ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

The heterogeneity of craniofacial morphology in Prader–Willi patients

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Abstract

Prader–Willi syndrome is a complex genetic disorder with narrow spectrum of facial phenotypic signs, which make the clinical diagnosis difficult in some cases. There are several reports describing the craniofacial appearance of Prader–Willi patients, but there are only a few cephalometric studies for these patients. In this study were included 18 patients with Prader–Willi syndrome and a control group of 18 subjects of both sexes selected based on specific criteria. The cephalometric radiographs of the patients were taken using the standardized technique with centric teeth in occlusion and lips in relaxed position. Angular, horizontal and linear measurements were analyzed for the study group and for the control group. We established that in Prader–Willi patients, there is a decrease of the majority of parameters but the degree of this reduction varies widely between patients and clinically typical facies not always have smaller measurements which can be found in an unusual facies. Facial dysmorphism in Prader–Willi patients varies a group ranging from miss proportions that do not alter the facial architecture as regard of facial typology, skeletal class and pattern of development to a severe disturbance of those. There is a degree of clinical heterogeneity between subjects with Prader–Willi syndrome on clinical evaluation and cephalometric study confirms the heterogeneity for this patients. Because the identification of smaller dimensions for majority of parameters in children and adults, the possibility of developmental delay or growth retardation delay can be excluded. These findings are important for the orthodontist for optimum timing of orthodontic management of patients with Prader–Willi syndrome.

Keywords: Prader–Willi syndrome, cephalometry, orthodontic management.

Introduction

Prader–Willi syndrome, a rare genetic condition with an incidence between 1 in 25 000 and 1 in 10 000 live births was first described in literature by Langdon–Down in 1887 [1]. Later, in 1956, Andrea Prader, Heinrich Willi, Alexis Labhart, Andrew Ziegler, and Guido Fanconi reported several cases exhibiting the same phenotype. Ledbetter DH *et al*., who identified the microdeletion 15q11-13 as being responsible for Prader–Willi syndrome [2], revealed the etiopathogeny in 1981.

Prader–Willi syndrome is a complex genetic disorder because there are several genetic models for this condition: microdeletion of paternal chromosome 15q11-13, uniparental disomy, sporadic mutations, imprinting defects, chromosome translocations, and gene deletions [3–6]. There is a narrow spectrum of facial phenotypic signs, which make the clinical diagnosis difficult in some cases. When the facial pattern associates narrow bifrontal diameter, almond shaped eyes, thin upper lip, downturn corner of the mouth and the patient also presents obesity, severe hypotonia, short stature, hypogonadism, hyperphagia, cognitive disabilities and behavior problems the diagnosis of Prader–Willi syndrome can be raised. Holm VA *et al.* established the clinical diagnostic criteria in 1993, which were later confirmed by Gunay-Aygun M *et al.* [7, 8].

There are several reports describing the craniofacial appearance of Prader–Willi patients, but there are only a few cephalometric studies for these patients. Until present, there are five reports about the cephalometric and orofacial pattern in Prader–Willi patients. Two studies were done by Meany FJ and Butler MG in 1987, the first presents the anthropometric parameters in Prader–Willi patients and the second described the craniometric variability of those patients [9, 10]. Another study was performed by Schaedel R *et al.*, in 1990, and analyzed the cephalometric parameters for Prader–Willi patients [11].

In 2007, Bailleul-Forestier I *et al.* studied the orofacial phenotype of 15 patients with Prader–Willi

syndrome [12]. The latest study was those of Saeves R *et al.* and analyzed the orofacial dysfunction [13].

By using the cephalometry in Prader–Willi patients, for establishing the craniofacial growth tendencies, the orthodontics, dentists and pediatricians may identify more easily facial growth problems in the antero-posterior, vertical and transversal dimension, through a simple clinical assessment method. In the absence of treatment, these problems can lead to aesthetic and functional disturbances, thus, these must be managed by various means in a limited period.

