UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

RAYANE DE OLIVEIRA PINTO

Evaluation of facial profile and airway in individuals with Richieiri-Costa-Pereira syndrome

Avaliação do perfil facial e vias aéreas em indivíduos com a síndrome de Richieri-Costa-Pereira

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Dissertação constituída por artigo apresentada ao Hospital de Reabilitação em Anomalias Craniofaciais da Universidade de São Paulo para obtenção do título de Mestre em Ciências da Reabilitação, na área de concentração Fissuras Orofaciais e Anomalias Relacionadas.

Orientador: Drª. Gisele da Silva Dalben.

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HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

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Rayane de Oliveira Pinto

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“Mas na profissão, além de amar tem de saber.

E o saber leva tempo pra crescer.”

Rubem Alves

ABSTRACT

ABSTRACT

Evaluation of facial profile and airway in individuals with Richieri-Costa-Pereira Syndrome

The Richieri-Costa Pereira Syndrome (RCPS) is an autosomal recessive acrofacial dysostosis characterized by mandibular cleft comprising other craniofacial anomalies as limb defects, Robin Sequence, microstomia, absence of mandibular central incisors, minor ear anomalies, clubfeet and learning disability. This present study was designed to compare cephalometric measurements between 9 individuals with RCPS and 9 controls, matched for gender and age and was conducted at the Hospital for Rehabilitation of Craniofacial Anomalies at the University of São Paulo, Bauru, Brazil. Lateral cephalometrics were used to assess craniofacial and airway linear and angular measurements. In statistical analysis were used t test for analysis of means and Levene's equality of variances. The syndrome group presented severe mandibular hypoplasia and retrognathism, and greater facial convexity, compared with the control group. No statistical differences were detected in airway dimensions The focus of this article was to assess and describe the craniofacial morphology in RCPS, aiming to improve the diagnosis and elaboration of treatment plan in order to keep individuals with RCPS healthy and socially integrated.

Key-words: dysostoses, craniofacial abnormalities, cephalometry.

Resumo

RESUMO

Avaliação do perfil facial e vias aéreas em indivíduos com a Síndrome de Richieri-Costa-Pereira

A Síndrome de Richieri-Costa Pereira (SRCP) é uma disostose autossômica acrofacial caracterizada pela fissura mandibular e pode estar associada a outras anomalias craniofaciais como defeitos nos membros, Sequência de Robin, microstomia, ausência de incisivos inferiores, anomalias de orelha menor, pés tortos e dificuldades de aprendizado. O objetivo deste estudo foi comparar as medidas cefalométricas de 9 indivíduos com SRCP e 9 controles pareados em gênero e número. Este estudo transversal restrospectivo foi conduzido no Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo, Bauru, Brasil. Foram utilizadas radiografias cefalométricas em norma lateral, as quais foram digitalizadas e analizadas em um software para obtenção de medidas angulares e lineares. Foram aplicados na análise estatística o teste t e teste de Levene's para igualdade de variâncias. O grupo sindrômico apresentou severa hipoplasia e retro gnatismo mandibular e convexidade facial aumentada, comparados ao grupo controle. Não foram detectadas diferenças estatísticas nas dimensões de vias aéreas. O foco deste trabalho foi acessar e descrever a morfologia craniofacial de pacientes com SRCP, com o objetivo de melhorar as condições de diagnóstico e elaboração de plano de tratamento para que estes indivíduos permaneçam saudáveis e integrados socialmente.

Descritores: disostoses, anormalidades craniofaciais, cefalometria.

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1 Introduction

1 INTRODUCTION

The Richieri-Costa-Pereira syndrome (RCPS) is an acrofacial dysostosis that comprises median mandibular cleft, Robin sequence, laryngeal alterations, tibia and radius disorders associated with clubfeet. It is a rare syndrome with autosomal recessive inheritance. The main clinical findings include short stature, pre- and postaxial hand anomalies, hypodontia of mandibular central incisors, laryngeal abnormalities and minor ear malformations. Language and learning disabilities are also reported in more than 50% of affected individuals (FAVARO FP et al., 2011).

The RCPS was first described in Brazil in 1992 (RICHIERI-COSTA -PEREIRA 1992, OMIM 2004) and was reported in individuals living in a restricted area in the state of São Paulo.

Since the reports occurred in a restricted region, the authors suggested that it would be a rare mutation with a common founder effect (RICHIERI-COSTA, PEREIRA., 1993). However, an isolated report was published outside Brazil (WALTER-NICOLET et al., 1999).

Currently, there are 32 reported cases in Brazil (RASKIN S et al., 1999). A published study on 28 cases revealed as common factor the cities of birth of these individuals, being that 19 out of 25 families investigated were from the “Vale do Ribeira”, an old and isolated rural region in the state of São Paulo. Consanguinity was observed in 11 families, and recurrence among siblings and cousins occurred in 9 investigated families. The phenotype could be assigned to an autosomal recessive gene; a rare mutation with common founder effect, and the case reported outside Brazil would be an isolated mutation, without correlation with Brazilian cases (FAVARO FP et al., 2011).

Aiming to understand the etiology of the syndrome, 497 polymorphic markers were assessed by linkage analysis with direct sequencing of exons for 10 candidate genes. No evidence of shared alleles or mutation loci were found (FERREIRA DE LIMA RL et al., 2003).

The most recent study of Favaro et al detected that the etiology of RCPS is related with mutations in the EIF4A3 gene, which is involved in RNA metabolism and plays a role in the morphogenesis of structures affected in the syndrome: mandible, larynx and limbs (FAVARO FP et al., 2014).

Some studies were conducted to map the phenotype of RCPS. In the study of Severini JM et al. (2012) on panoramic radiographs, the authors observed high prevalence of hypodontia, especially at the region of mandibular incisors and premolars. The prevalence of hypodontia was high, as well as the frequency of enamel opacities.

It should be highlighted that one of the alterations found in RCPS is the Robin sequence (RS), which is described in the literature as a triad of anomalies characterized by micrognathia, glossoptosis, with or without cleft palate (ELLIOTT MA et.,1995).

In the neonatal period, there commonly is respiratory and feeding difficulties in individuals with these characteristics (FIGUEROA et al., 1991). Several treatment options are described in the literature to enhance the deficient respiratory pattern: postural treatment (the child is placed in prone positioning), nasopharyngeal intubation, glossopexia, tracheostomy and mandibular distraction (MARQUES IL et al 2001). The clinical observation of gradual improvement in breathing, combined with cephalometric reports, provide support to the concept of mandibular catch-up growth in individuals with RS, reaching cephalometric values close to normality (DASKALOGIANNAKIS et al 2001), yet this concept is still controversial in the literature (MACKAY DR, 2011).

There are no scientific evidences in the literature that individuals with RCPS may present mandibular catch-up growth with age, alike individuals with RS.

In 1996, Tabith and Bento-Gonçalves described 5 individuals (TABITH E BENTO-GONÇALVES et al., 1996), and 2 individuals in 2003 (TABITH E BENTO-GONÇALVES et al., 2003), aiming to analyze the laryngeal alterations in individuals with RCPS. The study was conducted using nasolaryngoscopy and achieved similar outcomes in both studies: reduced laryngeal space, absence or hypoplastic epiglottis, hypertrophic arytenoids and aryepiglottic folds, and a fold in the posterior

laryngeal region, above the glottal level. The study also detected voice alterations as marked coarseness and soprosity. Miguel et al. (2012) analyzed 17 cases using the same methodology of previous study and demonstrated the same defects.

However, no studies have conducted on cephalometric analysis of the head and airway in individuals with RCPS, quantifying the malformations as compared to normal individuals. Therefore, this study aims to broaden the investigation on these aspects, to enhance the treatment of these individuals and provide better knowledge on their alterations.

2 Objectives

2 OBJECTIVES

To evaluate the cephalometric characteristics of individuals with Richieri-Costa-Pereira Syndrome (SRCP) on lateral cephalograms obtained from the files of the Radiology Sector of HRAC / USP, compared to a control group without morphofunctional alterations, matched for gender and age.

Overall objective

To numerically define the craniofacial characteristics of individuals with SRCP by variables obtained from cephalometric analyses created for this purpose.

