CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

MORFOLOGIA DA BASE DO CRÂNIO EM INDIVÍDUOS COM SÍNDROME DE APERT

Dissertação apresentada à Universidade Católica Portuguesa
para obtenção do grau de Mestre em Medicina Dentária

Por:
Aline Cássia Inocêncio

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Orientador: Susana Silva
Coorientador: Ana Lídia Ciamponi

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Epígrafe

"Quanto mais aumenta nosso conhecimento,
mais evidente fica nossa ignorância". (John F. Kennedy)

Dedicatória

Dedico esse trabalho ao meu amado esposo André que sempre me apoiou na realização dos meus sonhos.

Agradecimentos

Aos doentes portadores de Síndrome de Apert , agradeço à disposição em contribuir com esse estudo que visa aprimorar o tratamento ortodôntico cirúrgico e com isso almejamos oferecer melhor qualidade de vida . Sem a participação de vocês esse estudo não seria possível . Deixo aqui registado o meu MUITO OBRIGADA!

Agradeço a minha orientadora Susana Silva pela colaboração nesse estudo .

Agradeço a minha co- orientadora Ana Lídia Ciamponi pelos ensinamentos e que me fez adquirir o interesse pela odontopediatria . Que sua voluntariedade em ajudar no tratamento dentário das crianças com necessidades especiais continue e que você brilhe mais e mais .

À Universidade Católica Portuguesa meu muito obrigada por tornar esse sonho possível .

À Universidade de São Paulo e Universidade Paulista Júlio de Mesquita Filho agradeço imensamente pela minha formação profissional.

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Resumo

A Síndrome de Apert é caracterizada por craniossinostoses e sindactilia dos dedos das mãos e dos pés. Os genes mais frequentemente mutados nas craniossinostoses sindrômicas são FGFRs que causam alteração nas células de fibroblastos e aumenta a taxa de diferenciação óssea. Essas malformações causam diminuição do crescimento da base do crânio com hipoplasia da face associada a severa retrusão maxilar. O tratamento inclui vários procedimentos cirúrgicos que são adaptados às necessidades do indivíduo afetado. O objetivo desse estudo foi avaliar comprimento, a largura e a rotação da base do crânio de maneira a verificar se estas teriam influência sobre a disposição das estruturas esqueléticas faciais.

Materiais e Métodos: Foram analisadas imagens obtidas de Tomografia Computadorizada Feixe Cônico e as grandezas cefalométricas angulares e lineares foram mensuradas pelo Software Dolphin (USA). A amostra foi composta por 22 indivíduos que foram divididos em 2 grupos: O Grupo 1 foi composto por 11 indivíduos com Síndrome de Apert com idade média de 15,6 anos e o grupo 2 foi composto por 11 indivíduos não sindrômicos pareados por sexo e idade com perfil facial equilibrado e em classe I.

Resultados: Foram calculados coeficiente de correlação intraclasses para verificar reprodutibilidade e confiabilidade das medidas. A comparação entre os grupos G1 e G2 foram realizadas pelo teste t student e mostrou diferença significativa nas grandezas N.S.Ba (p = 0.006), Fcrant ant dir- Fcrant ante esq (p= < 0.0001), F crant med dir - Fcrant med esq (p = 0,0001) , S-N / largura da fossa craniana anterior (p= 0.0420) , S-Ba / largura fossa craniana média (p= 0.0087). Não houve diferença significativas nas medidas N-S e N- Ba.

Conclusão: A base craniana dos indivíduos com síndrome de Apert possui alterações morfológicas importantes. O crânio é mais largo e curto e a maxila possui rotação mais vertical que favorece um posicionamento mais retruído influenciando o tipo de mal oclusão CIII.

Palavras chave: Apert, Síndrome de Apert, Craniossinostoses, Acrocefalodactilia

Abstract

Objective: The aim of this study was to evaluate the length, width and rotation of the base of the skull in order to verify whether these factors influence the disposition of skeletal structures.

Settings and Sample Population: The sample consisted of 22 individuals who were divided into two groups: AS group, composed of 11 individuals with Apert Syndrome (mean age of 15.6 years), and a control group.

Materials and Method: Images obtained from cone bean computed tomography were analysed and angular and linear cephalometric measurements were measured using Dolphin Software (USA). A comparison between groups was performed via T Student's.

Results: The morphology of the skull base of individuals with Apert syndrome is different to that of the normal population and it showed a significant difference in magnitudes for N.S.Ba ($p = 0.0062$), Fcrant ant right- Fcrant ant left ($p \leq 0.0001$), F crant med right- Fcrant med left ($p = 0,0001$) , S-N / width cranial anterior fossa ($p= 0.0420$) and S-Ba / width cranial median fossa ($p= 0.0087$).