Although not a common pathology, through this study we aimed to better understand the Prader–Willi phenotype and research results will allow an improvement in patients quality of life by increasing therapeutic compliance, with treatment of orodental problems in early stages, decreasing complications and correction of orthodontic defects at optimal time.

Patients and Methods

Subjects' selection

The study group included 18 patients aged between 4 and 33 years, mean age 16.42±9.71 years. Gender distribution of patients reveals a slight preponderance of female patients compared to males.

Genetic investigations including standard cytogenetic analysis, molecular cytogenetic technique (FISH), deletions analysis using MLPA, DNA methylation analysis and arrayCGH were performed for establishing the genetic diagnosis and etiopathogeny for each patient included in the study group. Cytogenetic and molecular analysis confirmed Prader–Willi syndrome diagnosis for all the patients included in this report.

The control group comprised 18 subjects of both sexes selected based on the following criteria: similar age, skeletal Class 1, normal transversal occlusion, normal overjet and overbite, dental arches without dental crowding or congenital anomalies, straight profile, without facial asymmetry and without orthodontic history.

Cephalometric assessment

The cephalometric radiographs of the patients were taken using the standardized technique with centric teeth in occlusion and lips in relaxed position. The subjects were standing with the Frankfurt plane parallel to the floor with the auricular rod slightly inserted into the external auditory canal to stabilize the position during exposure. The distance between anode, the sagittal plane and film respectively was 150 cm, and 15 cm leading to a linear magnification factor of 10% the median. There has been no correction of X-rays.

The radiographic technique was very complicated for the study group because the patients were uncomfortable with the metallic portion, they had to stay still for a long period and the combine effort of the investigator and the parents was necessary in order to obtain radiography of good quality (Figures 1–3).

CephX software (CephX Inc., Las Vegas, USA) was used for cephalometric traces of the digital cephalograms and for obtaining the linear and angular measurements necessary for evaluating the craniofacial morphology. This software allowed us to obtain the necessary measurements even for the cases with radiographs of poor quality.

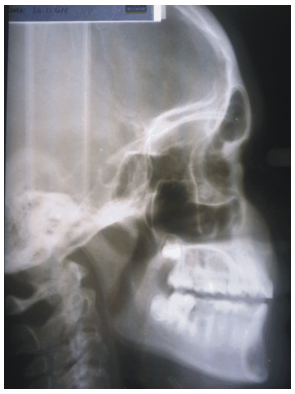

Figure 1 – ***Patient D cephalogram (11-year-old).***

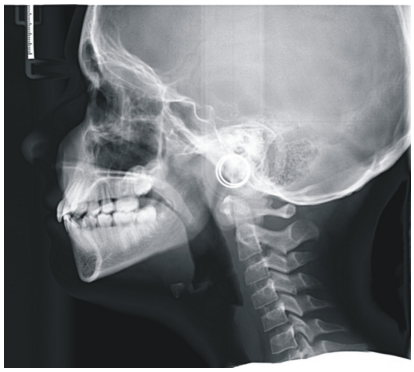

Figure 2 – ***Patient DF cephalogram (9-year-old).***

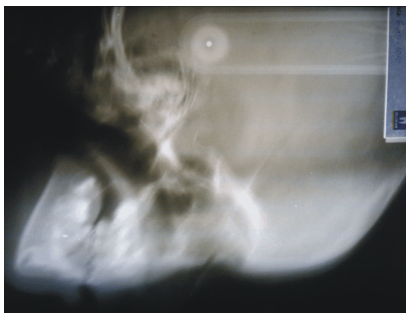

Figure 3 – ***Patient S cephalogram (4-year-old).***

For a comprehensive cephalometric evaluation, we took in consideration several cephalometric analyses. Each cephalometric parameter was compared in minimum two cephalometric analyses. The cephalometric analysis used for assessment of the craniofacial morphology in Prader–Willi patients are: Bjork–Jarabak Analysis, Busrstone Analysis, Harvold Analysis, McGann Analysis, Heb Uni. Analysis, Ricketts Analysis, Steiner Analysis, Modified Steiner Analysis.

