UNIVERSIDADE DE SÃO PAULO HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

ISABELLA DE OLIVEIRA LIMA PARIZOTTO PAULA

# Clinical characterization of anophthalmic and microphthalmic cavities in individuals with craniofacial anomalies

Caracterização clínica das cavidades anoftálmicas e microftálmicas em indivíduos com anomalias craniofaciais

BAURU

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Dissertação constituída por artigo apresentada ao Hospital de Reabilitação de 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. Dr. Cristiano Tonello

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Orientador: Prof. Dr. Cristiamo Tonello

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# DEDICATÓRIA

Dedico este trabalho aos pacientes do Centrinho (Hospital de Reabilitação de Anomalias Craniofaciais – Universidade de São Paulo) e a todos que possam se beneficiar de seus frutos. Dedico também à minha família pelo exemplo e por não poupar esforços para que eu chegasse a esta etapa da minha vida.

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"Feliz é aquele que transfere o que sabe e aprende o que ensina."

Cora Coralina\*

<sup>\*</sup> trecho do poema Exaltação de Aninha de Cora Coralina. In: Vintém de cobre: as meias confissões de Aninha. 9. ed. São Paulo: Global; 2007."

#### ABSTRACT

*Objective* Measure the frequency of anophthalmic and microphthalmic patients with craniofacial anomalies (FCAs). Design Descriptive, cross-sectional, retrospective study. Setting Hospital for Rehabilitation in Craniofacial Anomalies of the University of São Paulo (HRAC-USP, Bauru, São Paulo, Brazil). Patients The medical records of patients treated at HRAC from 2000 to 2012 with a diagnosis of anophthalmia or congenital microphthalmia were examined. Patients were excluded for secondary anophthalmia, incomplete medical records, or information that could not be accessed. Outcome Measures Frequency of anophthalmia and microphthalmia; the proportions and diagnoses of associated FCAs; impairment of ocular appendages; extracranial or facial anomalies; genetic alterations; and surgical approach. Results A total of 56 patients had anophthalmia (52.3%), 35 had microphthalmia (32.7%), and 16 patients had both (15%). Individuals with FCAs associated with microphthalmia, anophthalmia, or both totaled 74, corresponding to 69.2%. Anophthalmia was more likely than microphthalmia to be accompanied by FCAs, at 76.4% of patients (p < 0.05). Cleft lip and palate were the main malformations associated with anophthalmia (23.64%), with microphthalmia (45%), and with both (44.44%). Reconstructive surgery was done in 63.6% of cases. The ocular attachments were compromised in 71% of cases. Extracraniofacial malformations were found in 9.3% of patients. Only seven records contained karyotypes, and no changes directly related to anophthalmia or microphthalmia were found. Conclusion Anophthalmia is more frequent than microphthalmia and is more often accompanied by FCA. Cleft lip and cleft palate are the most frequent concomitant malformations.

**KEYWORDS:** anophthalmos, microphthalmos, craniofacial abnormalities, orbit.

#### RESUMO

# Caracterização clínica de cavidades anoftálmicas e microftaálmicas em indivíduos com anomalias craniofaciais

*Objetivo:* Frequência de pacientes anoftálmicos e microftálmicos com as anomalias craniofaciais (ACF). Desenho Estudo descritivo, transversal e retrospectivo. Local: Hospital de Reabilitação em Anomalias Craniofaciais da Universidade de São Paulo (HRAC-USP). Bauru, São Paulo, Brasil. Pacientes: Prontuários de pacientes atendidos no HRAC no intervalo do ano de 2000 a 2012 com diagnóstico de anoftalmia ou microftalmia congênita. Excluiu-se anoftalmia secundária, prontuários incompletos ou cujas informações não possam ser acessadas. Desfechos estudados: Frequência de anoftalmia e microftalmia, proporção e diagnóstico de ACF associadas. Comprometimento de anexos oculares, anomalias extracranianas ou faciais, alterações genéticas e abordagem cirúrgica. Resultados: Total de 56 pacientes com anoftalmia (52,3%), 35 com microftalmia (32,7%) e 16 que apresentavam ambos (15%). Indivíduos com ACF associadas a microftalmia, anoftalmia ou ambos somaram 74, correspondendo a 69,2%. Em anoftalmia foi encontrado maior tendência a associar-se com ACF com 76,4% (p<0.05). Fissura labiopalatina foi a principal malformação associada à anoftalmia 23,64%, microftalmia 45% e ambos 44,44% em todas as situações. A cirurgia reparadora ocorreu em 63,6% dos casos. Os anexos oculares foram comprometidos em 71% dos casos. Em 9,3% dos pacientes encontrou-se malformações extra craniofaciais. Apenas 7 prontuários contavam análise de cariótipo e nenhuma alteração diretamente relacionada com a anoftalmia ou microftalmia foi encontrada. Conclusão: Conclui-se que a anoftalmia é mais frequente e que mais se associa a ACF. As fissuras labiopalatinas são as malformações concomitantes mais frequentes.

