49)	50.50†	±7.38				
−1.79	16.30	VWSG (7)	63.33†	±9.97	0.016§*	8.21	2.22	14.21
		CG2 (49)	55.11†	±7.02				
−1.72	9.02	VWSG (7)	39.56†	±3.68	1.000§	1.05	−3.76	5.86
		CG2 (49)	38.51†	±6.16				
		VWSG (7)	58.00‡	10	0.026¶*			
		CG2 (49)	47.70‡	7				
1.82	8.73	VWSG (7)	33.23†	±2.14	0.020§*	4.70	1.15	8.24
		CG2 (49)	28.53†	±4.58				
−0.07	15.52	VWSG (7)	66.87†	±6.62	0.004§*	8.08	3.00	13.16
		CG2 (49)	58.79†	±6.23				
0,87	8.21	VWSG (7)	4.91†	±4.95	0.180§	−2.24	−4.85	0.36
		CG2 (48)	2.40†	±2.43				
8.69	24.52	VWSG (7)	85.34†	±7.29	0.002§*	11.95	4.98	18.92
		CG2 (49)	73.39†	±8.75				
		VWSG (7)	106.00‡	7	0.014¶*			
		CG2 (49)	93.30‡	16.3				
−1.13	12.89	VWSG (7)	62.96†	±6.87	0.396§	3.70	−2.00	9.39
		CG2 (49)	59.26†	±7.05				
−6.39	2.86	VWSG (7)	85.64†	±6.24	0.456§	−2.77	−7.31	1.78
		CG2 (49)	88.41†	±5.53				
−5.27	3.36	VWSG (7)	45.57†	±6.65	0.732§	2.01	−2.41	6.43
		CG2 (49)	43.56†	±5.29				
−7.48	3.78	VWSG (7)	34.36†	±7.87	1.000§	1.51	−4.00	7.02
		CG2 (49)	32.85†	±6.66				

(Continues)

TABLE 4 (Continued)

				Equal variances assumed	
				Student's *T*-test / Mann–Whitney *U* test	
Variable	**Group (*n*)**	**Mean/ Median**	**±SD/ IQR**	***p*-Value**	**Mean difference**
Angulation of the mandibular corpus relative to the mandibular ramus (°)	VWSG (7)	28.50†	±5.84	0.452§	−2.79
	CG1 (49)	31.29†	±5.60		
Total gonial angle (°)	VWSG (7)	134.71†	±6.13	0.154§	5.41
	CG1 (49)	129.31†	±7.56		
Upper gonial angle (°)	VWSG (7)	55.93†	±3.25	0.154§	3.60
	CG1 (49)	52.33†	±5.12		
Lower gonial angle (°)	VWSG (7)	78.79†	±7.56	0.986§	1.87
	CG1 (49)	76.92†	±6.59		
Nasomaxillary height (°)	VWSG (7)	59.64†	±6.21	1.000§	0.98
	CG1 (49)	58.66†	±4.32		
Maxillary inclination relative Po-Or plane (°)	VWSG (7)	2.14†	±4.78	1.000§	0.92
	CG1 (49)	1.22†	±4.76		
Cranial base angulation relative to Po-Or plane (°)	VWSG (7)	28.64†	±1.70	1.000§	0.41
	CG1 (49)	28.24†	±2.95		
Angulation between anterior and posterior cranial base (°)	VWSG (7)	131.14†	±3.98	1.000§	0.31
	CG1 (49)	130.84†	±7.18		
SNA angle (°)	VWSG (7)	81.14†	±7.35	0.152§	3.98
	CG1 (49)	77.16†	±5.15		
SNB angle (°)	VWSG (7)	74.29†	±17.22	1.000§	−1.39
	CG1 (49)	75.67†	±4.94		
Anterior facial height takes away posterior facial height	VWSG (7)	41.00‡	33.5	0.156¶	
	CG1 (49)	62.10‡	6.5		
ANB angle (°)	VWSG (7)	5.43†	±4.36	0.084§	3.90
	CG1 (49)	1.53†	±4.66		
Maxillomandibular relationship index (mm)	VWSG (7)	14.70‡	15	0.370¶	
	CG1 (49)	23.50‡	8		
Dental analysis					
Position of the maxillary incisor (mm)	VWSG (7)	2.00‡	4	0.564¶	
	CG1 (49)	2.60‡	5		
Position of the mandibular incisor (mm)	VWSG (7)	−2.04†	±2.69	0.028§*	−3.48
	CG1 (49)	1.44†	±3.47		
Inclination of the maxillary incisor (°)	VWSG (7)	15.36†	±10.29	1.000§	−2.83
	CG1 (49)	18.18†	±14.11		
Inclination of the mandibular incisor (°)	VWSG (7)	13.50‡	10	0.000¶*	
	CG1 (49)	21.00‡	10		
Angulation between maxillary and mandibular incisors (°)	VWSG (7)	155.14†	±16.89	0.062§	15.84
	CG1 (49)	139.31†	±17.78		

