UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

DIOGO DOS SANTOS DA MATA REZENDE

LESÕES SINCRÔNICAS DOS MAXILARES: UM ESTUDO MULTICÊNTRICO RETROSPECTIVO.

SYNCHRONOUS JAWBONE DISEASES: A MULTICENTRIC RETROSPECTIVE STUDY.

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutor em Estomatopatologia, na Área de Patologia.

Thesis presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Oral Medicine and Oral Pathology, in Pathology area.

ORIENTADOR: PROF. DR. HELDER ANTONIO REBÊLO PONTES
CO-ORIENTADOR: PROF. DR. FELIPE PAIVA FONSECA

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RESUMO

O objetivo deste estudo foi descrever as características imaginológicas, aspectos clínicos e análises bioquímicas das lesões sincrônicas dos maxilares. Foi realizado um estudo transversal nos prontuários de 3 centros independentes de diagnóstico bucal e maxilofacial de 2 regiões do Brasil (Norte e Sudeste) de janeiro de 2007 a dezembro de 2019. Setenta e duas lesões sincrônicas dos maxilares foram incluídas neste estudo, os dados coletados foram analisados e tabulados pelos autores; os pacientes foram classificados de acordo com o tipo de lesão. Displasia óssea florida, síndrome de Gorlin-Goltz, querubismo, mieloma múltiplo e o tumor marrom do hiperparatireoidismo foram as lesões mais frequentes constatadas nesta série de casos. Além disso, a região posterior da mandíbula foi a principal região de ocorrência. Displasia óssea florida e síndrome de Gorlin-Goltz representaram dois terços da nossa amostra. Com a utilização de informações demográficas, clínicas e radiológicas adequadas é possível estabelecer o correto diagnóstico da maioria das lesões sincrônicas dos maxilares. Em alguns casos, porém, exames complementares são necessários, como analises histopatológicas, imuno-histoquímica e bioquímicas.

Palavras-chave: Patologia bucal, Estomatologia, Mieloma múltiplo, Hiperparatireoidismo, Maxilares.

ABSTRACT

The aim of this study is to describe the image features, the clinical descriptions, and the biochemical analysis of synchronous jawbone diseases. Data of patients seen over 13 years were extracted from the files of three Oral Radiology and Pathology diagnostic centres in Brazil. The clinical, radiographic and laboratory characteristics were tabulated and analysed by the authors; the patients were described according to lesion type. Seventy-two synchronous jawbone diseases were included in this study. Florid osseous dysplasia, Gorlin-Goltz syndrome, cherubism, multiple myeloma and brown tumour of hyperparathyroidism were the most frequent disorders reported in this case series. In addition, the posterior mandible area was the main site of manifestation. Florid osseous dysplasia and Gorlin-Goltz syndrome represented two-thirds of our samples. With the utilization of adequate demographic, clinical, and radiologic information, it is possible to diagnosis most of the synchronous lesions of jawbones. Sometimes, however, we need complementary exams, such as histopathologic, immunohistochemical reactions and biochemical analysis.

Keywords: Pathology, Oral medicine, Multiple myeloma, Hyperparathyroidism, Maxilla.

SUMÁRIO

1 INTRODUÇÃO

São classificadas como lesões sincrônicas aquelas patologias que afetam mais de uma região simultaneamente ou com uma diferença máxima de 6 meses entre elas. Estas diferem das lesões metacrônicas, as quais ocorrem após seis meses entre o prévio diagnóstico. Porém, em ambos os casos, deve-se excluir a possibilidade de recorrência ou metástase (Panosetti E, 1989; Znhag Q, 2011).

Em virtude da baixa ocorrência, heterogeneidade destas patologias, poucos dados epidemiológicos, com amplo aspecto radiográfico e não específicos (podem se apresentar como imagens radiolúcidas, radiopacas e/ou mistas, com limites definidos ou indefinidos) e muitas vezes com informações clínicas limitadas, estabelecer o correto diagnóstico pode representar um verdadeiro desafio profissional. (MacDonald D, 2020; Behere R, 2009).

Considerando que, nas bases de dados consultadas, os estudos disponíveis na literatura sobre lesões sincrônicas dos maxilares se limitaram a estudar um tipo específico de lesão, propomos relatar uma série de casos avaliando diferentes grupos de patologias. Nesta série de casos, descreveremos variadas alterações com ocorrência sincrônicas nos ossos maxilares, enfatizando a importância de correlacionar os aspectos clínicos, radiográficos, demográficos e, em alguns casos, também as análises histológicas, imuno-histoquímicas e bioquímicas, para estabelecer o correto diagnóstico.

2 ARTIGO

SYNCHRONOUS JAWBONE DISEASES: A MULTICENTRIC RETROSPECTIVE STUDY.

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ABSTRACT

The aim of this study is to describe the image features, the clinical descriptions, and the biochemical analysis of synchronous jawbone diseases. Data of patients seen over 13 years were extracted from the files of three Oral Radiology and Pathology diagnostic centres in Brazil. The clinical, radiographic and laboratory characteristics were tabulated and analysed by the authors; the patients were described according to lesion type. Seventy-two synchronous jawbone diseases were included in this study. Florid osseous dysplasia, Gorlin-Goltz syndrome, cherubism, brown tumour of hyperparathyroidism and multiple myeloma were the most frequent disorders reported in this case. In addition, the posterior mandible area was the main site of manifestation. Florid osseous dysplasia and Gorlin-Goltz syndrome represented two-thirds of our samples. With the utilization of adequate demographic, clinical, and radiologic information, it is possible to diagnosis most of the synchronous lesions of jawbones. Sometimes, however, we need complementary exams, such as histopathologic, immunohistochemical reactions and biochemical analysis.

Keywords: synchronous disease, jawbones, florid osseous dysplasia, Gorlin-Goltz syndrome, cherubism, brown tumour of hyperparathyroidism.

INTRODUCTION

Two or more lesions are considered synchronous when they affect more than one site at the same time, or have a maximum of six months difference between diagnoses, and are referred to metachronous when they occur at separate times (excluding the possibility of recurrence or metastasis)[1,2]. The diagnostic can represent a challenge for radiologist due to the uncommon occurrence, heterogeneity of these disorders, similar radiologic features, and the limited clinical and demographic information available about the patient at the time imaging[3]. The image exams can show a range of bone alterations including osteolytic, sclerotic, or mixed injuries in appearance[4].

Since the descriptions of the jaws synchronous disorders reported in the literature have been limited to the specific lesions, we propose to report in this study a series of cases on these conditions. In this case series, we describe a group of synchronous jawbone diseases (SJBD), emphasizing the importance of correlating the parameters of images with clinical, demographic, and some cases with histological and biochemical analysis to achieve the correct diagnosis.