PALAVRAS- CHAVE: anoftalmia, microftalmia, anomalias craniofacias, órbita.

### ILLUSTRATIONS LIST

# Figure list

Figure 1-	Ocular embryological evelopment	17
Figure 2-	Scanning electron micrograph of an optic vesicle (dorsal is at the top of the image; optical rod cavity on the left)	18
Figure 3 -	Ocular ultrasound showing an eyeball with reduced dimensions and calcifications	20
Figure 4 -	Left microphthalmia with ocular prothesis on CT examination	21
Figure 5 -	Left anophthalmia on CT examination	21

# Photograph list

Photograph 1-	A- Bilateral anophthalmia B- Palate cleft associated	19
Photograph 2 -	Left microphthalmia	20
Photograph 3-	Orbital implant with progressive expansion	22
Photograph 4-	Dermofat graft surgery	22

### LIST OF TABLES

Table 1-	Correlation of anophthalmia, microphthalmia and bothwith laterality	29
Table 2-	Ocular patology and craniofacial malformations	31
Table 3-	Genetic changes in craniofacial malformation	32

### SUMMARY

1- Introduction and literature review	15
2- Objectives	24
3- Article	25
4- Overall conclusion	38
References	39
Appendix	43

#### INTRODUCTION AND LITERATURE REVIEW

Anophthalmia and microphthalmia are, respectively, an absence and a reduced size of the eyeball compared to the age-adjusted mean of the population. The two conditions can overlap because they are part of the same clinical spectrum, so their respective phenotypes can be difficult to delineate<sup>.1</sup>The prevalence of microphthalmia and anophthalmia is 1:7000 and 1:30,000 live births, respectively. <sup>2</sup>Although anophthalmia or microphthalmia may occur as an isolated finding, without systemic characteristics Extraocular findings are reported in 33-95% of these patients, suggesting that ocular findings are part of a broader pattern of developmental defects in many patients. The diagnosis of a syndrome can be made in 20-45% of patients with anophthalmia or microphthalmia. The extraocular systems most frequently affected are the craniofacial region (anomalies of the face, ear), the neck, and the limbs (musculoskeletal system).<sup>3</sup>

Congenital ocular anomalies are common among craniofacial malformations because they are usually compatible with life. Neural crest cells make key contributions to facial, dental, and cranial structures. The main congenital factors that affect the eyes and their appendages act between the 4th and 8th weeks of embryonic development. Facial changes such as cleft lip and palate occur between the 4th and the 12th week. In other words, there is an overlap period between the 6th and 8th week in which ocular and oral changes occur.<sup>4</sup> For this reason, syndromes that arise from inadequate development of the neural crest (e.g., Goldenhar syndrome) usually involve the eye as well as facial, dental, and cranial abnormalities.<sup>5</sup>

Frequently, anophthalmia occurs as part of other congenital syndromes. The most common syndromes are manifestations of chromosomal anomalies, with frequent association with Patau syndrome (chromosome 13) and Edward syndrome (chromosome 18), whose multiple malformations include anophthalmia.<sup>6</sup> Exceptionally, these malformations may manifest in association with bilateral cleft lip and palate and rare facial clefts.<sup>7</sup>

The primordia of the eye arise from the neural folds on the 22nd day of gestation on average. Following the neuroectoderm, two excavations are formed on each side of the midline, an optical groove, where the optic vesicles will be formed. The narrow neck of these vesicles connects them with the developing anterior brain. Once the optic vesicle touches the inner part of the surface ectoderm, it invaginates to form the optic calyx, which at this time has two layers. The inner layer forms the neural retina, and the outer layer forms the retinal pigment epithelium.<sup>5,8</sup>