Specific objectives

The specific objectives of the present research will be to test the following hypotheses (H0):

1- The craniofacial morphology of individuals with Richieri-Costa-Pereira Syndrome does not present measurements with statistically significant differences compared to the control group;
2- Individuals with Richieri-Costa-Pereira Syndrome present similar airway morphology as the control group;

3 Article

3 ARTICLE

The article presented in this Dissertation was written according to the Journal of Oral and Maxillofacial Pathology instructions and guidelines for article submission (Annex A).

Title of the article: Evaluation of the maxillofacial morphological characteristics of Richieri-Costa-Pereira Syndrome

Abstract:

Context: The Richieri-Costa Pereira Syndrome (RCPS) is an autosomal recessive acrofacial dysostosis characterized by mandibular cleft comprising other craniofacial anomalies as limb defects, Robin Sequence, microstomia, absence of mandibular central incisors, minor ear anomalies, clubfeet and learning disability.
Aims: To compare cephalometric measurements between 9 individuals with RCPS and 9 controls, matched for gender and age.
Settings and Design: This retrospective cross-sectional study was conducted at the Hospital for Rehabilitation of Craniofacial Anomalies at the University of São Paulo, Bauru, Brazil.
Methods and Material: The study was conducted on lateral cephalograms that were digitized and then analyzed on a software to obtain the linear and angular mesurements.
Statistical analysis used: t test for analysis of means and Levene's equality of variances.
Results: The syndrome group presented severe mandibular hypoplasia and retrognathism, and greater facial convexity, hyoid bone is below and antero-positioned in syndrome group compared with the control group.
Conclusions: The focus of this article was to assess and describe the craniofacial morphology in RCPS, aiming to improve the diagnosis and elabotation of treatment plan, in order to keep individuals with RCPS healthy and socially integrated.

Key-words: dysostoses, craniofacial abnormalities, cephalometry.

Introduction:

The Richieri-Costa-Pereira syndrome (RCPS, OMIM 268305) was first described by Richieri Costa and Pereira in 1992 as a new syndrome of acrofacial dysostosis, and the related studies showed characteristics of both autosomal and recessive inheritances [1,2,3,4,5]. The main clinical features are short stature, cleft mandible, retromicrognathia with absence of mandibular incisors and limb defects [5].

RCPS may exhibit the triad of Pierre Robin Sequence (PRS) (retrognathia, glossoptosis, with or without overt or submucous cleft palate), high-arched palate, prominent nose, minor ear anomalies, microstomia and hypoplastic mandible[1,2,5].

Although a wide spectrum of phenotypes can be expressed, including as clinical signs alterations in the larynx (short and round larynx, absent or hypoplastic epiglottis, hypertrophy of arytenoids, aryepiglottic folds and voice alterations)[5] and limbs (hypoplastic thumbs and radius and distal part of the tibias, proximal and lateral displacement of the fibulas, clubfoot, clinodactyly of the fifth digit and hypoplastic hand bones). Learning and language disabilities were also prevalent, reported in more than 50% of affected individuals[6].

Among the 34 RCPS cases described in the literature, 33 are Brazilians [1,2,3,5,6,7,8,9,10,11,12] and one is French [13], which raised the possibility of a common ancestry [6].

The most recent attempt to identify the causative gene of this syndrome performed homozygosity mapping including 7 syndromic individuals from 4 consanguíneos families from Brazil and found the only extended region of homozygosity at chromosome 17q25.3. The results suggested that RCPS is caused by mutations in EIF4A3 gene and showed that this gene is involved in RNA metabolism and affects the mandible, larynx and limb morphogenesis [14].

A study revealed occurrence of dental anomalies in 100% of individuals analyzed, ranging from 4 to 22 dental anomalies per individual, especially hypodontia of mandibular incisors and premolars and enamel opacities [15].

The literature on craniofacial morphology in RCPS is limited to anatomical descriptions, with emphasis to the severe retromicrognathia.

The literature addressing the skeletal morphology in non-syndromic PRS reports shorter posterior cranial base, proportionate retrusion of the maxilla and mandible, shorter mandibular length, resulting in convex facial profile [16]. However, this

craniofacial evaluation on individuals with RCPS has never been described and remains unclear. The aim of this retrospective study was to evaluate the maxillofacial morphological characteristics in individuals with diagnosis of RCPS. For this purpose, children with RCPS were compared with a control group matched for age and gender.

Subjects and Methods:

This retrospective study was conducted at the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC-USP), Bauru, Brazil. The study was approved by the Institutional Review Board, according to the Brazilian Health Ministry no. 196/96 resolution. Informed consent was obtained from at least one parent or legal caretaker.

All individuals were Caucasoid, descendants of Brazilian parents and grandparents, and none had undergone craniofacial trauma or surgery, orthodontic procedures, or hormonal growth therapy.

Molecular genetic analysis was not applied in these individuals, thus sample selection was based on clinical evaluation of this syndrome, based in cardinal characteristics as the presence of cleft mandible and limb defects as mandatory factors for investigation of more anomalies, which together characterize the complete diagnosis.

Individuals with clinical diagnosis of Richieri-Costa Pereira Syndrome were first identified by a search on the Hospital database in June 2016, to retrieve the number of affected individuals.

Until study onset, 33 individuals were registered on the database. The exclusion criteria were unavailability of lateral cephalograms (17 individuals); death (2 individuals); individuals younger than 6 years (2 individuals); individuals for whom lateral cephalograms were not available (17 individuals); previous craniofacial surgical treatment (2 individuals); clinical diagnosis not confirmed by the Genetics sector (1 individual). Thus, the study included 9 individuals (Table 1) with mean age 10 years and 3 months (range: 8 years and 1 month to 13 years and 2 months) with lateral cephalograms available at the files of HRAC-USP.

The control group comprised 9 subjects with mean age 10 years and 6 months (range: 8 years and 1 month to 13 years and 7 months) and who had available cephalograms. This group presented Class I malocclusion in mixed or young permanent dentition and well-balanced faces on frontal and lateral photograph analysis. This group of non-syndromic individuals were retrospectively selected, matched for gender and age to the syndrome group, from a partner Institution (Sociedade de Promoção Labial do Fissurado Labio-Palatal (PROFIS), São Paulo, Bauru, Brazil).

The cephalograms were taken in standing position and adequately protected, with the teeth in centric occlusion, Frankfurt plane parallel to the floor and lips relaxed.

All radiographs were scanned with the help of a Dolphin ruler (Dolphin 9.0, Dolphin Imaging & Management Solutions, California / USA) used to correct magnification of the radiographic image, caused during cephalometric film exposure. Then, the radiographs were analyzed on a software (Radiocef 2.0 , Radio Memory, Brazil) to obtain the measurements.

A total of 24 cephalometric points were identified (Fig. 1 and Table 2) Based on the t test, the age of both groups did not present statistically significant difference (10.3+-1.6 years for the syndrome group and 10.6 +-1.9 years for the control group; t=0.3623, p= .7218) and ranged from 8.1 to 13.7 years.

Error Analysis

To determine the reliability of the cephalometric method, all cephalometric radiographs from both groups were traced and measured twice with a 20 days interval by the same investigator. The random error was calculated by intraclass correlation coefficient.

Statistical Analysis

The Levene’s variance homogeneity test was applied and revealed homogeneity of variance between groups, except for CePog'MLS. Statistical evaluation of cephalometric values between groups was performed using a parametric test. The

results of the study and control groups were compared by the t test. SPSS software (version 16.0, SPSS Inc, Chicago, Ill) for Windows was used for statistical analysis. Statistical significance was set at P< 0.05.

Results:

The angular and linear cephalometric measurements for the RCPS and control groups and the statistical difference between them are shown in Table 3. Statistical differences between the syndrome and control groups were found in 11 of all measurements analyzed (p<0.05), all demonstrating pronounced differences (p<0.01). Mandibular linear dimensions of RCPS were shorter than those observed in the control group (Go-Pog and C3-Me; p<0.01), also in sagittal position of the mandibular apical base (SN-Pog; p<0.01). Mandibular plane angle was similar with the control group.

Angular and linear measurements were similar for both RCPS and control groups with no statistical difference in maxillary length (Ans-Pns) and position (SNA), inclination of maxillary incisors (1SN), maxillary occlusal plane (SN-U6U1a) and maxillary plane angle (SN-AnsPns).