MATERIALS AND METHODS

Study design and ethical approval

All cases in which patients had jawbones synchronous manifestations were retrospectively retrieved from the files from the Oral Medicine, Oral Pathology, and Oral and Maxillofacial Surgery Departments of the João de Barros Barreto University Hospital (Belém, Brazil), Piracicaba Dental School of the University of Campinas (Piracicaba, Brazil), and Clinics Hospital of the Medical School of the University of São Paulo (São Paulo, Brazil) from January 2007 to December 2019. The clinical data included sex, age, signs and symptoms, as well as the oral and maxillofacial affected sites. The available image findings of panoramic radiograph (PR), computed tomography (CT), or magnetic resonance imaging (MRI) were

registered. In some cases, biochemical analysis and histopathological information were necessary for diagnosis.

Apical periodontitis lesions, periodontitis, and disorders with inconclusive diagnosis were excluded. This study followed the guidelines proposed in the Helsinki Declaration and was approved by the local Institutional Ethical Committee.

RESULTS

Over 12 years, 72 SJBD cases were identified at the study centres. A total of 48 cases were excluded from the samples because they represented inflammatory diseases. The clinical and radiographic characteristics of each disorder founded in this sample are summarized in Table 1. The most frequent diseases were florid cemento-osseous dysplasia (FCOD) (33 cases; 45.8%), Gorlin-Goltz syndrome (GGS) (11 cases; 15.2%), and cherubism (6 cases; 8.3%). The lesions were more prevalent in females than males, with a male:female ratio of 1:2. The mean age of the patients was 37.6 years (range: 5-84 years).

FCOD was identified in 33 cases, representing 45.8% of all cases. The mean age was 51 years (range: 11-84). This group demonstrated a prevalence for female patients, with a male:female ratio of 1:32. The main diagnostic criteria were clinical exam (CE), PR, and CT (21 cases; 63.3%). Under radiographic evaluation, a well-defined image and dense radiopacities surrounded by radiolucent rims was demonstrated more frequently (23 cases, 69%). The patients were more affected in two quadrants for this injury (20 cases; 60.6%). The second most prevalent disease was GGS, with 11 cases (15.2%). The mean age was 23 years (range: 08–74). The male:female ratio was 8:3, demonstrating a prevalence for male patients. The lesions' diagnostic criteria included CE and PR in all 11 cases, and a clinical exam, PR, and CT in 6 cases (54.5%). The most observed radiographic aspects were well defined, unilocular,

radiolucent image (eight cases; 72.7%). The lesion showed mainly two affected quadrants (8 cases; 72.8%) followed by four affected quadrants (3; 27.2%).

Cherubism was found in 6 cases (8.3%). Cherubism did not demonstrate any sex predominance, with a male:female ratio of 1:1 and a mean age of 14.6 years (range: 5-36). The main diagnostic criteria for this lesion were CE and PR (6 cases; 100%). Radiographically, all lesions were presented as multilocular radiolucencies (6 cases; 100%). Four quadrants were affected for this syndrome in 5 cases (83.4%). Brown tumour of hyperparathyroidism (BTH) corresponded four cases (5.5%). BTH demonstrated a strong sex predominance for males (4 cases; 100%) at a mean age of 53 years (range: 29-64). Regarding the diagnostic criteria, CE, RP, CT, laboratory examination (LE), and biopsy were performed in all four cases. The most observed radiographic aspect was multiple radiolucencies (4 cases; 100%). BTH showed two affected quadrants in two cases and three quadrants in two cases.

Multiple myeloma was observed in four cases (5.5%). They were mainly seen in male patients with a mean age of 65 years old (range 54-84 years old). Diagnostic criteria evidenced CE, PR, CT, CT and biopsy were explored in all cases. Radiographic aspects showed radiolucent multilocular lesions in all analysed patients. MM evidenced four affected quadrants in four cases and two quadrants in two cases. Simple bone cyst (SBC) were found in three cases (4.1%). SBC was observed mainly in male patients (2 cases; 66.6%) and one case, the sex information was not reported; the mean age was 15 years (range: 13–19). In two cases, the diagnostic criteria were CE, PR, and CT (66.6%). The radiographic aspect mainly demonstrated a well-defined, unilocular, radiolucent image (two cases; 66.6 %). All cases had two affected quadrants.

Dentigerous cysts (DC) were seen in 2 cases (2.7%), both being male at a mean age of 8.5 years (range: 5–12). Radiographically, all cases presented were well-defined, unilocular,

radiolucent images associated with the crowns of an unerupted permanent tooth, and the diagnostic criteria were CE and PR (two cases; 100%). All cases had two affected quadrants. Langerhans cell histiocytosis (LCH) corresponded to 2 cases (2.7%). All cases occurred in males at a mean age of 14.5 years (range: 11–18). Under the main diagnostic criteria, CE, PR, and biopsy were performed in two cases (100%). All two cases presented an ill-defined, radiolucent image, and had four affected quadrants.

Paget's disease (PD) were found in 2 cases (2.7%). PD did not demonstrate any sex predominance (male, one case; female, one case), at a mean age of 49 years (range: 48–58). The main diagnostic criteria were CE, PR, CT, and LC. When radiographically evaluated, all lesions showed cotton wool-like radiopacity. Considering the affected quadrants, 1 case presented four affected quadrants, and the other case presented two quadrants that were affected. Gardner syndrome (GS) (2 cases; 2.7%) occurred exclusively in female at mean age 15.5 years (range: 13–18). In 1 case, the diagnostic criteria were CE and PR, and in the other, the criteria were CE, PR, and CT. Radiographically, the images presented were well-defined, unilocular, and dense radiopacities in one of the cases and an ill-defined, multilocular, radiolucent image in the other. Considering the affected quadrants, 1 case presented four affected quadrants (50%) and 1 case presented 2 affected quadrants (50%).

Central ossifying fibroma (OF) represented 1.38% (one case) of our sample: a 21-year-old woman, who underwent CE, PR, CT, LE, and biopsy. The radiographic aspect was a well-defined, unilocular, radiolucent image, and two mandibular quadrants were affected. Osteitis fibrosa cystica (OFC) was found in one case (1.38%), a 27-years-old man. Radiographs showed multiple radiolucencies and the diagnostic criteria were CE, PR, CT, LE, and biopsy; four quadrants were affected. Idiopathic osteosclerosis was observed in one case (1.38%) in a 74-years-old male patient. PR showed a generalized irregular radiopacity. Diagnosis was based on CE and PR, and lesion affected four quadrants of the patients.

DISCUSSION

To the best of our knowledge, this is the first description of a series of cases with different types of synchronic diseases of the jawbones. Although, all of us agree that it is imperative to have a holistic approach that combines the demographic, biochemical analysis, clinical and radiologic information with the diagnostic of SJBD, the discussion proposed by us is focused on image features with the other necessary data to complete the diagnosis of each disease shown in Table 2.