Conclusion: The cranial base of the individuals with Apert Syndrome underwent important morphological alterations. The skull was wider and shorter, and the maxilla had a more vertical rotation that favoured a more retruded position which influences the type of malocclusion.

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Lista de Abreviações

2D	Bidimensional
3D	Tridimensional
Cl III	Classe III de Angle
DICOM	Digital Imaging and Comunications in Medicine
FOV	Field of View
HV	Horizontal verdadeira
PHV	Plano Horizontal Verdadeiro
PNC	Posição Natural da Cabeça
SA	Síndrome de Apert
TCFC	Tomografia Computadorizada de Feixe Cônico
Voxel	Volume Element (Elemento de Volume)
VV	Vertical Verdadeira

Introdução

As craniossinostoses sindrômicas são raras e são caracterizadas pela fusão das suturas cranianas em pacientes sindrômicos e sua prevalência é de 1:100.000 nascidos vivos. Causam restrição no crescimento do crânio e da base do crânio associados à hipoplasia do terço médio da face e dimorfismos[1].

A Síndrome de Apert foi descrita por Èugene Charles Apert em 1906 e o fenótipo dessa Síndrome inclui sinostoses bilaterais coronais da sutura, fontanela anterior ampla, hipoplasia da maxila, sindactilia de mãos e pés, perda de audição, hiperidrose, acne e anomalias da coluna vertebral. Os genes mais frequentemente mutados são os FGFRs, gerando manifestações clínicas conhecidas como síndrome de Apert, Crouzon e Pfeiffer [2 3]. O padrão de herança autossômica dominante é bem documentado, apesar da reduzida incidência familiar, relacionado ao baixo valor adaptativo desses indivíduos, predominando a ocorrência esporádica dos casos[4 5].

Pacientes com craniossinostoses sindrômicas manifestam hipoplasia maxilar muitas vezes tratada pelo avanço do terço médio da face[6].

A falta de crescimento e desenvolvimento maxilar causados pela craniossinostose resulta em aglomeração, impactação, perda prematura de dentes decíduos, erupção dentária tardia e erupção ectópica. Estas características bucais são encontradas em ambos as arcadas, mas são mais graves na maxila [7 8]. A mandíbula é indiretamente influenciada pela ausência de deslocamento primário e secundário dos ossos do complexo maxilar e da base craniana[9].

A Orthodontics and Craniofacial Research foi o jornal de escolha para a publicação desse estudo, pois tem o objetivo de publicar artigos relacionados com a genética, biologia do desenvolvimento, sindromologia, cirurgia, fala e audição e outras disciplinas

biomédicas relacionadas à ortodontia clínica e crescimento e desenvolvimento craniofacial normal e anormal. Portanto, esse estudo se adequa aos objetivos do jornal escolhido e pode contribuir para a comunidade científica.

Morphology of the cranial base in individuals with Apert syndrome: A cross-sectional study

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Título:

Morphology of the cranial base in individuals with Apert syndrome: A cross-sectional study

Introduction

Syndromic craniosynostosis is rare and is characterised by the premature fusion of the cranial sutures in syndromic patients; its prevalence is 1:100,000 live births. It causes restriction in the growth of the skull and the base of the skull, associated with the hypoplasia of the middle third of the face and dimorphisms [1 2].

Apert syndrome (AS) (OMIM # 101200) was initially described by Èugene Charles Apert in 1906 and also known as acrocephalosyndactyly. It is characterised by a phenotype that includes bilateral suture synostosis, broad anterior fontanelle, maxillary hypoplasia, complex symmetric syndactyly of the hands and feet, hearing loss, hyperhidrosis, acne and spinal anomalies. The most frequently mutated genes are FGFRs, generating clinical manifestations known as Apert, Crouzon and Pfeiffer syndrome [3 4 5].

The autosomal dominant inheritance pattern is well documented, despite its low family incidence, related to the low adaptive value of these individuals, with the sporadic occurrence of cases predominating. Patients with syndromic craniosynostosis show maxillary hypoplasia, which is often treated by advancing the middle third of the face. The benefits of facial advancement through osteogenesis, or through distraction, have been studied thoroughly, but complications of infectious origin related are reported, and those responsible for such patients should be aware of the risk involved in the procedure [6].

The dysmorphology of the maxillary growth and development caused by craniosynostosis results in agglomeration, impaction, premature loss of deciduous teeth, late eruption of the teeth and ectopic eruption. These buccal characteristics are found in both arches, but are more severe in the maxilla [7 8]. The mandible is indirectly influenced by the absence of primary and secondary displacement of the bones of the maxillary complex and the cranial base. The cranial base has a great influence on the face and occlusion, since its inclination can modify the position of the maxilla and mandible,

favouring certain types of malocclusion and influencing the pattern of the facial skeleton[9] [10].