Note: SD, standard deviation; IQR, interquartile range; VWSG, case group; CG1, control group 1; CG2, control group 2;
*, statically significant value; mm, millimetres; °, degrees.

Bonferroni's correction applied.

†, mean; ‡, median; §, Student's *T*-test for parameters following normal distribution; ¶, Mann–Whitney *U* test for non-normal parameters.

					Equal variances assumed			
					Student's *T*-test / Mann–Whitney *U* test			
95% confidence interval							95% confidence interval	
Min	Max	Group (*n*)	Mean/ Median	±SD/ IQR	*p*-Value	Mean difference	Min	Max
−7.34	1.775	VWSG (7)	28.50†	±5.84	0.060§	−5.32	−10.10	−0.53
		CG2 (49)	33.82†	±5.92				
−0.60	11.42	VWSG (7)	134.71†	±6.13	0.000§*	10.64	5.32	15.97
		CG2 (49)	124.07†	±6.63				
−0.40	7.61	VWSG (7)	55.93†	±3.25	0.002§*	5.50	2.22	8.78
		CG2 (49)	50.43†	±4.13				
−3.56	7.30	VWSG (7)	78.79†	±7.56	0.074§	5.18	0.33	10.04
		CG2 (49)	73.60†	±5.77				
−2.72	4.68	VWSG (7)	59.64†	±6.21	1.000§	0.70	−2.70	4.10
		CG2 (49)	58.94†	±3.87				
−2.94	4.77	VWSG (7)	2.14†	±4.78	0.472§	1.13	−1.13	4.50
		CG2 (49)	0.46†	±3.28				
−1.89	2.70	VWSG (7)	28.64†	±1.70	1.000§	−0.52	−2.64	1.60
		CG2 (49)	29.16†	±2.70				
−5.28	5.89	VWSG (7)	131.14†	±3.98	1.000§	0.12	−3.85	4.10
		CG2 (49)	131.02†	±5.01				
−0.42	8.38	VWSG (7)	81.14†	±7.35	1.000§	0.79	−2.82	4.40
		CG2 (49)	80.36†	±3.95				
−7.38	4.60	VWSG (7)	74.29†	±17.22	0.722§	−2.61	−8.30	3.08
		CG2 (49)	76.90†	±4.29				
		VWSG (7)	41.00‡	33.5	0.734¶			
		CG2 (49)	61.80‡	17.5				
0.15	7.64	VWSG (7)	5.43†	±4.36	0.348§	1.85	−0.68	4.28
		CG2 (49)	3.58†	±2.94				
		VWSG (7)	14.70‡	15	1.000¶			
		CG2 (49)	20.20‡	7				
		VWSG (7)	2.00‡	4	0.002¶*			
		CG2 (49)	5.00‡	4				
−6.22	−0.74	VWSG (7)	−2.04†	±2.69	0.006§*	−3.52	−5.79	−1.26
		CG2 (49)	1.48†	±2.80				
−13.96	8.30	VWSG (7)	15.36†	±10.29	0.006§*	−13.37	−21.90	−4.83
		CG2 (49)	28.72†	±10.56				
		VWSG (7)	13.50‡	10	0.000¶*			
		CG2 (49)	26.00‡	10				
1.52	30.16	VWSG (7)	155.14†	±16.89	0.000§*	28.71	16.22	41.21
		CG2 (49)	126.43†	±15.24				