Using these analyses, the following relationships were evaluated:

▪ Skeletal relationships: horizontal linear measurements: anterior cranial base (NS) and posterior cranial base (S-Ar), anteroposterior position of the jaw, the position of jaw and chin; angular measurements: position of cranial flexion angle N/S/Ar and cranial base angle N/S/Ba; vertical skeletal relationships: linear measurements of anterior (N-Me) and posterior (S-Go)

facial heights, anterior upper face height (N-ANS) and the anterior lower facial height (ANS-Me) and the proportions between them.

▪ Angular measurements for evaluating the vertical relationship of the mandible to the SN plane (SN/MP) and to the plane Frankfurt (FMA).

▪ Evaluation of the jaw: linear by jaw length (Co-A), palate size (ANS-PNS) and angular jaw relationship to the skull by the angle S/N/A.

▪ Evaluation of mandible: linear length of the mandible (Co-Gn), mandibular ramus size (Ar-Go), mandibular body (Go-Pg) and angular: gonial angle (Ar/Go/Gn) and mandibular relationship to the skull by angles of S/N/B and S/Ar/Go.

▪ Relationships in the complex maxillo-mandibular by using the angle A/N/B.

Statistical analysis

Statistical analysis was done using the program SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics used mean values and standard deviation for all variables measured on study groups. Angular, horizontal and linear measurements were analyzed for the study group and for the control group. The cephalometric parameters between study group and control group, using Student's *t*-test, were compared in order to detect differences between these groups. The *p* two-tailed values were processed. Differences were considered statistically significant if *p*-value was ≤0.05.

Results

The cephalometric measurements of the Prader–Willi patients were compared with those of the control group and the mean values as well as the standard deviations are presented in the Tables 1 and 2.

For all these parameters, the statistic significance was evaluated and the *p*-values are also presented in Tables 1 and 2.

We also present images of Ricketts analysis for patient DF, Bjork–Jarabak analysis for patients V and McGann analysis for patient B (Figures 4–6).

Table 1 – *Cephalometric parameters evaluating cranial base and facial heights for the Prader patients and the control group*

Parameters	Study group mean (SD)	Control group mean (SD)	*P*
Anterior cranial base (S-N)	75.83 mm (1.75 mm)	70.19 mm (3.89 mm)	<0.0001
Posterior cranial base (S-Ar)	36.4 mm (2.75 mm)	33.22 mm (1.34 mm)	<0.0001
Cranial base angle (N/S/Ba)	127.2^0 (4.53^0)	130.68^0 (1.6^0)	0.02
Cranial flexion angle (N/S/Ar)	118.15^0 (5.26^0)	123.07^0 (0.58^0)	<0.0001
Posterior facial height (S-Go)	71.93 mm (8.44 mm)	73.6 mm (6.49 mm)	0.513
Anterior facial height (N-Me)	111.46 mm (7.34 mm)	115.5 mm (3.07 mm)	0.038
Upper anterior facial height (N-ANS)	53.02 mm (4.48 mm)	54.25 mm (1.3 mm)	0.275
Lower anterior facial height (ANS-Me)	58.04 mm (4.1 mm)	61.36 mm (1.74 mm)	0.003

Table 2 – *Cephalometric parameters evaluating mandibula and maxilla for the Prader patients and the control group*

Parameters	Study group mean (SD)	Control group mean (SD)	*P*
Maxillary length (Co-A)	83.45 mm (2.13 mm)	86.21 mm (1.84 mm)	<0.0001
Palate length (ANS-PNS)	55.48 mm (2.14 mm)	55.21 mm (2.27 mm)	0.716
Mandibular length (Co-Gn)	111.24 mm (5.01 mm)	112.57 mm (4.12 mm)	0.357
Mandibular corpus length (Go-Pg)	80.6 mm (3.45 mm)	82.2 mm (2.7 mm)	0.137
Mandibular ramus length (Ar-Go)	39.48 mm (4.28 mm)	44.18 mm (3.45 mm)	<0.0001
SN/MP	32.37^0 (1.98^0)	34.06^0 (1.23^0)	0.004
FMA	25.56^0 (2.42^0)	28.79^0 (0.77^0)	<0.0001
Gonial angle (Ar/Go/Gn)	124.63^0 (2.36^0)	127.11^0 (4.05^0)	0.31
S/N/A	83.85^0 (1.83^0)	81.83^0 (0.6^0)	<0.0001
S/N/B	80.11^0 (1.81^0)	79.16^0 (1.22^0)	0.074