The aim of this study was to evaluate the length, width and rotation of the skull base in order to verify whether these influence the disposition of skeletal structures.

Material and Methods

This cross-sectional study was approved by the Local Ethics Committee (No. 1.366.060). Participants were included in the research after the signing of the Informed Consent Form.

The criteria for the inclusion of patients were as follows: individuals diagnosed with AS; ages between 10 and 21, did not experience any type of surgery involving advancement of the middle third of the face (monobloc advancement or bone stretching with distractors); did not use orthodontic and orthopaedic appliances prior to the study. From a total of 53 patients with AS attending the SOBRAPAR hospital, third-three were younger or older than 10-21 years old, seven had already undergone orthognatic surgery and two did not consent to participate in the study. Therefore, a total of eleven (11) adolescents and young adults with AS composed de study group (AS group).

After selection of the syndromic population, eleven healthy teenagers and young adults, paired by gender and age with AS group, were selected to compose de control group. The criteria for the inclusion of patients in this group were the following: Class I occlusion for both canines and molars; without the absence of permanent teeth; good relation between bone bases, without facial asymmetry; the presence of a lip seal and balanced facial profile, following photographic and clinical evaluation; matched in gender and age to the individuals in AS group; consented to participate in the study, by means of the signing of the Informed Consent Term.

The patients were submitted to the cone beam 3-D dental imaging system (i-Cat® - Imaging Sciences Int. USA) in a FOV 23 cm x 17 cm of 360 °, 600 image bundles, 120 kVp; 5 mA in 26 seconds, with extended height protocol. The data were saved in DICOM (Digital Imaging and Communications in Medicine) format with a voxel size of 0.25 mm. Before the tomography was performed, the patient was dressed with a plumbing apron. The patient's head was positioned and stabilised at the forehead with the aid of a Velcro strip and the patient was instructed to stand still, with lips relaxed and to swallow.

Following this, we began the extended height exam protocol. In order to evaluate the images in the software, it was necessary to import the files of the images of the Cone Been into a DICOM extension. Once the data were imported, the three-dimensional image of the patient's head was oriented in the virtual space, in order to obtain the X-ray images, as with the cephalostat. The advantage of positioning the head virtually lies in the fact that we can visualise the three planes of space in order to avoid any kind of rotation (Figure 1). In this research, the images were oriented in the natural head position to generate lateral cephalograms and facilitate both linear and angular measurements (Figure 2). This position uses the visual axis as an external reference for positioning, and it has been reported in the literature as being more suitable for orthodontic diagnosis and planning (9).

The cephalometric measures described in Table 1 were performed in an independent work station (Samsung, South Korea). Dolphin 3-D ® software (version 11.96, Dolphin Imaging and Management Solutions, Chatswost, CA - USA) was used. The examiner was trained and calibrated by a second experienced examiner to analyse and measure computed tomography available via Dolphin software. Tomographic measurements were performed twice, with a two-week interval.

Intra-reliability was tested by a single examiner. The intraclass correlation coefficient was calculated to evaluate the level of agreement between the measurements in these two different moments. Cephalometric measurements were analysed for normality via the Shapiro-Wilk test and for the homoscedasticity of the sample via the Levene test for homoscedasticity of the sample. The measurements showed adhesion to the normality curve, and homogeneity of variances were submitted to the comparisons by the T Student-test.

Results

Initially, the intraclass correlation coefficient was verified by the two measurements performed at two different moments (Table 2), which presented values very close to 1, all of them being above 0.9, and low confidence intervals for all measures.

In Table 3, the values N.S.Ba, Fcrant ant dir- Fcrant ante esq, F crant med dir - Fcrant med esq, S-N / width of the anterior cranial fossa, S-Ba / cranial fossa width and

the mean show significant differences when compared to the control group. The N.S.Ba angle presented smaller values when compared to the control group. Regarding the other values related to the shape of the skull base, the values are higher for the AS group compared to control group.

Discussion

This study was carried out with the purpose of comparing the morphology of the cranial base of individuals with Apert syndrome with non-syndromic individuals with balanced faces. The morphology of the skull base of individuals with Apert syndrome is different to that of the normal population, but it has been shown that variations in skull morphology do not affect the accuracy of cephalometrics [11].

This study was performed with concomitant computed tomography (CT) and its indication is excellent for evaluating changes in the cranial base that are difficult to assess via conventional radiographs, but are clearly observed in three-dimensional examinations on patients with complex craniomaxillofacial deformities [9].

When evaluating the cranial base, we intended to evaluate its angulation, length and width and to determine whether these measures have an influence on the disposition of skeletal structures [11].