The facial convexity (N'PnPog', in degrees) and soft tissue convexity (N'SnPog', in degrees) were markedly smaller for the RCPS group (p<0.05). The nasolabial angle (PnSnLs) did not present statistical differences (p=0.07).

Statistical analysis revealed that the mandible-cervical convexity (CePog'SML) and mentolabial angle (LiMLSPog') were larger than in normal individuals (p<0.01).

RCPS had extremely decreased upper lip protrusion (Ls-Sn.Pog') and lower lip protrusion (Li-Sn.Pog') (p<0.01).

he vertebrae relationship was similar in both groups. The hyoid presented more inferior and anterior positioning in the syndrome group.

Data from this paper indicate that significant craniofacial differences are present between RCPS and non-syndromic individuals with balanced face.

Discussion:

Cephalometric radiography is a standardized method of production of skull radiographs, which provides elaborate information for diagnosis and treatment planning. Recently, cone-beam computed tomography (CBTC) has proved its value

in dental practice when conducting craniofacial measurements[17]. However, 2D digital lateral cephalometry is still the gold standard for cephalometric measurements[18]. This study describes the lateral cephalometric analysis between RCPS and a control group.

Considering the studies published so far, Favaro et al.[6] achieved the largest sample size, with a total of 34 individuals, making an overview of cases previously known. In this study, only 9 individuals met the inclusion criteria and had radiographs of sufficient quality for inclusion in the study.

Our sample was composed of 6 females and 3 males. In the review of Favaro el al.[6], the sex ratio showed a deviation toward females (1:8F:1M); however, when they considered all affected individuals in the families, including those who died earlier before medical assistance, the sex-ratio deviation decreased to 1.3F:1M.

The features observed in a review study of 18 individuals included microstomia (100%), micrognathia (100%), cleft palate/Robin Sequence (78.5%), absent mandibular central incisors (80%), minor ear anomalies (92.8%), hypoplastic thumbs (96.2%), hypoplastic thenar/hypothenar region (83.3%), mesomelic shortening of upper (51.8%) and lower limbs (88.8%), hypoplastic halluces (92.5%), and clubfeet (100%). Learning disability was observed in 84%, and language disorders in 77%.

Consistent with all published studies[1-3,5,6-12], individuals with RCPS exhibited severe mandibular retrognathism, with shortened mandibular length. Furthermore, the mandible is also posteriorly positioned, as evidenced by the decreased SN-Pog angle and the reduced distance from Me to C3 vertebrae.

The severe facial convexity is consistent with overall mandibular retrognathia. The decreased facial and soft tissue convexity were influenced by the mandibular malformation, as well as the increased mandible-cervical and mentolabial angle. All measurements that involved the Pog point (mandibular points, profile points and lip position points) to form angles in the methodology were statistically significant, due to the severe retromicrognathia.

Paradoxically, the nasolabial angle (PnSnLs) did not present statistical differences ($p=0.07$), which was expected with the few maxillary alterations examined. There was increase in mentolabial angle (LiMLSPog') and mandible-cervical convexity (CePog'SML), which was previously clinically described as webbed neck[11].

Individuals with RCPS did not present differences in anterior and posterior cranial base length and cranial base length, in contrast with the velocardiofacial syndrome that present reduced length of the skull base[19].

The sagittal position of the maxilla was statistically more anterior (prognathic) than normal. This is in contrast with some reports on Pierre Robin Sequence[20,21] but agrees with a study on syndromic PRS[22]. Although the differences were statistically significant, the clinical relevance is small; this minor degree of anterior maxillary positioning may make the mandibular retrognathism appear more visible.

The finding of decreased maxillary length (ANS to PNS) yet without statistical significance supports the absence of maxillary hypoplasia. The individuals did not present significant maxillary alterations in measurements compared to controls, which has not been reported until now[1-3,5,6-12]. This result differs from Shen et al.[16] in individuals with Pierre Robin Sequence (PRS), who described statistical differences in maxillary length and SNA angle between non-syndromic PRS, control group and isolated cleft palate; individuals with Robin Sequence presented maxillary retrognathia, with the PRS group showing slower maxillary growth rate than isolated cleft palate, and proportionate sagittal jaw deficiency. However, according to Rogers et al.[22] the cephalometric measurements are variable in Robin sequence, based on the presence and type of associated syndromic diagnosis.

Pierre Robin Sequence is described as a triad of micrognathia, glossoptosis, and airway obstruction; the smaller mandible displaces the tongue posteriorly, resulting in airway obstruction and formation or not of cleft palate[23]. PRS is not a syndrome, but a sequence, with one abnormality causing the next. It is related to several other craniofacial malformations and may appear with a syndromic diagnosis, such as velocardiofacial, Stickler, craniofacial microsomia, RCPS and Treacher Collins Syndrome[19,24].

Alike the Treacher Collins (TC) syndrome, the most important consideration in an infant with RCPS could be the management of an inadequate airway and respiratory compromise[24]. The majority of reported cases describe neonatal respiratory distress[12]. In most severe cases, tracheostomy is required to manage the airway[24]. Severe mandibular retrognathism also plays a role in airway compromise, leading to posterior and superior tongue malpositioning that affects the airway by obstruction of nasopharyngeal, oropharyngeal and hypopharyngeal spaces[24].

A previous study associated the increased airway size (hyocervical distance) with greater distances of C3 from the menton[25]. Inversely proportional, the present study revealed a reduced distance of C3 from the menton, which is consistent with the findings of Ogando el al.[26], who described a RCPS case with airway obstruction, and Souza et al.[11] in two siblings.

The present results did not exhibit statistical significance in airway measurements. However the mean difference of 2 mm found in study group could be clinically relevant. The small sample size could have influenced the statistical test. Additional studies with larger sample sizes are warranted for a reliable interpretation.

The hypothesis of "partial mandibular catch-up growth" in infants with PRS supports that the increased growth rate in infants with PRS improves the airway dimension, which might be partly responsible for the natural resolution of respiratory distress. This theory could justify the improvement in airway conditions in individuals in this study, which was conducted in individuals between 8 and 13 years old[27]. Besides, not all PRS cases necessarily present compromised airway due to glossoptosis[28].

Measurements of mandibular incisors were not included in methods because of the high prevalence of hypodontia of mandibular central incisors in this sample. The occlusal plane measurement was more obtuse in the syndrome group. The absence of occlusal contact between maxillary and mandibular incisors because of the retrognathic mandible could have favored the extrusion of maxillary incisors. In a growing individual, the main approach of the multidisciplinary team involves repairing the mandibular cleft using grafts obtained from ribs, calvaria, or iliac crest, and fixing the graft in its position using wire, screw, or miniplates[28]. The orthodontic treatment in RCPS is usually focused in the mandibular arch, addressing the absence of mandibular incisors and the mandibular atresia. The syndrome is variable, but in the end-stage correction of the skeletal pathology, individuals with RCPS often require bimaxillary orthognathic surgery at skeletal maturity, similar to the TC syndrome[24].

A recent report identified mutation of the *EIF4A3* gene as the causal effect of RCPS. The *EIF4A3* deficiency leads to abnormal development of most pharyngeal arches, resulting in altered mandible and laryngeal morphogenesis[14]. This study revealed altered position of the hyoid bone, a structure originated from the second and third arch mesenchyme[29].

In individuals with RCPS, the hyoid bone is below and anteriorly positioned compared to controls. Many studies have showed that the hyoid position is

determined by the skeletal relationship, facial profile, posture, mouth breathing and forward head positioning[30].

According to authors, individuals with Class II have the longest length distance of the hyoid bone body from the vertebrae[30], in agreement with the present results that revealed a great distance of hyoid from C4 vertebrae in the syndrome group compared to controls. Our results also contrast with the findings of Trenouth and Timms (1999), which described positive correlation between the length of the mandible (measured from the points of Gon-Me) with the distance between the third cervical vertebra and hyoid bone (C3H)[31]. In this study, the syndrome group with mandibular hypoplasia had the greatest hyoid-vertebrae distances.