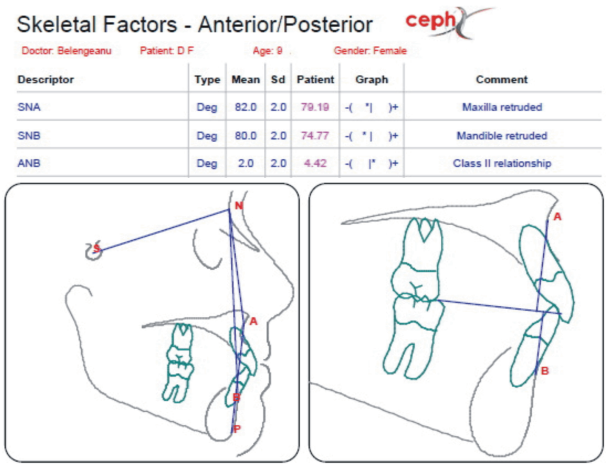

Figure 4 – *Ricketts analysis for patient DF (9-year-old).*

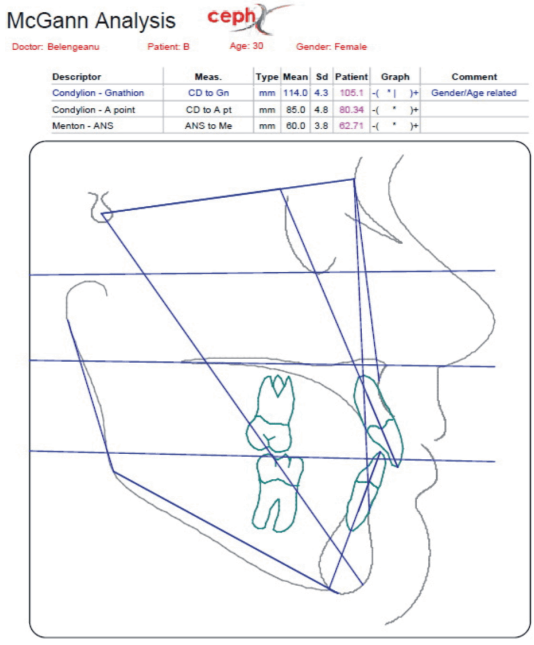

Figure 5 – *McGann analysis for patient B (30 years old).*

Bjork-Jarabak Analysis ceph

Doctor: Belengeanu Patient: V Age: 13 Gender: Male

Descriptor	Meas.	Type	Mean	Sd	Patient	Graph	Comment
SADDLE ANGLE	N-S-Ar	Deg	123.0	4.0	119.27	-(*)+	
ARTICULAR ANGLE	S-Ar-Go	Deg	143.0	5.0	145.84	-(*)+	
GONIAL ANGLE	Ar-Go-Gn	Deg	130.0	5.0	131.56	-(*)+	
SUM OF ANGLES		Deg	396.0	20.0	396.67	-(*)+	
UPPER GONIAL ANGLE	Ar-Go-N	Deg	53.0	2.0	51.22	-(*)+	
LOWER GONIAL ANGLE	N-Go-Gn	Deg	73.0	3.0	80.33	-(| *)+	
ANT. CRANIAL BASE	N-S	mm	71.0	10.0	87.45	-(|*)+	
POST. CRANIAL BASE	S-Ar	mm	32.0	5.0	40.98	-(|*)+	