There was a significant difference for the angle of the cranial base (N.S.Ba) between the groups ($p = 0.0062$), for the age of studied patients. Even though Lu et al. [12] [13] observed normal cranial base angle for young children (0 to 6 years of age), they described a CT for a 24-year-old patient with a widened cranial base angle in the sagittal plane, suggesting a potentially flatter cranial base. The prematurely fused spheno-occipital syncrondosis seems to influence such angulation. Sanggarnjanavanich [14], Gkantidis [15] and Andria [16] agree that the reduction of the cranial base angulation is a factor related to mandibular prognathism. The measurements of the anterior cranial base length (N-S) and total length of the cranial base (N-Ba) showed that the AS group presented smaller values compared to control group, but without significant differences ($p = 0.16$ and $p = 0.18$) respectively. Cohen [17] and Kreiborg [18] state that 15% of individuals with Apert or Crouzon syndrome have lowest skull base length when compared to the normal population. The shorter length of the skull base is probably caused by decreased growth of the spheno-occipital synchondroses and the sphenofrontal suture [19]. The base of the

short skull may influence the most anterior position of the condyle, thus establishing a Cl III occlusion [8].

The width of the anterior cranial fossa presented a significant difference between groups ($p < 0.0001$), being wider in individuals with AS. This value is in agreement with the literature, which suggests that in individuals with Cl III occlusion, the anterior fossa is wider than normal [19]. According to Lu et al [13] the widened anterior cranial fossa is the earliest and the most remarkable deformity in AS.

The proportion of the length with width of the anterior cranial fossa was different between groups ($p = 0.042$). Reports in the literature state that patients with Cl III occlusion have an increase in width and height than length [20]. The cranial fossa length and width ratio indicated a significant difference ($p = 0.0087$) and confirmed the predominance of greater skull width than skull length in patients with AS [19 21 22].

However, the angle of flexion of the base of the reduced skull (N-S-Ba) indicates a more vertical position, which favours the projection of the mandible. The length of the skull base, although showing no significant difference, showed lower values than in control group. The width of the base of the skull is greater than its length; that is, the morphology of the base of the skull is altered in patients with AS.

Conclusion

The morphology of the skull base is altered due to a more vertical rotation that changes the position of the maxilla which has a strong influence on occlusion. The skull of adolescents and young adults with Apert syndrome is wider and shorter if compared to non-syndromic individuals.

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midface, and mandible. *Scand J Plast Reconstr Surg Hand Surg*. 2009;43(2):109-112.

Table 1

Table 1: Cephalometric measures of the cranial base

Variable	Measure
Angle N.S.Ba	Angle of Cranial Base
N-S	Anterior cranial base length
N-Ba	Total cranial base length
Fcran ant.right - Fcran ant.left	Width of the anterior fossa
Fcran mid.right – Fcran mid.left	Width of the middle cranial fossa
N-S / anterior cranial fossa width	Proportion of the anterior cranial length with width of the anterior cranial fossa
N-Ba / middle cranial fossa width	Proportion of the total cranial length with width of the middle cranial fossa

Table 2

Table 2: Intraclass correlation coefficient

Variable	Intraclass Correlation	CI (95%)	
		Minimum	Maximum
N.S.Ba	0.97	0.94	0.98
N-S	0.96	0.90	0.98
N-Ba	0.96	0.90	0.98
Fcran ant.right- Fcran ant.left	0.99	0.98	1.00
Fcran mid.right - Fcran mid.left	0.99	0.97	0.99
N-S / width of the anterior fossa	0.98	0.96	0.99
N-Ba / width of the middle cranial fossa	0.98	0.95	0.99

Table 3

Table 3: Comparison of angular and linear measurements for AS and control groups

Variable	Groups						
	AS group			Control group			
	Media	DP	N	Media	DP	N	Value P
N.S.Ba	120.70	10.975	11	131.04	3.423	11	0.0062*
N-S	62.08	6.693	11	66.47	5.584	11	0.1632
N-Ba	76.78	12.213	11	85.39	16.389	11	0.1840
Fcran ant.right- Fcran ant.left	158.28	12.19	11	118.47	20.308	11	< 0.0001*
Fcran mid.right - Fcran mid.left	162.23	12.528	11	125.93	20.901	11	0.0001*
N-S / width of the anterior fossa	68.75	7.550	11	60.86	10.882	11	0.0420*
N-Ba / width of the middle cranial fossa	151.54	5.252	11	120.44	1.822	11	0.0087*

