UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

MARCOS LOYOLA BORÉM GUIMARÃES

# Ear Anomalies in Apert and Crouzon Syndromes – The Description and Classification of Radiology Evaluation

# Anomalias do Ouvido nas Síndromes de Apert e Crouzon – a Descrição e Classificação da Avaliação Radiológica

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Dissertação constituída pelo artigo apresentado 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: Prof.º Dr.º Cristiano Tonello

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BAURU
2022

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**HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS**

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# DEDICATÓRIA

Aos meus amados pais, Jane e Marcos, pela vida e por me guiarem nesta caminhada…

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“Um sonho sonhado sozinho é um sonho. Um sonho sonhado junto é realidade.”

**Yoko Ono**

# RESUMO

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Guimarães, MLB. Anomalias do ouvido nas Síndromes de Apert e Crouzon – a Descrição e Classificação da Avaliação Radiológica. [Dissertação]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2022.

**Introdução:** Craniosinostose é uma fusão prematura das suturas cranianas e pode estar associada a síndromes raras. Essas síndromes tem pelo menos 150 genes identificados e comumente estão relacionadas ao gene FGF. Apesar de haver algumas anormalidades de orelha externa, media e interna nestas síndromes, há uma escassez na literatura a respeito das principais anormalidades do osso temporal nos exames de imagem e a sua frêquencia nas Síndromes de Apert (SA) e Sindrome de Crouzon (SC)

**Objetivos:** Descrever as principais alterações do osso temporal nos exames de tomografia computadorizada (TC), classifica-las e aferir sua frequência nas SA e SC

**Métodos:** Avaliar as estruturas do osso temporal usando imagens de TC. Alterações envolvendo a orelha externa, media e interna, os grandes vasos (jugular e carótida) e nervo facial, assim como outras alterações significativas do osso temporal foram avaliadas e classificadas em cada segmento.

**Resultados:** Anormalidades da orelha externa foram encontradas em 64,3% nas orelhas da SA e 81,9% nas orelhas da SC, anormalidades da orelha média foram encontradas em 92% na SA e 81% nas orelhas da SC, anormalidades da orelha interna foram encontradas em 69,6% nas orelhas da SA e 9% nas orelhas da SC, o nervo facial estava anormal em 48,3% nas orelhas da SA e 47,8% das orelhas na SC, a veia jugular estava anormal em 37,5% nas orelhas da SA e 54,6% das orelhas da SC, a artéria carótida estava anormal em 14,3% das orelhas da SA e 20,5% das orelhas na SC.

**Conclusão:** A frequência das principais anomalias do osso temporal foi demonstrada nessas raras condições clinicas. O manejo global destas síndromes necessita abranger a avaliação do osso temporal em particular com exames de imagem. A frequência destas alterações faz com que possamos considerar fenotípico estas alterações nestas síndromes e podem compor protocolos de descrição delas. Ainda podemos avaliar o quão desafiador pode ser abordar o osso temporal destes pacientes.

**Descritores:** Craniossinostose, Síndrome de Apert, Síndrome de Crouzon, orelha/anormalidades, tomografia computadorizada

# ABSTRACT

# ABSTRACT

Guimarães, MLB. Ear Anomalies in Apert and Crouzon Syndromes – The Description and Classification of Radiology Evaluation [Dissertation]. Bauru: Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo; 2022.

**Introduction:** Craniosynostosis (CS) is a premature fusion of cranial sutures associated with rare syndromes. Those syndromes have at least 150 genes identified, and the most common syndromes are associated with FGF. Although there are some abnormalities of external, middle and inner ear in those syndromes, there is a shortage in the literature about the main anomalies in the temporal bone (TB) on imaging examinations and their frequency in patients with Apert syndrome (AS) and Crouzon syndrome (CS).

**Objectives:** describe the main alterations in the temporal bone on Computed Tomography (CT) scans, classify them and their frequency in the AS and CS.

**Methods:** evaluation of the structures of the temporal bone using CT scans. Anomalies involving the external, middle and inner ear, large vessels, facial nerve, as well as other significant temporal bone anomalies were evaluated and classified by means of specific classifications and descriptive findings associated with each segment.

**Results:** Anomalies in the external ear were found 64,3% of AS ears and 81,9% CS ears, the middle ear anomalies were found 92% of AS ears and 81% of CS ears, the inner ear anomalies were found 69,6% of AS ears and 9% of CS ears, the facial nerve was abnormal 48,3% of AS ears and 47,8% of CS ears, the jugular was abnormal 37,5% of AS ears and 54,6 of CS ears the carotid artery was abnormal 14,3% of AS ears and 20,5% of CS ears.

**Conclusion:** The frequency of the main anomalies in the TB were demonstrated on these rare clinical conditions. The global management of those patients needs to embrace an evaluation of the TB with imaging exams. These findings can be considered phenotypic of the syndromes, and can compose protocols for their description. Furthermore, one can measure how challenging it can be to approach the TB of those patients.

**Key words:** craniosynostosis, Apert Syndrome, Crouzon Syndrome, ear/abnormalities, computed tomography

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# SUMMARY

# 1 INTRODUCTION

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Craniosynostosis is a premature fusion of one or more cranial sutures with an estimated incidence of 1 to 2,000-2,500 live births. It can be spontaneous, syndromic or familial and may present in different forms (DI ROCCO, ARNAUD, RENIER, 2009). Only 8% of craniosynostosis are syndromic or familial (GOVERNALE, 2015). Apert syndrome (AS) and Crouzon syndrome (CS) are syndromic craniosynostosis (SC), with an incidence of 1: 65,000-200,000 in SA and 1: 60,000 in SC. (Irene et al. 2015) (Fearon et al. 2003)

SC often show mutations in six genes: FGFR2, FGFR3, TWIST1, EFNB1, TCF12 and ETS2 repressor factor (ERF) - with more than 150 identified forms. Mutation of the Fibroblast Growth Factor (FGF) gene leads to the most common SC, such as AS and CS. Others syndromes also have FGF mutations like Muenke Syndrome, Pfeiffer Syndrome, Beare Stevenson Syndrome, Jackson-Wiess Syndrome. Others common genes are TWIST1 expressed in Saethre-Chotzen Syndrome and EFNB1 gene expressed in craniofrontonasal syndrome. Most syndromes are autossomal dominant (Apert, Crouzon, Muenke, Pfeiffer, Saethere-Chotzen), but also have some recessive syndromes like Beare-Stevenson and Jack-Weiss (WANG, NAGY, DEMKE, 2016) (WILKIE et al. 2017)

AS e CS share some clinical findings such as: midface hypoplasia, ocular proptosis and elevated intracranial pressure. AS typically presents with bilateral coronal suture synostosis, enlargement of the anterior fontanelle and complex symmetrical syndactyly of the hands and feet. Other findings include pointed narrow palate, ocular hypertelorism, and oropharyngeal narrowing. (COHEN, KREIBORG, 1996), (SPRUIJT et al. 2015) (WANG, NAGY, DEMKE, 2016). CS presents complex cranial suture synostosis, divergent strabismus due to shallow orbits and ocular hypertelorism (HELMAN et al. 2014). (WANG, NAGY, DEMKE, 2016).

Another classically alteration described is the audiological involvement in these syndromes. Agochukwu, Solomon and Muenke. (2014) demonstrated hearing loss in 80% in AS and in CS 74% of patients. Zhou, Schwartz and Gopen (2009) demonstrated 10% did not have hearing loss, 10% mixed deficit, and 80% conductive

deficit in a sample of 20 AS. Orvidas et al. (1999) demonstrated in 15 patients in CS, 33% did not have hearing loss, 27% sensorineural hearing loss, 27% conductive hearing loss and 13% mixed hearing loss.

However there is a scarcity in the literature that demonstrates the alteration on computed tomography (CT) scans of the temporal bone (external, middle and inner ear) in AS and CS that can justify the high prevalence of hearing loss in the literature.

Therefore, this study aims to describe the main changes in the external, middle, inner ear and large vessels of the temporal bone in CT scans, classify them and their frequecy in the AS and CS.

# 2 OBJECTIVES

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Describe the main anomalies of the external ear, middle ear, inner ear, the large vessels of the temporal bone on CT scans in patients with Apert Syndrome and Crouzon Syndrome.

# 3 ARTICLE

# 3 ARTICLE

Article presented in this Dissertation was written according to The Cleft Palate-Craniofacial Journal instructions and guidelines for article submission.

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## Abstract:

**Objective:** To describe the main anomalies in the temporal bone (TB) using Computed Tomography (CT); to classify them and their prevalence in Apert Syndrome (AS) and Crouzon Syndrome (CS).

**Study Design:** Descriptive retrospective chart review

**Setting:** Tertiary referral center.

**Patients**: Fifty consecutive patients diagnosed with AS and CS were divided into the groups of AS and CS, obtaining 28 patients with AS and 22 patients with CS, totaling 100 ears evaluated.

**Interventions:** Diagnosis of anomalies involving the TB with CT evaluation.

**Main Outcome Measure:** to classify and determine the prevalence of anomalies of external, middle and inner ear, large vessels, facial nerve, and other significant TB anomalies.

