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Análise da retrusão do terço médio da face e dismorfologia orbital em crianças portadoras das síndromes de Apert e Crouzon

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ANTONIO JORGE DE VASCONCELOS FORTE

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Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para a obtenção do título de Doutor em Ciências

Programa de Clínica Cirúrgica
Orientador: Prof. Dr. Nivaldo Alonso

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Aprovada em: _____ de _____ de 2017.

Banca Examinadora

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À minha amada esposa, à minha filha Alexa e aos meus queridos pais e irmãos.

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SUMMARY

LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ANS-PP	Anterior Nasal Spine- Pterygomaxillary Fissure
AP	Anteroposterior
AR	Articulare
BA	Basion
ES	Ethmosphenoidal
FGFR	Fibroblast Growth Factor Receptor
FGFR2	Fibroblast Growth Factor Receptor -2
N	Nasion
N-BA	Nasion-Basion
N-ES	Nasion- Ethmosphenoidal
N-S-AR	Nasion-Sella-Articulare
N-S-BA	Nasion-Sella-Basion
N-S-PP	Nasion-Sella- Pterygomaxillary Fissure
N-S-SO	Nasion-Sella-Sphenooccipital Synchondrosis
N-SO-BA	Nasion- Sphenooccipital Synchondrosis -Basion
PP	Pterygomaxillary Fissure
PPL	Left Pterygoid Plate
PPR	Right Pterygoid Plate
PPR-S-PPL	Right Pterygoid Plate -Sella- Left Pterygoid Plate
S	Sella
S-BA	Sella-Basion
S-SO	Sella- Sphenooccipital Synchondrosis
S-SO-BA	Sella- Sphenooccipital Synchondrosis -Basion
SO	Sphenooccipital Synchondrosis
SO-BA	Sphenooccipital Synchondrosis -Basion
CT	Computerized Tomography
ZML	Left Zygomaticomaxillary Suture
ZMR	Right Zygomaticomaxillary Suture
ZMR-ZML	Right Zygomaticomaxillary Suture - Left Zygomaticomaxillary Suture

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RESUMO

Forte AJV. Análise da retrusão do terço médio da face e dismorfologia orbital em crianças portadoras das síndromes de Apert e Crouzon [Tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2017.

Retrusão do terço médio da face é característica das disostoses sindrômicas. Falta de projeção e deficiência estrutural podem ser responsáveis pelo fenômeno, mas estes nunca foram avaliados adequadamente tridimensionalmente. O objetivo deste estudo é analisar a interface entre a base do crânio e a face, o volume dos ossos do terço médio da face e o volume e estrutura dos componentes da órbita, para fornecer uma compreensão da etiopatogenia da deficiência do terço médio da face e da dismorfologia ocular. Crianças com tomografia computadorizada, na ausência de qualquer intervenção cirúrgica, foram incluídas. As informações demográficas foram obtidas para três grupos (Apert, Crouzon, Controle). As tomografias computadorizadas foram digitalizadas e analisadas usando o software Materialise (Surgicase CMF ™). Dados craniométricas relativos ao terço médio da face, esfenóide e da órbita foram recolhido. Avaliação volumétrica do terço médio da face e órbita foi tabulada. A análise estatística foi realizada utilizando T-teste. Para a análise da retrusão do terço médio da face, trinta e seis tomografias foram incluídas (Controle n = 17, Crouzon / Apert n = 19). Todas as crianças estavam no período de dentição mista. A fossa anterior craniana é mais curta e mais larga em Crouzon/Apert versus Controles. Os ângulos da base do crânio medidos não foram estatisticamente diferentes entre os grupos. Crouzon/Apert mostrou ângulos mais obtusos entre as maiores asas do esfenóide, e mais obtusos entre as placas pterigóides. O ângulo formado pelo nasion-sela-fissura pterigomaxilar foi mais obtuso no grupo Crouzon e Apert comparado aos Controles. Não houve diferença volumétrica da maxila, zigoma e esfenóide comparando Crouzon/Apert aos Controles. Para a análise da dismorfologia orbital, trinta e uma tomografias computadorizadas foram incluídas (Controle n = 12, n = 9 Crouzon, Apert n = 10). A média de idade do grupo Apert foi de 5,31 ± 5 anos, Crouzon foi 5,77 ± 2,7 anos e Controle foi de 6,4 ± 3,6 anos (p = 0,6). O grupo de Crouzon era composto por 5 meninos e 4 meninas, o grupo de Apert continha 4 meninos e 6 meninas e o grupo Controle tinha 6 meninos e 6 meninas (p> 0,7). O comprimento da órbita óssea é 12% menor em Apert (p = 0,004) e 17% menor no grupo Crouzon quando comparado ao grupo Controle (p <0,0001). A altura da órbita é 14% maior no grupo de Apert (p <0,0001) e 7% maior no grupo Crouzon quando comparados com os Controles (p = 0,03). A largura da órbita não é

estatisticamente diferente no Crouzon ou grupo Apert quando comparados aos Controles (p = 0,1). O volume da órbita óssea é 21% menor nas crianças Apert (p = 0,0006) e 23% menor em Crouzon quando comparados aos Controles (p = 0,003). A projeção do globo é 99% maior em Apert e 119% maior em Crouzon quando comparados aos Controles (ambos p <0,0001). Volume projetado fora da órbita é 179% maior em ambos Crouzon e Apert grupo quando comparados aos Controles (ambos p <0,0001). O volume do globo ocular é 15% maior em Apert (p = 0,008) e 36% maior no grupo Crouzon quando comparado com o grupo Controle (p <0,0001). O volume da porção do globo ocular dentro da órbita é 27% menor em Apert (p = 0,03). O grupo Crouzon não apresentou diferença estatística em relação ao grupo Controle para essa variável(p = 0,47). O volume da periórbita é 18% menor em Apert (p = 0,027) e 27% menor em Crouzon (p = 0,039), quando comparado com o grupo Controle (p = 0,001). O volume total dos tecidos moles (globo mais periórbita) em ambos os grupos Apert e Crouzon não foi estatisticamente diferente de Controles. Em suma, retrusão do terço médio da face em pacientes com Crouzon e Apert é associado com deformidade do esfenóide, que consiste na retrusão das placas pterigóides, causando alargamento e deformidade maxilar amplo, sugerindo crescimento diminuição inferior e anteriormente. Não há deficiência volumétrica dos ossos do terço médio da face nos grupos Crouzon e Apert comparado com Controles. Além disso, a dismorfologia ocular está relacionada com um encurtamento da órbita óssea associado com diminuição do volume orbital, aumento do volume do globo e diminuição do volume de periórbita. Apesar desses pacientes apresentarem volume normal do conteúdo da orbita, os conteúdos são alteradas, e da órbita óssea é mais curta e tem menos volume, o que não se encaixa na descrição clássica de exoftalmia ou exorbitismo.