*p<0,05

Figure 1

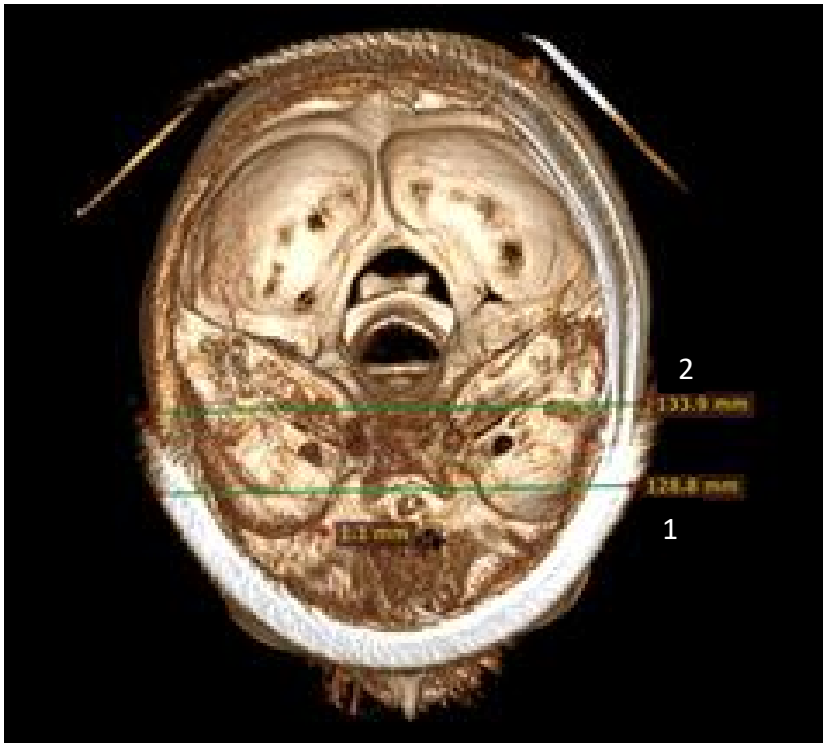

Figure 1- Representation of measurements of the width of the skull

1-Fcran ant.right- Fcran ant.left
2- Fcran mid.right - Fcran mid.left

Figure 2

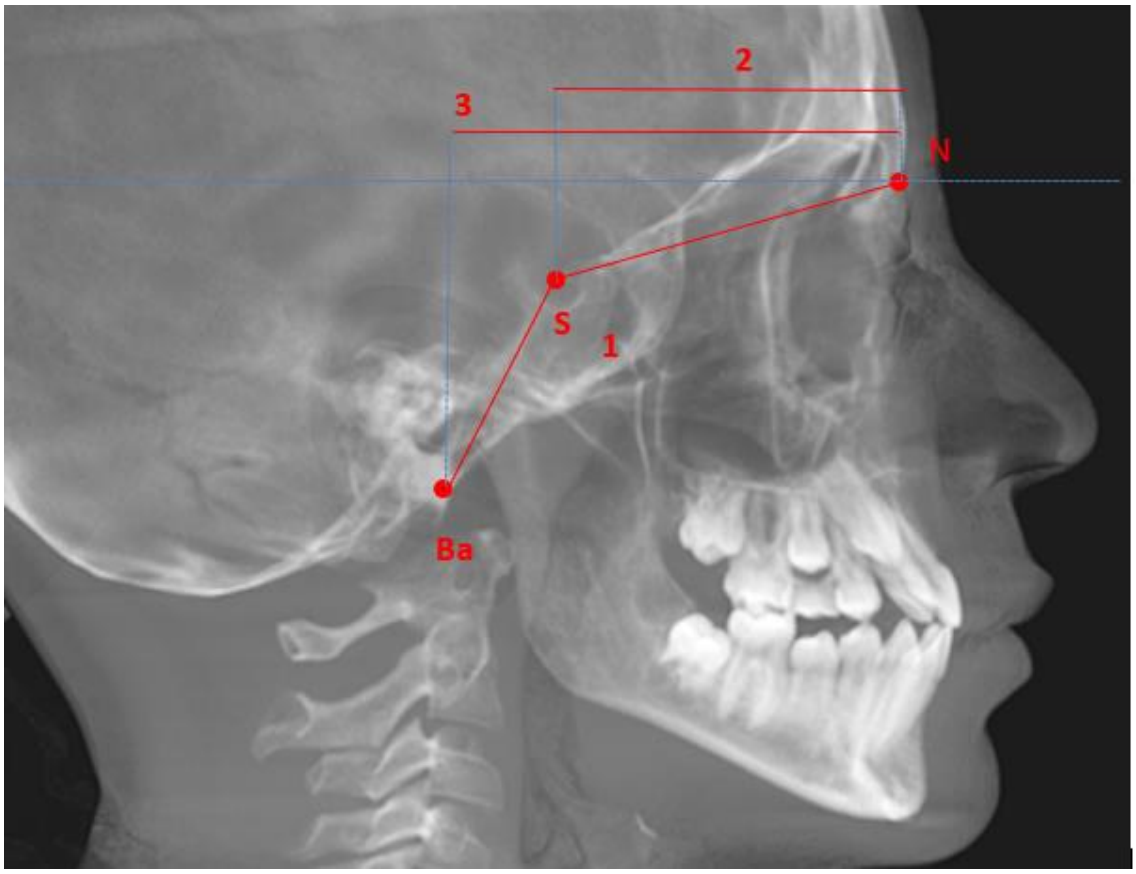

Figure 2- Representation of cephalometric measurements of cranial base

1- S.N.Ba
2- N-S
3- N-Ba

Cover Letter

Dear Editor,

We would like to submit the article entitled 'Morphology of the Skull Base in Individuals with Apert Syndrome'. This is a cross-sectional study carried out by the authors Aline Cassia Inocencio, José Rino Neto, Cassio Eduardo Raposo do Amaral, Fausto Mendes, Susana Silva and Ana Lidia Ciamponi.

The treatment protocol for this rare syndrome (1/100,000 live births) involves multidisciplinary therapy based mainly on surgical interventions on the skullcap, however the skull base is the most affected structure in these individuals.

