Revista Odontológica Mexicana
Facultad de Odontología
Vol. 16, No. 2 • April-June 2012
pp 88-97
ORIGINAL RESEARCH

Study of craniofacial growth in Pierre Robin Sequence (PRS) patients not subjected to osteogenic distraction (OD)

Estudio del crecimiento craneofacial en pacientes con Secuencia de Pierre Robin (SPR) no sometidos a distracción osteogénica (DO)

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ABSTRACT

A craniofacial growth study was conducted in Pierre Robin Sequence patients (not subjected to osteogenic distraction) (OD), with the aim of assessing the behavior of partial compensatory growth of the upper and lower jaw structures, and thus determine whether this growth can be considered within the parameters of established cephalometric standards. The study was descriptive, open, observational and retrospective. The study was conducted on 10 PRS patients not subjected to OD. The main researcher performed 220 cephalometric tracings in lateral x- rays of the skull, previously Kappa test calibrated, Harvold, Ricketts, Riedel and Jarabak cephaolmetric analysis measurements were included in the study. A $p < 0.05$ significance level Mann Whitney U test was used. Growth behavior in patients without OD presented tendency towards verticality. In patients 4, 5, 6 and 12 years old, growth was vertical. At 7 years of age, a patient showed tendency to normality and at 8 years of age growth was horizontal. Growth behavior of the upper jaw showed tendency to verticality, and was apparent in 80% of cases as supra-occlusion and retrusion. Angle C II was the predominating skeletal pattern. The values for facial depth were altered (Po-Or/N-Pg) and found to be under the norm in all 10 studied cases. PRS patients not subjected to OD were found to be under the ranges established by cephalometric norms.

RESUMEN

Se realizó un estudio del crecimiento craneofacial en pacientes con secuencia de Pierre Robin (SPR) no sometidos a distracción osteogénica (DO), con la finalidad de conocer el comportamiento del crecimiento compensatorio parcial del complejo maxilo-mandibular y determinar si este crecimiento se encuentra entre las normas cefalométricas establecidas. El tipo de estudio fue descriptivo, abierto, observacional y retrospectivo en 10 pacientes con SPR no sometidos a DO. El investigador principal realizó 220 trazos cefalométricos en radiografías laterales de cráneo, previa calibración a través de la prueba Kappa. Incluyendo medidas de los análisis cefalométricos de Harvold, Ricketts, Riedel y Jarabak. Se usó la prueba de U de Mann Whitney con un nivel de significancia de $p < 0.05$. El comportamiento del crecimiento en los pacientes sin DO presenta una tendencia a la verticalidad. A los 4, 5, 6 y 12 años el crecimiento fue vertical, mientras que a los 7 años un paciente mostró tendencia a la normalidad y a los 8 años el crecimiento fue horizontal. El comportamiento del maxilar en su crecimiento fue con tendencia vertical, manifestándose con supraoclusión y retrusión en el 80% de los casos. El patrón esquelético que predominó fue de clase II, encontrándose alterada el valor de la profundidad facial (Po-Or/N-Pg) debajo de la norma en los 10 casos estudiados. Los pacientes con SPR no sometidos a DO, se encuentran por debajo de los límites establecidos por las normas cefalométricas.

Key words: Pierre Robin sequence, craniofacial growth, cephalometric tracings, cephalometric measurements, osteogenic distraction.
Palabras clave: Secuencia de Pierre Robin, crecimiento craneofacial, cefalometría, distracción osteogénica.

INTRODUCTION

Pierre Robin Sequence is an embryological disturbance involving first and second branchial arches. It favors the development of mandibular deficiencies, which, as a result, secondarily causes the development of cleft palate.

HISTORY

Shukowsky first described PRS in 1911. Nevertheless, it was not until 1923 when Dr Pierre Robin reported the obstruction of airway accompanied by

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glossoptosis and mandibular hypoplasia, which he named Pierre Robin syndrome. Several authors, Cohen in 1981, Spranger 1982 and Jones, 1985, concurred in naming this growth alteration Pierre Robin Sequence (PRS), due to the manifestation of several defects, occurring simultaneously which derive from the primitive malformation: micrognathia, glossoptosis and cleft palate. In the newborn, these alterations are associated with respiratory disorders. Some of the congenital defects associated with this condition are: laryngomalacia, congenital heart disease, anomalies in ear defects, microcephaly, hydrocephaly and eye alterations.[1]

ETIOLOGY AND GENETICS

The theory has been proposed that the position of the tongue is the agent responsible for palate alterations hindering palatine processes fusion.[2,3] There is existing controversy with respect to micrognatia etiology and genetics. Deskalogiannakis, in 2001, mentioned the compressive theory (mechanical or positional) in which micrognathia is the result of an «in uterus» compression of the lower jaw against the sternum, a situation possibly associated to oligohydramnios.[4,5]