The results also revealed normal measurements for skull-vertebral angle, indicating a normal degree of head flexion or extension in relation to the cervical spine. A similar study determined the mean value of this angle in 101 ± 5 °. A value less than 96 ° would indicate posterior rotation or head extension and a value greater than 106 ° would indicate anterior rotation or head flexion [32]. However, Valenzuela et al., in a study on 50 individuals without craniofacial alterations showed that there is no relation between the degree of head flexion or extension and position of the hyoid bone[33].

Kaduk (2003) reported significantly more anterior and caudal values in the position of hyoid bones in children with clefts compared with children without clefts; this is explained as a mechanism of adaptive closure of velopharyngeal valves and swallowing[34]. Similar findings were identified in a study in children with Pierre Robin sequence , which agrees with this study on individuals with RCPS[35].

Although the focus of this article was to assess and describe the craniofacial morphology in individuals with RCPS, the objective was to improve the diagnosis and understanding of the etiopathogenesis, in order to keep individuals with RCPS healthy and socially integrated. It is expected that this knowledge will also assist orthopedic/orthodontic clinicians to offer esthetic and functional improvement for these individuals.

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Legends for Illustrations

Figure 1: Clinical aspects of typical form of RCPS.

(A) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Frontal View

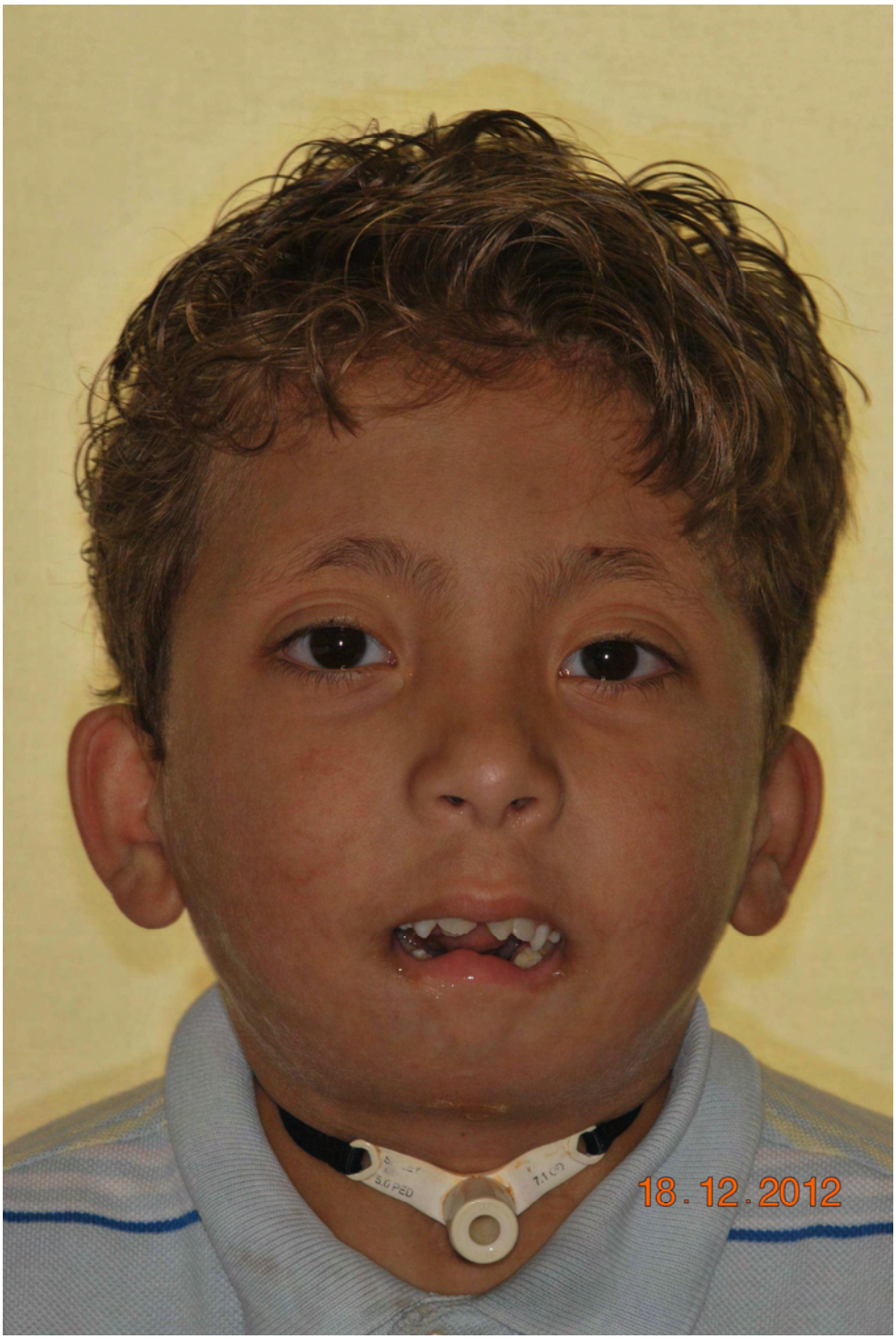

Figure 1: Clinical aspects of typical form of RCPS.

(B) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Lateral View

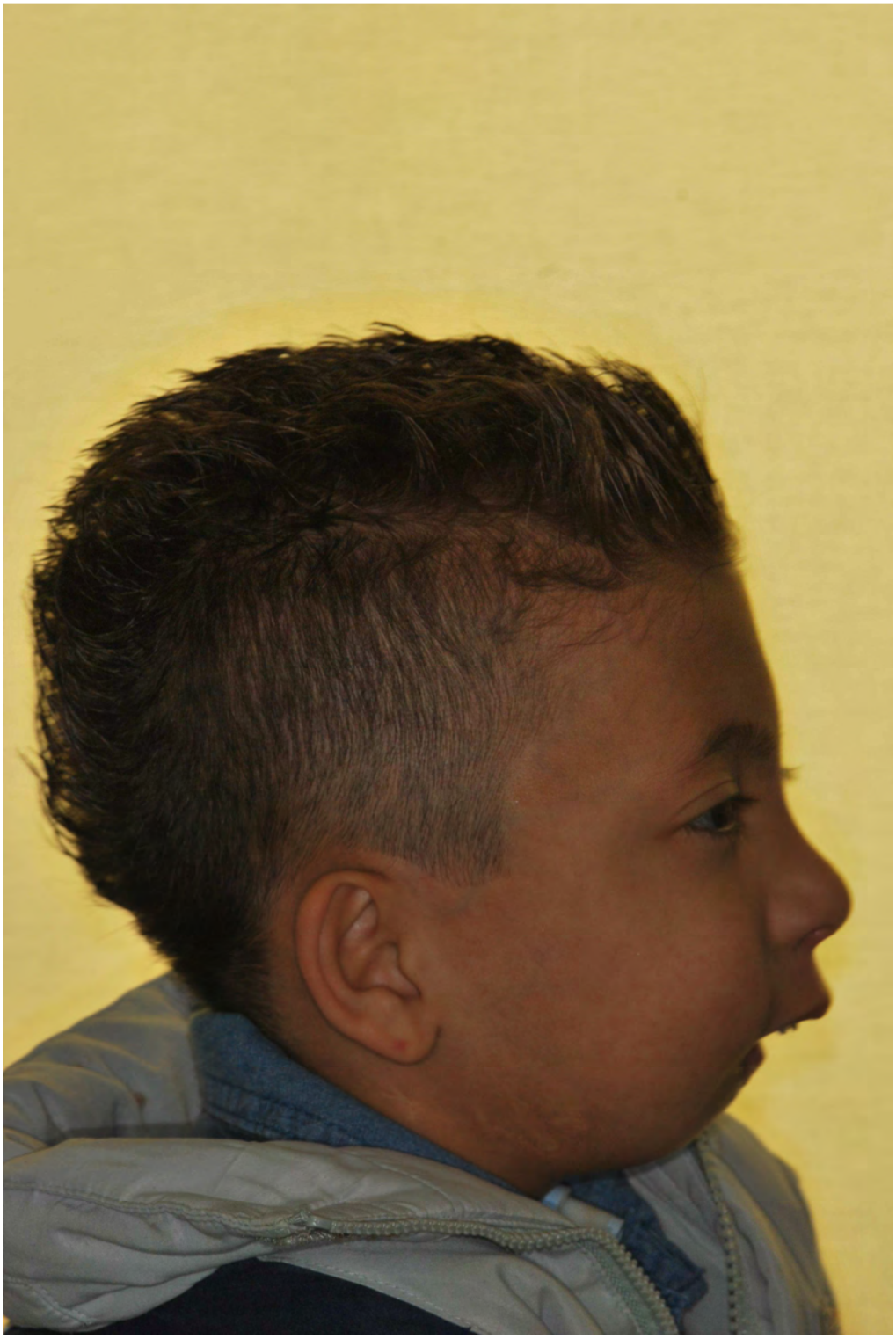

Figure 1: Clinical aspects of typical form of RCPS.