As the optical calyx is formed, two processes begin: the first is that the surface ectoderm invaginates to form the lens (crystalline); the second is that the region between the surface ectoderm and the calyx is filled with a combination of cells derived from the mesodermal and neural crest that form most of the anterior segment of the eye. In the area surrounding the posterior region of the optic calyx, the same group of cells forms the hyaloid, choroid, and sclera vessels. The invagination of the optical calyx occurs asymmetrically. The ventral fissure enables the entry of mesodermal and neural crest cells. The fissure closes first in its center and then both anteriorly and posteriorly (Figure 1). The failure at this closing point generates what we call coloboma.<sup>5</sup>

The orbit is made of seven bones: the maxillary, zygomatic, frontal, sphenoidal, palatine, ethmoid, and lacrimal bones. During the first 6 months of gestation, it undergoes changes in shape and size, growing mostly linearly, after which it grows rapidly accompanying the development of the eyeball.<sup>9</sup>

Embryogenesis proceeds in stages, each stage regulated by genetic programs that are activated by specific cell types in a predetermined order that are expressed in response to external signals. Thus, this process can be thought of as a series of events that are based on each other, each step creating a cascade effect for the subsequent steps. Often, the same genes can participate in different cascades and play different roles in different contexts.<sup>5</sup>



Figure 1 Ocular embryological development.

Source: Figure by Paul Schiffmacher. Adapted from Forrester JV, Dick AD Mc Menamin PG, Roberts F, Pearlman E. The Eye: Basic Sciences in Practice. 4th ed. Edinburgh: Elsevier; 2016: 104-105

A proposed theory about anophthalmia/microphthalmia is that they result from a lack of induction at the level of the primitive neural tube or a failure of the optical excavation to grow and form the optic vesicle.<sup>10</sup> Later suggestions included secondary regression of an ocular structure during development (instead of primary aplasia of the optic vesicle), explaining the variable presence of ocular vestigial tissue buried in human anophthalmic sockets seen on histological examination.<sup>11</sup> Additional propositions have included that anophthalmia occurs after failure of the induction of the lens, early differentiation or interruption of the retina, and extensive cellularmovements, which are essential for invagination of the optic vesicle. Asymmetric involvement is common, suggesting differences in the intensity and penetration of themechanisms involved.<sup>12</sup> Abnormal developmental processes can hinder the formationof different segments of the eye, resulting in lesions and dysgenesis of the posterior segment, as well as all eyeballs, leading to anophthalmia and microphthalmia.<sup>10,13</sup>

Some genes are known to be important in ocular development. *PAX6*, *SOX2*, and *RAX*, for example, are induced early to support normal ocular development. Figure 2 depicts the main genes involved in an electron microscopy image of the eye. Mutation in *PAX6* generates malformations and midline fusion defects. The absence of these genes leads to anophthalmia.<sup>8,13</sup>

In general, mutations in each gene explain only a small percentage of cases. According to the 2015 revision of GeneRViews, the main gene responsible for anophthalmia/microphthalmia is *SOX2*, representing 10-15% of affected individuals, usually those with a severe anophthalmia/microphthalmia phenotype.<sup>14</sup> The next most frequent genetic causes are changes in *OTX2* (2–5% of cases), *RAX* (3% of cases), *FOXE3* (2.5% of cases), and *PAX6* (2% of cases). In general, the genetic cause is determined in only 20-30% of microphthalmia patients per year, although this number is higher in cases of severe and/or bilateral anophthalmia/microphthalmia.<sup>12,14</sup> Common causes are defects in genes critical for normal development but also include aneuploidies, intrauterine exposure to exogenous teratogens, and obstetric complications (oligohydramnios).<sup>9</sup>

Figure 2 Scanning electron micrograph of an optic vesicle (dorsal is at the top of the image; optical rod cavity on the left).



Source: Forrester JV, Dick AD, Mc Menamin PG, Roberts F, Pearlman E. The Eye: Basic Sciences in Practice. 4th ed. Edinburgh: Elsevier; 2016: 110.