Duplication of the 2q chromosome has been found in PRS cases. FISH and cytogenetic analysis point out to duplication of chromosome 2q13-q22. According with Ounap´s (2005) study[6,7] conducted on patients afflicted with oral and facial clefts, it was demonstrated that the cause of these clefts was found in the locus of the 2q chromosome, and that the presence of gene overexpression in the chromosome 2q13-q21 could be the causal agent of cleft lip in PRS cases. In 2005, Johansen[8] published a study where he mentioned that in PRS a genetic base had been identified in the loci 2q24 1- 33.3, 4q32 –qter, 11q21-23.1 and 17q21 – 24.3. He in turn reported the existence of PRS identified genes: GAD67 in 2q31 gene, PVRL1 in11q23-q24 gene, and SOX9 in 17q24.3-q 25.1 gene.[6]

PRS AND CRANIOFACIAL GROWTH

PRS appears as a result of an abnormal development of the upper jaw before the fetus reaches 9 weeks of gestational age. Any changes taking place in the craniofacial complex bring repercussions in other sites of the same location which cannot be isolated. Dr Enlow referred it as a system of parts and counterparts; that is to say, when the lower jaw is affected, it produces a deficit in the upper jaw growth which in turn, predisposes to the development of upper and lower jaw rotations. These rotations bring as a consequence growth alterations in nearby sites, like the naso-maxillary structures, or the orbital structures to mention but a few.

During the first few months of age, the growth of the lower jaw corrects glossoptosis and growth continues in a compensatory fashion.[9] Herman in 2003[1] reported that in cases of non-syndromic PRS newborn subjects, craniofacial morphology and growth decreased during the two first years of life. He mentioned as well that neither glossoptosis nor cleft palate were present in all degrees of PRS expression. These facts must be taken into account when analyzing craniofacial growth in these patients.

PREVALENCE

Prevalence is found in one out of 8,500 newborn. Reported mortality is 5 to 30%.[4]

AIRWAY

PRS respiratory problems can be crucial for the prognosis, treatment and quality of life of affected children. This obstruction can be caused by many factors, it can especially be related to the micrognatia degree, which causes a posterior position of the base of the tongue, and therefore, obstruction of the retropharyngeal space. This is related to a decrease in size of the genioglossus muscle which then allows the tongue to place itself in a posterior position. In more severe cases, difficulties in feeding might be present. These might bring as a consequence vomiting or bronchial aspiration. In cases of persistence, this obstruction can cause edema or lymphatic organ hyperthophy, infection of upper airways as well as tendency of collapse in the oropharynx, and neurological endangerment due to constant hypoxia, and consequently, the death of the patient.[10]

TREATMENT

The type of treatment will depend on the severity of airway obstruction. This can be assessed when observing the child s behavior when crying, eating and sleeping. In most cases, discomfort can be controlled by placing the newborn in prone position until the improvement of the problem which should occur at 3 to 6 months of age.[10,11]

According to PRS expressiveness, growth control can be contemplated in cases where airways are not endangered. In more severe cases, other measures will have to be resorted to: oxygen saturation levels monitoring, temporary nasopharyngeal intubation, or placement of endotracheal tube. In severe cases, tracheostomy might be required.

Mandibular osteogenic distraction (OD) is a treatment alternative for PRS patients, with critical obstructive apnea secondary to mandibular hypoplasia.[12]

OD is a biological procedure implemented by Dr Gabriel Ilizarov in 1954, whereby, through the slow and progressive separation of two bone segments, new bone is generated between both, thus resulting in their elongation. With OD all tissues are elongated. This process includes periosteum, vessels, nerves, ligaments, muscle, mucosa and skin coverage.[13]

In 1954, Dr Samuel Prusanzky conducted a longitudinal study on growth in children with retrognathic mandible associated to PRS. In that study, he reached the conclusion that mandibular growth, given time, is proportionately adequate to improve retrognathic profile and provide better facial aesthetics[(5).] Figueroa, in 1991[14] conducted a follow-up on 17 non operated PRS patients. The study encompassed ages ranking from 3 months to two years of age. Patients were compared with normal control subjects as well as with cleft palate patients. The author concluded that PRS patients showed partial growth potential which never reached normal levels.

In 2001, Deskalogiannakis[4] concurred with Figueroa[14] when comparing lateral cephalometries taken from a group of PRS patients and concluded that PRS patients presented higher degree of micrognathia than patients afflicted with cleft palate solely.