Descritores: doença de Crouzon; síndrome de Apert; face; órbita; osso esfenoide; maxila.

ABSTRACT

Forte AJV. Analysis of midface retrusion and orbital dysmorphology in children with Apert and Crouzon syndromes [Thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2017.

Midface retrusion is the hallmark of the syndromic dysotoses. Lack of forward projection and structural deficiency could be responsible, but neither has been adequately 3-dimensionally assessed. The purpose of this study is to examine cranial base interface and midface volume to provide understanding of the etiopathogenesis of midface deficiency. Children with CT scans in the absence of any surgical intervention were included. Demographic information was recorded for three groups (Apert, Crouzon, Control). CTs were digitized and manipulated using Materialise software (Surgicase CMF™). Craniometric data relating to the midface, sphenoid and orbit was collected. Volumetric assessment of the midface and orbit were tabulated. Statistical analysis was performed using T-test. For the midface retrusion analysis, thirty-six CT scans were included (Control n=17, Crouzon/Apert n=19). All children were in the early mixed dentition. The anterior cranial fossa proved to be shorter and wider in Crouzon/Apert versus controls. The cranial base angles measured were not statistically different across the groups. Crouzon/Apert group showed angles more obtuse between the greater wings of the sphenoid, and more obtuse between the pterygoid plates. Nasion-sella-pterygomaxillary fissure angle was more obtuse in Crouzon/Apert. There was no volumetric difference in the maxilla, zygoma, and sphenoid comparing Crouzon/Apert to controls. For the orbital dysmorphology analysis, thirty-one CT scans were included (Control n=12, Crouzon n=9, Apert n=10). The mean age of the Apert group was 5.31 ± 5 years, Crouzon was 5.77 ± 2.7 years and Control was 6.4 ± 3.6 years (p=0.6). The Crouzon group consisted of 5 boys and 4 girls, the Apert group had 4 boys and 6 girls and the Control group had 6 boys and 6 girls (p>0.7). The bony orbit length was 12% shorter in Apert (p=0.004) and 17% shorter in the Crouzon group when compared to controls (p<0.0001). Orbital height was 14% higher in the Apert group (p<0.0001) and 7% higher in the Crouzon group when compared to controls (p=0.03). Orbital width was not statistically different in either Crouzon or Apert group when compared to controls (p=0.1). The bony orbital volume was 21% smaller in the Apert children (p=0.0006) and 23% smaller in Crouzon when compared to controls (p=0.003). The globe projection was 99% larger in Apert and 119% larger in Crouzon groups when compared to controls (both p<0.0001). Volume projected outside the orbit was

increased over 179% in both Crouzon and Apert group when compared to Controls (both $p<0.0001$). Globe volume was 15% larger in Apert ($p=0.008$) and 36% larger in Crouzon group when compared to Controls ($p<0.0001$). Globe volume inside the orbit was 27% smaller in Apert ($p=0.03$) and the Crouzon group presented no statistical difference when compared to Controls ($p=0.47$). Periorbita volume was 18% less in Apert ($p=0.027$) and 27% less in Crouzon ($p=0.039$) group when compared to Controls ($p=0.001$). Total soft tissue volume (globe plus periorbita) in both Apert and Crouzon groups was not statistically different from Controls. In summary, midface retrusion in Crouzon and Apert is associated with altered sphenoid morphology consisting of widened and retruded pterygoid plates, with a flatter and wider maxilla, suggesting diminished growth inferiorly and anteriorly. There is no volumetric deficiency in Crouzon/Apert versus controls. Orbital dysmorphology is associated with altered sphenoid morphology, shortened bony orbit with diminished orbital volume, increased globe volume and decreased volume of periorbita. Despite normal volume of the overall orbital contents, the contents are altered, and the bony orbit is shorter and holds less volume, which does not fit the classic description of either exophthalmos or exorbitism.

Descriptors: Crouzon's disease; Apert syndrom; face; orbit; sphenoid bone; maxilla.

1 INTRODUCTION

Midface retrusion and proptosis are hallmark features for Crouzon and Apert syndromes (1, 2). Multiple theories have attempted to explain midface retrusion in Crouzon's and Apert's Syndrome. However, they do not fully account for the spectrum of deformities, vayring from mild to severe, and have not been based on sophisticated 3D analysis. (3-12). The current theories don't appropriately predict what surgical technique will have the best long term functional and aesthetic outcome. In fact, better understanding of the abnormal anatomy and development of the cranial base is a necessary step for the evolution of the surgical treatment options, which could potentially provide patients safer and fewer operations. Enlow was one of the first researchers to report important descriptive findings regarding Crouzon and Aper Syndrome. In summary, he described such growth pattern as upwards and backwards using lateral cephalograms and counterpart analysis (10), which was the explanation accepted for decades justifying the midface retrusion in these patients.

Both Crouzon and Apert share similar genetic etiology and activating mutations in fibroblast growth factor-2 (FGFR-2) have been reported in almost all cases (13, 14). Fibroblast growth factor receptor (FGFR) abnormal function leads to bicoronal synostosis (13). More specifically, recent data demonstrates the role of FGFR2c-mediated ERK-MAPK signaling as a key mediator of craniofacial growth and coronal suture development (15). Similarly, the cranial base is also postulated to be aberrant with disruption of the normal midfacial growth, including the synchondroses and vomerine. It is believed that the spheno-occipital synchondrosis fuses earlier in syndromic patients compared with normal children, ant that there is a positive correlation between earlier fusion and degree of midface hypoplasia (16, 17).