According to our study, the most prevalence SJBD was FCOD, representing almost 50% of all cases. This condition occurs above the inferior alveolar canal, surround the root apices of teeth or in edentulous areas[5]. The process is confined to an alveolar process, including interdental and interradicular septa. Subsequently, the newly formed bone spreads to the periodontal space without compromising pulp vitality and radicular reabsorption or changes in the dental positions (Figure 1A)[6]. FCOD presents as a symmetrical pattern, affecting at least two and, in many cases, even four quadrants. In the early immature osteolytic stage, the radiographic features are entirely radiolucent with a round or ovoid configuration, mimicking an inflammatory periapical lesion. The intermediate stage is characterised by a mixed radiolucent and radiopaque appearance (cotton wool appearance). In the final stage, the lesion becomes a densely mineralised mass (radiopaque), usually with a radiolucent rim[7]. When an SBC is associated with the FOCD, multilocular radiolucency can be detected and may result in an expanded or perforated cortical, as seen in three cases in the present series[5]. The FOCD diagnostic can be achieved by PR[8]. CT and cone-beam computed tomography (CBCT) should be performed in lesions in maxilla due to the greater difficulty of diagnosis. Kato et al.[9] showed that on CT examination, FOCDs can present with the cortical bone intact, slight thinning,

expansion, and is less frequently perforated. In addition, in all cases, the mandible is involved, especially in posterior areas, as observed in this study.

OF presents as an oval shape in general unilocular, with corticated margins and without root resorption, and according to the degree of calcification, completely radiolucent or as mixed images (Figure 1B)[10]. Expansion without perforation of cortical and displacement teeth are associated with larger lesions [11].Synchronous OF tends to occur in the mandible and maxilla, with one lesion in each area. Simultaneous lesions in the mandible, as seen in our work, are unusual. It is noteworthy that synchronous OF can be a manifestation of hyperparathyroidism[12].

Multiples odontogenic keratocysts (MOK) are one of the main clinical features of naevoid basal-cell carcinoma syndrome (NBCCS) or GGS. MOK occur in 75% to 90% of patients with NBCCS. The most common radiographic characteristics are multiple well-defined, unilocular radiolucencies, and the lower jaw is more affected than the upper jaw (Figure 1C)[3,18]. Abnormalities in vertebrae (fused or bifid) and ribs (fused, bifid, splayed, or missing) can be found, and calcification of falx cerebri is pathognomonic (Figure 2A). Also, there is frontal and temporoparietal bossing, prominent supra-orbital ridges, and increased occipitofrontal circumference (Figure 2B, 2C). It is noteworthy that the syndrome is associated with benign neoplasia and other comorbidities. For this reason, it is vital to establish an early diagnosis. In light of this question, it is important to keep in mind that MOKs represent the first sign in the syndrome in 75% of patients[19].

By definition, DC is always associated with the crowns of an unerupted permanent tooth at the cementoenamel junction, and almost all cases of DC synchronous described are associated with the third molars[20]. Radiographically, DC shows a unilocular radiolucent lesion of corticated borders of more than 5 mm. Synchronous DCs are rare, for the most part, in association with cleidocranial dysplasia, basal cell nevus syndrome, or mucopolysaccharidosis type IV[21,22]. In general, DCs are diagnosed in routine radiographic examination or while

researching an asymptomatic swelling. A pathological exam is fundamental for the correct diagnosis, because other cysts, like keratocysts, can mimic the image appearance of DC. MRI provides correct detail on the lesion contents helping in the identification of cyst fluid, with hypointense image on T1 and hyperdense on T2-weighted images[22].

Osteopetrosis is an inherited metabolic bone disorder with a clinical spectrum ranging from mild to severe that shows uniform and generalised sclerosis of the skeleton due to a failure in bone resorption (impaired osteoclast activity or development). Parallel bands of dense bone in the vertebrae and the long bones give the impression of 'bone-within-bone'. The condition causes obliteration of medullary spaces, especially long bones, skull (macrocephaly, frontal bossing), and spine, with increased bony trabeculae and thickened cortices (Figure 2D)[15]. The condition in jawbones lead the micrognathia. Another important sign seen in our cases was a thickening of lamina dura as an early sign and an alteration in the medullar bone, which masks the roots[16]. Delayed tooth eruption, tooth agenesis, enamel hypoplasia, and osteomyelitis of the jaws after surgical procedure are common findings[17].

PD presents, in general, in polyostotic form involving many bones of skeletal, with jawbones being involved in 15% of cases (Figure 3A-3C)[13]. The upper jaw is more affected than the lower jaw. In the early phase (osteolytic phase), radiolucent areas predominate (ground glasses appearance), leading to the loss of the lamina dura when the lesion involves the roots of teeth and migration and resorption of the roots of teeth. Now, in the osteoblastic phase, the radiopacity spreads in most of the areas, leading to the enlargement of the jaws, with alveolar ridges become widened (cotton wool appearance). Focal loss of lamina dura and hypercementosis allows the differentiation of PD from hyperparathyroidism[14]. Bone scintigraphy (Figure 3D-3H) is recommended to delineate the alteration of bone in the mandible (Lincoln`s sign)[13].

The face of children affected with cherubism resembles cherubs from the Renaissance due to expansion of the cortical bone and consequent swelling of the cheek. Although there are reports of a unilateral manifestation, these cases are not fully accepted as cherubism by the entire scientific community[23]. Under radiographic evaluation, the images have a radiolucent, multilocular aspect and well-defined borders (soap bubble appearance) located in the posterior regions of the mandible more than the maxilla. The anterior regions and the adjacent bones can also be affected in the most severe cases of the disease. Bone alterations start in the angle and ascending ramus, expanding from the mandibular to the body. Complete obliteration of the sinus is expected in more aggressive cases, and involvement of the orbital cavity can occur (Figure 4A-4B). In the mandible, the body, corpus, and angle are affected, with preservation of condylar regions[24]. Tooth displacement, root resorption, or agenesis are common features. Tooth agenesis is associated with higher advanced disease[23,25]. The CT is the gold standard for evaluating the bone lesions of the jaws (Figure 4C-4D). In our sample, men and women had an equal prevalence, and the four quadrants were equally affected.

BTH represents the third most common endocrine disorder after diabetes mellitus and thyroid disease26. Radiographically, the condition presents as a multiple, hypodense image or as a multiple well-defined, uni or multilocular radiolucency that is soap bubble-like, with the cortical bone expanded (ground-glass appearance) (Figure 1D)[27]. Untreated secondary hyperparathyroidism can progress to renal osteodystrophy (RO), which can cause alterations in jawbones in the form of renal osteitis fibrosa (OFi). In 90% of patients undergoing dialysis, RO is present[28]. In PR, OFi shows a diffuse ill-defined ground glass with poor corticomedullary distinction and expansion of the cortical (Figure 5). The early radiographic appearance of jawbone involvement in OFi are thinning of the cortices and loss of the lamina dura[29]. Root reabsorption and obliteration of the inferior alveolar canal are commonly found[30].

SBC can occur in association with FOCD, and SBC can manifest synchronously in jawbones. An et al.[31] and Chrcanovic and Gomez[32], after a systematic review on synchronous SBC, showed the most of lesions were located in the posterior mandibular region (body mandibular) and have been diagnosed in routine radiographic analysis (asymptomatic lesions). Interradicular scalloping is characteristic. In addition, the authors determined that the most usual radiographic appearance in multifocal SBC was unilocular with well-demarcated borders. The expansion of bone without perforation is more frequent in synchronous lesions than in solitary disease[32]. Moreover, root resorption and the absence of lamina dura can occur[33].