We performed a study with cephalometric measures to determine if there was a difference in the morphology of the skull base compared with non-syndromic individuals. Our findings demonstrated that there is a difference in the morphology of the skull base of these patients and that they can influence future treatments, both surgical and orthodontic.

We declare that the present work is original and has not been published or forwarded for publication in any other periodical or scientific journal. In addition, there is no conflict of interest and there was no external funding for this study to be carried out.

Thank you for considering our manuscript for publication in Orthodontics and Craniofacial Research.

Best regards,

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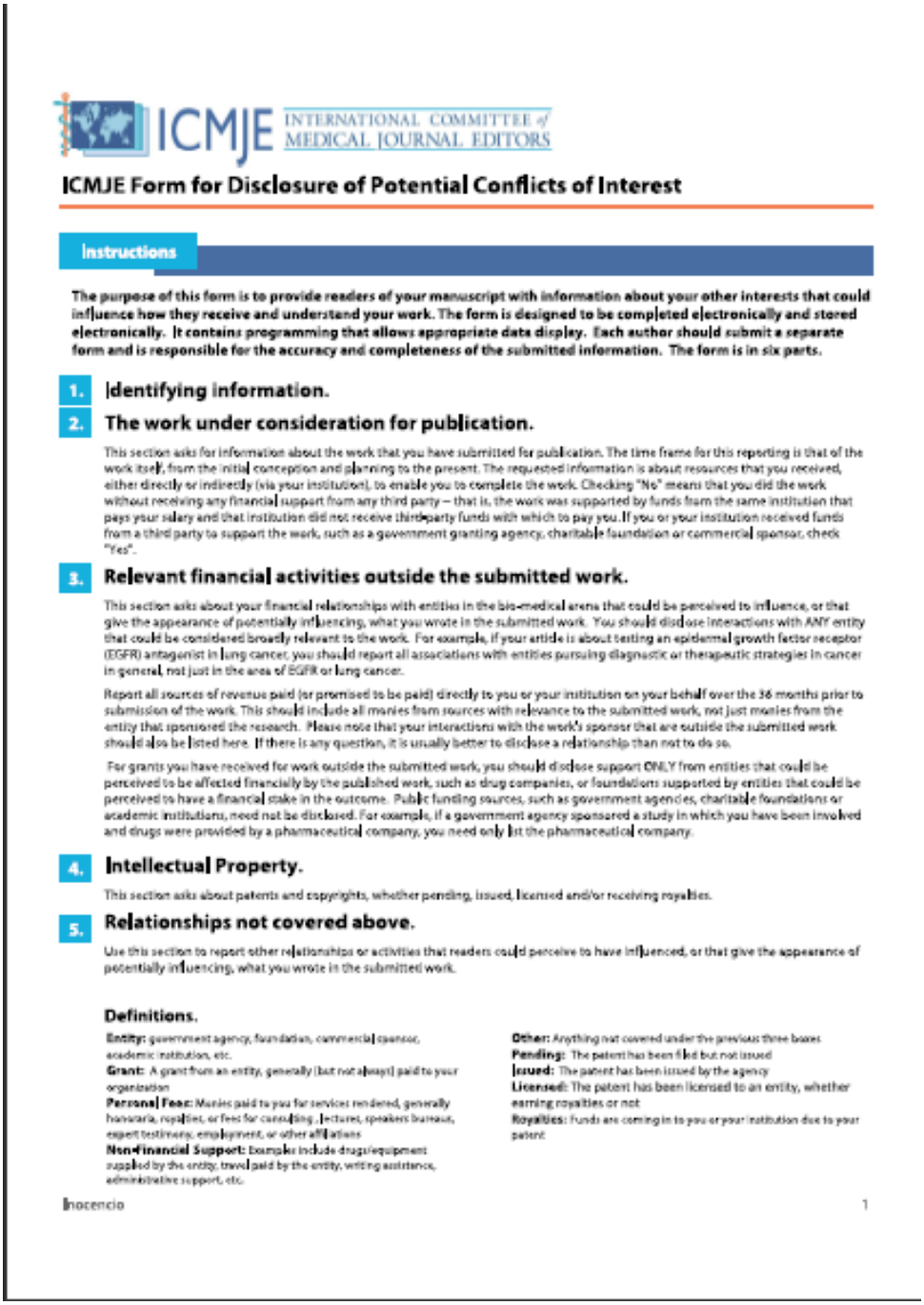
Disclosure of Potential Conflicts and Interests