(C-) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Intraoral view.

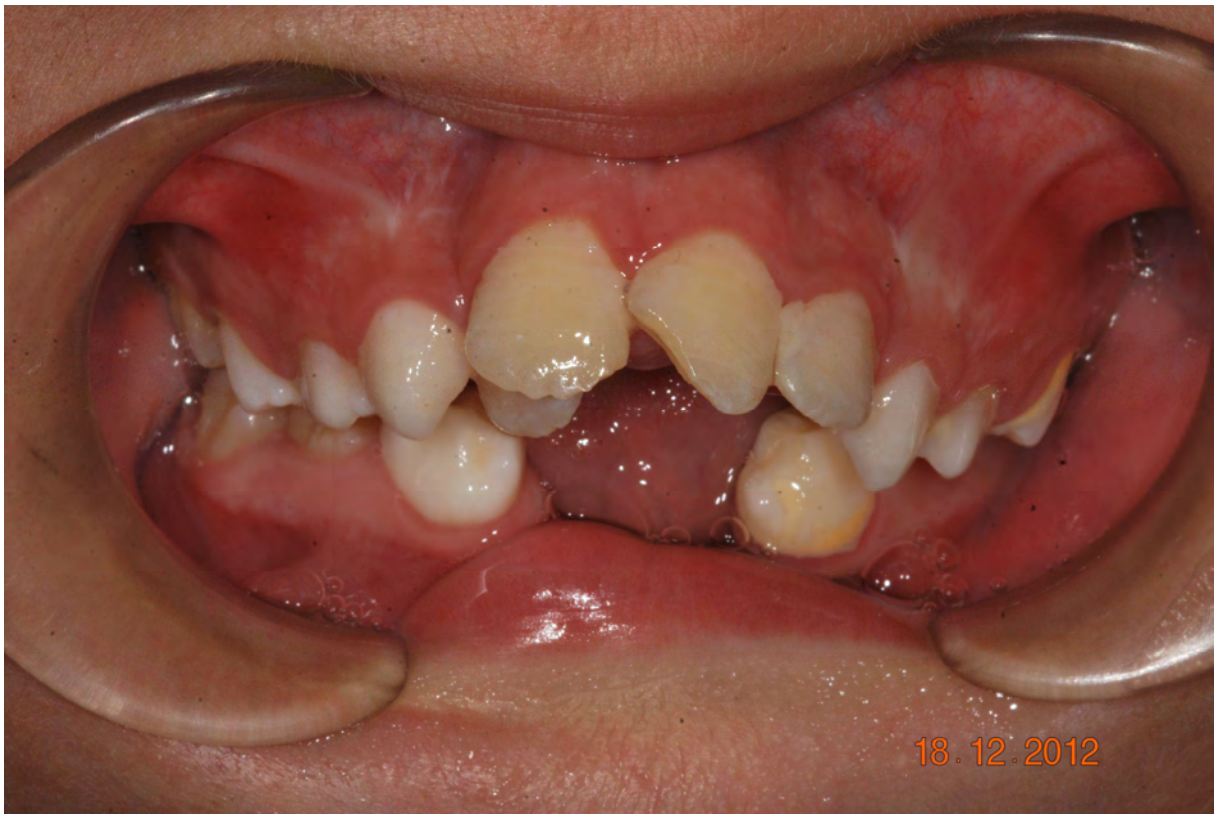

Figure 1: Clinical aspects of typical form of RCPS.

(D) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Oclusal intraoral view.

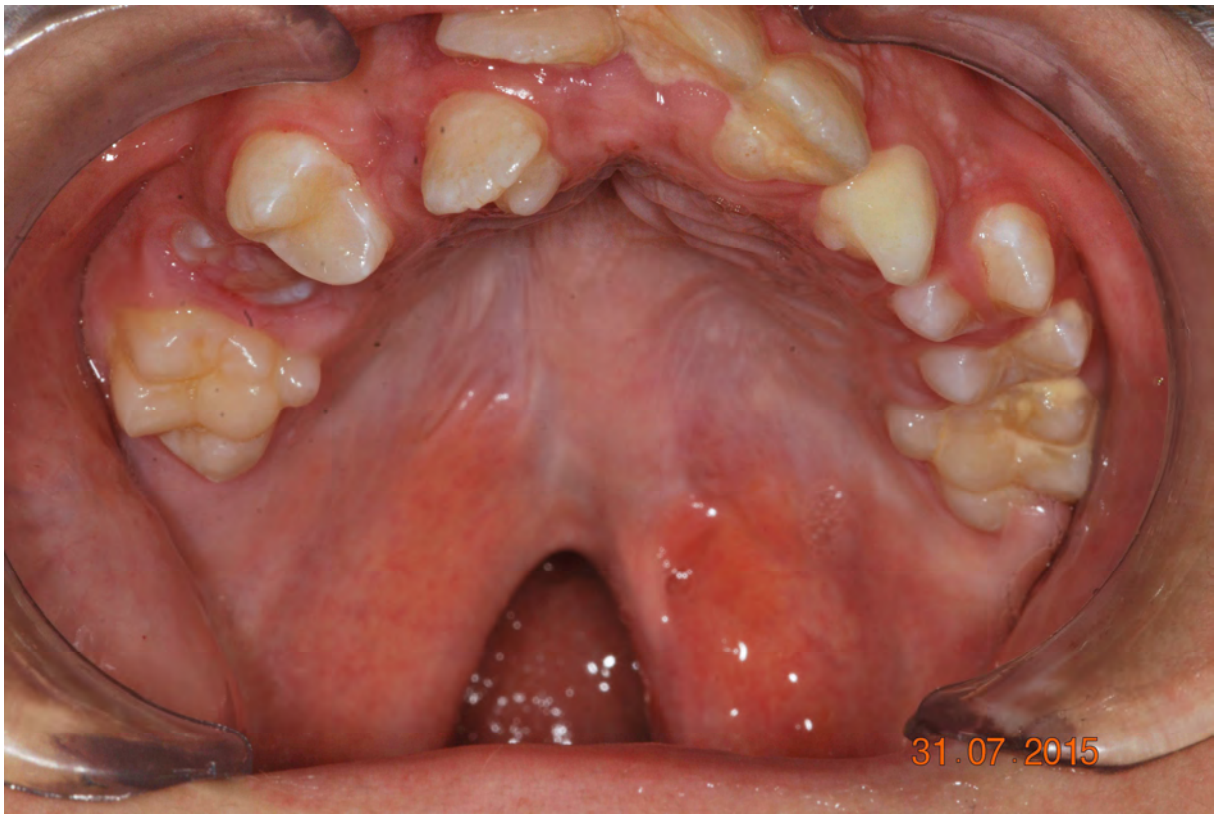

Figure 1: Clinical aspects of typical form of RCPS.

(E) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Cleft view.