**Results:** Anomalies in the external ear were found, 64.3% in AS and 81.9% in CS ears; anomalies in the middle ear were found, 92% in AS and 81% in CS ears; anomalies in the inner ear were found, 69.6% in AS and 9% in CS ears; anomalies in the facial nerve were 48.3% in AS and 47.8% in CS ears; jugular was abnormal, 37.5% in AS and 54.6 CS ears; the carotid artery was abnormal, 14.3% in AS and 20.5% CS ears.

**Conclusion:** The frequency of the main anomalies in the TB were demonstrated on these rare clinical conditions. The global management of those patients needs to embrace an evaluation of the TB with imaging exams. These findings can be considered phenotypic of the syndromes, and can compose protocols for their description. Furthermore, one can measure how challenging it can be to approach those patients` TB.

**Keywords:** Craniosynostosis, Apert syndrome, Crouzon syndrome, Ear Anomalies

## INTRODUCTION

Craniosynostosis is a premature fusion of cranial sutures with an estimated incidence of 1 to 2,000-2,500 live births. It can be spontaneous, syndromic, or familial and may present in different forms.[1] Only 8% of craniosynostoses are syndromic or familial.[2] Apert syndrome (AS) and Crouzon syndrome (CS) are syndromic craniosynostoses (SC), with an incidence of 1:65,000-200,000 in AS and 1:60,000 in CS. [3,4]

SCs often show mutations in six genes: FGFR2, FGFR3, TWIST1, EFNB1, TCF12 and ETS2 repressor factor (ERF) - with more than 150 forms identified. Mutation of the Fibroblast Growth Factor (FGF) gene leads to the most common SCs, such as and CS. [5,6]

AS e CS share some clinical findings, such as midface hypoplasia, ocular proptosis, and intracranial hypertension.[7] AS typically presents with bilateral coronal suture synostosis, enlargement of the anterior fontanelle, and complex symmetrical syndactyly of the hands and feet. Other findings include pointed narrow palate, ocular hypertelorism, and oropharyngeal narrowing.[8–11] CS presents complex cranial suture synostosis, divergent strabismus due to shallow orbits, and ocular hypertelorism [10,12,13]

Another classical alteration is the audiological involvement in these syndromes, demonstrated in the literature with hearing loss in 80% in AS and 74% in CS.[14] Other studies of AS demonstrated that 10% did not have hearing loss, 10% showed mixed deficits, and 80% conductive deficit in a sample of 20 patients. A sample of 15 patients of CS demonstrated that 33% did not have hearing loss, 27% had sensorineural hearing loss, 27% conductive hearing loss, and 13% mixed hearing loss.[15,16]

However, the anomalies of the TB (external, middle and inner ear) in AS and CS that can explain the high prevalence of hearing loss in the literature are poorly demonstrated on computed tomography (CT) scans.[12,14–18]

Therefore, this study aims to describe the main changes in the external, middle, inner ear and large vessels of the TB in CT scans, classify them and their prevalence in AS and CS.

## MATERIALS AND METHODS

This is a retrospective chart review of image exams describing the ear anomalies in a serial of cases of AS and CS, conducted at the Hospital for Rehabilitation of Craniofacial Anomalies of the University of São Paulo– HRAC/USP, the largest national reference for craniofacial anomalies in Brazil, and was approved by the ethics committee of HRAC/USP (2,993,880).

Inclusion criteria: consecutive patients diagnosed with AS and CS, who were evaluated in a specific outpatient clinic of the Craniofacial and Clinical Genetics team, and underwent (CT) of the temporal bones. Fifty medical records were analyzed, divided into the groups of AS and CS, obtaining 28 patients with AS and 22 patients with CS, totaling 100 ears evaluated (56 in AS and 44 in CS).

Exclusion criteria: Insufficient quality of the images to analyze ear structures, lack of images available in the medical record, lack of diagnosis, inconclusive diagnosis, or diagnosis of another syndrome.

### Imaging Exams:

The evaluation occurs through a analysis of the CT scans that was in a database made available by HRAC-USP, collected from different machines across the country. All CT scans were made for craniofacial preoperative purposes.

The evaluation of the structures used coronal, axial, and sagittal reconstructions of CT scans using the software RadiAnt DICOM Viewer. All CT scans have slices of 1mm or thinner and were analyzed by three ENT experts in craniofacial anomalies and otology and one ear anomalies expert radiologist.

Specific classifications and descriptive findings associated with each segment were used:

1. **External Ear:**

The classification described by Weerda[19] was used as reference for the following descriptive parameters:

A- Normality

B- Stenosis (type A of Weerda)

C- Atresia (Type B and C of Weerda)

D- Low ear insertion with cephalization of the external auditory canal (EAC)

2. **Middle Ear:**

The classification by Jahrsdoerfer[20] was used, in addition to the following descriptive parameters:

A- Evaluation of the tympanic cleft/middle ear space (It was evaluated with soft tissue content only or associated with hypoplasia/reduction of its dimensions, isolated hypoplasia, total absence of tympanic cleft, erosion of the tympanic bones)

B- Evaluation of the mastoid bone (evaluated for its pneumatization, size, development of the medullary bone, bone erosions, and soft tissue content).

C- Evaluation of the tympanic membrane (evaluated in its usual aspect, thickened or retracted.)

D- Evaluation of the ossicular chain (evaluated both in its integrity and in the presence of malformations)

E- Evaluation of the facial nerve (evaluated in its tympanic and mastoid portions, evident dehiscence, absence of nerve, double nerve, or anomalous path).

Jahsdoerfer scale: Scale of points of the middle ear structures and EAC, totaling 10 points:

- Presence of stapes (2 points),
- Presence of oval window (1 point),
- Space in the middle ear (1 point),
- Facial nerve in anatomical position (1 point),
- Hammer-anvil complex (1 point),
- Pneumatization of the mastoid (1 point),
- Anvil-stapes joint (1 point),
- Presence of a round window (1 point),
- Anomalous external ear (1 point).

### 3. Inner Ear

The classification by Sennaroglu[21] was used as reference for the following descriptive parameters:

A- Evaluation of the cochlea (presence of dysplasia/incomplete partitions, hypoplasia, common cavity and aplasia evaluated).

B- Evaluation of the vestibule (dilation, hypoplasia, aplasia or common cavity evaluated).

C- Evaluation of Semicircular Canal (Each canal was evaluated as absent, dilated, hypoplastic, or dehiscent).

D- Evaluation of the Cochlear Aqueduct (evaluated as enlarged following comparative parameters with the posterior semicircular canal and/or the absolute value above 1.5 mm).

E- Evaluation of the Vestibular Aqueduct (evaluated as enlarged following comparative parameters with the posterior semicircular canal and/or the absolute value above 1.5 mm)

F- Internal auditory canal (IAC) (Pathologically evaluated as atresic, dilated or stenotic, and morphologically as cylindrical, funnel- or bud-shaped).*

G- Evaluation of the relationship between the middle fossa and the inner ear, the lateral semicircular canal in the craniocaudal orientation.

*Classification used by Marques's for morphological classification of the normal IAC in cylindrical, bud-shaped, and funnel/cone shaped was used.[22]

**4. Large vessels (Jugular and carotid)**

The classification by Manjila[23] was used, in addition to the following descriptive parameters:

A- Jugular evaluation (evaluation of protrusion, dehiscence, stenosis, vascular malformations).

B- Carotid evaluation (evaluation of protrusion, dehiscence, stenosis, vascular malformations).

Classification by Manjila: Classifies the positional aspects of the jugular in the temporal bone as:

1) Normal jugular bulb;
2) High jugular bulb up to the lower margin of the posterior semicircular canal;
    a. without dehiscence for the middle ear and
    b. with dehiscence for the middle ear

3) Between the lower margin of the posterior semicircular canal and the margin of the internal auditory canal;
    a. without dehiscence for the middle ear and
    b. with dehiscence for the middle ear;
4) Above the lower margin of the internal auditory canal;
    a. without dehiscence for the internal auditory canal
    b. with dehiscence for the internal auditory canal;
5) Complex combination of dehiscences.

**RESULTS**

CTs of 50 patients were selected and 100 ears were evaluated (56 ears in the AS group and 44 ears in the CS group). Of these, 23 patients were female (14 AS and 9 CS) and 27 were male (14 AS and 13 CS). Ages ranging from 1 month to 34 years, 7 patients <1 years old, 11 patients between 1 – 5 years, 8 patients between 5 – 10 years, 9 patients between 10-15 years, 3 patients between 15-20 years, 5 patients between 20-25 years, 5 patients between 25-30 years and 2 patients between 30-34 years, with an average age of 11.2 years.

**EXTERNAL EAR**

The evaluation of the external ear focused on information about the EAC (Table 1). We can evaluate EAC stenosis (Werda Grade A) in 15 ears (8 in AS and 7 in CS). Incomplete (Werda Grade 2) or complete (Werda grade 3) atresia found in 7 ears (4 in AS and 3 in CS). We performed the evaluation of the low implantation of the ears in 50 ears (24 in AS and 26 in CS). (Figure 1)

**MIDDLE EAR**

Isolated malformations of the anvil were found in 4 ears in CS, stapes malformations were found in 6 ears (5 in AS and 1 in CS), fusion of the incudomalleolar joint was found in 9 ears (7 in AS and 2 in CS) and total chain malformation was found in 2 ears in CS (Table 1).