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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

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Dr. Inocencio has nothing to disclose.

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Dr. Ciamponi has nothing to disclose.

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Dr. do Amaral has nothing to disclose.

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Dr. Mendes has nothing to disclose.

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Author Guidelines

Sections

1. SUBMISSION

Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at https://mc.manuscriptcentral.com/ocr

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Orthodontics & Craniofacial Research is published to serve its readers as an international forum for the presentation and critical discussion of issues pertinent to the advancement of the specialty of orthodontics and the evidence-based knowledge of craniofacial growth and development. This forum is based on scientifically supported information, but also includes minority and conflicting opinions.

The objective of *Orthodontics & Craniofacial Research* is to facilitate effective communication between the research community and practicing clinicians. Original Papers of high scientific quality that report the findings of clinical trials, clinical epidemiology, and novel therapeutic or diagnostic approaches are appropriate submissions. Similarly, we welcome papers in genetics, developmental biology, syndromology, surgery, speech and hearing, and other biomedical disciplines related to clinical orthodontics and normal and abnormal craniofacial growth and development. In addition to original and basic research, the journal publishes Critical Commentaries, Short Communications, Reviews, Letters, and Meeting Reports.

Orthodontics & Craniofacial Research is published quarterly. The review of submitted papers will be coordinated by the editor and members of the editorial board. It is policy to review manuscripts within 4 to 6 weeks of receipt and to publish within 3 to 6 months of acceptance.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

i. Original Research Articles

Original Research Articles of high scientific quality that report the findings of clinical trials, clinical epidemiology, and novel therapeutic or diagnostic approaches are appropriate submissions. Similarly, we welcome papers in genetics, developmental biology, syndromology, surgery, speech and hearing, and other biomedical disciplines related to clinical orthodontics and normal and abnormal craniofacial growth and development. Only manuscripts reporting the results of original clinical or clinically relevant investigations are suitable for publication.

Word limit: 4,000 words maximum, excluding Title page, Abstract, References figure legends and Acknowledgment; including Introduction, Materials and Methods, Results, Discussion, Conclusions.

Abstract: 250 words maximum; must be structured, under the sub-headings: Objective(s), Materials and Methods (include design, setting, subject and main outcome measures as appropriate), Results, Conclusion.

References: Maximum of 40 references.

Figures/Tables: Total of no more than 6 figures and/or tables.

Main text structure: The main text should be structured under the headings Introduction, Material and Methods, Results, Discussion, Conclusions.

ii. Short Communications

Priority will be given to communications relating to primary research data. This section permits time-sensitive material to be published within 6 months of submission.

Word limit: 2,000 words maximum, excluding references.

Abstract: 150 words maximum.

References: Maximum 20 references.

Figures/Tables: Total of no more than 3 figures and/or tables.

Main text structure: The main text should be structured under the headings Introduction, Material and Methods, Results, Discussion, Conclusions.

iii. Reviews

Systematic reviews and meta-analyses are preferred above narrative reviews.

Word limit: 5,000 words maximum.

Abstract: 250 words maximum.

References: No limit.

Figures/Tables: Total of no more than 6 figures and/or tables.

Main text structure: Headings may be used as appropriate.

iv. Letters to the Editor

Letter to the Editor are encouraged to stimulate scientific discussions on recently published papers. The Editor will refer them to the authors. The readers' comments and authors' replies may subsequently be published together.

Word limit: 1,500 words maximum, excluding references.

References: Maximum 5 references.

Tables and Figures: Total of no more than 1 figure or table.

v. Meeting Reports

Proceedings of significant meetings may also be published at the discretion of the Editor-in-Chief.

Case Reports are no longer accepted.

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Cover letters are not mandatory; however, they may be supplied at the author's discretion.

Parts of the Manuscript

The manuscript should be submitted in separate files: title page; main text file; figures.

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The title page should contain:

i. A short informative title containing the major key words. The title should not contain abbreviations (see Wiley's **best practice SEO tips**);

ii. A short running title of less than 40 characters;

iii. The full names of the authors;

iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;

v. Acknowledgments.