4 | DISCUSSION

Since VWS was first described, few cases of this syndrome have been reported and clearly described (Tehranchi et al., 2017; Tokat et al., 2005). One of the inconveniences of studying a rare disease is the difficulty of gathering a large sample. Most of the articles address the study of one case, one or two families, denoting the low incidence of this syndrome (Angiero et al., 2018; Kaul et al., 2014; Tokat et al., 2005; Tripathi et al., 2014). This is perhaps due to either a lack of knowledge about the clinical features of this syndrome or to its variable expression and limited symptoms. Studies that manage to analyse a larger sample do so by bringing together patients from different institutions, from the same country or internationally; or by analysing the cases that occur over a very long period (Desmyter et al., 2010; Kondo et al., 2002; Onofre et al., 1997; Reardon et al., 2015; B C Schutte et al., 1999). Therefore, although the sample size of the present research is relatively small, we must consider that the prevalence of VWS is very low, ranging from 1:100.000 to 1:40.000 live births (Rizos & Spyropoulos, 2004). We have to highlight that our study is the first to be carried out in the Southern European population and provides a basis for future research.

Regarding the gender of the included patients, there is no consensus between studies up to date (Burdick, 1986; Cervenka et al., 1967; Schinzel & Kläusler, 1986). Many authors believe that there is a greater prevalence in women, due to their greater concern for aesthetic defects (Onofre et al., 1997; Watanabe et al., 1951). Our study indicates that the frequency of the syndrome in men is much higher than in women, accounting for 80% of the cases, coinciding with the study by Csiba et al., although he found that the syndrome is twice as frequent in males than in females (Csiba, 1966).

The information about craniofacial growth is limited, particularly very few studies analysed the cephalometric study of VWS-patients (Heliövaara et al., 2014; Kane et al., 2002; Oberoi & Vargervik, 2005). Heliövaara et al. compared the teleradiographs of 44 VWS individuals whose mean age was 6.6 years (range 5.9–8.2) (17 boys and 27 girls) with those of 73 non-syndromic fissured individuals whose mean age was 6.2 years (34 boys and 39 girls). They concluded that 6-year-old children with VWS and non-syndromic cleft palate had a similar craniofacial morphology (Heliövaara et al., 2014). This situation is not reproduced in our study. Although in both cases the patients have not completed their growth, and therefore, the facial morphology has not been fully established; the subsequent increased lack of growth in the Heliövaara et al. sample may affect more to the measurements and relationships between the different craniofacial structures, which may result in differences at this level between patients with VWS and non-syndromic cleft lip-palate. In both cases, we must consider that the final facial morphology is not fully determined until growth has ceased.

Similarly, Oberoi and Vargervik (Oberoi & Vargervik, 2005) studied 15 individuals with VWS aged between 9 and 10 years, with 15 matched controls with non-syndromic cleft lip and palate. The authors concluded that the individuals with VWS presented maxillary hypoplasia, particularly in the cases of more severe cleft palate. The measurements on the sagittal relationship between maxilla and mandible (ANB angle and Wits), were smaller in individuals with VWS than in matched controls. These authors highlighted that in patients with VWS, an increased mandibular angle was indicative of a marked tendency to vertical growth, a result that is reproduced in our study. In addition, in contrast with Oberoi and Vargervik, in the evaluation of the sagittal jaw relationship: The facial convexity, SNB and ANB angles indicated skeletal class II in the VWS, compared to the controls and the normal measurements established by the cephalometric studies.