Hypopneumatization was found in 41 ears (29 in AS and 12 in CS); hypopneumatization associated with soft tissue content was found in 20 ears (15 in AS and 5 in CS). Finally, due to some patients' age, some mastoid bones were still under development with a medullary bone in 8 ears (6 in AS and 2 in CS) (Table 1).

Thickening of the tympanic membrane was found in 6 ears (2 in AS and 4 in CS), retraction was found in 17 ears in AS. Due to the tomographic limitation, when there is complete atresia or soft tissue content, sometimes this hindered the correct evaluation of the tympanic membrane through the present method; therefore, 19 ears could not be evaluated on the tympanic membrane (13 AS and 6 in CS) (Table 1).

Hypoplasia of the tympanic cleft was found in 17 ears (10 in AS and 7 in CS); hypoplasia with soft tissue content was found in 21 ears (16 in AS and 5 in CS) (Table 1).

Dehiscence of the tympanic portion of the facial nerve was found in only 2 ears in AS and anomalous position of the facial nerve path (its position evaluated as more anterior and/or lateralized than usual) was found in 44 ears (23 in AS and 21 in CS). Two ears could not be adequately assessed for the facial nerve (Table 1).

Using the classification by Jahrsdoerfer, we found 2 ears in CS with a score of 2; 2 ears in AS with a score of 4; 4 ears with a score of 5 (3 in AS and 1 in CS); 7 ears with a score of 6 (6 in AS and 1 in CS); 26 ears with a score of 7 (16 in AS and 10 in CS); 31 ears with score of 8 (16 from AS and 15 from CS); 16 ears with score of 9 (9 from AS and 7 from CS); 12 ears with score 10 (4 from AS and 8 of CS) (Table 2).

**INNER EAR**

All 100 ears evaluated had cochleas within normal limits. Vestibular hypoplasia was found in 4 ears of AS and vestibular dilation was found in 34 ears of AS. Important hypoplasia of the

lateral canal was found in 31 ears of AS and 1 ear was associated with hypoplasia of the upper semicircular canal (Figure 2). Evident dehiscence of the upper semicircular canal was found in 2 ears of CS. (Table 1)

Two ears of CS had vestibular aqueduct enlargement. Cochlear aqueduct enlargement using similar parameters was demonstrated in 3 ears of AS (Table 1).

No pathological changes in the IAC were found in the 100 ears evaluated. Analysis of the IAC morphology found 44 ears (24 AS and 20 CS) with cylindrical shape, 46 ears (28 AS and 18 CS) with bud shape and 10 ears (4 AS and 6 CS) in funnel shape (Table 1).

Lowering of the middle cranial fossa beyond the lateral canal was found in 56 ears (31 in AS and 25 in CS). Four ears could not be properly evaluated (Table 1).

**LARGE VESSELS**

The carotid artery was found protruding in the middle ear in 15 ears (6 in AS and 9 in CS), and 2 ears in AS presented stenosis with reduced caliber. Alterations of the intratemporal jugular vein are more frequent, protruding in the middle ear in 30 ears (15 in AS and 15 in CS), dehiscence in 15 ears (6 in AS and 9 in CS) (Figure 3) (Table 1).

The evaluation using the classification by Manjila demonstrates that 23 ears were classified as 2a (10 in AS and 13 in CS), 7 ears as 2b (2 in AS and 5 in CS), 3 ears as 3a (1 in AS and 2 in CS), 5 ears as 3b (2 in AS and 3 in CS), 3 ears as 4a in AS, 3 ears as 4b (2 in AS and 1 in CS), with no ears with classification 5 (Table 3).

**DISCUSSION**

Systematic and standardized evaluation of the external, middle, inner ear, and large vessels (jugular and intratemporal carotid) in patients with AS and CS is limited in the

literature.[3,4,10,12,14–16,24] This study gathers a large sample of patients with these rare syndromes compared to the literature, bringing na detailed methodology for assessing changes in the TB, with specific classifications, and also individualizing the prevalence of each alteration found. This was only possible because the HRAC/USP hospital conducts CT scans not only of the TB, but of all craniofacial structures, allowing the assessment of changes in several areas.[7,11,13]

Anomalies in the external ear, both in AS and CS, are usually described through the physical examination and otoscopy. The description of EAC anomalies, such as stenosis and atresia, are often associated with ear implantation dystopias, typical of syndromic diseases[14,25,26]. Our study consistently evaluated the EAC using CT scans, in line with other studies, demonstrating stenosis, atresia, and low ear implantation in our patients. Specifically, the dystopia of the positioning of the ears was often found, leading to a cephalized EAC and distorted anatomy. These alterations themselves already make ordinary hearing rehabilitations difficult, and also hinder access via the transcanal of otological surgery and distort the anatomy of the middle ear, mastoid, and middle fossa.[18,27]

Alterations in the middle ear in AS include effusive otitis media, recurrent acute otitis media, changes in tubal dysfunction, ossicular adaptation (primary stapes adjustment), ossicle malformation or fusion, and chronic otitis media.[14,25] Alterations in the middle ear in CS include changes in the tympanic membrane (thickened, retracted, perforated or atrophic), tympanosclerosis, atresia of the auditory canal, malformation and fixation of the anvil, otitis media with effusion, otosclerosis and changes of the stapes with fusion to the promontory, ankylosis from the hammer towards the outer wall of the epitympanum, distortions of the middle ear space, absence of the tympanic membrane, and recurrent infections of the middle ear.[14,24]

The evaluation of the 56 ears of AS was consistent with the findings of the literature, showing changes in the middle ear in 92.8% of the ears. Our study also reinforces the findings of alterations in the middle ear (81.8% of them) of the 44 ears of CS patients. These changes may explain the high prevalence of conductive hearing deficits in patients with AS and CS, still leading to real challenges for the complete cleaning of inflammatory tissues in the middle ear and mastoid, making ossicle chain reconstruction surgeries difficult. [28]

The facial nerve in its tympanic and mastoid portion was evaluated mainly in terms of anomalous position (anterior and/or lateralized); these positions are frequent in patients with craniofacial anomalies and predispose to greater risks of injury to the facial nerve during otological procedures. This high incidence of changes (about 44.6% of the ears in AS and about 47.7% of the ears in CS) justifies the monitoring of the facial nerve in surgeries addressing these patients' TB. [29,30]

We used the Jahrsdoerfer classification to standardize scores on these patients' middle ear and EAC, as demonstrated in the literature. This classification is widely used to predict patients favorable to EAC reconstruction and placement of middle ear hearing prosthesis, surgical difficulties, and possible results.[31] We found a weighted average of 7.5 points for AS and 7.9 points for CS, with the majority of the ears with scores of 7 and 8 (lowest score was 2 and highest score was 10), demonstrating that these patients need detailed assessments of the middle ear structures, and that most of them have a satisfactory score for possible interventions if needed.[20,31]

Alterations of the inner ear are commonly found in patients with AS, frequently involving vestibular malformations. Alterations in the cochlear aqueduct, dilation of the vestibule, fusion of the bulbous vestibule with the lateral semicircular canal, cochlear hypoplasia, dehiscence of the posterior semicircular canal are described in the literature.[14,16] Our study reinforces the high

frequency of alterations in the inner ear in 69.6% of the ears of AS. These alterations are concentrated in the posterior labyrinth. Changes in the inner ear should always be investigated for these patients with hearing loss or alterations of neuropsycholinguistic abilities.[4,32] Our study demonstrated that there are no high frequency alterations in the inner ear of CS, which can serve as a basis for future comparisons.

The IAC of patients with AS and CS did not show pathological changes. We use a morphological classification used on a non-syndromic Brazilian population. This Brazilian study found a funnel shape in 58.3% of the ears, cylindrical shape in 30.9%, and a bud shape in 10.8% of them.[22] Our study found a high prevalence of bud-shaped IAC (46 ears in total), 50% of the ears in AS and 40.9% of ears in CS, meaning that this shape can be considered phenotypic of these syndromes. The cylindrical shape was found in 44 ears, the second most commonly found with a small difference from the bud shape.

The evaluation of the relation of the middle cranial fossa and the inner ear (lateral canal) is one of the parameters for preoperative assessment of surgeries with access to the mastoid bone to prevent iatrogenic lesion and later meningoencephalic herniation. The lowered fossae below the lateral semicircular canal can make access to the tympanic cleft difficult with a transmastoid approach.[33,34] Low middle cranial fossa has been frequently found in patients with craniofacial anomalies and our study found it at a high frequency in 56% of the ears (55% of the ears in AS and 56.8% of the ears in CS).