Acrocephaly, exophthalmos, hypertelorism, parrot-beaked nose, midface hypoplasia, cleft palate, low-set ears, and various central nervous system (CNS) abnormalities

are present in both conditions (18, 19). However, Apert is typified by syndactyly while Crouzon does not present any specific limb deformity. The skeletal distortions frequently involve the orbit and associated adnexa, which justify the need for care by an ophthalmologist. Interestingly, proptosis of the globe is a problem affecting nearly all Crouzon and Apert patients, rendering the eye more vulnerable to corneal injury and inflammation. Strabismus, ametropia and hypermetropia are regularly encountered (20), and visual impairment is reported in up to half of all patients (21-23).

Apert and Crouzon craniosynostosis syndromes often show ocular dysmorphology. Kreiborg and Cohen reported that Apert and Crouzon's syndromes display significant qualitative and quantitative differences in the oculo-orbital region (20). Apert syndrome is more asymmetric in nature and a more severe clinical entity than Crouzon's syndrome. Optic atrophy found and subluxation of the eye globe is present in some Crouzon patients and absent in Apert syndrome. Before and after fronto-orbital expansion, Crouzon patients were found to have smaller intraorbital volume than Apert counterparts (24).

Such complex patients require a multidisciplinary team approach and outcomes driven protocols provide important insight (25). A craniofacial team including plastic, dental orthodontic and orthognathic surgical management is advantageous (26). In the early days of craniofacial surgery, Tessier described several techniques to address these skeletal abnormalities (27-33). Among others, Posnick believes that staged surgical intervention for these patients will provide them with the best long-term functional and aesthetic outcome (34). Apert and Crouzon patients can also present hypertelorbitism, which can be addressed with local flaps and soft tissue rearrangements (35). Ultimately, it is important to measure the quality of life improvement experienced by patients. British researches indicated that a treated adult syndromic patient with similar cognitive capacity perceive their quality of life as better compared to normative data (36). Raposo-Amaral et al studied Apert patients' cohort quality

of life in Brasil and reported that highest-functioning Apert and Crouzon patients presented a satisfactory quality of life (37, 38).

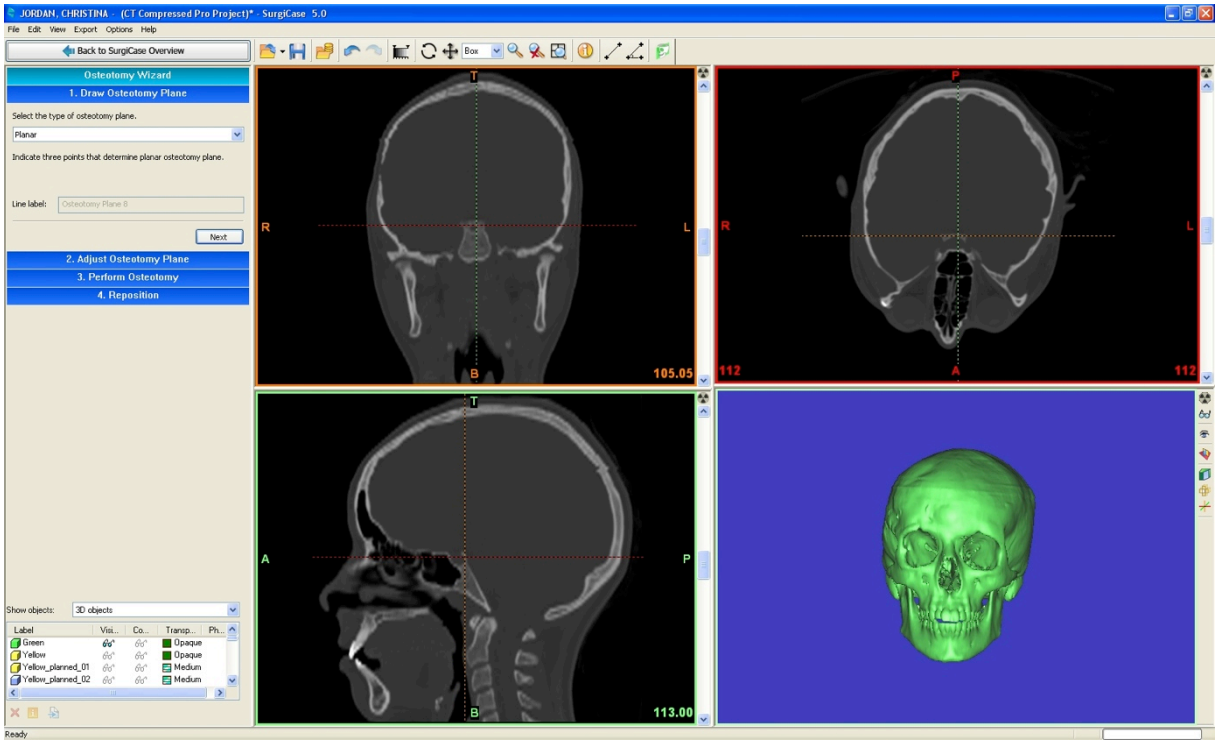
It is unclear whether overall orbital or globe volumes differ in Crouzon and Apert syndromes compared to normal controls. Fortunately, in depth analysis of three-dimensional (3D) structures are now possible due to advances in computed tomography (CT) and softwares capable of generating accurate 3D models. Recently, modern techniques in 3D CT reconstruction have been demonstrated to be a powerful method for defining both bony and soft-tissue morphology in a number of craniofacial abnormalities, and soft-tissue masks can be used to calculate the volume and morphology of bony cavities (39-41). For the first time, with this study, the application of the 3D CT analysis allows demonstration of morphologic differences in the syndromic orbits and the relation of the globes. Ko et al did use 3D CT for cephalometric evaluation of the orbital variations in Apert's and Crouzon's patients. Surprisingly, despite having the necessary technology to analyze the 3 dimensional space of the orbit, the group choose only to consider the orbit 2-dimensionally (42). Second, we compared our study results to untreated healthy, age and gender matched controls who also received 3D CT scans which were digitalized and manipulated using software. These controls strengthens the relevance of our study, since studies previously performed, such as Imai et al, did not match their own quantitative results (24, 43).