Langerhans cell histiocytosis (LCH) is a disorder characterised by abnormal proliferation of bone marrow-derived histiocytes. The condition can present focal or systemic manifestations. In jawbones, LCH manifest as solitary or multiple radiolucent circumscribed lesions affecting the alveolar or cortical bone, causing the appearance of floating teeth with disease evaluation. The overlying mucosa is ulcerated, with gingival inflammation. Bleeding, necrosis, recession, dental mobility, and premature loss of teeth are a common occurrence. In many cases, the diagnosis is established through oral lesions[34].

CONCLUSION

FOCD, GGS, cherubism, multiple myeloma and BTH were the most frequent disorders associated with synchronous jaw lesions in this case series. Also, the posterior mandible area was the main site of manifestation. The utilization of adequate demographic, clinical, and radiologic information allows the appropriate diagnosis of the most synchronous lesions of jawbones. Sometimes, however, we need complementary exams, such as histopathologic, immunohistochemical reactions and biochemical analysis.

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CONFLICT OF INTEREST STATEMENT

None.

TABLES

Table 1. Clinicopathologic and radiographic of the synchronous jaw lesions analysed in the present study.

Table 2. Definitions, etiology, clinical features and biochemical analysis of the synchronous jawbone lesions.

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FIGURE LEGENDS

Figure 1. (A) Panoramic radiograph of two ossifying fibromas. Well-delimited unilocular, primarily radiolucent containing diffuse calcifications can be seen bilaterally in the mandibular body and downward bowing of the inferior cortex of the mandible on the right side. (B) Mixed density lesions (arrows) consistent with florid osseous dysplasia. Note that the epicentre of the mandibular lesions is above the inferior alveolar canal. (C) Radiographic findings observed in a patient diagnosed as Gorlin-Goltz syndrome demonstrating multiple well-defined, radiolucent images in the posterior areas of the maxilla and mandible (white arrows), and a pathological mandibular fracture was also observed (yellow arrow). (D) Well-defined, radiolucent images (green arrows) extending from the roots of teeth 18-20 and the roots of teeth 30-31, diagnosed as brown tumour of hyperparathyroidism secondary to chronic kidney disease.

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Table 1. Clinicopathologic and radiographic of the synchronous jaw lesions analysed in the present study.

Lesions	Patients	Sex	Mean Age (range)	Radiographic Aspects	Diagnostic Criteria	Affected Quadrants
Florid cemento-osseous dysplasia	33 (45.8%)	32 F (96,9%) 1 M (3,03%)	51 (11-84)	23 cases (69%) Well-Defined, Dense Radiopacities Surrounded by Radiolucent Rims.	21 cases (63,3%) Clinical Examination, Panoramic Radiograph, Computed Tomography	2 Affected = 20 (60,6%) 3 Affected = 5 (15.1%) 4 Affected = 7 (21,2%) NR = 1 (3,03%)
Gorlin-Goltz syndrome	11 (15.2%)	3 F (27,2%) 8 M (72,7%)	23 (8-74)	8 Cases (72,7%) Well-Defined, Unilocular, Radiolucent Image	6 Cases (54,5%) Clinical Examination, Panoramic Radiograph, Computed Tomography 11 Cases (100%) Clinical Examination, Panoramic Radiograph	2 Affected = 8 (72,8%) 4 Affected = 3 (27,2%)

Cherubism	6 (8.3%)	3 F (50%) 3 M (50%)	14.6 (5-36)	6 Cases (100%) Multilocular Radiolucencies	6 Cases (100%) Clinical Examination, Panoramic Radiograph 1 Case (16,6%) Clinical Examination, Panoramic Radiograph, Computed Tomography	2 Affected = 5 (83,4%) 4 Affected = 1 (16,6%)
Brown tumor of hyperparathyroidism	4 (5.5%)	4 M (100%)	53 (29-64)	4 Cases (100%) Multiple Radiolucencies	4 Cases (100%) Clinical Examination, Panoramic Radiograph, Computed Tomography, Laboratory Examination, Biopsy	2 Affected = 2 (50%) 3 Affected = 1 (25%) 4 Affected = 1 (25%)

Multiple Myeloma	4 (5.5%)	3 M (75%) 1 F (25%(	65 (54-84)	4 cases (100%) Multilocular, Radiolucent	Clinical examination, Panoramic radiographic, Computed tomography, Biopsy	4 affected = 2 (50%) 2 affected = 2 (50%)
Simple bone cyst	3 (4.1%)	2 M (66,6%) 1 NR (33,3%)	15 (13-19)	2 Cases (66.6%) Well-Defined, Unilocular, Radiolucent Image 1 Case (33,3%) Ill-Defined, Unilocular, Dense Radiopaque Surrounded By Radiolucente Image	2 Cases (66.6%) Clinical Examination, Panoramic Radiograph, Computed Tomography 1 Case (33,3%) Clinical Examination, Panoramic Radiograph	2 Affected = 3 (100%)
Dentigerous cysts	2 (2.7%)	2 M (100%)	8.5 (05-12)	2 Cases (100%) Well-Defined, Unilocular, Radiolucent Image	2 Cases (100%) Clinical Examination, Panoramic Radiograph	2 Affected = 2 (100%)

Langerhans cell histiocytosis	2 (2.7%)	2 M (100%)	14.5 (11-18)	2 Cases (100 %) Ill-Defined, Radiolucent Image	2 Cases (100%) Clinical Examination, Panoramic Radiograph, Biopsy	4 Affected 2 (100%)
Paget's disease	2 (2.7%)	1 F (50%) 1 M (50%)	49 (48-58)	2 Cases (100%) Cotton-Woll Like Radiopacity	2 Cases (100%) Clinical Examination, Panoramic Radiograph Computed Tomography, Laboratory Examination	2 Affected = 1 (50%) 4 Affected = 1 (50%)
Gardner syndrome	2 (2.7%)	2 F (100%)	15.5 (13-18)	1 Case (50%) Well-Defined, Unilocular, Dense Radiopacities 1 Case (50%) Ill-Defined, Multilocular, Radiolucent Image	1 Case (50%) Clinical Examination, Panoramic Radiograph 1 Case (50%)	2 Affected = 1 (50%) 4 Affected = 1 (50%)

					Clinical Examination, Panoramic Radiograph, Computed Tomography	
Ossifying fibroma	1 (1,38%)	F	21 (-)	Well-Defined, Unilocular, Radiolucent Image	Clinical Examination, Panoramic Radiograph, Computed Tomography, Laboratory Examination, Biopsy	2 Affected
Osteitis fibrosa cystica	1 (1,38%)	M	27 (-)	Multiple Radiolucencies	Clinical Examination, Panoramic Radiograph, Computed Tomography, Laboratory Examination, Biopsy	4 Affected
Idiopathic Osteosclerosis	1 (1.38%)	M	74 (-)	Generalized irregular radiopacity	Clinical Examination, Panoramic radiographic	4 Affected

F, Female; M, Male; NR, Not Reported

Table 2. Definitions, etiology, clinical features and biochemical analysis of the synchronous jawbone lesions.