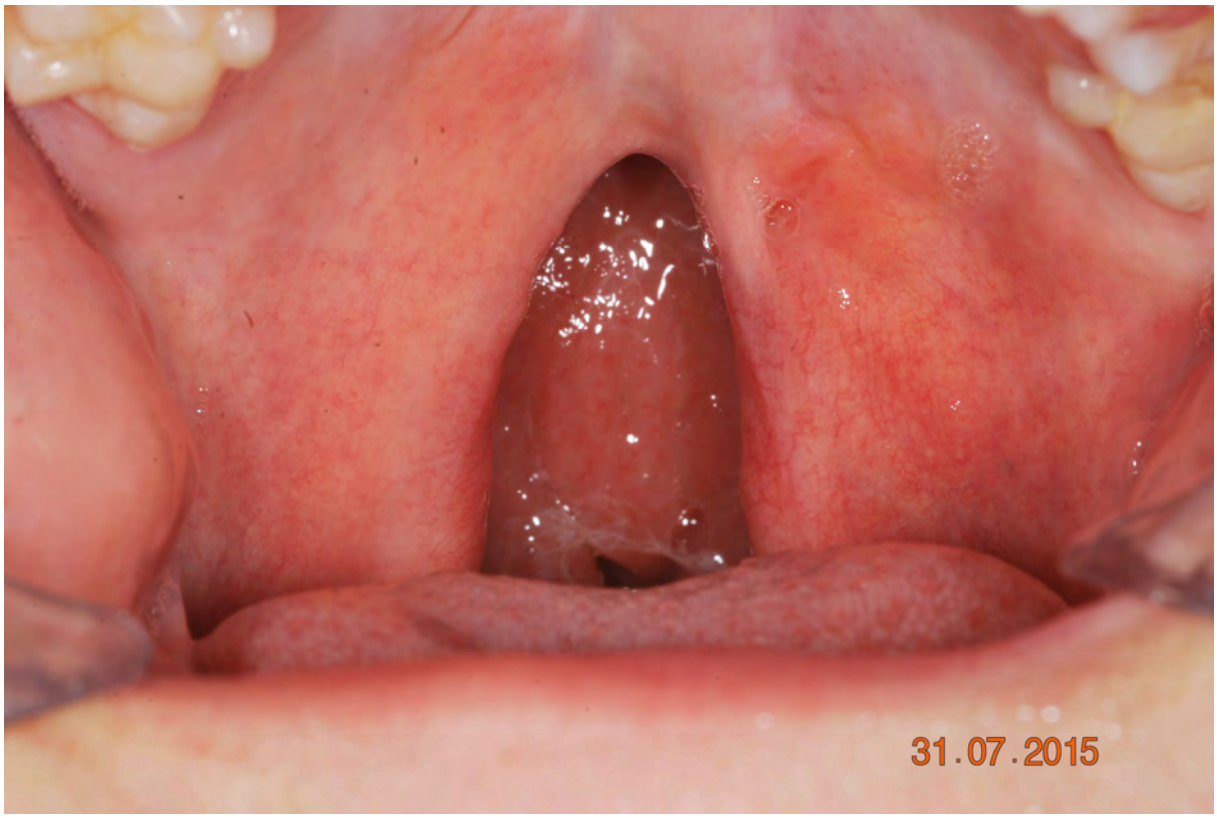

Figure 1: Clinical aspects of typical form of RCPS.

(F) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Limbs view.

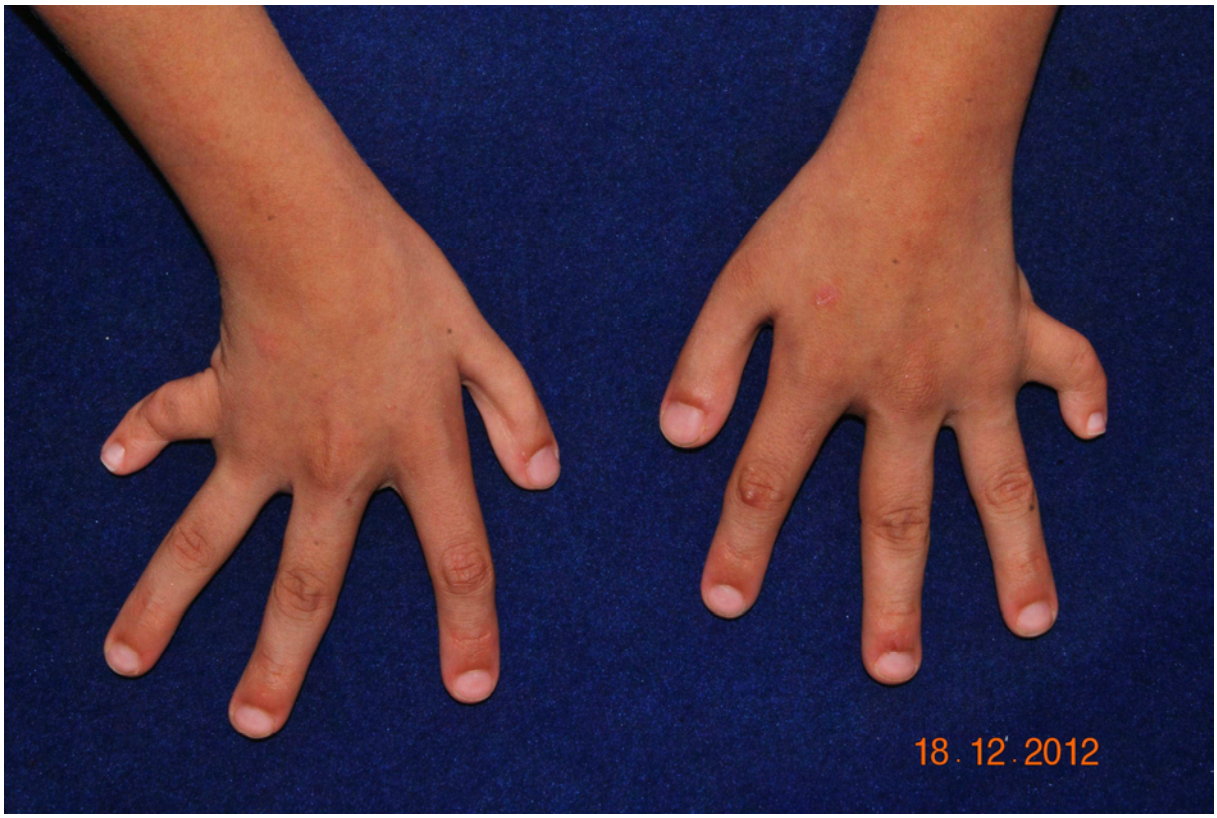

Figure 1: Clinical aspects of typical form of RCPS.

(G) Affected individual with 11 years of age, illustrating typical facial features including micrognathia and microstomia, abnormal fusion of the mandible, Robin Sequence, cleft palate and hypoplastic halluces and clubfeet. Limbs view.