Vascular lesions in surgical procedures are considered one of the most dramatic complications in neuro-otological surgeries and have to be accurately evaluated preoperative in search for the position of the great vessels in the TB. Lesions of the jugular vein or carotid artery can occur during surgeries such as otological microsurgery for placement of a ventilation tube or adjacent surgeries like temporomandibular joint procedures in patients with craniofacial anomalies.[35–38]

The protrusion or dehiscence of the jugular in the middle ear is often described in AS patients. A study describes 12 cases (24 ears) of 20 AS patients.[14,16] Jugular alterations are also frequently described in CS patients, with another study describing alterations of protrusion in the middle ear and dehiscence of the jugular of CS patients in 12 ears of 11 patients, making this condition highly prevalent, thus having to be always accounted for.[14,39] More rarely, other anomalies can also occur, such as stenosis and vascular malformations.[14,40]

A high prevalence of jugular protrusion and dehiscence was demonstrated in our study. This high prevalence requires attention when performing neuro-otological surgeries in patients with AS or CS so that there are no inadvertent jugular lesions. Our hospital proposed evaluation protocols with CT to address the middle ear, TB, glenoid fossa, and temporomandibular joint preoperative in these patients due to the high incidence of potentially serious alterations. Despite the high frequency of jugular alterations, these would be more concentrated in classification 2 (bulging and/or dehiscence that does not reach the posterior semicircular canal); thus, a transpetrous approach to the posterior fossa can be achieved in the majority of the patients, unlike types 3 and 4 that hinder the access due the height of the jugular bulb.[23]

This study showed a higher number of patients with rare syndromes (AS and CS) compared to the literature. We can consider as limitations not having a matched control group, the use of retrospective samples only, and not considering audiometry and clinical changes available in medical records.

## CONCLUSION

By evaluating a large sample of patients with AS and CS, the frequency of the main anomalies in the TB were demonstrated on these rare clinical conditions. Anomalies were categorized according to classifications established in the literature and their frequency was individualized according to each group and each segment. Based on these results, it is concluded that the global

management of these patients requires the inclusion of an extensive evaluation of the TB with imaging exams because of the high prevalence of anomalies found in these syndromes. There were also findings that can be considered phenotypic of these syndromes, and protocols can be developed for their proper evaluation, description and diagnosis. Furthermore, this study demonstrated how challenging it can be to manage the TB of AS and CS patients, and a detailed assessment of these anomalies with imaging exams is required.

**REFERENCES**


1. Di Rocco F, Arnaud E, Renier D. Evolution in the frequency of nonsyndromic craniosynostosis: Clinical article. *J Neurosurg Pediatr*. 2009;4(1):21-25.

2. Governale LS. Craniosynostosis. *Pediatr Neurol*. 2015;53(5):394-401.

3. Fearon JA. Treatment of the Hands and Feet in Apert Syndrome : An Evolution in Management. *Plast Reconstr Surg*. Published online 2002:1-12.

4. Mathijssen IMJ. Guideline for Care of Patients With the Diagnoses of Craniosynostosis : Working Group on Craniosynostosis. *J Craniofac Surg*. 2015;26(6):1735-1807.

5. Wilkie AOM, Johnson D, Wall SA. Clinical genetics of craniosynostosis. *Curr Opin Pediatr*. 2017;29(6):622-628. doi:10.1097/MOP.0000000000000542

6. Jezela-Stanek A, Krajewska-Walasek M. Genetic causes of syndromic craniosynostoses. *Eur J Paediatr Neurol*. 2013;17(3):221-224.

7. Tonello C, Cevidanes LHS, Ruellas ACO, Alonso N. Midface Morphology and Growth in Syndromic Craniosynostosis Patients Following Frontofacial Monobloc Distraction. *J Craniofac Surg*. 2021;1(32):87-91.

8. Cohen MM, Kreiborg SA, Cohen MM, Kreiborg S. A clinical study of the craniofacial features in Apert syndrome. *Int J Oral Maxillofac Surg*. Published online 1996:45-53.

9. Spruijt B, Rijken BFM, Joosten KFM, et al. Atypical presentation of a newborn with Apert syndrome. *Child's Nerv Syst*. 2015;31(3):481-486.

10. Wang JC, Nagy L, Demke JC. Syndromic Craniosynostosis. *Facial Plast Surg Clin*

*North Am*. 2016;24(4):531-543.

11. Lu X, Forte AJ, Park KE, et al. Morphological Basis for Airway Surgical Intervention in Apert Syndrome. *Ann Plast Surg*. 2021;87(1):59-64.

12. Helman SN, Badhey A, Kadakia S, Myers E. Revisiting Crouzon syndrome: reviewing the background and management of a multifaceted disease. *Oral Maxillofac Surg*. 2014;18(4):373-379.

13. Lu X, Forte AJ, Park KE, et al. Airway Growth in Preoperative Patients with Crouzon Syndrome. *Facial Plast Surg Aesthet Med*. 2021;23(3):191-197.

14. Agochukwu NB, Solomon BD, Muenke M. Hearing loss in syndromic craniosynostoses: Otologic manifestations and clinical findings. *Int J Pediatr Otorhinolaryngol*. 2014;78(12):2037-2047.

15. Orvidas LJ, Fabry LB, Diacova S, McDonald TJ. Hearing and otopathology in Crouzon syndrome. *Laryngoscope*. 1999;109(9):1372-1375.

16. Zhou G, Schwartz LT, Gopen Q. Inner ear anomalies and conductive hearing loss in children with apert syndrome: An overlooked otologic aspect. *Otol Neurotol*. 2009;30(2):184-189.

17. Staal FCR, Ponniah AJT, Angullia F, Ruff C, Koudstaal MJ, Dunaway D. Describing Crouzon and Pfeiffer syndrome based on principal component analysis. *J Cranio-Maxillofacial Surg*. 2015;43(4):528-536.

18. Chen K, Liu L, Shi R, Wang P, Chen D, Xiao H. Correlation among external auditory canal anomaly, temporal bone malformation, and hearing levels in patients with microtia. *Ear, Nose Throat J*. 2017;96(6):210-217.

19. Weerda H. Classification of Congenital Deformities of the Auricle. *FACIAL Plast Surg*. 1988;(October).

20. Jahrsdoerfer RA HJ 3rd. Congenital malformations of the ear. *Am J Otol*. 1986;7(4):267-269.

21. Sennaroglu L, Saatci I. A New Classification for Cochleovestibular Malformations. *Laryngoscope*. 2002;(December):2230-2241.

22. Marques SR, Ajzen S, D´Ippolito G, Alonso L, Isotani S, Lederman H. Morphometric Analysis of the Internal Auditory Canal by Computed Tomography Imaging. *Iran J Radiol*. 2012;9(2):71-78.

23. Manjila S, Bazil T, Kay M, Udayasankar UK, Semaan M. Jugular bulb and skull base pathologies: Proposal for a novel classification system for jugular bulb positions and microsurgical implications. *Neurosurg Focus*. 2018;45(1):1-8.

24. da Silva DL, Neto FXP, Carneiro SG, et al. Síndrome de Crouzon: revisão de literatura. *Arq int otorrinolaringol*. Published online 2008:436-441.

25. Rajenderkumar D, Bamiou D, Sirimanna T. Management of hearing loss in Apert syndrome. *J Laryngol Otol*. 2005;119(5):385-390.

26. Ko JM. Genetic syndromes associated with craniosynostosis. *J Korean Neurosurg Soc*. 2016;59(3):187-191.

27. Droessaert V, Vanspauwen R, Offeciers E, Zarowski A, Van Dinther J, Somers T. Surgical treatment of acquired atresia of the external auditory ear canal. *Int Arch Otorhinolaryngol*. 2017;21(4):343-346.

28. Luers JC, Hüttenbrink KB. Surgical anatomy and pathology of the middle ear. *J Anat*. 2016;228(2):338-353.

29. Leonetti JP, Smith PG, Matz GJ, Beck DL. Facial nerve monitoring in otologic surgery: Clinical indications and intraoperative technique. *Ann Otol Rhinol Laryngol*. 1990;99(11):911-918. doi:10.1177/000348949009901111

30. Thomas J, Ghate G, Kumar A. Anomalies of the facial nerve: a surgeon's nightmare. *Int J Otorhinolaryngol Head Neck Surg*. 2018;4(5):1202.

31. de Brito R, Ventura LMP, Jorge JC, Oliveira EB, Lourencone LFM. An implantable hearing system as rehabilitation for hearing loss due to bilateral aural Atresia: Surgical technique and audiological results. J Int Adv Otol. Published online 2016;12(3):241-246.

32. Maximino LP, Ducati LG, Abramides DVM, Corrêa C de C, Garcia PF, Fernandes AY. Syndromic craniosynostosis: neuropsycholinguistic abilities and imaging analysis of the central nervous system. *Arq Neuropsiquiatr*. 2017;75(12):862-868.

33. Sergi B, Paludetti G. Transmastoid Approach to Repair Meningoencephalic Herniation in the Middle Ear. *J Neurol Surg Part B Skull Base*. 2012;73(S 02):97-101.

34. Peris-Celda M, Perry A, Carlstrom LP, Graffeo CS, Driscoll CLW, Link MJ. Key anatomical landmarks for middle fossa surgery: A surgical anatomy study. *J Neurosurg*. 2019;131(5):1561-1570.