Hayakawa, in 2005[15] conducted a study on mandibular growth in PRS patients subjected to mandibular OD. He found that facial characteristics and dimensions in these patients subjected to mandibular distension are slightly under standard values.

APPROACH OF THE PROBLEM

The question arises about whether there is compensatory craniofacial growth in PRS patients not subjected to OD which could be compared to established cephalometric standards.

JUSTIFICATION

Current treatment of PRS patients bears as a reference point the severity of respiratory alterations. In severe cases, treatment of choice is osteogenic distraction. Its aim is the correction of the obstructive problem, increased size and mandibular position, which in turn causes changes in the position of the tongue thus facilitating swallowing and respiration. PRS patients who do not present respiratory problems and are thus not candidates for early osteogenic distraction, show a partial compensatory growth in the upper and lower jaw structures. It is yet unknown whether this growth is similar or not to growth achieved through distraction. The aim of this study was to ascertain the behavior of the aforementioned growth and establish a comparative parameter with established cephalometric standards.

OBJECTIVE

Determination of craniofacial structures compensatory growth in PRS patients not subjected to OD.

ETHICAL CONSIDERATIONS

All procedures complied with Rulings of the General Health Law on the Matter of Health Research (Reglamento de la Ley General de Salud en Materia de Investigación para la Salud) Title 2, Chapter I, Article 17, Section I. Research devoid of risk, does not require informed consent.

METHODS

The design of the study was descriptive, open, observational and retrospective. The study group was composed by PRS patient files. Patients were male and female, ranking from 4 to 12 years of age. Patients were required to present the following characteristics: possess cranial lateral radiographs, and not be candidates to OD. Files were gathered from the Clinical Archive of the Stomatological-Orthodontic Division of the General Hospital Manuel Gea González, during the period spanning from 1990 to December 2006.

The sample was sequentially selected among all files of patients presenting PRS who were not subjected to OD. The former was calculated based on a 5 mm difference among groups, alpha 0.05 and 95% test potency. According to the statistical test we had a total of n = 6 cases, nevertheless, cases were increased to ten with the aim of presenting craniofacial growth behavior.

INCLUSION CRITERIA

PRS patients files. Patients were selected from a 4-12 years rank, not subjected to OD, and with radiographic records (lateral x-rays of the skull). Patients were of both genders and could not be afflicted with cleft palate.

EXCLUSION CRITERIA

PRS patients who did not possess clear lateral skull radiographic records, as well as patients afflicted with cleft palate. PRS patients with completed craniofacial growth were excluded, as well as files of patients who no longer attended consultation at the Stomatological-Orthodontic Division.

On the lateral skull radiographs, the main researcher traced each one of the radiographs, after having consulted with other examiners. This was conducted following the Kappa test. Cephalometric analysis measurements of: Harvold. Ricketts, Riedel and Jarabak were included, since they were applicable to subjects experiencing growth in ages ranking 5-20 years. Measurements thus obtained were compiled in a data sheet for analysis, graphic expression and presentation of results.

Inferential and descriptive statistics were applied, which determined the degree of study reliability and validity.

Descriptive statistics were used, with central tendency and dispersion measurements, rank, median, mode, standard deviation, proportions or percentages.

Non parametric statistics with Mann Whitney U test were used. Significance level to reject the null hypothesis was $P < 0.05$.

The following cephalometric variables were measured:

MEASUREMENTS OF THE UPPER JAW

From Ricketts` s analysis: Lower facial height (Ena-XiPm), facial depth (Po-Or/N-Pg) facial axis (Ba-Na/PgG), maxillary height (N-Cf-A), cranial deflection (Ba-Na/Po-Or).

From Riedel s analysis: SNA angle

From Jarabaks analysis Sella angle (N-S-Ar), posterior facial height (S-Go), anterior facial height (N-Pl.Man).

MEASUREMENTS OF THE LOWER JAW

Measurements from **Riolo analysis** were selected. To measure the degree of mandibular rotation the SNB angle was applied. To measure mandibular length (Co-Gn) was used and distance (Co-Pg). Ramus growth was measured with the variable Co-Go, Co-Me, Co-B were also measured. To measure mandibular body growth the following were used: Go-Id, Go-B, Go-Pg, Go-Gn. To measure the distance of the symphysis measure Me-Id was applied.

Total growth percentages were determined according to Jarabak.

RESULTS

The prevailing growth pattern was vertical in 7 out of the 10 studied cases. At ages 4, 5, 6 and 12 years, growth presented a vertical behavior, while at 7 years of age, one patient presented tendency to normal growth, and in this patient, at 8 years of age, the tendency shifted to horizontal growth. When considering gender, male patients presented higher tendency to vertical growth (75%) as compared with female patients (67%). Female patients presented 33.3% tendency to growth within the ranges of normal standards.