Disease	Definition	Etiology	Signs and Symptoms	Age Group	Sex/Race	Other Comorbidies	Biochemical Analysis
Florid osseous dysplasia	Reactive or dysplastic process characterized by the substitution of normal bone by fibrous connective tissue, with subsequent immature bone deposition that gradually becomes sclerotic.	Unknown	Asymptomatic or painful swelling in edentulous areas, with bone exposure or after extractions.	Fifth to sixth decades of life.	Female/Black people.	Not reported.	Not reported.
Central ossifying fibroma	Benign neoplasm, which arises from mesenchymal blast cells of the periodontal ligament.	Unknown	Asymptomatic	Second and third decades of life.	Female/No predilection.	Hyperparathyroidism Association	Not reported.

Paget's disease	Polyostotic metabolic disorder caused by osteoclast dysfunction leading to an altered bone remodeling.	Mutation in the SQSTM-1 gene	Pain in the affected bones during all course of the disease.	After the fifth decade of life, been rare before the age 40.	Male/White people.	Facial paralysis and deafness associated with due to the narrowing of skull foramina. Sacrum, pelvis, skull and femur are the most affected bones.	Elevated alkaline phosphatase.
Nevoid basal-cell carcinoma syndrome	Autosomal dominant inheritable condition.	Mutation in the Patched gene	Asymptomatic	First and second decade of life.	No predilection/ No predilection.	Multiple nevoid basal-cell carcinomas and palmar or plantar pits. Abnormalities in vertebrae (fused or bifid) and ribs (fused, bifid, splayed	Not reported.

						or missing) and calcification of cerebral falx. Frontal and temporoparietal bossing, prominent supra-orbital ridges and increased occipitofrontal circumference.	
Cherubism	Autosomal dominant genetic condition which giant cell lesions replace the bone.	Mutation in SH3BP2 gene (80% of cases).	Painful lesions due to nerves compression.	First decade of life.	Males slightly more affected/No predilection.	Lymph node involvement.	Elevated alkaline phosphatase
Brown tumor of hyperparathyroidism	The disorder caused by elevated levels of parathyroid hormone.	Tumor in parathyroid gland or	Painful or asymptomatic lesions.	Fourth decade of life	No predilection/No predilection.	Lesion in the parathyroid gland and/or advanced	Hypophosphatemia, elevated levels of serum calcium

		advanced chronic kidney disease				chronic kidney disease.	and parathyroid hormone.
Simple bone cyst	Empty or fluid-filled cavity that develops within bone.	Unknown.	Asymptomatic.	Second decade of life.	Female/No predilection.	Not reported.	Not reported.
Dentigerous cyst	Cyst associated with the crowns of permanent teeth.	Unknown	Asymptomatic	First and second decades of life.	No predilection/No predilection	Association with cleidocranial dysplasia, basal cell naevus syndrome or mucopolysaccharidosis type IV.	Not reported.
Osteopetrosis	The genetic disorder which presents the bone formation normal but	Mutations in the TCIRG1,	Bone fracture.	Severe infantile or malignant type: At birth or	No predilection/	Severe infantile or malignant type:	Low serum Ca2+ levels associated

bone reduced resorption resulting in the presence of excessive calcified tissue	SNX10, OSTM1, PLEKHM, *TNFSF11* *TNFRSF11* *A* and CLCN7 genes.	at the first months of infancy.	Osteopetrosis with renal tubular acidosis and cerebral calcifications: Early childhood.	No predilection.	anaemia hepatomegaly, splenomegaly, lymphadenopathy, blindness, hydrocephalus, exophthalmos, small thorax and hypertelorism and problems during tooth eruption.	with secondary hyperparathyroidism ; carbonic anhydrase 2 deficiency in the osteopetrosis with renal tubular acidosis and cerebral calcification form; levels of alkaline phosphatase, 1,25-dihydroxyvitamin D_3 and lactate dehydrogenase vary from patient to patient and are (unreliable as
			Benign osteopetrosis or Albers-Schönberg disease: Adults		Osteopetrosis with renal tubular acidosis and cerebral calcifications:	

				Intermediate type osteopetrosis: Children and adults.		Short stature and mental retardation. Benign osteopetrosis or Albers-Schönberg disease: Without symptoms.	biomarkers for the disease); elevated levels of lactate dehydrogenase, aspartate aminotransferase, correlate with autosomal dominant.
Langerhans cell histiocytosis	Abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells) which comprise an unusual group of disorders with focal or systemic manifestations.	Unknown	Pain and mucosa overlying of the gingival and of the hard-palate presents ulcerated	Predominantly seen in children, particularly during early infancy	Slight predominance in man.	Cervical lymphadenopathies. Skull and femoral lesions children younger than age 10, patients older than	Not reported

						age 20 lesions in the ribs, shoulder girdle, and mandible. Seborrheic dermatitis or eczematous eruption on the scalp and trunk. Hepatomegaly Splenomegaly.	
Multiple myeloma	Cancer of plasma cells, a type of white blood cell that normally produces antibodies.	Unknown.	Swelling and pain.	Older than 60 years old.	Man is more affected.	The lesion is commonly associated with anemia, impaired	Multiple myeloma can produce all classes of immunoglobulin, but

						kidney function, infection and neurological symptoms.	IgG paraproteins are most common. Light and or heavy chains (the building blocks of antibodies) may be secreted in isolation: κ- or λ-light chains or any of the five types of heavy chains (α-, γ-, δ-, ε- or μ-heavy chains).
Osteitis fibrosa cystica	Is a skeletal disorder resulting in replacement of bone to fibrous tissue and the formation of cyst-	Hyperparathyroidism	Bone pain or tenderness, bone fractures and skeletal deformities.	Before age 40.	No sex predilection.	Weight loss, appetite loss, vomiting, polyuria, and polydipsia.	High levels of calcium, parathyroid hormone and

	like brown tumors in and around the bone.						alkaline phosphatase.
Idiopathic Osteosclerosis	A reaction to past trauma or infection.	Unknown.	Focal radiodensity of the jaw which is not inflammatory, dysplastic, neoplastic or a manifestation of a systemic disease.	Teens and those in their 20s	No sex predilection.	None.	None.