35. De Carvalho GM, Guimarães AC, Vega F, Iwakura C, Paschoal JR, Pfeilsticker LN. Surgical disaster in temporomandibular joint: Case report. *Rev Esp Cir Oral y Maxilofac*. 2014;36(3):113-118.

36. Atmaca S, Elmali M, Kucuk H. High and dehiscent jugular bulb: Clear and present danger during middle ear surgery. *Surg Radiol Anat*. 2014;36(4):369-374.

37. Muderris T, Bercin S, Sevil E, Cetin H, Kiris M. A Potentially Catastrophic Anatomical Variation: Aberrant Internal Carotid Artery in the Middle Ear Cavity. *Case Rep Otolaryngol*. 2013;2013(Figure 3):1-3.

38. Brodish BN, Woolley AL. Major vascular injuries in children undergoing myringotomy for tube placement. *Am J Otolaryngol - Head Neck Med Surg*. 1999;20(1):46-50.

39. Van Die A, de Groot JAM, Zonneveld FW, Vaandrager JM, Beck FJA. Dehiscence of the Jugular Bulb in Crouzon`s Disease. *Laryngoscope*. 1995;105:432-435.

40. Dolores MP, Vander Woude DL, Barnes PD, Scott RM, Mulliken JB. Jugular foraminal stenosis in crouzon syndrome. *Pediatr Neurosurg*. 1997;25(5):252-255.

**FIGURES**

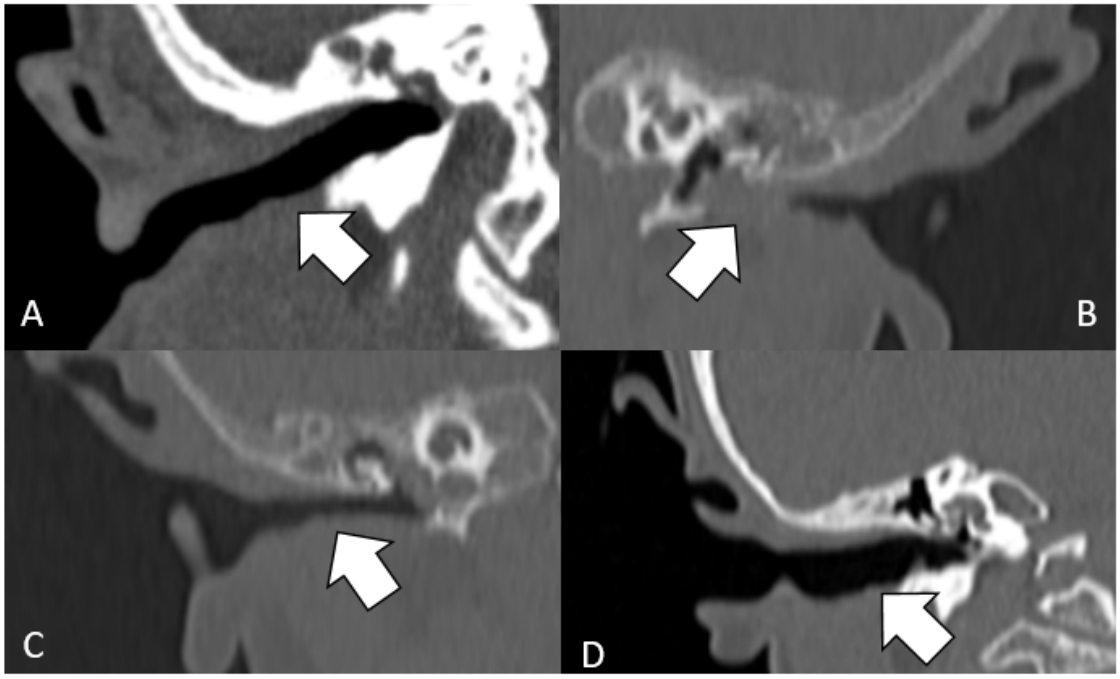


Figure 1: Coronal reconstruction of TC scan of the External Ear A: a low implantation of the ear with cephalization of EAC B- Atresia of the EAC C- Stenosis of the EAC D- Normal EAC

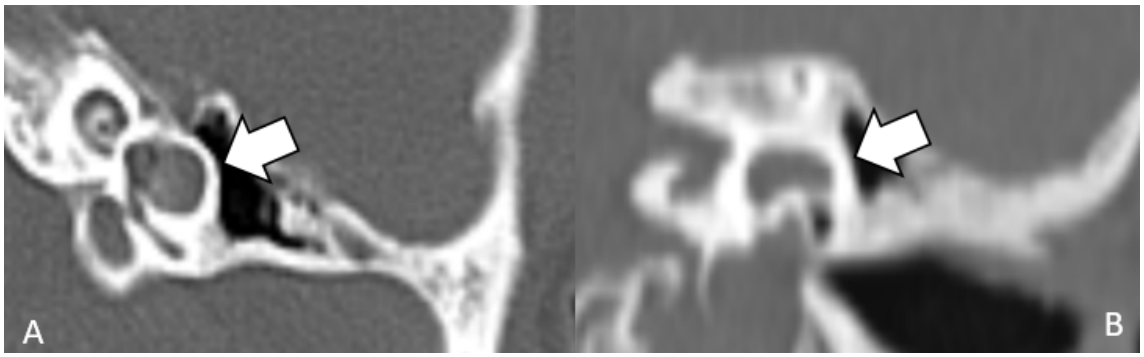


Figure 2: Axial and Coronal reconstruction of TC scan of the Inner ear showing vestibular dilatation with dilatation of the lateral semicircular canal

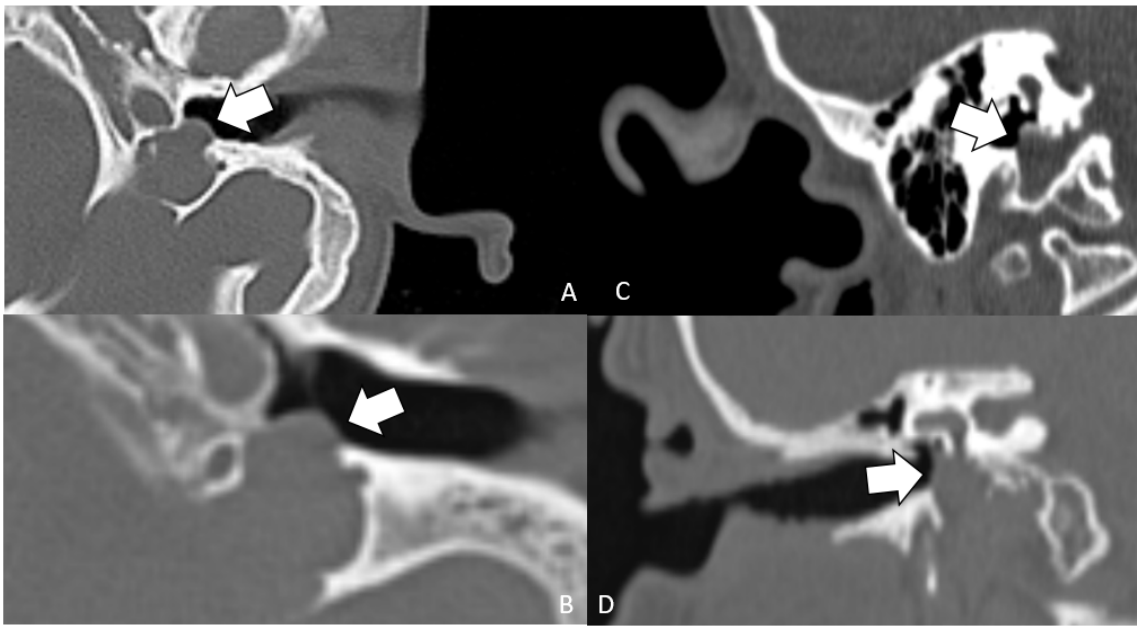


Figure 3: A & B- Axial reconstruction of TC scan of the Jugular vein protruding in the temporal bone C & D- Coronal reconstruction of TC scan of the Jugular vein dehiscent in the temporal bone.

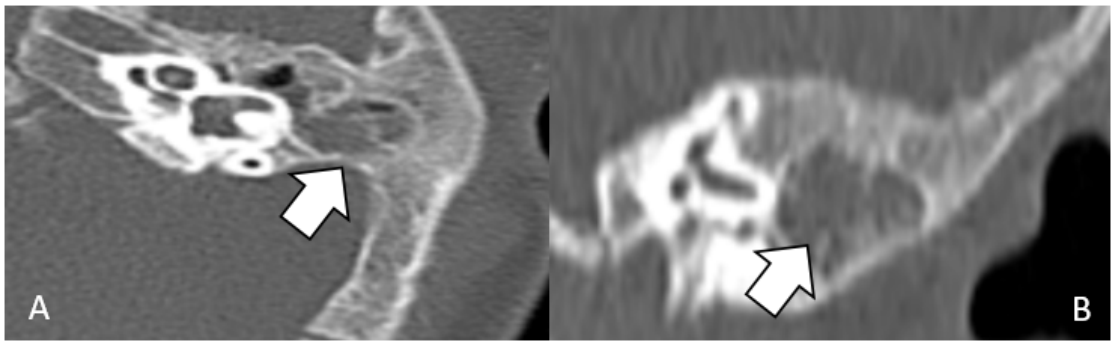


Figure 4: Axial and Coronal reconstruction of TC scan showing Hypopneumatized mastoid bone with soft tissue content.