MEASUREMENTS OF THE UPPER JAW

Out of 100 measurements, 6% were found to be within normal standards, 47% below standard. And 47 above standard *(Figure 1)*.

MEASUREMENTS OF THE LOWER JAW

Out of 120 measurements, 94.16% were found to be below cephalometric standard, and 5.84% above standard *(Figure 2)*.

Due to the reduced size of the sample, data were not significant except for the following variables: SNA, S-Ar-Go, S-Go and SNB, Go-Id, Me-Id with $p < 0.05$.

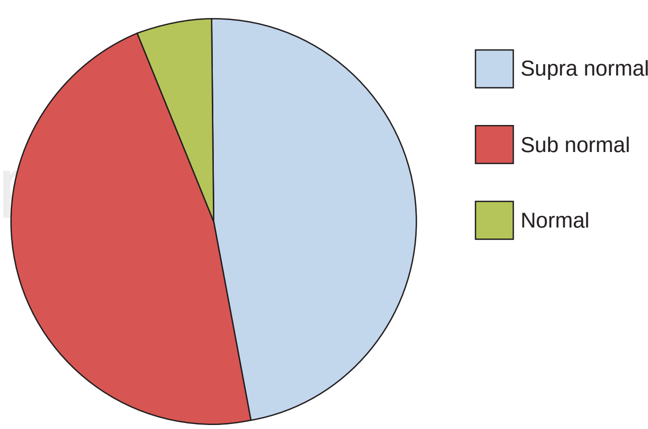

Figure 1. Percentile distribution of upper jaw measurements according to cephalometric standards.

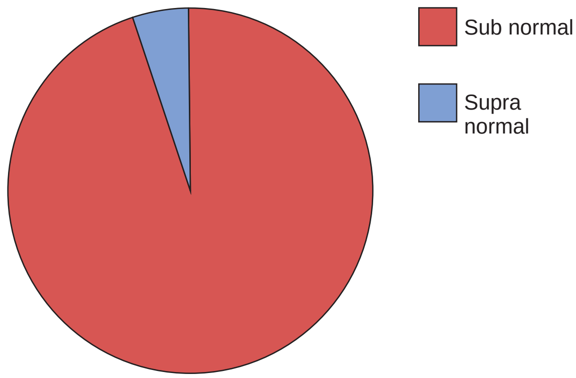

Figure 2. Percentile distribution of lower jaw measurements according to cephalometric standards.

Percentile values obtained from Rickets, Riedel and Jarabak analyses were graphically observed, as well as Riolo analysis values applied to the lower jaw *(Figures 3, 4, 5, 6, 7 and 8)*.

Values obtained for rank, average, and standard deviation are shown in detail in the tables of cephalometric values differences in upper and lower jaws *(Tables I to VI)*.

DISCUSSION

In published studies on craniofacial growth in non operated PRS patients, most authors use mandibular growth behavior as a basis, isolating growth of the lower jaw. The present study incorporated cephalometric values which allowed us to correlate the behavior of

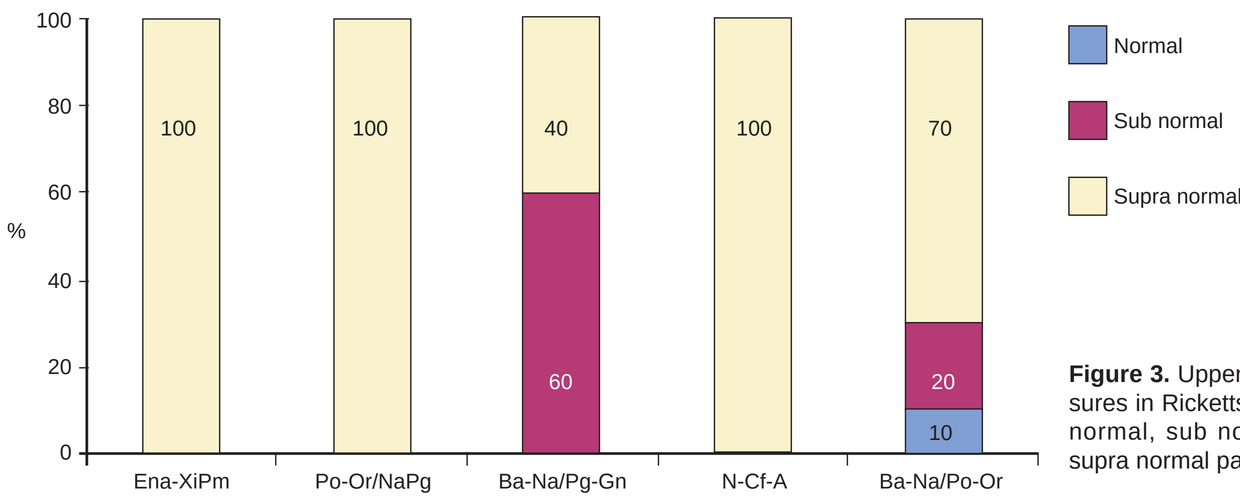

Figure 3. Upper jaw measures in Ricketts analysis: normal, sub normal and supra normal patterns.