Several known environmental factors may increase the risk of anophthalmia and microphthalmia, such as thalidomide, ethyl alcohol, and retinoic acid used by the mother during pregnancy. Viral infections with rubella virus, Epstein–Barr virus, Parvovirus B19, toxoplasmosis, and cytomegalovirus are also responsible for ocular malformations.<sup>6</sup> True anophthalmia occurs when ocular development is aborted at the stage of development of the optic vesicle, at approximately 3-4 weeks of gestation, leading to the absence of the eye, optic nerve, and chiasm, which can be confirmed by magnetic resonance imaging (MRI) examinations of the brain and orbit. Often, a small cystic remnant is detectable, called clinical anophthalmia, which occurs when the optic vesicle forms but then degenerates; therefore, a hypoplastic optic nerve, chiasma, or tract may be present (Photograph 1).<sup>15</sup>

Photograph 1 A- Bilateral anophthalmia B- Palate cleft associated.



Source: HRAC photographic archive.

In microphthalmia, the eye has a smaller volume, which may be associated with a reduced corneal diameter (microcornea, defined as a cornea with a horizontal diameter less than 9 mm in a newborn and less than 10 mm in children older than two years). Axial length less than 19 mm at 1 year of age or less than 21 mm in an adult as measured on B-scan ultrasound (Figure 3), representing 2 standard deviations below normal, define microphthalmia.<sup>16</sup>

#### Photograph 2 Left microphthalmia



Source: HRAC photographic archive.

Microphthalmia and anophthalmia can be distinguished through clinical evaluation and imaging exams, such as ultrasound, computed tomography (CT)(Figure 4 and Figure 5) and MRI. The distinction between clinical and true anophthalmia can only be made by histopathology.<sup>1</sup>

Figure 3 Ocular ultrasound showing an eyeball with reduced dimensions and calcifications.



Source HRAC photographic archive.



Figure 4 Left microphthalmia with ocular prothesis on CT examination

Source: HRAC photographic archive.



Figure 5 Left anophthalmia on CT examination

Source: HRAC photographic archive.

The approach to microphthalmic cavities can be conservative in cases of microphthalmia with a visual prognosis even with a prognosis of amblyopia, and it is important to perform refraction to provide the best vision potential for this eye. The eyeball triples in volume from birth to adolescence, and the growth of the orbit reflects the growth of the globe. Microphthalmia and anophthalmia constitute a smaller orbital volume than the normal volume of people of the same age, causing facial asymmetry. Treatment strategies are based on improving soft tissue expansion and bone asymmetry.<sup>17</sup>

Treatment should start early. The less severe microphthalmia can be treated conservatively with conformators (ocular prostheses) that are periodically changed to larger ones to promote orbital development. The most severe microphthalmia or anophthalmia should be treated within weeks of birth with cavity shapers to increase the eyelid cleft and promote orbital growth. The endo-orbital volume can be supplemented with static or progressively expanding orbital implants (Photograph 3) that can be complemented or replaced by dermofat implants (Photograph 4) from 6 months of age.<sup>18</sup>





Source: HRAC photographic archive

Photograph 4 Dermofat graft surgery



Source: HRAC photographic archive.

Cystic microphthalmia is usually operated on at 5 years or older, when the benefit of the cyst volume is beneficial for the development of the orbital bones, and then surgery is indicated for better rehabilitation of the orbital cavity.<sup>1</sup>

Varieties of pathogenic mutations in *YAP1* have been described in patients with anophthalmia, microphthalmia, iris colobomas, and chorioretinitis in addition to cataracts. Extraocular manifestations such as cleft lip and palate, bifid uvula, hearing loss, developmental delay, and Asperger's syndrome with reduced penetrance were found. YAP1 is a transcriptional coactivator that is a major effector of the hypothalamic pathway that regulates organ size and is directly regulated by SOX2. YAP1 can also affect  $\beta$ -catenin-dependent signaling and interacts with a number of genes and proteins that are implicated in anophthalmia, microphthalmia, and coloboma.<sup>19</sup>

Cleft lip and cleft palate are related to anophthalmia/microphthalmia, and their related genes are OTX2, STRA6, BMP4, BCR, TFAP2, PORCN, and YAP1.<sup>2</sup>

The group of rare facial fissures was classified by Paul Tessier. They are malformations caused by errors in embryogenesis in the first 12 weeks.<sup>20</sup> These fissures use the orbit as a reference point because it is a point of confluence between the skull and the face. There are 15 fissures: those below the orbit are numbered 0-8, and those above the orbit 9-14.<sup>21</sup> The clefts that have a special involvement with the ocular, eyelid, and orbital regions are among the rarest and are clefts 3, 4, and 5 consecutively.<sup>22</sup>

The literature on facial malformations and eye development defects is scarce. Most studies have sought to correlate genetic causes and external factors during pregnancy to explain their occurrence. Thus, this study seeks to detail, among the cases of congenital anophthalmia and microphthalmia, the main changes in craniofacial development and correlate them with genetic causes.