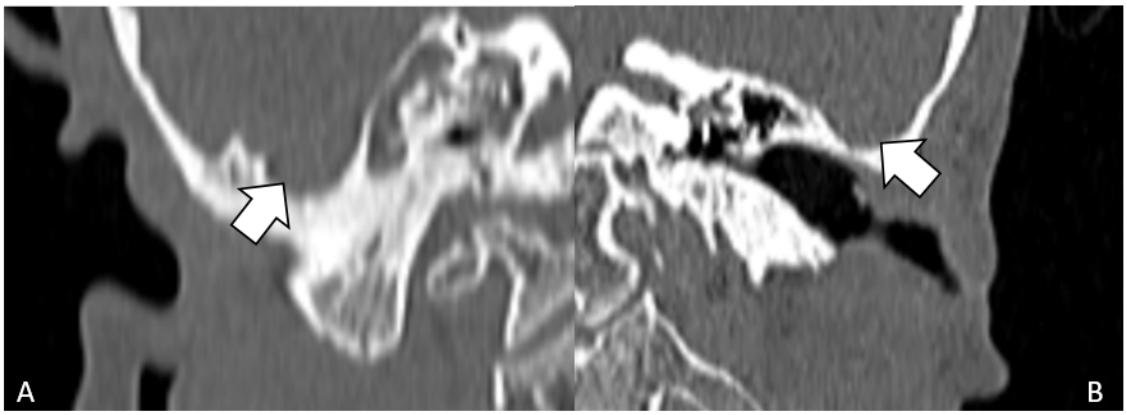


Figure 5: Coronal reconstruction of TC scan demonstrating lowered middle cranial fossa

## TABLES

### Table I. Age group

| Age | Apert Syndrome | Crouzon Syndrome | Total |
|---|---|---|---|
| <1 Year | 5 | 2 | 7 |
| 1 – 5 Year | 8 | 3 | 11 |
| 5 – 10 Year | 5 | 3 | 8 |
| 10 -15 Year | 4 | 5 | 9 |
| 15-20 Year | 1 | 2 | 3 |
| >20 Year | 5 | 7 | 12 |

### Table II. External, Middle, inner Ear and large vessels alterations

| External Ear | | Apert Syndrome | Crouzon Syndrome | Total |
|---|---|---|---|---|
| **External Auditory Canal** | | | | |
| | Normal | 20 (35,7%) | 8 (18,1%) | 28 |
| | Stenosis | 8 (14,2%) | 7 (15,9%) | 15 |
| | Atresia | 4 (7,1%) | 3 (6,8%) | 7 |
| | Low ear insertion | 24 (42,8%) | 26 (59,0%) | 50 |
| **Middle Ear** | | **Apert Syndrome** | **Crouzon Syndrome** | **Total** |
| **Ossicles** | | | | |
| | Normal | 44(78,5%) | 35(79,5%) | 79 |

| | | | | |
|---|---|---|---|---|
| | Anvil Malformation | 0 | 4(9%) | 4 |
| | Stapes Malformation | 5(8,9%) | 1(2,2%) | 6 |
| | Total malformation | 0 | 2(4,5%) | 2 |
| | Malleolus-Anvil Joint Fusion | 7(12,5%) | 2(4,5%) | 9 |
| **Mastoid Bone** | | | | |
| | Normal | 6(10,7%) | 25(56,8%) | 31 |
| | Hypopneumatized | 29(51,7%) | 12(27,2%) | 41 |
| | Hypopneumatized with soft tissue content | 15(26,7%) | 5(11,3%) | 20 |
| | under development | 6(10,7%) | 2(4,5%) | 8 |
| **Tympanic Membrane** | | | | |
| | Normal | 24(42,8%) | 34(77,2%) | 58 |
| | Thickened | 2(3,5%) | 4(9%) | 6 |
| | Retracted | 17(30,3%) | 0 | 17 |
| | Not evaluable | 13(23,2%) | 6(13,6%) | 19 |
| **Tympanic Cleft** | | | | |
| | Normal | 20(35,7%) | 30(68,1%) | 50 |
| | Soft Part Content | 10(17,8%) | 2(4,5%) | 12 |
| | Hypoplastic | 10(17,8%) | 7 (15,9%) | 17 |
| | Hypoplastic with soft tissue content | 16(28,5%) | 5(11,3%) | 21 |
| **Facil Nerve** | | | | |
| | Normal | 29(51,7%) | 23(52,2%) | 52 |
| | Dehiscent | 2(3,5%) | 0 | 2 |
| | Anomalous position (anterior / lateralized) | 23(41%) | 21(37,5%) | 44 |
| | Not evaluable | 2(3,5%) | 0 | 2 |
| **Inner Ear** | | **Apert Syndrome** | **Crouzon Syndrome** | **Total** |
| **Cochlea** | | | | |
| | Normal | 56(100%) | 44(100%) | 100 |
| **Vestibule** | | | | |
| | Normal | 18(32,1%) | 44(100%) | 62 |
| | Hypoplastic | 4(7,1%) | 0 | 4 |
| | Enlarged | 34(60,7%) | 0 | 34 |
| **Semicircular Canal** | | | | |

| | | | | |
|---|---|---|---|---|
| | Normal | 25(44,6%) | 42(95,4%) | 67 |
| | Hypoplasia of lateral semicircular canal | 30(53,5%) | 0 | 30 |
| | Hypoplasia of lateral and superior semicircular canal | 1(1,7%) | 0 | 1 |
| | Dehiscence of the upper semicircular canal | 0 | 2(4,5%) | 2 |
| **Vestibular Aqueduct** | | | | |
| | Normal | 56(100%) | 42(95,4%) | 98 |
| | Enlarged | 0 | 2(4,5%) | 2 |
| **Cochlear Aqueduct** | | | | |
| | Normal | 53(94,6%) | 44(100%) | 97 |
| | Enlarged | 3(5,3%) | 0 | 3 |
| **Internal Auditory Canal Morphology** | | | | |
| | Cylindrical | 24(42,8%) | 20(45,4%) | 44 |
| | Bud Shaped | 28(50%) | 18(40,9%) | 46 |
| | Funnel | 4(7,1%) | 6(13,6%) | 10 |
| **Relation of the Middle Cranial Fossa with the Inner Ear** | | | | |
| | Normal | 21(37,5%) | 17(38,6%) | 38 |
| | Lowered Middle Cranial Fossa | 31(55,3%) | 25(56,8%) | 56 |
| | Not evaluable | 4(7,1%) | 0 | 4 |

| **Large Vessels** | | **Apert Syndrome** | **Crouzon Syndrome** | **Total** |
|---|---|---|---|---|
| **Carotid** | | | | |
| | Normal | 48(85,7%) | 35(79,5%) | 83 |
| | Protruding | 6(10,7%) | 9(20.4%) | 15 |
| | Stenosis | 2(3,5%) | 0 | 2 |
| **Jugular** | | | | |
| | Normal | 35(62,5%) | 20(45,4%) | 55 |
| | Protruding | 15(26,7%) | 15(34%) | 30 |
| | Dehiscence | 6(10,7%) | 9(20,4%) | 15 |

**Table III. Jahrsdoerfer Scale**

| Jahrsdoerfer Scale | Apert Syndrome | Crouzon Syndrome | Total |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 1 | 0 | 0 | 0 |
| 2 | 0 | 2 | 2 |
| 3 | 0 | 0 | 0 |
| 4 | 2 | 0 | 2 |
| 5 | 3 | 1 | 4 |
| 6 | 6 | 1 | 7 |
| 7 | 16 | 10 | 26 |
| 8 | 16 | 15 | 31 |
| 9 | 9 | 7 | 16 |
| 10 | 4 | 8 | 12 |
| **Weighted Average** | 7,5 | 7,9 | 7,68 |

**Table IV. Jugular Classification (Manjila)**

| Jugular Classification | Apert Syndrome | Crouzon Syndrome | Total |
|---|---|---|---|
| 1 | 35(62,5%) | 20(44,4%) | 55 |
| 2a | 10(17,8%) | 13(29,5%) | 23 |
| 2b | 2(3,5%) | 5(11,3%) | 7 |
| 3a | 1(1,7%) | 2(4,5%) | 3 |
| 3b | 2(3,5%) | 3(6,8%) | 5 |
| 4a | 3(5,3%) | 0 | 3 |
| 4b | 2(3,5%) | 1(2,2%) | 3 |
| 5 | 0 | 0 | 0 |

# 4 FINAL CONSIDERATIONS

# 4 FINAL CONSIDERATIONS

1. The external, middle and inner ear of Apert and Crouzon Syndrome have abnormalities in each segment with a high frequency;
2. The large vessels of the temporal bone have a high frequency of alterations especially the jugular vein;
3. Those alterations can be part of the description of those syndromes;
4. The alterations need to be evaluated properly for the proper management of those syndromes;
5. The methodology we use can be used on other syndromes due to it detailed classifications and evaluations

# REFERENCES

## REFERENCES

AGOCHUKWU NB, SOLOMON BD, MUENKE M. **Hearing loss in syndromic craniosynostoses: Otologic manifestations and clinical findings**. International Journal of Pediatric Otorhinolaryngology, v. 78, n. 12, p. 2037–2047, 2014. Disponível em: <http://dx.doi.org/10.1016/j.ijporl.2014.09.019>.