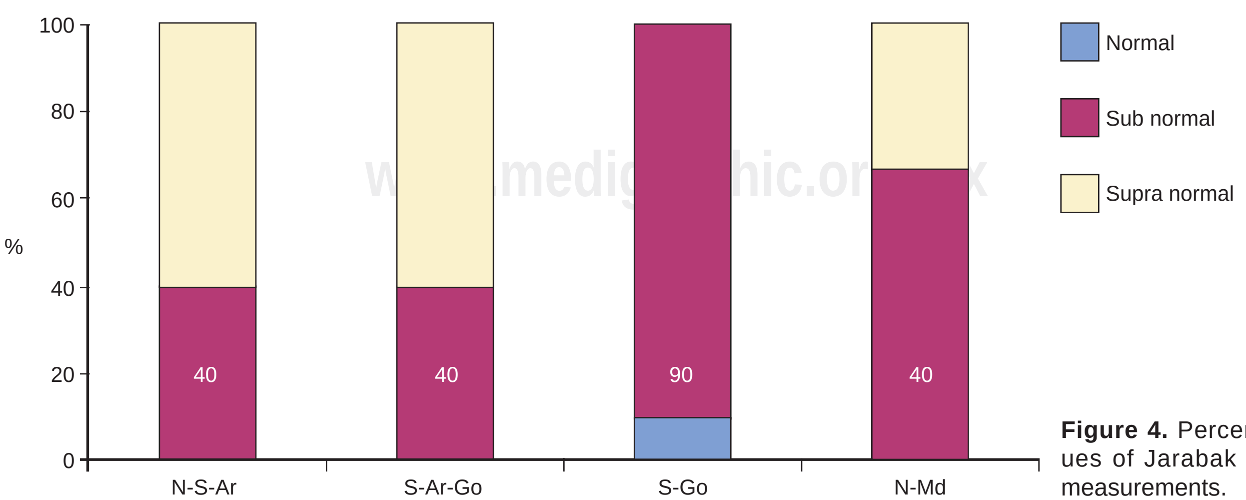

Figure 4. Percentile values of Jarabak analysis measurements.

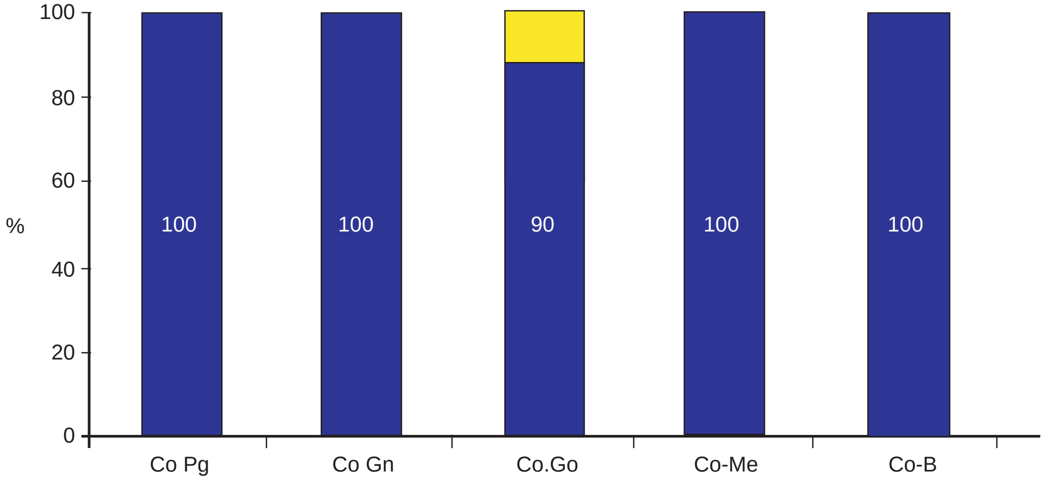

Figure 5. Percentile representation of Co Pg, Co-Gn, Co-Go, Co-Me, Co-B; normal, subnormal and supranormal patterns.