### **OBJECTIVES**

**Primary**: To clinically characterize anophthalmic and microphthalmic patients with craniofacial anomalies.

#### Secondary:

- to establish the percentage of anophthalmia and microphthalmia within thedefined sample as well as its laterality and severity of involvement;
- to define the craniofacial malformations associated with anophthalmia andmicrophthalmia;
- to calculate the frequency of craniofacial malformations in patients withanophthalmia and microphthalmia;
- to describe the percentage of patients surgically treated for anophthalmicand microphthalmic cavities
- to correlate previously identified genetic alterations with ocular alterations and craniofacial malformations

#### ARTICLE

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

# Clinical characterization of congenital anophthalmic and microphthalmic cavities in individuals with craniofacial anomalies

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#### ABSTRACT

*Objective* Measure the frequency of anophthalmic and microphthalmic patients with craniofacial anomalies (FCAs).

Design Descriptive, cross-sectional, retrospective study.

Setting Hospital for Rehabilitation of Craniofacial Anomalies of the University of São Paulo (HRAC-USP, Bauru, São Paulo, Brazil).

*Patients* The medical records of patients treated at HRAC from 2000 to 2012 with a diagnosis of anophthalmia or congenital microphthalmia were examined. Patients were excluded for secondary anophthalmia, incomplete medical records, or information that could not be accessed.

*Outcome Measures* Frequency of anophthalmia and microphthalmia; the proportions and diagnoses of associated FCAs; impairment of ocular appendages; extracranial or facial anomalies; genetic alterations; and surgical approach.

*Results* A total of 56 patients had anophthalmia (52.3%), 35 had microphthalmia (32.7%), and 16 patients had both (15%). Individuals with FCAs associated with microphthalmia, anophthalmia, or both totaled 74, corresponding to 69.2%. Anophthalmia was more likely than microphthalmia to be accompanied by FCAs, at 76.4% of patients (p < 0.05). Cleft lip and palate were the main malformations associated with anophthalmia (23.64%), with microphthalmia (45%), and with both (44.44%).

Reconstructive surgery was done in 63.6% of cases. The ocular attachments were compromised in 71% of cases. Extracraniofacial malformations were found in 9.3% of patients. Only seven records contained karyotypes, and no changes directly related to anophthalmia or microphthalmia were found.

*Conclusion* Anophthalmia is more frequent than microphthalmia and is more often accompanied by FCA. Cleft lip and cleft palate are the most frequent concomitant malformations.

#### INTRODUCTION

Anophthalmia and microphthalmia are, respectively, the absence and the reduced size of the eyeball compared to the age-adjusted mean of the population. The two can overlap because they are part of the same clinical spectrum, so theirrespective phenotypes can be difficult to delineate.<sup>1</sup> The prevalence of microphthalmia and anophthalmia is 1:7000 and 1:30,000 live births, respectively.<sup>2</sup>Although anophthalmia or microphthalmia may occur as an isolated finding, without systemic characteristics, extraocular findings are reported in 33-95% of these patients, suggesting that ocular findings are part of a broader pattern of developmental defects many patients. The diagnosis of a syndrome can be made in 20-45% of patients with anophthalmia or microphthalmia. The extraocular systems most frequently affected arethe craniofacial region (anomalies of the face, ear), the neck, and the limbs (musculoskeletal system).<sup>3</sup>

Congenital ocular anomalies are common among craniofacial malformations because they are usually compatible with life. Neural crest cells make key contributions to facial, dental, and cranial structures. The main congenital factors that affect the eyes and their appendages act between the 4th and 8th weeks of embryonic development. Facial changes such as cleft lip and palate occur between the 4th and the 12th week. In other words, there is an overlap period between the 6th and 8th week in which ocular and oral changes occur.<sup>4</sup> For this reason, syndromes that arise from inadequate development of the neural crest (e.g., Goldenhar syndrome) usually involve the eye as well as facial, dental and cranial abnormalities.<sup>5</sup> Exceptionally, these malformations may manifest in association with bilateral cleft lip and palate and rare facial clefts.<sup>7</sup>

The main objective of this study is to detail the cases of congenital anophthalmia and microphthalmia at the hospital and link the main changes in craniofacial development with their genetic causes.