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Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section 'Conflict of Interest' in the **Editorial Policies and Ethical Considerations section** below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

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1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book

2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

Internet document

3. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf Accessed March 3, 2003

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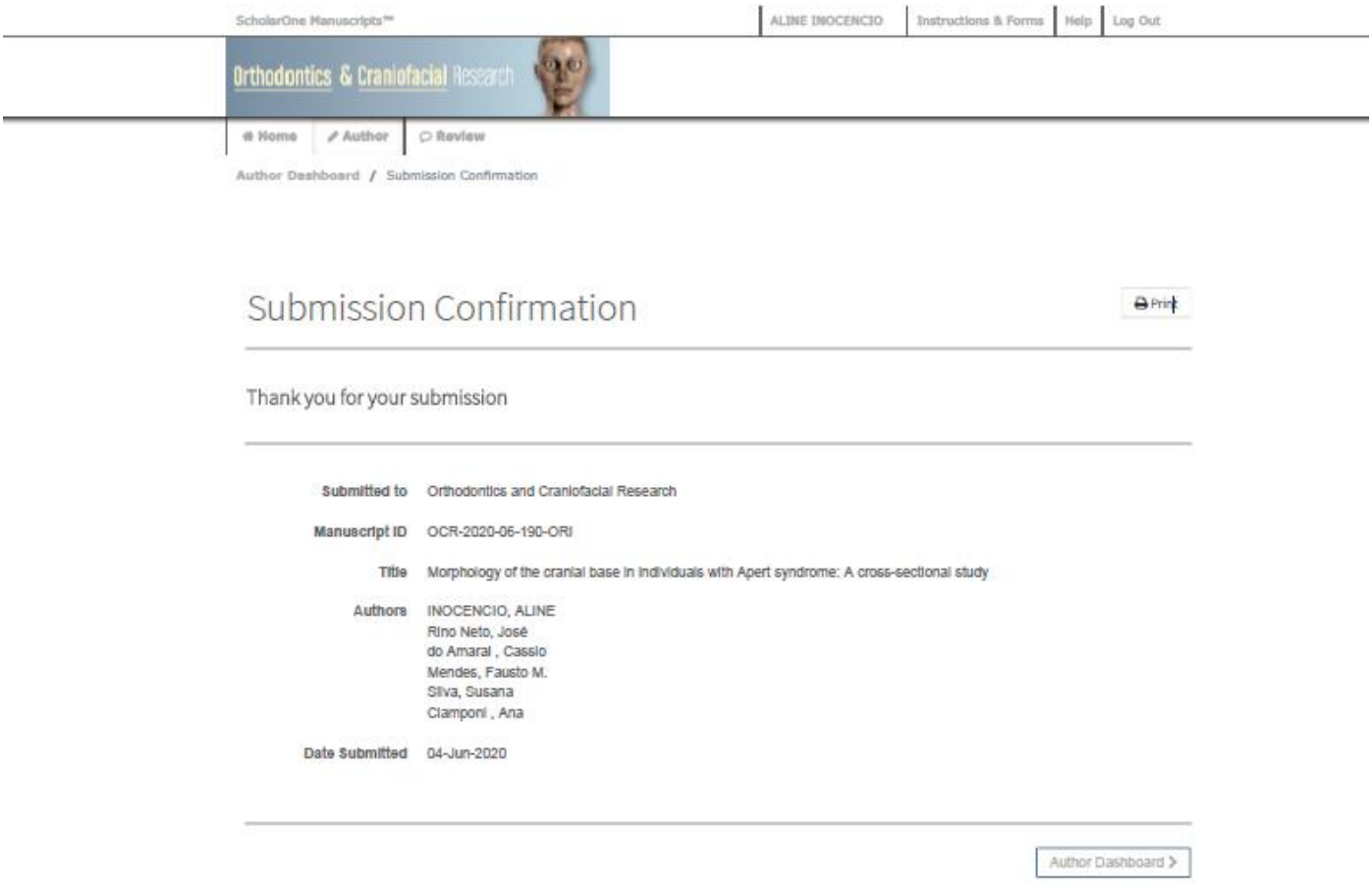

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COMITÊ DE ÉTICA EM PESQUISA

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Protocolo 1.366.060

CAAE: 50825415.8.0000.0075

Com base em parecer de relator, o Comitê de Ética em pesquisa **APROVOU** o protocolo de pesquisa Crescimento Craniofacial e padrão de apinhamento dentário em pacientes com Síndrome de Apert de responsabilidade da Pesquisadora Aline Cássia Inocêncio sob orientação da Professora Ana Lídia Ciamponi.

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São Paulo 30 de maio de 2016

Profa.Dra. Maria Gabriela Haye Biazevic

Coordenadora do CEP-FOUSP