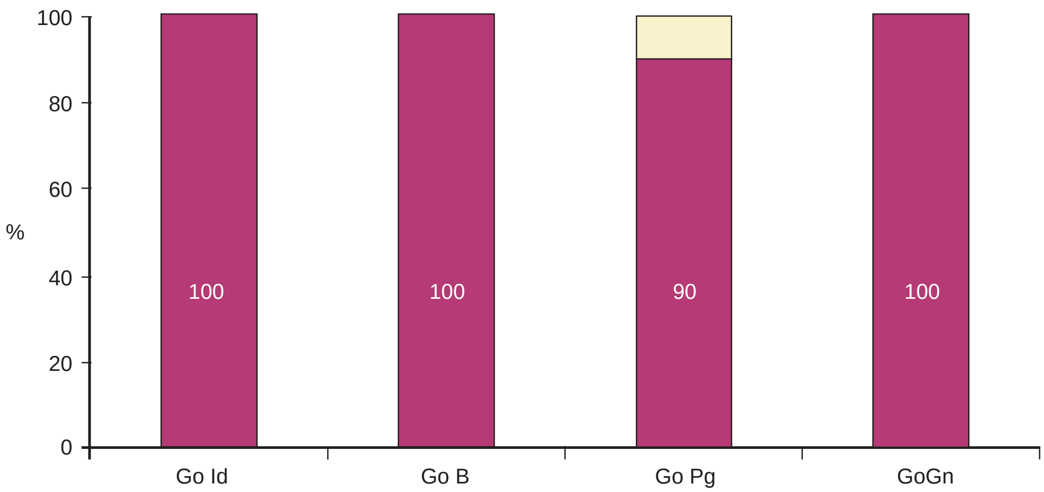

Figure 6. Percentile representation of Go Id, Go-B, Go-Pg, Go-Gn; normal, subnormal and supranormal patterns.

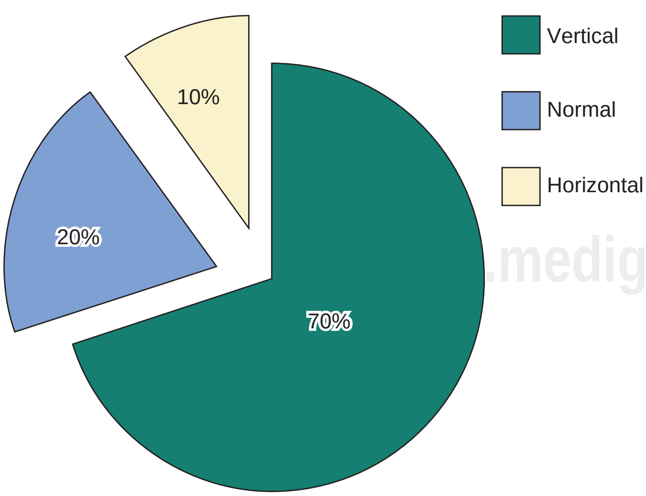

Figure 7. Percentile distribution of craniofacial growth in PRS patients not subjected to OD.

this growth, taking reference points from the skull and upper and lower jaws.

It was found that growth behavior in PRS patients not subjected to OD presented tendency towards verticality, this concurs with what Hermann[1] reported in 2003, in non operated patients. In 80% of cases, the upper jaw presented supra occlusion and tendency to retrognathia. Posterior facial height was found to be decreased. This concurred with the 1991 findings of Hermann[1] and Figueroa[14] which observed limited upper and lower jaw growth in PRS, non operated patients.

Patients in our study presented flat cranial base in 70% of cases, as mentioned by Hermann in 2003[1] who referred that, PRS non operated patients presented differences in cranial base morphology and length, with a tendency of cranial base. This fact can be correlated to the greatly divergent growth patterns found in our study.