### MATERIALS AND METHODS

This was a descriptive, cross-sectional, retrospective study based on the analysis of medical records of individuals regularly treated at the Hospital for

Rehabilitation of Craniofacial Anomalies of the University of São Paulo (HRAC-USP). The study was approved by the Human Research Ethics Committee of HRAC-USP under opinion number 4,371,477.

For the diagnosis of anophthalmia and microphthalmia, the medical evaluation of the Craniofacial Surgery and Genetics team of HRAC-USP was considered. The diagnosis was confirmed by data available in medical records. The evaluation was performed using descriptive data contained in the medical records, imaging findings on CT or MRI, and the photographic archives of the institution.

The inclusion criteria were:

- diagnosis of congenital anophthalmia or microphthalmia
- treatment between 2000 and 2012

The exclusion criteria were secondary (acquired) anophthalmia, incomplete medical records, or incomplete/inaccessible information (photographs or imaging results).

### Selection of medical records

Medical records were selected sequentially according to the record of care by the surgeons of the HRAC outpatient clinic.

A total of 107 medical records were suitable for the study, featuring anophthalmia, microphthalmia, or both congenitally, were identified. The time interval of care was from 2000 to 2012.

### Data analyzed

The individuals were classified as having anophthalmia or microphthalmia and had the following characteristics analyzed:

- diagnosis of anophthalmia or microphthalmia
- laterality
- diagnosis of craniofacial malformation
- impaired ocular attachments
- extrafacial or cranial involvement
- performance of reconstructive surgery

• genetic changes, depending on availability in the medical records.

#### Analysis of results

The data obtained were tabulated and analyzed through descriptive and analytical statistics and the chi-squared test.

#### RESULTS

The total of 107 patients had their medical records selected for analysis, which reflects approximately 28.6% of the initial sample of the outpatient clinic in the defined period.

A total of 56 patients with anophthalmia (52.3%), 35 patients with microphthalmia (32.7%), and 16 patients with both diagnoses, anophthalmia in one eye and microphthalmia in the other eye, were identified, corresponding to 15% of the patients. These patients who had both pathologies were not classified into the anophthalmia group or the microphthalmia group. Laterality was analyzed according to pathology and is shown in Table 1.

Malformation and laterality	Frequency	Percent
Anophthalmia, right eye	28	26.2
Anophthalmia, left eye	18	16.8
Microphthalmia, right eye	14	13.1
Microphthalmia, left eye	12	11.2
Microphthalmia, both eyes	9	8.4
Anophthalmia, both eyes	10	9.3
Microphthalmia and anophthalmia	16	15.0
Total	107	100.0

Table 1-. Correlation of anophthalmia, microphthalmia and both with laterality

Regarding sex, 44% were male and 56% were female. Female sex was more prevalent in cases of anophthalmia, microphthalmia, and both. Patients with

craniofacial anomalies associated with microphthalmia, anophthalmia, or both totaled 74, corresponding to 69.2%. Thus, 30.8% of patients had the isolated form of anophthalmia or microphthalmia.

The involvement of ocular adnexa was present in 71% of the cases, including alterations in the eyelids, lacrimal pathways, extraocular muscles and glands.

Genitourinary and renal alterations, tegmental alterations, alterations in the extremities (fingers and limbs) were found in 9.3% of the patients as part of a broader syndromic picture.

When analyzing the main craniofacial changes in patients with anophthalmia, microphthalmia, and both, it was noted that there was a higher frequency of cleft lip, cleft palate, and rare clefts. Other abnormalities found were nose malformations (hemiarhinia, arhinia, nasal hypoplasia, nasal coloboma), ear malformations (complete absence of the flag, partial malformations), changes in the central nervous system (holoprosencephaly, hydrocephalus, encephalocele, agenesis of corpus callosum, arachnoid cyst), amniotic banding sequence, Goltz–Gorlin syndrome, Delleman syndrome, Saethre–Chotzen syndrome, and oculoauriculovertebral spectrum. The changes in regions already covered by the description of the syndrome were not tabulated separately. Table 2 shows the frequency of these changes in anophthalmia, microphthalmia, and both.