Our main goal was to understand how the craniofacial skeletal distortions impact the projection of the midface and orbital dysmorphology. Therefore, we designed a retrospective analysis performed in concordance with the Yale University Human Investigation Committee (HIC 1101007932). It consisted of an analysis of the patient of the Craniofacial Surgery Clinic in Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAPPesq Protocol 13130).

We decided to use CT scans, obtained from subjects without previous surgical intervention to correct midface retrusion, to generate 3D models, which could allow us better understand the anatomical deformity and obtained more reliable measurement data. In order to do that, DICOM data was digitized and manipulated using Surgicase CMF® software (version 5.0.0.32, Materialise, Leuven, Belgium). All variables were obtained and analyzed by the same observer in both control and study groups.

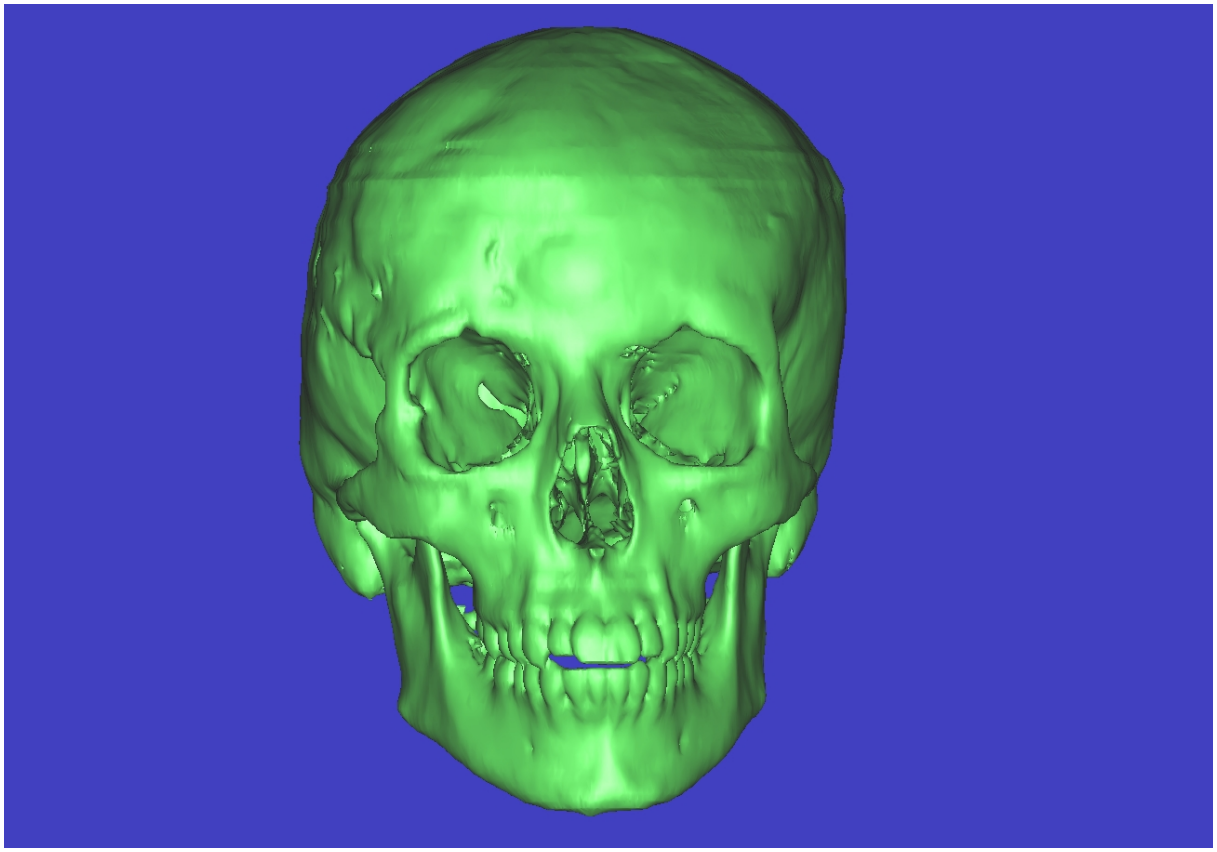
Soon after the CTs are digitalized into Surgicase CMF® (Figure 1), the software transforms pixels into voxels, what allows for the creation of renderized 3D models of the cranial bones and soft tissue (Figure 2, 3, 4). Based on the Hounsfield scales, the software is able to identify and isolate the different components of the craniofacial region (Figure 5). This process is called segmentation (Figure 6).

Figure 1 - Overview of the Surgicase CMF® interface.



Source: Created by Author

Figure 2 - Example of a 3D model of a skull of a normal subject

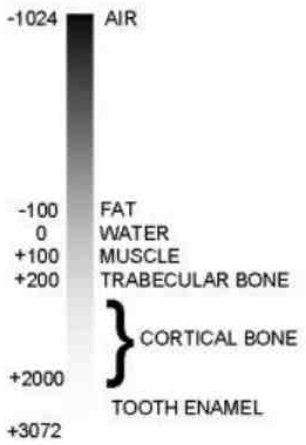


Source: Created by Author

Figure 3 and 4 - Photo of a Crouzon patient whose 3D soft tissue model is represented in Figure 4