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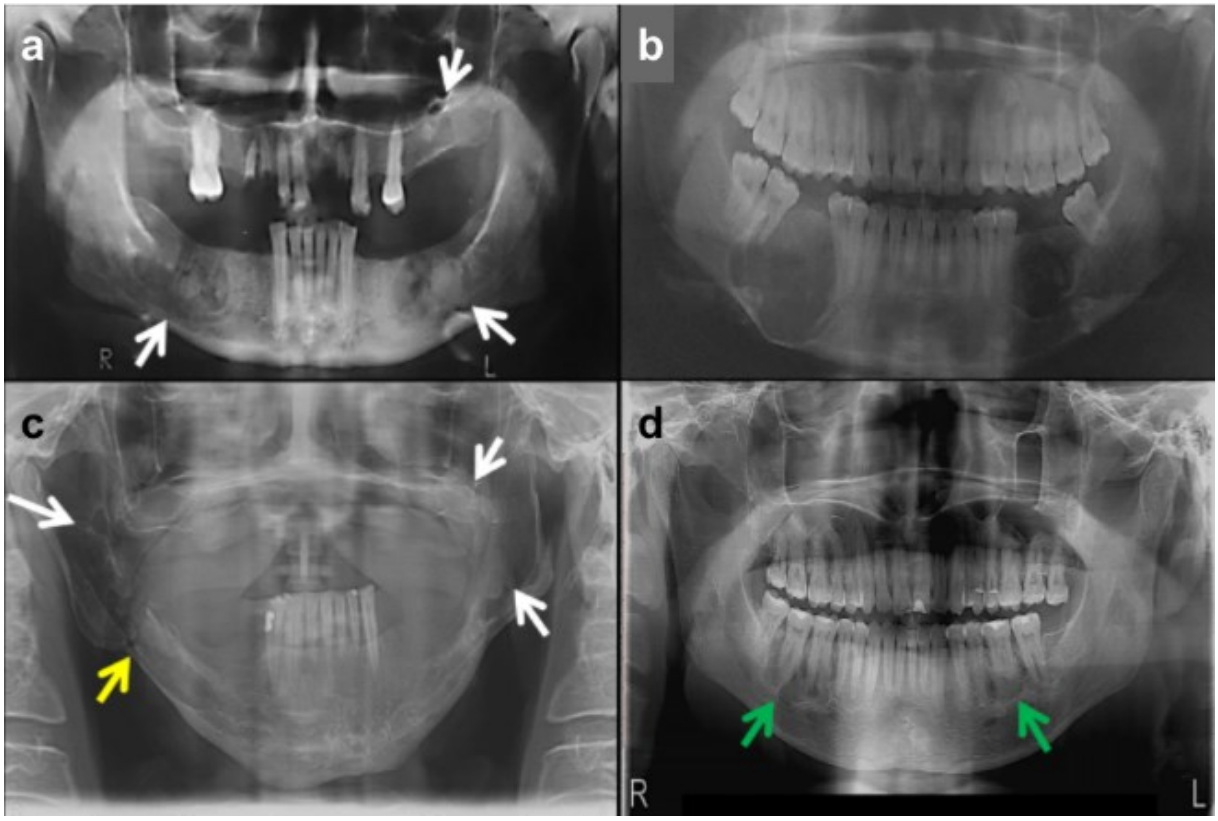

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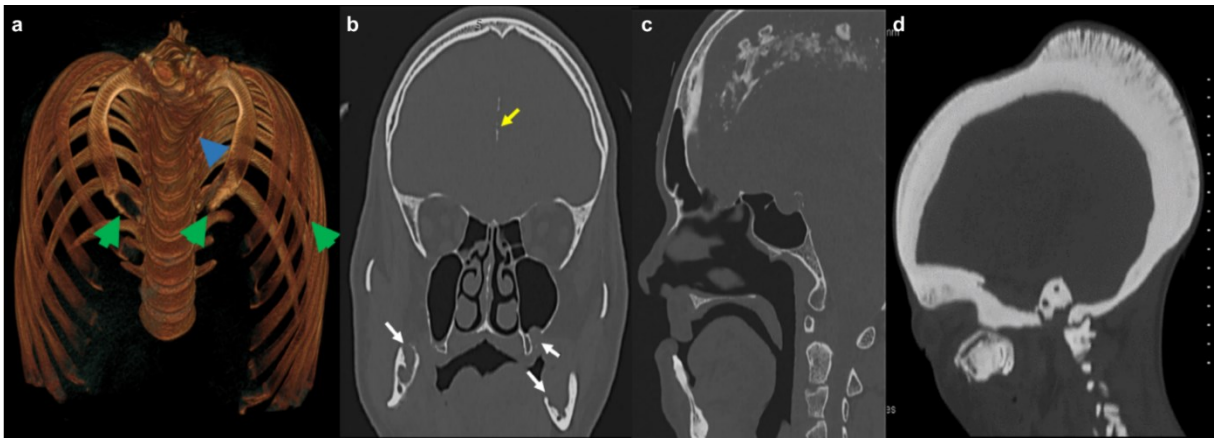

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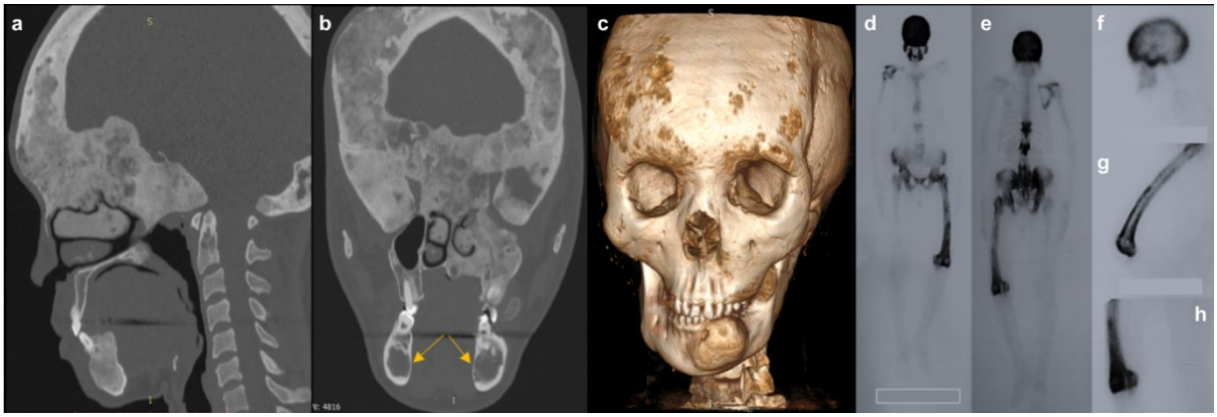