With regard to the length of the maxilla, Kane et al. (Kane et al., 2002) compared celaphometrically 17 VWS individuals with controls in a cross-sectional and longitudinal study with age groups of 5 years, 7 years, 9 years, 11 years, and 13 years or greater. They found that the anteroposterior length of the maxilla (described from the anterior nasal spine to the posterior nasal spine) is shorter in the older age group with VWS. Their longitudinal growth analysis showed that the position of point B was vertically lower in controls. Furthermore, the soft tissue analysis demonstrated that the VW-cases had a most protruding lower lip in each age group. The results of our research agree with the data over the position of the lower lip, much more protruding in the VWS. In contrast, in our sample, the total maxillary length (measured from the condylion to the A point) was greater in VWSG than in the controls, with a mean value of 85.34mm, almost at the lower limit set by cephalometric norm (90.5 mm $\pm$4). Therefore, our results indicate that the presence of cleft palate affects to a lesser extent the longitudinal development of the maxilla. Furthermore, the measurements that determine the growth pattern indicated a greater vertical pattern in the VWS than in non-syndromic cleft patients (with a mean age of 12 years).

Interestingly, although the VW-patients of our sample show a marked tendency to the class II, the lower lip is very prominent relative to the Sn-Pg line, with respect to the cephalometric norm and the control groups, more related to the class III. It should be at least partly explained due to the fact that the presence of pits in the lower lip of these patients is the main cause of lip protrusion, giving volume to the lower lip and generating this defect at the profile level. Moreover, the differences found in our sample with respect to other cohorts could be due to ethnic differences. The Southern European population might present a more elongated face and a greater tendency to class II (Campos Peña et al., 1993; Travesí Gómez, 1992). Nevertheless, we should be aware when treating patients with cleft palate orthodontically, that we cannot take a standard treatment based on the thought that these patients may need disjunction and maxillary traction with a face mask due to maxillary hypoplasia. A complete diagnosis must always be carried out, analysing the clinical history, orthopantomography, tele-radiography and performing a functional exploration to establish the correct treatment. This is one of the first pieces of research to provide with valuable craniofacial characterization of VW-patients compared with matched control cohorts in a Southern European population.

5 | CONCLUSIONS

Based on the results described, we conclude that:

1. The patients with VWS present a skeletal maturation according to chronological age as compared to the matched control cohorts.
2. According to the cephalometric findings and the comparison, patients with VWS present a characteristic craniofacial morphology with vertical component in the growth, skeletal class II caused by mandibular retrognathism and dental bi-retrusion. At the profile level, we can highlight an open nasolabial angle and a more protruding lower lip.
3. The scarcity of scientific and clinical data regarding SVW in the literature is by far one of the biggest barriers for their adequate access to oral health. The greater the knowledge that the professional possesses about orofacial pathology associated with the syndrome and its treatment needs, the better the quality of care that can be provided.

ACKNOWLEDGEMENTS

The authors report no conflicts of interest and gratefully acknowledge the collaboration of the stomatology departments of the Virgen Macarena University Hospital of Seville and 12 de Octubre University Hospital of Madrid and the support of the stomatology department of the dentistry college of the University of Seville and of the dental clinical specialist department of Complutense University of Madrid.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Blanca Estévez-Arroyo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing. **Ignacio Gómez Mendo:** Data curation; Funding acquisition; Investigation; Project administration; Supervision; Validation; Writing – review & editing. **Enrique Solano-Reina:** Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing. **Alejandro Iglesias-Linares:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/odi.14187.

ORCID

Blanca Estévez-Arroyo https://orcid.org/0000-0002-8410-8742
Enrique Solano-Reina https://orcid.org/0000-0002-4477-0934
Alejandro Iglesias-Linares https://orcid.org/0000-0001-9063-1612

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How to cite this article: Estévez-Arroyo, B., Gómez-Mendo, I., Romero-Maroto, M., Solano-Reina, E., & Iglesias-Linares, A. (2022). Craniofacial characteristics in Van der Woude syndrome. *Oral Diseases*, *00*, 1–12. https://doi.org/10.1111/odi.14187