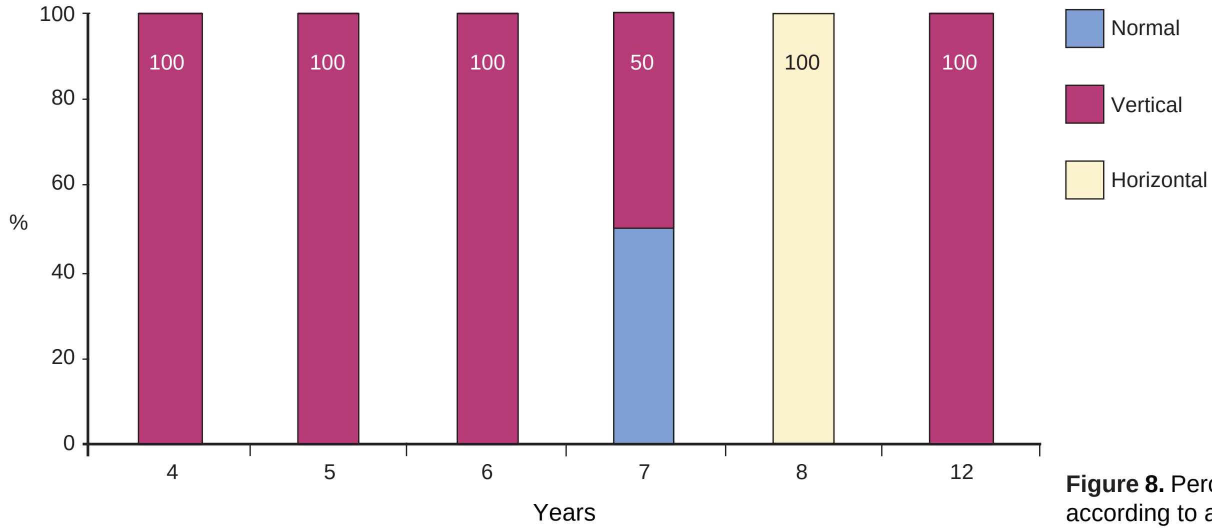

Figure 8. Percentile growth according to age.

Table I. Results of upper jaw measurements in each Rx traced.

Cephalometric measurement	Norm	PX 1	PX 2	PX 3	PX 4	PX 5	PX 6	PX 7	PX 8	PX 9	PX 10
Ena–XiPm Ricketts	47°	55°	54	63	57	55	57	51	60	58	55
Po-Or/N-Pg	87°	82°	79	75	77	72	77	77	79	73	73
Ba-Na/Pg Gn	90°	75°	86	75	74	94	78	100	72	98	100
N-Cf-A	53°	58°	61	56	63	62	62	65	62	60	55
Ba-Na/Po-Or	27°	36°	30	28	28	19	32	27	30	22	28
SNA Riedel	82°	80°	66	72	68	74	79	101	72	75	84
N-S-Ar Jarabak	123°	126°	120	140	120	120	130	127	128	130	122
S-Ar-Go	143°	145°	145	135	150	130	120	153	145	140	145
S-Go	70 – 85 mm	55	57	57	60	66	77	66	65	63	49
N-Me	105 – 120 mm	103	103	109	105	110	122	122	120	102	89

Table II. Central tendency measures in every upper jaw measurement.

Cephalometric measure	Average	Mean	DS	Mode	Median	Maximum	Minimum
Ena–XiPm Ricketts	53.0	52.96	2.82	55	56.0	63	51
Po-Or/N-Pg	74.5	74.45	3.53	77	77.0	79	72
Ba-Na/Pg Gn	97.0	96.95	4.24	100	82.0	100	72
N-Cf-A	63.5	63.48	2.12	62	61.5	65	55
Ba-Na/Po-Or	23.0	22.64	5.65	28	28.0	32	19
SNA Riedel	87.5	86.45	19.09	72	74.5	101	66
N-S-Ar Jarabak	63.0	63.00	0.00	120	126.5	140	120
S-Ar-Go	123.5	123.45	4.94	145	145.0	153	120
S-Go	141.5	141.03	16.26	66	61.5	77	49
N-Me	66.0	66.00	0.00	122	107.0	122	89

Table III. Statistical test values in upper jaw variables.

Cephalometric measure	P Value
Ena-XiPm Ricketts	0.157
Po-Or/N-Pg	0.370
Ba-Na/Pg Gn	0.857
N-Cf-A	0.598
Ba-Na/Po-Or	0.000
SNA Riedel	-0.240
N-S-Ar Jarabak	0.240
S-Ar-Go	-0.140
S-Go	0.010**
N-Me	-0.650

Pruzansky, mentioned by Figueroa in 2000[9] refers in PRS patients, the presence of a mandibular partial compensatory growth, which corrected micrognatia. This compensatory growth continues and becomes evident when patients reach the 4-6 year age bracket. This can then be correlated to findings of our study in a female patient of the sample, who presented tendency to normal growth at 7 years of age.

In lower jaw measurements we found differences with respect to the study conducted by Hayakawa[15] in 2005, in patients subjected to OD. In our sample, it was found that in all 10 cases SNB measurement was found to be below the standards as well as S-N-Pg.

Table IV. Results of lower jaw measurements for each Rx traced.