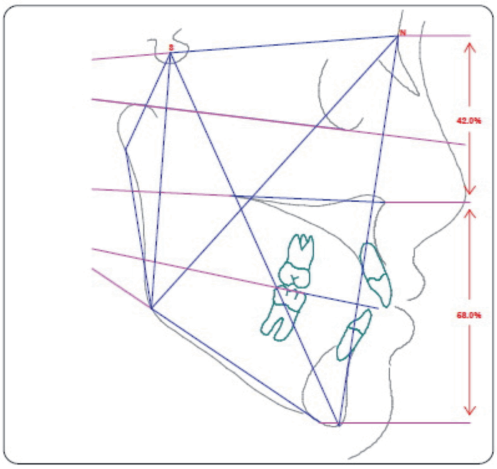

Figure 6 – ***Bjork–Jarabak analysis for patient V (13-year-old).***

For the skeletal horizontal relationships the Prader–Willi patients present reduced mean values for the angular parameters (N/S/Ba, N/S/Ar) and increased mean values of the linear measurements (S-N, S-Ar). Anterior and posterior cranial base lengths and the cranial flexion angle measurements, revealed *p*-values <0.0001, the differences being statistically very significant. If the anterior cranial base presented a very low variability, for the posterior cranial base, the cranial base angle and the cranial flexion angle we found great intragroup variability in Prader–Willi patients.

Regarding the vertical skeletal parameters, all the parameters were shorter for study group when compared with the control group. The difference between the mean values of anterior facial height (N-Me) and the anterior lower facial height (ANS-Me) of Prader–Willi patients and the control group were statistically significant. A great variability was found for the dimensions of anterior (N-Me) and posterior (S-Go) facial heights, anterior upper face height (N-ANS).

The linear measurements of the mandible and maxilla with the exception of the palatal length showed shorter dimensions in the Prader–Willi group as compared with the control group.

The mandibular plane angle (SN/MP), F/M/A and the gonial angle (Ar/Go/Gn) were found smaller in Prader–Willi group comparative with the control group. The angles evaluating the interrelationship between maxilla and cranial base (S/N/A), mandible and cranial base (S/N/B) and sagittal interrelationship between the maxillary and mandibular apical bases (A/N/B) were wider in Prader–Willi patients. Statistically significant differences were found for SN/MP, F/M/A, S/N/A and A/N/B angles. A great variability of the measurements was found for the SN/MP, S/N/A, S/N/B angles.

Discussion

Cephalometry is important for the practitioner in order to correctly evaluate the parameters and craniofacial relations between them, for the implementation of an appropriate treatment plan and also for orthodontic surgery, if it is sustained by clinical and cephalometric evaluation.

The study group is numerically limited but still relevant, considering that Prader–Willi syndrome is a rare disease and the study group included a homogeneous group of patients regarding the ethnicity, aged between 5 and 32-year-old, which allowed us to appreciate childhood, as well as adult state of these patients.

An important issue when evaluating patients with Prader–Willi syndrome was the fact that the cooperation was very difficult and implied a combined effort of the investigator and sometimes patients parents in order to perform a cephalometric radiography.

For the majority of the parameters evaluated we recorded reduced dimensions when compared with the control group. Our results are consistent with those obtain by Schaedel R *et al.* [11] regarding the linear measurements of posterior cranial base, facial heights, linear measurements of mandible and maxilla. The anterior cranial base was found to have normal values in Schaedel R *et al.* [11] study, for our group we recorded larger dimension of this segment. Regarding the variability of the measurements great heterogeneity for Prader–Willi patients was found for almost all the parameter with exception of anterior cranial base and anterior lower face height. For the angular measurements, there is no other study available at this moment for comparison.

Some authors suggest that the cranial base has a role in craniofacial disharmonies [14]. Cranial base, exerts considerable influence on facial growth, and plays an integral role in coordinated craniofacial growth. Evaluation of cranial base dimensions is important in order to establish the possible effects on facial floors heights [15].