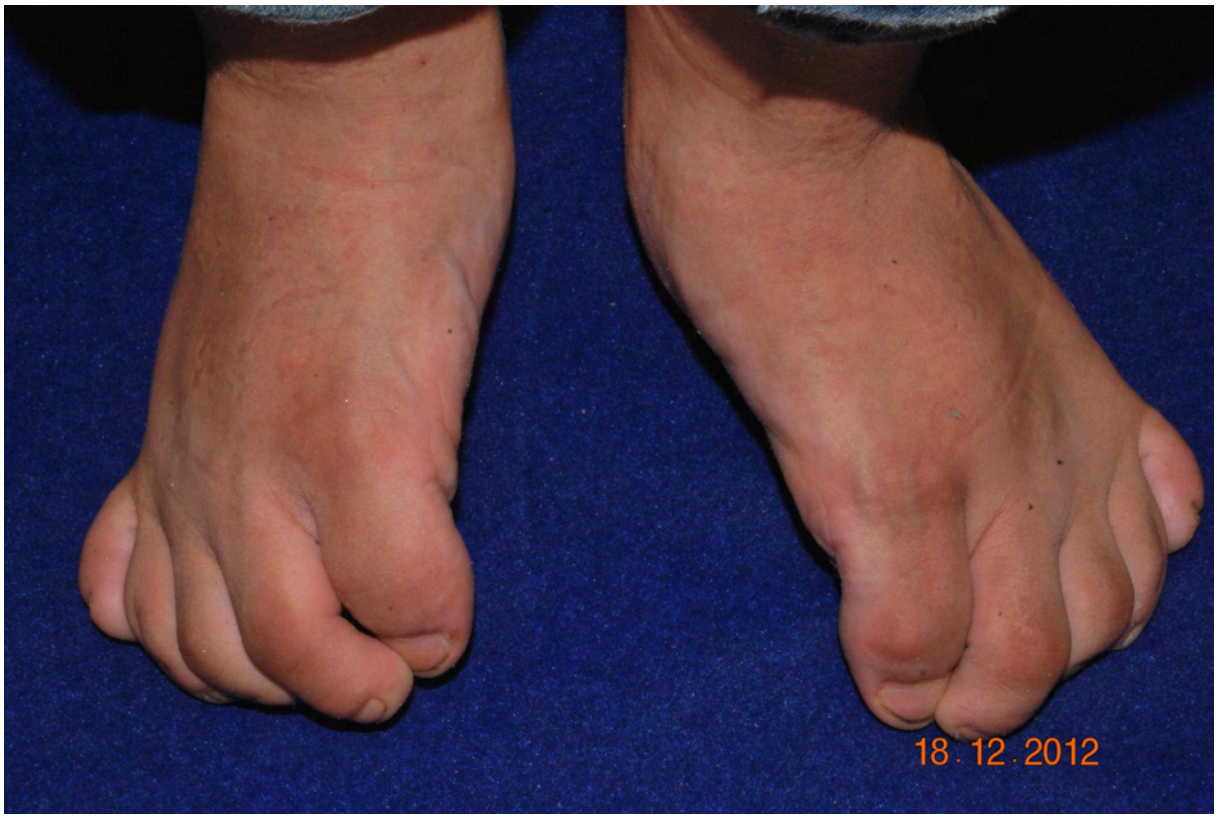

Figure 2: Points employed in the cephalometric analysis. 1. Soft tissue gnathion (Gn'): most anterior point on the soft tissue contour of the mentum. 2. Nasion (N): most anterior point of frontonasal suture. 3. Sella (S): Geometrical center of the sella túrcica. 4. Pronasale (Pr): most anterior point of the nose. 5. Subnasale (Sn): intersection between the pronasale and the upper lip. 6. Labrale superius (Ls): most anterior point of the upper lip. 7. Labrale inferius (Li): most anterior point of the lower lip. 8. Mentum lip sulcus point (SML): Most posterior point of the soft tissues between lower lip and mentum. 9. Soft tissue mentum (Me'): most inferior point below the soft tissue contour of the mentum. 10. Anterior nasal spine (ANS): Tip of the anterior nasal spine. 11. Posterior nasal spine (PNS): Tip of posterior nasal spine. 12. Ápex of maxillary incisor (U1a): Point on ápex of maxillary incisor. 13. Incisal tip of maxillary incisor (U1t): point on incisal tip of maxillary incisor. 14. Mesial cusp tip of the maxillary first molar (U6): point on mesial cusp tip of the maxillary first molar. 15. Gnathion (Gn): the most anterior and inferior points of the bone mentum. 16. Mentum (Me): most inferior point in the contour of the mandibular symphysis. 17. C2up: the most posterior and upper point on the border of the body of C2. 18. asNPW: A point on anterior wall on superior nasopharynx. 19. psNPW: A point on posterior wall of superior nasopharynx. 20. aiNPW: A point on anterior wall of inferior nasopharynx. 21. piNPW: A point on posterior wall of inferior nasopharynx. 22. asOPW: A point on anterior wall of superior oropharynx. 23. psOPW: A point on posterior wall of superior oropharynx. 24. pmOPW: A point on posterior wall of medium oropharynx. 25. amOPW: A point on anterior wall of medium oropharynx. 26. piOPW: A point on posterior wall of inferior oropharynx. 27. aiLPW: A point on anterior wall of inferior oropharynx. 28. Throat point (Th): Most posterior point on the neck curve. 29. Hyoid (H): most anterior and superior point of the hyoid bone. 30. C2lp: the most lower and the most posterior point on border of the body of C2. 31. C3ua: the most upper and anterior point on the border of the body of C3. 32. C4lp: the most posterior point on the lower border of the body of C4. 34. Basion (Ba): most inferior point of the anterior border of the foramen magnum.

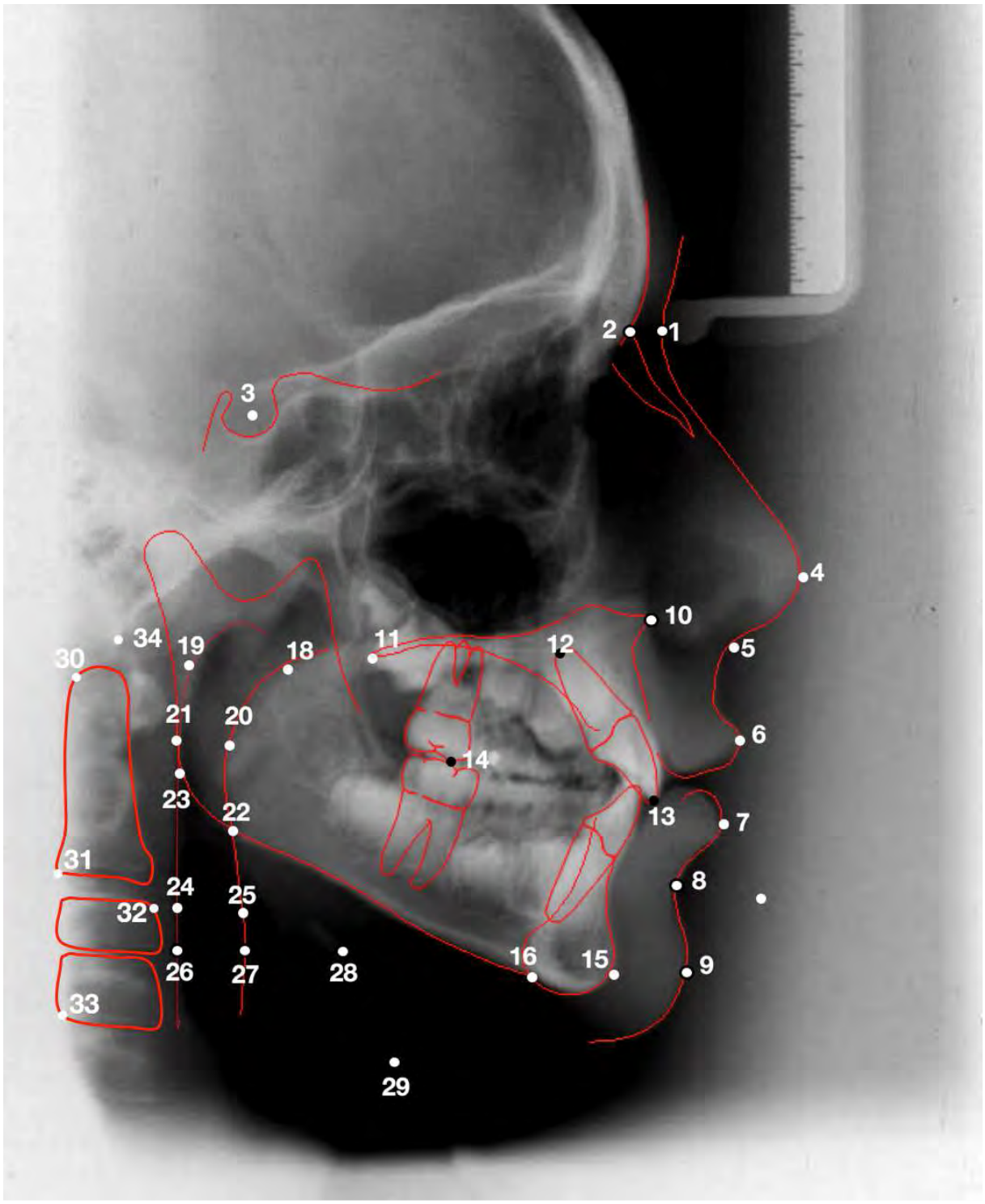
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Table 1: Age, Gender and Standard Deviation of Syndromic (RCPS) and Control groups.

	RCPS			*Control*		
Gender	Female	Male	Both	Female	Male	Both
n	6	3	9	6	3	9
Mean	9.7	11.5	10.3	9.8	12.0	10.6
Standard Deviation	1.2	2.0	1.6	1.4	2.2	1.9
Minimum	8.1	9.2	8.1	8.1	9.5	8.1
Maximum	11.3	13.2	13.2	11.9	13.7	13.7

Table 2: References of constructed points and lines.

asNPW, psNPW	Intersection of palatal plane (ANS-PSN) and anterior and posterior pharyngeal wall
aiNPW, piNPW	Intersection of oclusal plane (U1t-U6) and anterior and posterior pharyngeal wall
asOPW, psOPW	Intersection of mandibular plane (Go-Me) and anterior and posterior pharyngeal wall
amOPW, pmOPW	Intersection of a line on the most upper border of the body of C3 and anterior and posterior pharyngeal wall
aiOPW, piOPW	Intersection of a line between the C4lp and H points and anterior and posterior pharyngeal wall

Table 3: Results of Cephalometric Parameters in Richieri-Costa Pereira Syndrome (RCPS; n=9) and control (n=9) groups.