ATMACA S, ELMALI M, KUCUK H. **High and dehiscent jugular bulb: Clear and present danger during middle ear surgery**. Surgical and Radiologic Anatomy, v. 36, n. 4, p. 369–374, 2014.

BRODISH BN, WOOLLEY AL. **Major vascular injuries in children undergoing myringotomy for tube placement**. American Journal of Otolaryngology - Head and Neck Medicine and Surgery, v. 20, n. 1, p. 46–50, 1999.

CHEN K, et al. **Correlation among external auditory canal anomaly, temporal bone malformation, and hearing levels in patients with microtia**. Ear, Nose and Throat Journal, v. 96, n. 6, p. 210–217, 2017.

COHEN MM, Kreiborg S. **A clinical study of the craniofacial features in Apert syndrome**. Int. J. Oral Maxillofac. Surg, p. 45–53, 1996.

TONELLO C, CEVIDANES LHS, RUELLAS ACO, et al. **Midface Morphology and Growth in Syndromic Craniosynostosis Patients Following Frontofacial Monobloc Distraction**. J Craniofac Surg, v. 1, n. 32, p. 87–91, 2021.

DI ROCCO F, ARNAUD E, RENIER D. **Evolution in the frequency of nonsyndromic craniosynostosis: Clinical article**. Journal of Neurosurgery: Pediatrics, v. 4, n. 1, p. 21–25, 2009.

DIE, VA, et al. **Dehiscence of the Jugular Bulb in Crouzon`s Disease**. Laryngoscope, Van die, A.; et al. Dehiscence of the jugular bulb in Crouzon`s Disease. Laryngoscope v105, p. 432-435, 1995, v. 105, p. 432–435, 1995.

DOLORES MP, et al. **Jugular foraminal stenosis in crouzon syndrome**. Pediatric Neurosurgery, v. 25, n. 5, p. 252–255, 1997.

DROESSAERT V, et al. **Surgical treatment of acquired atresia of the external auditory ear canal**. International Archives of Otorhinolaryngology, v. 21, n. 4, p. 343–346, 2017.

FEARON JA. **Treatment of the Hands and Feet in Apert Syndrome : An Evolution in Management**. PLASTIC AND RECONSTRUCTIVE SURGERY, p. 1–12, 2002.

GOVERNALE LS. **Craniosynostosis**. Pediatric Neurology, v. 53, n. 5, p. 394–401, 2015.

GUPTA S, et al. **Imaging the Facial Nerve: A Contemporary Review**. Radiology Research and Practice, v. 2013, p. 1–14, 2013.

HELMAN SN, et al. **Revisiting Crouzon syndrome: reviewing the background and management of a multifaceted disease**. Oral and Maxillofacial Surgery, v. 18, n. 4, p. 373–379, 2014.

JAHRSDOERFER RA, HALL JW 3rd. **Congenital malformations of the ear.** The American Journal of Otology, v. 7, n. 4, p. 267–269, 1986.

JEZELA-STANEK A e KRAJEWSKA-WALASEK M. **Genetic causes of syndromic craniosynostoses**. European Journal of Paediatric Neurology, v. 17, n. 3, p. 221–224, 2013. Disponível em: <http://dx.doi.org/10.1016/j.ejpn.2012.09.009>.

KO JM. **Genetic syndromes associated with craniosynostosis**. Journal of Korean

Neurosurgical Society, v. 59, n. 3, p. 187–191, 2016.

LEONETTI JP, et al. **Facial nerve monitoring in otologic surgery: Clinical indications and intraoperative technique**. Annals of Otology, Rhinology & Laryngology, v. 99, n. 11, p. 911–918, 1990.

LIU C, et al. **The molecular and cellular basis of Apert syndrome**. Intractable & Rare Diseases Research, v. 2, n. 4, p. 115–122, 2013.

DE BRITO R, VENTURA LMP, JORGE JC, OLIVEIRA EB, LOURENCONE LFM. An implantable hearing system as rehabilitation for hearing loss due to bilateral aural Atresia: Surgical technique and audiological results. J Int Adv Otol. Published online 2016;12(3):241-246..

LU X, FORTE AJ, PARK KE, et al. Morphological Basis for Airway Surgical Intervention in Apert Syndrome. *Ann Plast Surg*. 2021;87(1):59-64.

LUERS JC, HÜTTENBRINK KB. **Surgical anatomy and pathology of the middle ear**. Journal of Anatomy, v. 228, n. 2, p. 338–353, 2016.

DE CARVALHO GM, et al. **Surgical disaster in temporomandibular joint: Case report**. Revista Espanola de Cirugia Oral y Maxilofacial, v. 36, n. 3, p. 113–118, 2014. Disponível em: <http://dx.doi.org/10.1016/j.maxilo.2012.06.006>.

MANJILA S, et al. **Jugular bulb and skull base pathologies: Proposal for a novel classification system for jugular bulb positions and microsurgical implications**. Neurosurgical Focus, v. 45, n. 1, p. 1–8, 2018.

MARQUES SR et al. **Morphometric Analysis of the Internal Auditory Canal by Computed Tomography Imaging**. Iranian Journal of Radiology, v. 9, n. 2, p. 71–78, 2012.

MATHIJSSEN IMJ. **Guideline for Care of Patients With the Diagnoses of Craniosynostosis : Working Group on Craniosynostosis**. J Craniofac Surg, v. 26, n. 6, p. 1735–1807, 2015.

MAXIMINO LP, et al. **Syndromic craniosynostosis: neuropsycholinguistic abilities and imaging analysis of the central nervous system**. Arquivos de Neuro-Psiquiatria, v. 75, n. 12, p. 862–868, 2017.

MUDERRIS T, et al. **A Potentially Catastrophic Anatomical Variation: Aberrant Internal Carotid Artery in the Middle Ear Cavity**. Case Reports in Otolaryngology, v. 2013, n. Figure 3, p. 1–3, 2013.

ORVIDAS LJ. e et al. **Hearing and otopathology in Crouzon syndrome**. Laryngoscope, v. 109, n. 9, p. 1372–1375, 1999.

PERIS-CELDA, M, et al. **Key anatomical landmarks for middle fossa surgery: A surgical anatomy study**. Journal of Neurosurgery, v. 131, n. 5, p. 1561–1570, 2019.

RAJENDERKUMAR D, BAMIOU D, SIRIMANNA T. **Management of hearing loss in Apert syndrome**. Journal of Laryngology and Otology, v. 119, n. 5, p. 385–390, 2005.

RODRIGUEZ, K, SHAH, RK, KENNA M. **Anomalies of the Middle and Inner Ear**. Otolaryngologic Clinics of North America, v. 40, n. 1, p. 81–96, 2007.

SENNAROGLU L e SAATCI I. **A New Classification for Cochleovestibular Malformations**. The Laryngoscope, n. December, p. 2230–2241, 2002.

SERGI B, PALUDETTI G. **Transmastoid Approach to Repair Meningoencephalic Herniation in the Middle Ear**. Journal of Neurological Surgery Part B: Skull Base, v. 73, n. S 02, p. 97–101, 2012.

Da SILVA DL, et al. **Síndrome de Crouzon: revisão de literatura**. Arq. int. otorrinolaringol. (Impr.), p. 436–441, 2008.

SPRUIJT B, et al. **Atypical presentation of a newborn with Apert syndrome**. Child's Nervous System, v. 31, n. 3, p. 481–486, 2015.

STAAL, FCR, et al. **Describing Crouzon and Pfeiffer syndrome based on principal component analysis**. Journal of Cranio-Maxillofacial Surgery, v. 43, n. 4, p. 528–536, 2015. Disponível em: <http://dx.doi.org/10.1016/j.jcms.2015.02.005>.

THOMAS J, GHATE G, KUMAR, A. **Anomalies of the facial nerve: a surgeon's nightmare**. International Journal of Otorhinolaryngology and Head and Neck Surgery, v. 4, n. 5, p. 1202, 2018.

TONELLO, Cristiano (Medical School/USP). **Three-dimensional image evaluation of midface morphological features and growth in syndromic craniosynostosis patients following frontofacial monobloc distraction [thesis]**. 2016.

WANG JC, NAGY L, DEMKE, JC. **Syndromic Craniosynostosis**. Facial Plastic Surgery Clinics of North America, v. 24, n. 4, p. 531–543, 2016. Disponível em: <http://dx.doi.org/10.1016/j.fsc.2016.06.008>.