Variations of the cranial base angle influence the facial type and jaws position. A reduced cranial base angle, as found in the study group is associated with the brachyfacial model [16], which is the characteristic face pattern for Prader–Willi patients.

The concept of facial harmony implies a certain ratio between the facial heights [17]. For the Prader–Willi patients all the facial heights have reduced dimensions but for the anterior face height and anterior lower face height, we found a statistically significant difference comparative with the control group. The reduction of the anterior face height is due mostly to the reduction of the lower floor height, which determines an alteration of the heights ratio and a perturbation of the facial harmony. The reduction of the mandibular plane angle is in concordance with the reduced dimensions of the anterior face height and of the anterior lower face height. The reduction of the mandibular plane angle was also correlated with the increase of the ratio between the posterior and anterior face height that we have established for the Prader–Willi patients.

The reduced dimensions of the maxilla and ramus are typical for the Prader–Willi patients, these parameters were found to be significantly statistic shorter when comparing with the control group. The presence of a hypotonic tong in conjunction with the reduction of mandibular and maxillary dimensions predisposes the Prader–Willi patients to sleep apnea. Sleep apnea is one of the consequences of the perturbations in orofacial morphology with important impact in patients well being and for some Prader–Willi patients therapeutic measures are needed for improving the respiratory function.

Gonial angle has an important role in facial profiling. Gonial angle reflects the vertical development of the mandible, which is dependent of the mandibular ram increscent and is correlated directly with lower face floor [18]. As the gonial angle reflects the proportion between the facial height and ramus height, for the Prader–Willi patients the smaller gonial angle revealed a miss proportion of those parameters. The reduction of the mandibular plane angle and the gonial angle are associated with the short face, which might be a characteristic of Prader–Willi patients.

For the Prader group we found a smaller FMA angle as compared with the control group, which can be correlated with small teeth and decrease vertical dimension of occlusion. For the study group, the reduced dimension of FMA angle is in concordance with the brachycephalic pattern [19] and an aspect less convex of these patients profile.

S/N/A, S/N/B and A/N/B angles are important for establishing the skeletal class [20]. A more obtuse S/N/A angle found for Prader–Willi patients correlates with brachyfacial type in concordance with the literature [10] reports that established that for this syndrome the brachyfacial type is characteristic. This facial type also associates an enlargement of the S/N/B angle, also characteristic for the hypodivergent pattern. The mesofacial model is correlated with a mean value $2^0 \pm 2$ of the A/N/B angle. For the Prader–Willi group this angle had a mean above 4^0, which is an indicator of class II skeletal pattern. Even if the differences between the means of the angular parameters for the study group and control group were small, yet they showed variations, which for some patients determined a pathological facial type.

We established that in Prader–Willi patients, there is a decrease of the majority of parameters but the degree of this reduction varies widely between patients and clinically typical facies not always have smaller measurements, which can be found in an unusual facies. Facial dysmorphism in Prader–Willi patients varies a group ranging from miss proportions that do not alter the facial architecture as regard of facial typology, skeletal class and pattern of development to a severe disturbance of those.

As with many other syndromes there is a degree of clinical heterogeneity between subjects and clinical diagnosis is based on clinical evaluation and cephalometric study confirms the clinical heterogeneity in terms of patients.

Conclusions

Because in both children and adults, most parameters analyzed had values lower than the control group, we cannot sustain a normal development pattern for the Prader–Willi patients, and the achievement of peak values corresponding to patient's age. Due to the identification of smaller dimensions for majority of parameters in children and adults, the possibility of developmental delay or growth retardation delay can be excluded. These findings are important for the orthodontist for optimum timing of orthodontic management of patients with Prader–Willi syndrome.

Acknowledgments

We would like to thank the patients with Prader–Willi syndrome included in the study, their families for accepting to take part in this research, to the voluntaries that where included in the control group and Mrs. Dorica Dan, President of Prader–Willi Association Romania. We had a very good collaboration with DentaVis – Radiology Center and we also thank Dr. Vlad George Tudericiu.

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Received: April 4th, 2012

Accepted: August 20th, 2012