		RCPS		Control				
		Mean	S.D.	Mean	S.D.	Dif	p	Error
Maxilla	SNA	100.29	5.59	83.91	4.64	16.38	0.001*	1.00
	ANS-PNS/SN	11.93	3.96	10.52	2.50	1.41	0.475	0.99
	U1tU6/SN	27.80	5.21	22.66	3.03	5.14	0.014*	0.99
	U1aU1t/SN	99.15	5.53	101.58	5.58	-2.43	0.294	0.99
	ANS-PNS	46.37	4.75	50.13	3.65	-3.76	0.068	0.99
Mandible	SNPog	108.16	3.45	102.43	3.34	5.73	0.009*	0.99
	SN.Go-Me	39.18	6.55	38.19	3.63	0.98	0.664	1.00
	Go-Pog	56.79	6.71	70.31	4.80	-13.52	0.001*	1.00
	C3-Me	54.81	8.23	71.51	5.52	-16.70	0.001*	1.00
Hyoid	H-S	102.57	9.63	90.48	8.51	12.10	0.003*	1.00
	H-C4lp	32.87	5.95	45.22	4.04	-12.35	0.001*	0.98
	H-Me	42.25	7.25	41.08	5.61	1.18	0.720	0.95
Posture	C2up. C2lp/SN	104.36	8.69	106.84	3.74	-2.47	0.820**	0.99
	C4lp.C2up/SN	103.82	8.56	109.00	2.48	-5.19	0.301	0.99
Airway	sNPW	12.91	4.27	17.32	4.84	-4.41	0.158	0.99
	iNPW	10.11	2.43	12.17	2.08	-2.06	0.106	0.96
	sOPW	10.88	3.20	13.95	3.18	-3.07	0.076	0.99
	mOPW	9.36	3.22	11.32	3.95	-1.96	0.289	0.99
	iOPW	9.63	3.67	12.61	3.82	-2.98	0.132	0.98
Soft Profile	N'PnPog'	59.43	5.74	48.56	4.22	10.87	0.003*	1.00
	N'SnPog'	33.68	7.20	22.43	4.63	11.26	0.004*	0.99
	PnSnLs	63.38	7.39	58.13	7.34	5.25	0.138	0.99
	LiSMLPog'	26.74	15.51	45.81	6.39	-19.07	0.001*	1.00
	CePog'SML	154.62	15.25	107.47	3.67	47.16	0.001*	1.00
Lips	Ls-SnPog'	9.32	2.78	5.33	1.10	4.00	0.002*	0.97
	Li-SnPog'	8.64	3.06	4.91	1.29	3.73	0.023*	0.98
Cranial Base	N-S	65.65	3.04	64.93	4.68	0.72	0.733	1.00
	S-Ba	40.71	5.91	42.54	4.79	-1.84	0.415	0.98
	N.S.Ba	130.95	4.06	132.87	2.53	-1.91	0.291	0.99

*Statistically significant differences ($p<.05$) according to paired t test.

** Measurement without normal distribution, Wilcoxon test.

4 Final Considerations

4 FINAL CONSIDERATIONS

The craniofacial morphology of individuals with Richieri-Costa-Pereira Syndrome presents measurements with statistically significant differences compared to the control group. Individuals with Richieri-Costa-Pereira Syndrome present reduced airway dimensions compared to the control group, without statistical significance yet with clinical relevance.

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ANNEXES

ANNEX A – Guidelines for The Journal of Oral and Maxillofacial Pathology

The Editorial Process

The manuscripts will be reviewed for possible publication with the understanding that they are being submitted to one journal at a time and have not been published, simultaneously submitted, or already accepted for publication elsewhere.

The Editors review all submitted manuscripts initially. Manuscripts with insufficient originality, serious scientific flaws, or absence of importance of message are rejected. The journal will not return the unaccepted manuscripts.

Other manuscripts are sent to two or more expert reviewers without revealing the identity of the authors to the reviewers. Within a period of eight to ten weeks, the contributors will be informed about the reviewers' comments and acceptance/rejection of manuscript. Articles accepted would be copy edited for grammar, punctuation, print style, and format. Page proofs will be sent to the first author, which has to be returned within five days. Correction received after that period may not be included. All manuscripts received are duly acknowledged.

Types of Manuscripts and word limits

Original research articles
Randomised controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response rate. Up to 2500 words excluding references and abstract.

Short Communication
Up to 1000 words excluding references and abstract and up to 5 references.

*** Enigmatic Morphoinsight**

Up to 1000 words excluding references and abstract.

Guidelines for enigmatic morphoinsight:

1. The Enigmatic Morphoinsight is a new feature introduced in the JOMFP issues by the Editorial Board from 2013 onwards.
2. It is a short update on any enigmatic histopathology that includes any rare patterns of histology, cellular or nuclear morphologies, or any histopathological features.
3. It contains contributing author's details, text, images, acknowledgement, source of data and references.
4. First page file which includes details of the single contributing author and a duly signed, valid copyright form is MANDATORY and should be uploaded from JOMFP author account.
5. Text should not exceed 1000 words.
6. Images should not exceed 4 histopathological images along with a hand-drawn illustration of one of the histopathological image – COMPULSORY
7. Image clarity should be at its best – size of the image should not exceed 300dpi or 100 MB.
8. Source of data should be acknowledged in the acknowledgement form and uploaded along with text and images – MANDATORY
9. Number of authors should not exceed one.

Case reports
New / interesting / very rare cases can be reported. Cases with clinical significance or implications will be given priority, whereas, mere reporting of a rare case may not be considered. Up to 2000 words excluding references and abstract and up to 15 references.

Review articles
Systemic critical assessments of literature and data sources. Up to 3500 words excluding references and abstract.

Letter to the Editor
Should be short, decisive observation. They should not be preliminary observations that need a later paper for validation. Up to 400 words and 4 references.

Announcements of **conferences**, **meetings**, **courses**, **awards**, and other items likely to be of interest to the readers should be submitted with the name and address of the person from whom additional information can be obtained. Up to 100 words.

Authorship criteria

All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article.

Authorship credit should be based only on

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of the version to be published.

Conditions 1, 2, 3 and 4 must all be met. Acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship.

The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed. Once submitted the order cannot be changed without written consent of all the authors.

For a study carried out in a single institute, the number of authors should not exceed six. For a case-report and for a review article, the number of authors should not exceed four. For short communication, the number of authors should not be more than three.

Only those who have done substantial work in a particular field can write a review article. A short summary of the work done by the authors (s) in the field of review should accompany the manuscript. The journal expects the authors to give post-publication updates on the subject of review. The update should be brief, covering the advances in the field after the publication of article and should be sent as letter to editor, as and when major development occur in the field.

Sending the Manuscript to the Journal

Articles should be submitted online from http://www.journalonweb.com/jomfp. New authors will have to register as author, which is a simple two step procedure.

1. **First Page File:** Prepare the title page, covering letter, acknowledgement, etc., using a word processor program. All information which can reveal your identity should be here. Do not zip the files.
2. **Article file:** The main text of the article, beginning from Abstract till References (including tables) should be in this file. Do not include any information such as acknowledgement, your names in page headers, etc., in this file. Do not zip the files. Limit the file size to 400 kb. Do not incorporate images in the file. If the file size is large, graphs can be submitted as images separately without incorporating them in the article file to reduce the size of the file.
3. **Images:** Submit good quality color images. Each image should be less than 400 kb in size. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to 1200 x 800 pixels or 5 inches). All image formats (jpeg, tiff, gif, bmp, png, eps, etc.) are acceptable; jpeg is most suitable. Do not zip the files
4. **Legends:** Legends for the figures/images should be included at the end of the article file.

The authors' form and copyright transfer form has to be submitted to the editorial office by post, in original with the signatures of all the authors within two weeks of online submission. Images related to the articles should be sent in a 'compact disc' or as hard copies to the journal office at the time of acceptance of the manuscript. These images should of high resolution and exceptional quality.

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