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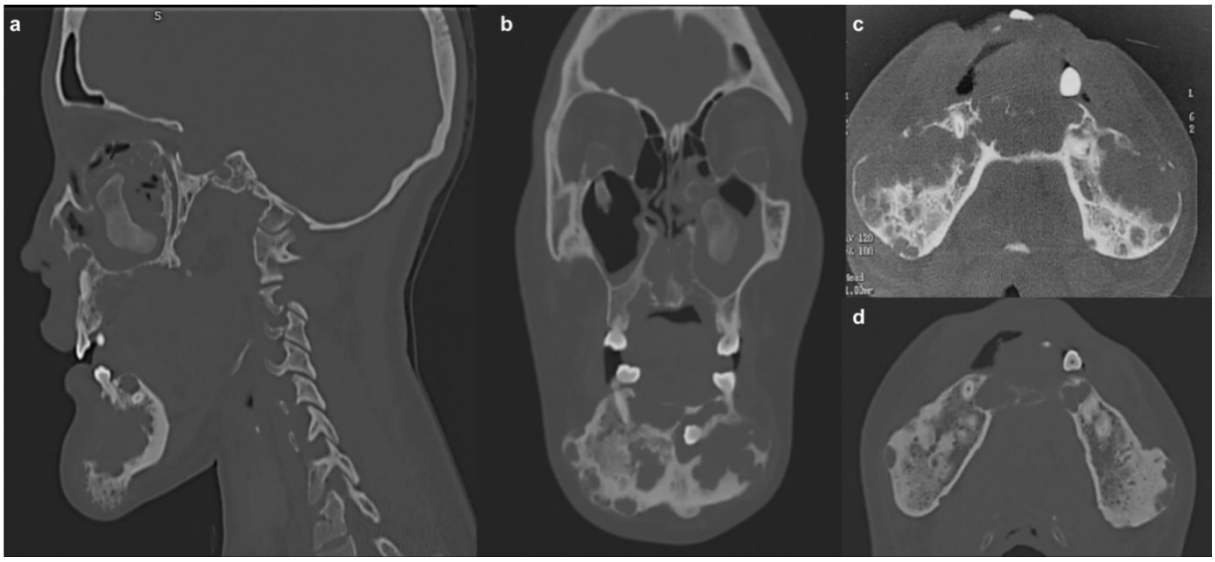

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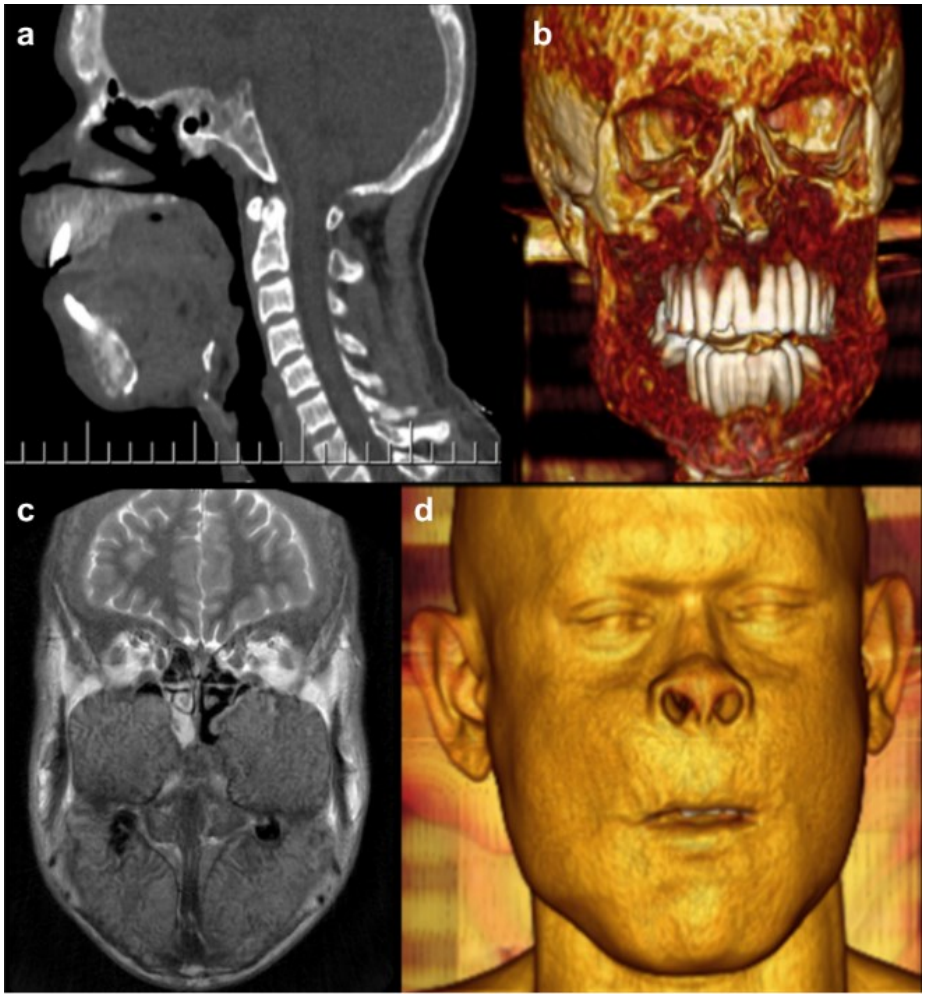
a
b
c
d

3 CONCLUSÃO

Lesões sincrônicas dos maxilares mais frequentes encontradas nesta série de casos foram a displasia óssea florida, síndrome de Gorlin-Goltz, querubismo e o tumor marrom do hiperparatireoidismo. Além disto, a região posterior da mandíbula foi o sítio de maior ocorrência. A adequada utilização dos dados epidemiológicos, descrição clínica e característica de imagem permite o correto diagnóstico da maioria das lesões sincrônicas dos maxilares. Contudo, em alguns casos, sejam necessários exames complementares como analise histopatológica e bioquímica dos níveis séricos de cálcio, fosforo e fosfatase alcalina.

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ANEXOS

Anexo 1 - Verificação de originalidade e prevenção de plágio

SYNCHRONOUS JAWBONE DISEASES: A MULTICENTRIC RETROSPECTIVE STUDY

RELATÓRIO DE ORIGINALIDADE

15%	11%	12%	3%
ÍNDICE DE SEMELHANÇA	FONTES DA INTERNET	PUBLICAÇÕES	DOCUMENTOS DOS ALUNOS

FONTES PRIMÁRIAS

1	Flávia Sirotheau Corrêa Pontes, Márcio Ajudarte Lopes, Lucas Lacerda de Souza, Diogo dos Santos da Mata Rezende et al. "Oral and maxillofacial manifestations of chronic kidney disease–mineral and bone disorder: a multicenter retrospective study", Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 2018 Publicação	2%
2	Rodrigo Neves-Silva, Diego Tetzner Fernandes, Felipe Paiva Fonseca, Helder Antonio Rebelo Pontes et al. "Oral manifestations of Langerhans cell histiocytosis: A case series", Special Care in Dentistry, 2018 Publicação	1%
3	en.wikipedia.org Fonte da Internet	1%

Anexo 2 - Certificado do Comitê De Ética em Pesquisa

UFPA - HOSPITAL UNIVERSITÁRIO JOÃO DE BARROS BARRETO DA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE E PREVALÊNCIA DAS LESÕES BUCAIS SINCRÔNICAS EM CAVIDADE ORAL: APRESENTAÇÃO CLÍNICA, RADIOGRÁFICA E HISTOLÓGICA DAS LESÕES BILATERAIS DE RARA MANIFESTAÇÃO NOS OSSOS GNÁTICOS.