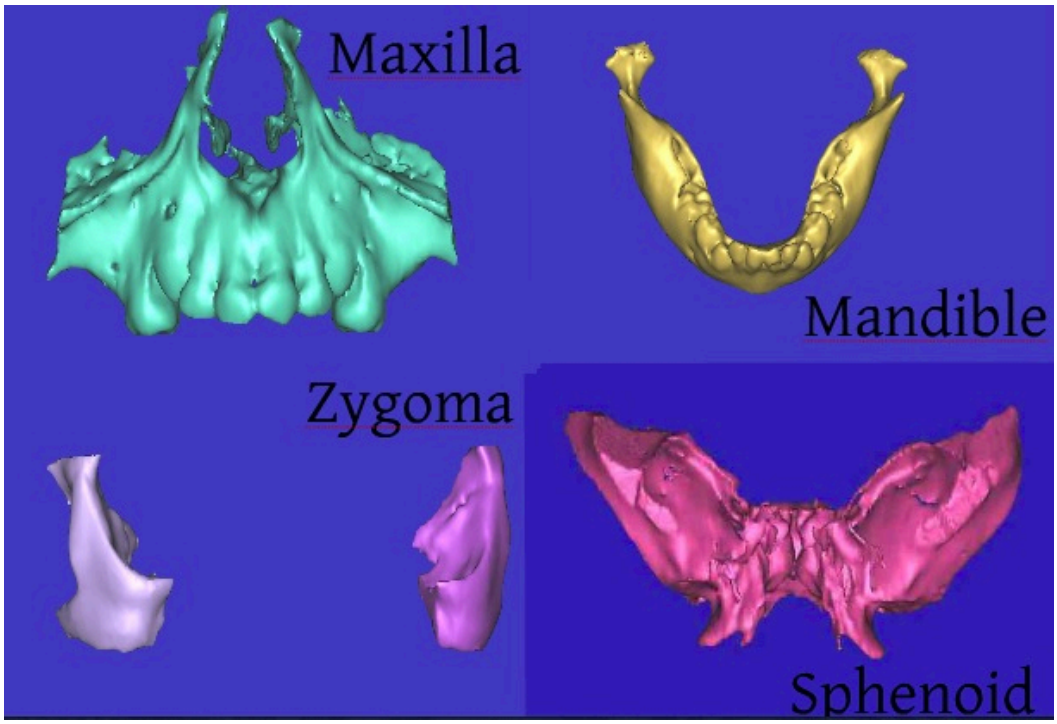
Source: Created by Author

Figure 5 - Different tissue densities are represented in the Hounsfield Scale



Following segmentation, craniometric and volumetric analyses were performed (1). The reference points used had been previously defined and validated in the literature (44). For volumetric analysis, right and left sides were measured for zygoma, mandible, maxilla, orbit and globe. Volume in cubic centimeters (mL, cc or cm3) was obtained for each structure.

Figure 6 - Multiple 3D model of different bones as a result of the segmentation process



Source: Created by Author

The same observer chose the points, with independent verification by two additional observers (all plastic surgeons). An interobserver analysis was performed in a series of test subjects prior to completing the complete data analysis. The software GraphPad Prism® version 6.0f for Mac OS X® (GraphPad Software, San Diego, California, USA, 2014) was used for the statistical analysis. Student's *t* test (nonpaired, two-tailed) was performed for the statistical analysis ($p \leq 0,05$ was considered statistically significant).

2 CAPPesq APPROVED PROJECT IN PORTUGUESE

PROJETO 13130 - Cadastrado em 26/11/2014, Aprovado em 11/02/2015

RESUMO

Retrusão do terço médio da face e proptose ocular são marcas das disotoses sindrômicas (Crouzon e Apert). Falta de projeção e / ou deficiência estrutural poderiam ser responsáveis, mas essas variáveis nunca foram avaliadas adequadamente tridimensionalmente. O objetivo deste estudo é analisar tanto a interface base cranial-face, e volume do terço médio da face, para fornecer uma compreensão da etiopatogenia da deficiência do terço médio da face e da dismorfologia das órbitas.

Métodos: Crianças com tomografia computadorizada, na ausência de qualquer intervenção cirúrgica, serão incluídas. As informações demográficas serão registradas para os três grupos (Apert, Crouzon, Controle). Tomografias computadorizadas serão digitalizadas e manipulados usando o software Materialise (Surgicase CMF ™). Dados craniométricos relativos ao terço médio da face e esfenóide serão recolhidos. Avaliação volumétrica do terço médio da face e da órbita e globo serão tabulados. A análise estatística será realizada utilizando T-teste.

INTRODUÇÃO:

Retrusão do terço médio da face é característica na síndrome de Crouzon e Apert. Fibroblast receptor growth factor (FGFR) exerce um papel fundamental no desenvolvimento da doença, e está relacionado com a sinostose bicoronal. A base do crânio também é tida como aberrante com a interrupção do crescimento midfacial normal, incluindo as sincondroses e o vomerino.

Várias teorias têm sido propostas para explicar a retrusão do terço médio da face nas Síndromes de Crouzon e Apert, mas estas não explicam completamente o fenótipo observado, e não foram baseadas em sofisticada análise 3-D.

O objetivo deste estudo é analisar objetivamente a retrusão do terço médio da face em uma série de crianças não tratadas de Crouzon e Apert e compará-las com um grupo controle. Especificamente, esperamos entender a dismorfologia facial e potêncial interrupção do crescimento usando recursos craniométricos e volumétricos para estudar a base do crânio e da anatomia do terço médio da face.

MATERIAL E MÉTODOS:

Esta é uma análise retrospectiva. Tomografias serão obtidas de indivíduos sem a intervenção cirúrgica prévia para corrigir retrusao facial. Serão incluidos pacientes com Síndrome de Crouzon ou Apert, e serão obtidos controles pareados em idade e sexo, sem nenhuma patologia. As informações demográficas serão tabuladas. Dados DICOM será digitalizado e manipulados usando software Surgicase CMF (versão 5.0.0.32, materializa, Leuven, Bélgica). Todas as variáveis serão obtidas e analisadas pelo mesmo observador, em ambos os grupos controle e estudo.