	Anophthalmia	%	Microphthalmia	%	Both	%
Cleft lip and palate	13	23.64	9	45.00	8	44.44
Rare cleft	13	23.64	1	5.00	3	16.67
Ear malformations	8	14.55	0	0.00	3	16.67
Malformations of the						
central nervous system	4	7.27	4	20.00	1	5.56
Malformations of the nose	8	14.55	3	15.00	1	5.56
Amniotic bridging						
sequence	1	1.82		0.00		0.00
Goltz–Gorlin syndrome	0	0.00	1	5.00	1	5.56
Dellman syndrome	0	0.00		0.00	1	5.56
Oculoauriculovertebral						
spectrum	7	12.73	2	10.00		0.00
Saethre-Chotzen						
syndrome	1	1.82		0.00		0.00
TOTAL	55	100	20	100.00	18	100.00

Table 2 Ocular patology and craniofacial malformations

An inferential statistical analysis was performed between the ocular malformations and the accompanying craniofacial abnormalities, adopting a significance level of 95% (p < 0.05), and the nonparametric chi-squared test was applied. In the anophthalmia group, p < 0.02 was found, showing that there was a statistically significant association between the occurrence of anophthalmia and craniofacial malformations. For microphthalmia, the association was not statistically significant (p = 0.170).

Up to the time of reading the medical records, 68 of the 107 patients (63.6%) had undergone some surgical procedure related to the ophthalmic cavity in the HRAC service. The fact that 39 patients (36.4%) had not undergone any procedure may be due to the lack of medical indication, impossibility due to issues related to the patient's health or the logistics of the service, or the lack of authorization by the patients or their caregivers.

Few medical records have karyotype analysis or molecular analysis in their body for the identification of specific genes. Seven karyotype and molecular analyses were found, of which four had normal karyotypes and three had translocations or alterations that did not fit into syndromes and were not compatible with known genes related to anophthalmia and microphthalmia.

Craniofacial malformations	Karyotype + molecular analysis
Hemiarhinia + rare fissure + ear alteration + right-eye anophthalmia	45,XY, dic(13;14)(p11;p11),
Cleft lip and palate + anophthalmia in both eyes	46,XY, inv(9)(p11;q13),
Saethre–Chotzen syndrome + right- eye anophthalmia	46,XX, add (7)(p21)

Table 3 Genetic changes in craniofacial malformation

#### DISCUSSION

The laterality in this analysis was predominantly unilateral (67.2%), 58.3% being right-side and 41.7% left-side, and bilaterality (combined microphthalmia and anophthalmia or only one of the changes on both sides) occurred in 32.7%. In a prevalence study with a sample determination different from ours, Forrester and Merz (2005) analyzed cases of children born alive in Hawaii with ocular defects, of whom 54.7% had bilateral ocular defects and 45.3% unilateral. Of the unilateral patients, 55.2% had the right side affected and 44.8% the left side.<sup>23</sup>

Regarding sex, no significant difference was found between females and males, in agreement with Kallen et al. (1996) in their epidemiological study of anophthalmia and microphthalmia. In absolute numbers, females do predominate.<sup>3</sup>In the article published by Chambers et al. (2018), the female sex predominated despite there being a small difference between them.<sup>24</sup>

In 2017, Chambers et al. found, in a study on the prevalence of live births in Texas between 1999 and 2009, that children with anophthalmia more often have other malformations than children with microphthalmia, 58.6% versus 42.5%.<sup>24</sup> In the current study, the rate of craniofacial malformations associated with anophthalmia was higher, and the statistical test confirmed the greater tendency to have malformations. Of the anophthalmic patients, 75% exhibited an associated craniofacial malformation, while 62.8% of the microphthalmic patients and 81.2% of those with both exhibited associated craniofacial anomalies. Overall, anophthalmia or microphthalmia was associated with other craniofacial malformations in 72% of our patients, so 28% of the cases were isolated. Bermejo and Martinez-Frias (1998) indicated that 21% of the cases were isolated forms of anophthalmia or microphthalmia.<sup>25</sup>

Genetic regulation is essential for embryogenesis. Two genes have been described as critical in ocular development: *PAX6* (chromosome 11p13) and the *RAX* gene (chromosome 18). Both genes are expressed in cell proliferation. PAX6 mutations are related to aniridia, congenital cataract, Peters' anomaly, and midline fusion defects. The absence of these genes leads to anophthalmia.<sup>4</sup> In the present study, the genetic changes found were not specifically related to the anophthalmia or microphthalmia phenotype.