Pesquisador: HÉLDER ANTÔNIO REBELO PONTES

Área Temática:

Versão: 1

CAAE: 82049318.2.0000.0017

Instituição Proponente: Hospital Universitário João de Barros Barreto - UFPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.480.116

Apresentação do Projeto:

Lesões sincrônicas são consideradas incomuns no organismo humano. Ao analisar a prevalência dessas lesões na cavidade oral por meio de estudos em grandes centros de referência em patologia bucal, é observado que os casos são publicados individualmente, porém não existem
estudos que avaliem a prevalência e características de lesões bilaterais em cavidade oral, que muitas vezes apresentam-se como um grande desafio diagnóstico para o cirurgião dentista especialista em Patologia Bucal, Radiologista e Cirurgião Buco Máxilo Facial e principalmente para o cirurgião dentista clínico. O cirurgião dentista precisa ter conhecimento de lesões que afetam a cavidade oral, pois apesar de raras, esse tipo de doença é uma realidade na rotina desse profissional. Dessa forma, esse estudo busca caracterizar clinicamente, radiograficamente e histologicamente as diversas lesões que apresentam essa característica sincrônica/bilateral afim de facilitar o diagnóstico e o tratamento mais adequado. Lesões Sincrônicas são lesões que se manifestam num intervalo de tempo de 6 meses depois de uma lesão primária. Portanto, na cavidade Oral essas lesões têm apresentação bilateral. Esse diagnóstico é válido clinicamente, radiograficamente, e por outros exames complementares como a tomografia computadorizada.Trata-se de um estudo descritivo retrospectivo com abordagem quantitativa a ser desenvolvida no Centro de Referência de Patologia Bucal do Hospital Universitário João de Barros Barreto (HUJBB).

Endereço: RUA DOS MUNDURUCUS 4487
Bairro: GUAMA **CEP:** 66.073-000
UF: PA **Município:** BELEM
Telefone: (91)3201-6754 **Fax:** (91)3201-6663 **E-mail:** cephujbb@yahoo.com.br

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar a prevalência das lesões bucais bilaterais/sincrônicas de pacientes atendidos no centro de referência de patologia bucal do Hospital Universitário João de Barros Barreto (HUJBB).

Objetivo Secundário:

- Avaliar os padrões clínicos (localização, idade, gênero) e a evolução das lesões bilaterais de pacientes atendidos no HUJBB.
- Avaliar quais lesões apresentam a maior prevalência de lesões bilaterais na cavidade oral.

Avaliação dos Riscos e Benefícios:

Riscos:

Os riscos com a pesquisa em questão serão mínimos. Estes são em relação ao risco de quebra da confidencialidade e privacidade dos usuários. Entretanto, serão tomadas todas as medidas necessárias para proteção e minimização dos mesmos. Os pesquisadores envolvidos garantem que
não utilizarão das informações coletadas nos prontuários para manter qualquer contato com os usuários e/ou familiares.

Benefícios:

Os benefícios com a realização da pesquisa e análise dos resultados incluem a identificação das principais lesões bucais que tem uma apresentação bilateral/sincrônica, facilitando o diagnóstico dessas lesões e o melhor tratamento.

Comentários e Considerações sobre a Pesquisa:

Pesquisa pretende a identificação das principais lesões bucais que tem uma apresentação bilateral/sincrônica, facilitando o diagnóstico dessas lesões e o melhor tratamento.

Considerações sobre os Termos de apresentação obrigatória:

Os termos de obrigatórios foram apresentados e estão de acordo com as legislações do Sistema CEP - CONEP/CNS/MS.

Recomendações:

Recomendamos a coordenação que mantenha atualizados todos os documentos pertinentes ao projeto.
Deverá também ser informado ao CEP:
Relatório Semestral;

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Relatório Final;
Envio de Relatório de Cancelamento;
Envio de Relatório de Suspensão de projeto;
Comunicação de Término do projeto na Plataforma Brasil.

Conclusões ou Pendências e Lista de Inadequações:

Pesquisa aprovada neste Colegiado.

Considerações Finais a critério do CEP:

Diante do exposto, este Colegiado manifesta-se pela APROVAÇÃO do protocolo de pesquisa por estar de acordo com a Resolução nº466/2012 e suas complementares do Conselho Nacional de Saúde/MS.
Ainda em atendimento a Res. 466/2012 esclarecemos que a responsabilidade do pesquisador é indelegável, indeclinável e compreende os aspectos éticos e legais. Além de apresentar o protocolo devidamente instruído ao CEP ou à CONEP, aguardando a decisão de aprovação ética, antes de iniciar a pesquisa; de elaborar o Termo de Consentimento Livre e Esclarecido;
Cabe ainda ao pesquisador:
1- desenvolver o projeto conforme delineado;
2- Em acordo com a Resolução 466/12 CNS, ítens X.1.- 3.b. e XI.2.d, os pesquisadores responsáveis deverão apresentar relatórios parcial semestral e final do projeto de pesquisa, contados a partir da data de aprovação do protocolo de pesquisa. Os relatórios deverão ser inseridos no Sistema Plataforma Brasil pelo ícone "Inserir Notificação" disponível para projetos aprovados.
3- apresentar dados solicitados pelo CEP ou pela CONEP, a qualquer momento;
4- manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período de 05 anos após o término da pesquisa;
5- encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico integrante do projeto;
6- justificar fundamentadamente, perante o CEP ou a CONEP, interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação

Endereço: RUA DOS MUNDURUCUS 4487
Bairro: GUAMA **CEP:** 66.073-000
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Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1057175.pdf	03/01/2018 04:42:54		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	03/01/2018 04:41:45	HELDER ANTONIO REBELO PONTES	Aceito
Orçamento	orcamento.jpg	03/01/2018 04:36:42	HELDER ANTONIO REBELO PONTES	Aceito
Declaração de Pesquisadores	termo.pdf	03/01/2018 04:31:01	HELDER ANTONIO REBELO PONTES	Aceito
Projeto Detalhado / Brochura Investigador	projeto.docx	03/01/2018 04:22:10	HELDER ANTONIO REBELO PONTES	Aceito
Folha de Rosto	folha.pdf	03/01/2018 04:19:42	HELDER ANTONIO REBELO PONTES	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELEM, 31 de Janeiro de 2018

Assinado por:
João Soares Felicio
(Coordenador)

Anexo3 - Documento de submissão do artigo

Brazilian Oral Research

SYNCHRONOUS JAWBONE DISEASES: A MULTICENTRIC RETROSPECTIVE STUDY.

Journal:	*Brazilian Oral Research*
Manuscript ID	BOR-2020-1285
Manuscript Type:	Original Research Report
Specialties:	Oral Pathology, Stomatology
Category--Select your categories from the <A HREF='http://www.nlm.nih.gov/mesh/MBrowser.html' target='_new'> MeSH or <A HREF='http://decs.bvs.br/' target='_new'> DeCS lists.:	Oral, Pathology, Mandible, Maxilla

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