WEERDA, H. **Classification of Congenital Deformities of the Auricle**. FACIAL PLASTIC SURGERY, n. October, 1988.

WILKIE AOM, JOHNSON D, WALL SA. **Clinical genetics of craniosynostosis**. Current Opinion in Pediatrics, v. 29, n. 6, p. 622–628, 2017.

XIAONA L, et al. **Airway Growth in Preoperative Patients with Crouzon Syndrome**. Facial Plast Surg Aesthet Med, v. 23, n. 3, p. 191–197, 2021.

ZHOU G, SCHWARTZ LT, GOPEN Q. **Inner ear anomalies and conductive hearing loss in children with apert syndrome: An overlooked otologic aspect**. Otology and Neurotology, v. 30, n. 2, p. 184–189, 2009.

# ANNEXES

**ANEXO 1 – Declaração de uso exclusivo de artigo a ser publicado em periódico de língua inglesa**

**DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS**

We hereby declare that we are aware of the article (Ear Anomalies in Apert and Crouzon Syndromes – The Description and Classification of Radiology Evaluation) will be included in Dissertation of the student Marcos Loyola Borém Guimarães were not used and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.

Bauru, de 2022 .

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| Luiz Fernando Manzoni Lourençone |  |
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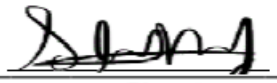
| Silvio Garcia Meira Junior |  |
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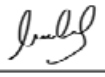
| Michele Madeira Brandão |  |
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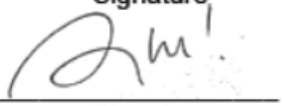
| Rubens Vuono de Brito Neto |  |
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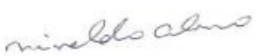
| Nivaldo Alonso |  |
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| Cristiano Tonello |  |
| Author | Signature |

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## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Alterações Otológicas e Auditivas em Pacientes com Craniossinostose
**Pesquisador:** Marcos Loyola Borém Guimarães
**Área Temática:**
**Versão:** 2
**CAAE:** 98138718.9.0000.5441
**Instituição Proponente:** Hospital de Reabilitação de Anomalias Craniofaciais da USP
**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 2.993.880

**Apresentação do Projeto:**
Trata-se da segunda versão do projeto de Pesquisa de Atualização, de autoria de Marcos Loyola Borém Guimarães sob orientação de Dr. Luiz Fernando Manzoni Lourençone e co-orientação de Dr. Critiano Tonello. Trata-se de um estudo retrospectivo de análise de prontuários e exames de imagens. O estudo será conduzido no Hospital de Reabilitações de Anomalias Craniofaciais da Universidade de São Paulo – HRAC/USP, após aprovação do Comitê de Ética em Pesquisa desta instituição. Serão selecionados pacientes com diagnóstico de craniossinostoses sindrômicas que foram avaliados em ambulatório específico da equipe craniofacial e que se submeteram a tomografia computadorizada (TC) e ressonância nuclear magnética (RNM) de crânio e ossos temporais. Exames de Imagem A avaliação das estruturas se dará com cortes coronais, axiais e/ou sagitais. Serão avaliadas anomalias envolvendo a orelha média e interna, assim como outras alterações do osso temporal significativas. A avaliação acontecerá por meio de estudo do exame de imagem que conste em anexo a prontuários dos pacientes, o qual serão analisados por três otorrinolaringologistas experientes.
Audiometria:Avaliação audiométrica será analisada através de dados de prontuário com a atenção para tipo e grau de perda auditiva.
Critérios de Exclusão:Qualidade insuficiente das imagens para analisar estruturas da orelha.

**Objetivo da Pesquisa:**
Objetivo Primário:

**Endereço:** Rua Silvio Marchione, 3-20
**Bairro:** Vila Nova Cidade Universitária **CEP:** 17.012-900
**UF:** SP **Município:** BAURU
**Telefone:** (14)3235-8421 **Fax:** (14)3234-7818 **E-mail:** cephrac@usp.br

Descrever as alterações do otológicas em pacientes com craniossinostose sindrômicas.

Objetivo Secundário:
Descrever as alterações auditivas em pacientes com craniossinostose sindrômicas.

**Avaliação dos Riscos e Benefícios:**
Riscos:
Não se aplica por envolver seres humanos indiretamente por dados obtidos em prontuários.
Benefícios:
Melhor compreensão das alterações otológicas e auditivas em pacientes com craniossinostose sindrômicas.

**Comentários e Considerações sobre a Pesquisa:**
Os pesquisadores atenderam as pendências solicitadas:

Pendência 1: Descrever na Metodologia o número de prontuários que serão analisados, tanto na Plataforma Brasil como no projeto detalhado.
a. Resposta: Acrescentado na Metodologia do projeto detalhado o número de prontuários que serão analisados. Ciente que esse número é uma estimativa média pela demanda do ambulatório. PENDÊNCIA ATENDIDA

Pendência 2: Esclarecer se haverá ou não a utilização de imagens de pacientes na publicação e em caso afirmativo, incluir no projeto o documento "Termo de Permissão para uso de Registros para Fins Científicos.
a. Resposta: O que está descrito na metodologia é descrever os principais achados, não estão programados imagens ilustrativas. Mas, visto a observação, optamos por incluir o termo de permissão para uso de registros para fins científicos. PENDÊNCIA ATENDIDA

Pendência 3: Adequar o cronograma na Plataforma Brasil. O início da coleta de dados deverá ser realizado somente após aprovação do projeto pelo CEP.
a. Resposta: Cronograma adequado na Plataforma Brasil. PENDÊNCIA ATENDIDA

**Considerações sobre os Termos de apresentação obrigatória:**
Carta de encaminhamento;
Formulário HRAC;

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Continuação do Parecer: 2.993.880

Folha de Rosto da Plataforma Brasil;
Justificativa de Dispensa de TCLE;
Termo de Compromisso, Confidencialidade e Autorização de Utilização de Dados em Projetos de Pesquisa
Termo de Compromisso de Tornar Públicos os Resultados da Pesquisa e Destinação de Materiais ou Dados Coletados;
Termo de Compromisso do Pesquisador Responsável;
Termo de permissão para uso de registros para fins científicos.

**Recomendações:**
Não há.

**Conclusões ou Pendências e Lista de Inadequações:**
Os pesquisadores atenderam as pendências solicitadas, sugiro ao CEP a aprovação do projeto.

**Considerações Finais a critério do CEP:**
O pesquisador deve atentar que o projeto de pesquisa aprovado por este CEP refere-se ao protocolo submetido para avaliação. Portanto, conforme a Resolução CNS 466/12, o pesquisador é responsável por "desenvolver o projeto conforme delineado", se caso houver alterações nesse projeto, este CEP deverá ser comunicado em emenda via Plataforma Brasil, para nova avaliação.
Cabe ao pesquisador notificar via Plataforma Brasil o relatório final para avaliação. Os Termos de Consentimento Livre e Esclarecidos e/ou outros Termos obrigatórios assinados pelos participantes da pesquisa deverão ser entregues ao CEP. Os relatórios semestrais devem ser notificados quando solicitados no parecer.

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1211354.pdf | 21/10/2018 17:22:30 | | Aceito |
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| Projeto Detalhado / Brochura Investigador | Projeto_Craniossinostoses.docx | 19/10/2018 16:09:11 | Marcos Loyola Borém Guimarães | Aceito |
| Cronograma | cronograma.docx | 19/10/2018 | Marcos Loyola | Aceito |

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| Cronograma | cronograma.docx | 16:09:00 | Borém Guimarães | Aceito |
| Outros | Checklist_Prot_Pesq_67_2018.pdf | 11/09/2018 16:30:08 | Rafael Mattos de Deus | Aceito |
| Orçamento | orcamento.pdf | 10/09/2018 20:52:46 | Marcos Loyola Borém Guimarães | Aceito |
| Projeto Detalhado / Brochura Investigador | Projeto_Craniossinostoses1.pdf | 10/09/2018 20:45:53 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Term_Comp_Tornar_Publico_Dest_Mat.pdf | 10/09/2018 20:45:00 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Carta_Encaminham.pdf | 06/09/2018 22:27:17 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Form_Cadastro_HRAC.pdf | 06/09/2018 22:17:21 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Term_Aquiesc.pdf | 06/09/2018 22:16:44 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Term_Comp_Conf_Aut_Dados.pdf | 06/09/2018 22:15:20 | Marcos Loyola Borém Guimarães | Aceito |
| Outros | Term_Comp_Pesq_Resp.pdf | 06/09/2018 22:14:36 | Marcos Loyola Borém Guimarães | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | Justif_Dispensa_TCLE.pdf | 06/09/2018 22:06:44 | Marcos Loyola Borém Guimarães | Aceito |
| Folha de Rosto | Folha_Rosto.pdf | 06/09/2018 22:04:57 | Marcos Loyola Borém Guimarães | Aceito |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

BAURU, 31 de Outubro de 2018

**Assinado por:**
**Renata Paciello Yamashita**
**(Coordenador(a))**