Após a segmentação, análises craniométricas e volumétricas serão realizadas. Os pontos craniofaciais e medidas lineares e angulares serão obtidas em ambos os grupos sindromicos e no grupo controle. O comprimento da fossa anterior e a largura serão obtidos a partir de uma

imagem sagital na linha média, considerando uma linha do nasion até a porção mais inferior do processo clinóide posterior, e à distância mínima entre as orbita no nível do globo posterior. O comprimento do esfenóide na fossa craniana anterior será obtido subtraindo-N-ES do comprimento ântero-posterior da fossa craniana.

Para a análise volumétrica, nos lados direito e esquerdo serão medidos o zigoma, mandíbula, maxila e órbitas. Volume em centímetros cúbicos (mL, ou cc cm3) será obtido para cada estrutura.

Os pontos (e ângulos gerados) serão escolhidos pelo mesmo observador, com verificação independente por dois observadores adicionais (todos os cirurgiões plásticos). Uma análise interobservador será realizada em uma série de assuntos de teste antes de concluir a análise de dados completo.

RESULTADOS ESPERADOS

Será observada as alterações do esfenóide e deformidades do terço médio da face e globo ocular.

Análise crítica de riscos e benefícios

Os riscos associados ao estudo são inexistentes, tendo em vista que este é um trabalho retrospectivo usando apenas tomografias computadorizadas. Já em relação aos benefícios, com o melhor entendimento da patologia e da dismorfologia facial, podemos desenvolver técnicas cirurgicas mais precisas que possam melhorar os resultados estético e funcional.

Duração total da pesquisa

Estima-se duração de 2-3 semanas para obtenção dos dados e 2 meses para a análise dos dados e publicação do trabalho.

Local da pesquisa

Esta pesquisa será realizada nas instalações do Departamento de Cirurgia Plástica da Faculdade de Medicina da Universidade de São Paulo.

Orçamento

Não haverá nenhum custo para a Faculdade de Medicina – USP.

Destino dos dados coletados

A partir dos dados coletados, sejam eles favoráveis ou não, será elaborado artigo para publicação em revista médica específica.

3 PUBLISHED PAPERS

After extensive data analysis, we published our results (1, 2) and will further discuss our findings in this thesis. In accordance to Wolters Kluwer Journals Author's Permission Guidelines (Appendix A), the links are available below:

Analysis of midface retrusion in Crouzon and Apert syndromes.

Forte AJ, Alonso N, Persing JA, Pfaff MJ, Brooks ED, Steinbacher DM.

Plast Reconstr Surg. 2014 Aug;134(2):285-93. doi: 10.1097/PRS.0000000000000360.

PMID: 25068327

Link:

http://journals.lww.com/plasreconsurg/Abstract/2014/08000/Analysis_of_Midface_Retrusion_in_Crouzon_and_Apert.26.aspx

Orbital Dysmorphology in Untreated Children with Crouzon and Apert Syndromes.

Forte AJ, Steinbacher DM, Persing JA, Brooks ED, Andrew TW, Alonso N.

Plast Reconstr Surg. 2015 Nov;136(5):1054-62. doi: 10.1097/PRS.0000000000001693.

PMID: 26505706

Link:

http://journals.lww.com/plasreconsurg/Abstract/2015/11000/Orbital_Dysmorphology_in_Untreated_Children_with.23.aspx

4 DISCUSSION

The synchondroses of the cranial base and cartilaginous growth centers are believed to direct midfacial growth (45). The position of the maxilla in space is influenced by growth of orbital contents, formation of maxillary sinuses and alveolar stimulation and apposition. It has been demonstrated that removal of nasal septum is shown to diminish midfacial growth in rabbits (46). Previous studies have called the midface hypoplastic in Crouzon and Apert patients. This term implies a decrease in volume, as opposed a retruded position in space. This expression was coined based on 2-D cephalograms, the only tools available decades ago. Determination of true hypoplasia would require 3-D models. Therefore, in our studies, in addition to volume, the 3-D shape of the maxilla and midface, and linear measurements compared to controls, were used to better understand the craniofacial deformation (1, 2). 2D and 3D methods have been used to study patients with Crouzon's and Apert's syndrome (10, 11, 47, 48). Some authors even use principal component analysis to describe Crouzon syndrome subjects (49). However, none of these studies measured the volumes of the midface bones, which contributed to dissemination of the term midface hypoplasia throughout the literature. The correct descriptor would be midface retrusion and maxillary deformity. In facts, we demonstrated that in these patients the maxilla is shorter in the anteroposterior dimension and rotated posteriorly, which gives the false impression that the midface is hypoplastic.

Similarly, most studies related to ocular and orbital deformity in Crouzon and Apert syndromes come from 2D imaging. These syndromes share similar orbital morphologies (50, 51). However, the globe proptosis and subsequent ocular morbidity is thought to differ in the two syndromes. Researchers believe that Crouzon syndrome proptosis

is caused by retrusion of the lateral and inferior orbital margins, while Apert proptosis is a result of extreme protrusion of the lateral orbital wall and shallow orbit posteriorly (20, 50, 51). It has remained unknown, in previous studies, whether the actual orbital or globe volume differs from normal in these conditions. Previously, 2D-cephalometrics based studies stated that the morphology of the orbit in Crouzon and Apert syndromes differs considerably from the population norm (20). Kreiborg et al.'s most notable finding was the marked protrusion of the lateral orbital wall caused by anterior displacement in the greater wing of the sphenoid in Apert. Fries and Katowitz describe compensatory expansion of the middle cranial fossa (52), and suggest this irregular expansion of the anterior and middle fossae in Apert syndrome causes orbital hypoplasia via displacement of the medial wall. Further studies, also employing 2D imaging, described the contribution of the anterior displacement of the greater sphenoid wing, lateral expansion of ethmoidal cells, and impaired growth of the maxilla and zygoma to a reduced orbital volume. They continued to suggest that the shortening of the anterior cranial base reduces the sagittal length of the orbital floor (53). Cephalometric techniques used by Kreiborg and Cohen demonstrated that both syndromes share an increase in interorbital distance and in orbital height, and shorter orbital floors with downward slant (11, 20, 50, 51). Fearon et al. concluded that the orbital cavity in patients with unoperated Crouzon and Apert syndrome tend to increase the degree of proptosis during growth (54).