Cephalometric measure	Norm	PX 1	PX 2	PX 3	PX 4	PX 5	PX 6	PX 7	PX 8	PX 9	PX 10
SNB	76.6	66.0	65.0	62	68	75	71.0	71	67	68	65
S-N-Pg	76.0	67.5	64.5	60	67	74	72.5	70	66	66	63
Co-B	94.8	77.0	76.0	82	85	92	96.0	104	100	85	71
Co-Pg	101.8	83.0	80.0	87	91	98	105.0	108	102	88	74
Co-Gn	103.0	84.0	80.0	89	93	99	107.0	112	115	90	76
Co-Me	99.4	79.0	75.0	81	88	90	100.0	109	103	79	64
Co-Go	48.7	41.0	32.0	45	51	42	54.0	53	44	40	35
Go-Id	67.5	59.0	56.0	58	44	68	73.0	68	66	28	46
Go-B	64.5	51.0	54.0	59	50	65	65.0	70	66	55	44
Go-Pg	66.1	54.0	56.0	57	52	69	71.0	73	69	56	45
Go-Gn	65.4	52.0	57.0	53	53	65	68.0	74	64	58	48
Me-Id	28.5	33.0	32.0	35	27	35	24.0	32	31	28	25

Table V. Central tendency measures for each of the lower jaw measurements.

Cephalometric measure	Average	Mean	DS	Mean	Mode	Maximum	Minimum
SNB	67.8	67.70	3.73	65	67.5	75	62
S-N-Pg	67.0	66.92	4.23	66	66.5	74	60
Co-B	86.8	86.18	10.92	85	85.0	104	71
Co-Pg	91.6	90.96	11.30		89.5	108	74
Co-Gn	94.5	93.65	13.41		91.5	115	76
Co-Me	86.8	85.78	13.96	79	84.5	109	64
Co-Go	43.7	43.13	7.33	0	43.0	54	32
Go-Id	56.6	54.74	13.80	68	58.5	73	28
Go-B	57.9	57.33	8.43	65	57.0	70	44
Go-Pg	60.2	59.51	9.53	56	56.5	73	45
Go-Gn	59.2	58.69	8.25	53	57.5	74	48
Me-Id	30.2	29.95	3.96	32	31.5	35	24

Table VI. Statistical test values for lower jaw variables.

Cephalometric measure	P Value
SNB	*-0.110
S-N-Pg	0.960
Co-B	0.190
Co-Pg	0.350
Co-Gn	0.430
Co-Me	0.320
Co-Go	0.210
Go-Id	-0.009**
Go-B	0.305
Go-Pg	0.330
Go-Gn	0.449
Me-Id	-0.630

Mandibular length Co-Po distances were found to be beneath established cephalometric standards, in this, our study did not concur with Hayakawa[15] who reported 56% for Co-Gn and 55% for Co-Po.

In both cases we concur with Figueroa,[14] Hermann[1] and Daskalogiannakis[4] since we found a decrease in mandibular proportions in non operated patients.

CONCLUSIONS

PRS patients not subjected to OD are found to be below limits established by cephalometric standards. They report a 94.16% growth deficit in lower jaw proportions. Patients in our study showed the following:

- 70% tendency to vertical growth
- At ages 4, 5, 6 and 12 years, growth presented vertical behavior. Meanwhile, at age 7 years one patient of the studied sample showed tendency to normal growth, and at 8 years of age in this same patient, tendency was shown to shift towards horizontal growth.
- According to gender, male subjects presented higher tendency towards vertical growth (75%) while 67% of female patients cases presented the aforementioned tendency.
- 33% of female patients cases presented tendency to growth found to be within normal standards.
- Behavior of growth in the upper jaw showed tendency to vertical excess. This was manifested in 80% of studied cases with supra occlusion and retrusion.
- Angle C II was the predominant skeletal pattern encountered in the studied sample. This fact is confirmed by a 100% alteration below cephalometric standards found in the facial depth variable (Po-Or/N-pg).

The relationship between anterior and middle cranial base was reflected by a 70% predominance of flat cranial base in 70% of cases and posterior glenoid fossa.

These results confirm Dr Enlow´s craniofacial growth and development concepts, which state that any repercussion of growth cannot be isolated and involves a system of parts and counterparts, which, under the influence of growth spurts and functional matrix define the final growth model. As mentioned by Dr Moss, function describes form.

It is proposed that although there is compensatory mandibular growth in PRS patients, it is limited and below results obtained by osteogenic distraction. Nevertheless, in these patients, early treatment based on myofunctional orthopedics must not be discarded. The treatment would have as first aim to perform mandibular propulsion, and at a later point to re-program the position of muscles and tongue. All this would be performed by taking advantage of the growth potential as well as favoring mandibular growth as much as possible. This, in turn would result into the growth of craniofacial structures. It is equally proposed to follow-up on the growth of these patients with the assistance of a longitudinal study which would allow us to continue with our research in PRS patient not subjected to OD.

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