The morphological relationship between the brain, orbit, periorbita and globe has important implications on the development of the eye (55). For example, as the cerebrum expands downward in infancy, the orbital roof moves inferiorly (56). The relationship between the orbital and globe volume invites elucidation, since current evidence suggests that globe growth has no influence on the orbit in humans (57), despite the contraditory clinical evidence: increased orbit in buphthalmos and decreased orbital volume in anophathalmia

compared to healthy controls (58). This contradiction has stimulated our research group to investigate this complex relationship in our patient population.

The cranial base angle is also a frequently studied parameter in craniometrics. Platybasia has been described associated with velocardial facial syndrome, with malar flattening and long face (59, 60). However, the cranial base angle has been shown in a younger population subset to not correlate with maxillary hypoplasia or SNA angle (61). Our findings indicate that, even though there is significant shortening of the anterior cranial fossa, the cranial base angles in the Crouzon/Apert group were not statistically different from those of the normal control children. This contradicts Enlow's theory that superior and posterior rotations at the cranial base are the reason for midface retrusion. Instead, we found that the posterior rotation of the pterygoid plates and its articulation with the maxilla play an important role in midface retrusion. The posteriorly rotated plate brings the maxilla and entire midface posteriorly, causing retrusion. In a similar fashion, Wilhelm et al also demonstrated that the mandibular and maxillary positional differences do not necessarily lie within the cranial base angulation, but rather in structural and potential growth differences of these structures (62).

Enlow’s Counterpart Analysis was designed to describe aberrant midfacial growth that could not be appropriately studied using conventional cephalometrics. 2-D cephalometrics contain inherent inaccuracies due to superimposition of bilateral structures, and altered points secondary to variations in head position. Therefore, cephalometric angles and measurements are also not able to independently describe patterns of growth (3, 5-8, 10). 3-D cephalometrics have been proven to be more effective than conventional cephalometrics, especially when assessing asymmetric conditions (63-66). 3-D digital analysis also allows for visualization of a single structure from multiple vantage points and segmentation of said structures (67-70).

Goldberg et al, studied patients with Apert's and Crouzon's Syndrome, using Counterpart Analysis, concluding that midface hypoplasia was derived from a superior and posterior rotation of middle cranial fossa, with a foreshortened anterior cranial fossa, which constrained nasomaxillary growth (10). Similarly, Reitsma et al reported an increasing counterclockwise rotation of the palatal plane in relation to the anterior cranial base in patients with Crouzon and Apert's syndrome (71). Additional studies concluded that the constricted anterior cranial base resulted both in coronal synostosis and diminished midface projection (72). The 2-D analytic methods available at the time could neither corroborate nor refute these statements. Our publications differ from previous studies by using 3-D volumetric renderized models, which allow a more precise multi-vantage point inspection of irregular structures. Furthermore, our papers investigated a group of Crouzon and Apert subjects without the presence of previous, confounding surgical intervention, and compared them to untreated age/gender-matched controls. The mixed-dentition, circa 6-year-old, age group was chosen for several reasons: maxillary and midface growth is almost completed by this age, and the eruption of permanent dentition influences alveolar projection and height. Moreover, midface surgical intervention occurs at this time for both psychosocial and functional reasons: to provide globe protection, reduce airway obstruction, and improve the occlusion.

During our research, we raised the question: which abnormality is primary? Does maxillary widening lead to the sphenoid deformity and splayed pterygoid plates or does the abnormal sphenoid growth lead to maxillary widening? Based on our data, which shows that both the maxilla and the sphenoid are deformed, and on Enlow's assertion that adjacent bones influence bone growth, we published that the sphenoid growth center is responsible for the process. If the maxilla intrinsically caused the deformity, we would expect the pterygoid plates to be rotated anteriorly. However, our findings show the pterygoid plates rotated posteriorly, indicating the sphenoid as the likely etiology, pulling the maxilla back in space.

This corroborates other reports pointing to the sphenoid as main culprit of an abnormal facial growth and projection (12). The sphenoid also likely contributes to the orbital deformity. Initially, it was thought that exorbitism in patients with Crouzon and Apert syndromes represented a relative proptosis secondary to maxillary retrusion (21). However, recent data indicate that most ocular pathologies occur secondary to shallow orbits, resulting in true exorbitism (73). In reality, there is a lack of consensus in the literature when describing the orbital dysmorphology in Crouzon and Apert patients as either exophthalmos or exorbitism (20, 24, 74, 75). Interestingly, our findings indicate that this deformity does not correlate to either of these classifications, and stands alone as a separate entity where patients have characteristics of both exorbitism and exophthalmos. These patients present with decreased orbital volume but also an increase in the globe.

Early midface distraction has been shown to enlarge the airway and improve obstructive respiratory disorders in syndromic patients (76). Midface distraction has been shown to achieve and maintain stability of the advanced midfacial skeleton if it is done up to 24mm (77). However, due to the differential growth rate of the midface and mandible, the facial profile becomes concave and patients require secondary midface correction postoperative year 5 to 10 (78). Furthermore, it was investigated if there was any difference in outcome based on the fixation used. The patients were divided in 3 groups: one underwent interosseous wiring and intermaxillary fixation, the other group had rigid plate fixation and the final group had a rigid external fixation device. One year after surgery, there was no difference in outcome (79). While surgeons achieve good outcomes using a standard Le Fort II and III for Crouzon patients (80), recent reports have showed improved outcomes when Apert patients are treated with a different technique. Dunaway's group recommends front facial bipartition distraction in Apert patients and believes that the relatively high perioperative complication rate is outweighed by the functional and aesthetic benefit (81).

Similarly, Hopper et al suggest the use of Le Fort II distraction with simultaneous zygomatic repositioning in the treatment of the Apert midface deformity (82, 83). Some authors have addressed the orbital hypoplasia using Le Fort III or fronto-orbital advancement (FOA) with cranial distraction (84, 85). FOA demonstrates dilation of the upper orbit only (21). Two studies compared the pre-operative and post-operative orbital volumes of patients with Apert or Crouzon syndrome after LeFort procedure (53, 86). Interestingly, Imai et al reported a significant increase in orbital volume and reduction of pre-operative ophthalmic symptoms despite there being no direct surgical remodeling of the orbital area (24). This is thought to be secondary to remodeling of the orbit following midface advancement (24, 85). Still, the full mechanism by which this apparent remodeling occurs remains uncertain.

Based on our findings, we would favor frontofacial monobloc advancement as a technique to potentially generate the best surgical outcome long-term, since it distracts the cranial base and appropriately repositions the face. Early reports from 1998 showed and important case of correction of proptosis and midface retrusion after undergoing a monobloc full face disjunction without repositioning. The patient was fitted with two springs for postoperative facial advancement and excellent results were noticed postoperatively (87). However, this procedure has been associated with complications such as cerebrospinal fluid leakage, infection, bone resorption and transient bilateral amaurosis (88). Raposo-Amaral et al report multiple variations of the Monobloc procedure that were performed to treat a family of Crouzon patients (89). Some authors advocate a combined monobloc Le Fort III distraction osteogenesis procedure, producing favorable clinical and functional outcomes (90). Recently, researchers investigated patient pre and postoperatively using 3D morphological analysis and showed that monobloc-distraction for Crouzon and bipartition-distraction in Apert Syndrome specifically address the morphological characteristics of the two syndromes (91). In previously operated adolescents with residual craniofacial deformation, frontofacial monobloc

advancement with simultaneous cranioplasty seemed to be an appropriate technique (92). Alonso's team also described normalization of the orbital volume in patients undergoing either Le Fort III or monobloc osteotomy (93). Finally, Bradley et al described the use of a keystone fixation for facial bipartition with monobloc distraction, allowing for excellent functional and aesthetic results and minimal relapse (94).

Apert and Crouzon present different features, but we strived to find a common trait in both groups responsible for the midface deformity, the link that could explain the midface retrusion regardless of the specific phenotype of each syndrome. In our first study, we felt that a subgroup analysis would shed additional light on our findings (1). In summary, our subgroup analysis showed that the anterior cranial fossa is shorter in both Apert and Crouzon when compared to control groups. It also showed that the cranial base distances are shorter in both Apert and Crouzon when compared to control groups. More importantly, it showed that the sphenoid angle of divergence is significantly more obtuse in both groups when compared to controls and that the pterygoid plates are posteriorly rotated in both Apert and Crouzon groups, which seems to be the common anatomical finding directing midface retrusion. Finally, we detected that Apert patients have a shorter maxilla compared to controls with similar width to controls, and Crouzon patients have a wider maxilla compared to controls, but similar length to controls. We believe that this can be explained by the noticeable splaying of angle of the pterygoid plates in the Crouzon patients (1).

Our assessment of orbital dimensions in both Crouzon and Apert syndromes demonstrates similar decreases in orbital length and increases in orbital height, corroborating the Krieborg and Cohen’s findings. However, our results contrast with other studies that have reported the opposite: that orbital morphology is not abnormal in the syndromic craniosynostoses (74, 95).

Perhaps the most interesting finding of our second study is that the globe volume is significantly greater in Apert and Crouzon patients than in the normal population (2). The role of mutations in FGFR-2 has been shows to cause immature cells to become bone cells during embryonic development (14, 96). FGFR-2 and associated receptors are also known to be involved in eye development (97-100). Therefore, globe development could be affected, given the extensive connective tissue involvement seen with FGFR-2 mutations, including the role of FGFR-2 in the formation of corneal epithelium and periocular mesenchyme (100, 101). However, understanding the mechanism by which the globe volume would be increased in these conditions is less apparent. It is known that periocular mesenchyme gives rise to specialized structures that are responsible for aqueous humor drainage in the eye (102-105). Therefore, abnormal development of the periocular mesenchymal cells can lead to dysgenesis of the anterior segment of the eye and compensatory increase in globe volume. Since our studies were not designed to collect clinical data from Crouzon and Apert patients, any theories as to why globe volume is increased in these conditions remains speculative and warrants further investigation. It also raises the question whether the protrusion is a result of exorbitism or exophthalmos (1, 12, 14, 16, 106). According to our data, the orbital dysmorphology observed in these patients does not fit the classic description of either exophthalmos or exorbitism (2).

There were strengths and novelties in our published papers (1, 2). One striking advantage we had at our disposal was the use of 3D analysis and cephalometrics, which was proved to be superior to the convention 2D cephalometrics (63-70). In 2D analysis, inaccuracies arise due to superimposed structures and variation in patient position (107). However, 3D analysis allows for multi-vantage point visualization of the globe and orbit and produces volumetric data (67-69). Another relative strength of our study is that the approximate age of our patients was 6 years, providing more morphological information than

what has been available, since it is unusual in the developed countries to encounter unoperated patient at that age bracket.

There were multiple limitations regarding our studies: bias related to small sample size, retrospective analyses and potential for patient selection biases. However, given the paucity of data on Crouzon and Apert patients presenting at age 5-6 years who are untreated, and the lack of consensus and understanding of the ocular pathology in these conditions, we believe that our study is unique in providing valuable data to providers and families.

5 CONCLUSION

Midface retrusion in Crouzon/Apert is associated with widened and posteriorly rotated pterygoid plates in association with a flatter and wider maxilla, suggesting diminished growth inferiorly and anteriorly. There is no bony volumetric deficiency in either Crouzon or Apert versus Controls. Additionally, orbital dysmorphology in Crouzon and Apert syndromes is associated with a shortened bony orbit, less orbital and periorbita volume, and an increased volume of the globe in both conditions. Despite normal volume of the overall orbital contents, the contents are altered, and the bony orbit is shorter and holds less volume, which does not fit the classic description of either exophthalmos or exorbitism.

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