The inversion of chromosome 9, found in one of the patients, often does not imply loss of genetic information but simply reorganizes the order of genes. According to some studies, 1-3% of the general population may have this change, and its phenotype is not clear. Pericentric inversions of chromosome 9, written as "inv(9)(p11q12)/(9)(p11q13)", are so common that geneticists consider them to be normal variants.<sup>26</sup> The patient with the karyotype 46,XX, add (7)(p21) had a mutation related to the *TWIST* gene located in 7p21-p22, related to Saethre–Chotzen syndrome.<sup>27</sup> The karyotype 45,XY, dic(13;14)(p11;p11) has no relation to any specific malformation syndrome.

In the present study, 9/20 patients with microphthalmia had cleft lip and palate, and 1 patient (5%) had rare cleft. Among patients with both microphthalmia and anophthalmia, the frequency of cleft lip and palate was 44% and rare clefts 16.6%. The anophthalmia and both anophthalmia and microphthalmia groups had the same rates of rare clefts and cleft lip and palate.

Orofacial malformations are the most common congenital anomalies in the world. Among them, the most prevalent is cleft lip with or without cleft palate, which may occur in isolation or in association with syndromes.<sup>28</sup> Clefts may be associated with other structural anomalies and soft tissues of the face, such as ears, eyes, nose, teeth, and brain. Almost all bone and soft tissues of the craniofacial region are derived from neural crest cells. Nasser et al. (2016), in a systematic review on ophthalmological changes in patients with cleft lip and cleft palate, concluded that there is no consensus about the most frequent ocular changes in patients with nonsyndromic cleft lip and palate, and the same is true of articles that relate these changes with cleft lip and palate as embryological concepts.<sup>4</sup>

As already reviewed, the most important and severe malformations occur between the 4th and 8th weeks of the embryological period, while clefts occur between the 4th or 6th and 8th weeks. It would then be this overlap period that would lead to a greater association of these malformations affected by similar external and genetic factors.<sup>9</sup> Anchlia et al. 2012 evaluated patients with clefts associated with ocular changes. In their patient group, they found microphthalmia in 6.9% of patients.<sup>28</sup>

The craniofacial cleft exists in a multitude of patterns, varying in degrees of severity. Tessier presented the classification of rare cleft that are not related to the

incisive foramen and are numbered from 0 to 14 from the orbit, which is considered the reference landmark because it is common to the skull and face.<sup>29</sup>

Microphthalmia is associated with clefts directed through the orbit. According to Tessier, 1976, the relationship between microphthalmia and rare clefts would be more frequent in clefts 10, 11, and 12, with anophthalmia being the main malformation and microphthalmia appearing frequently at 5, 9, and 8.<sup>30</sup> According to Binet et al. (2019), rare clefts with ocular involvement are rare, and the most often related clefts are 3, 4, and 5.<sup>22</sup>

Goldenhar syndrome, oculoauriculovertebral spectrum (OAVS), is a rare congenital disease resulting from the abnormal development of the first and second gill arches. Its incidence is between 1:3500 and 1:5600, with a male:female ratio of 3:2.<sup>31</sup> This condition is characterized by a classic triad: mandibular hypoplasia resulting in facial asymmetry, ocular and auricular malformations, and vertebral anomalies. The ocular changes are most commonly represented by upper-eyelid colobomas associated with iris/chorioretinal coloboma, epibulbar choristoma, subconjunctival dermoid, and, less frequently, microphthalmia/anophthalmia, strabismus, cataract, or inequality of eyelid cleft.<sup>32</sup>

Cantor et al. (2018) discussed the association of syndromes of inadequate development of the neural crest, such as Goldenhar syndrome.<sup>5</sup> Anophthalmia and microphthalmia are relatively rarely associated with OAVS, which was confirmed in this study: 9 patients had OAVS, 12.16% of the malformations recorded, and it was more frequently found in our patients with anophthalmia. A systematic review published in 2020 by Rooijers et al. showed that the prevalence of microphthalmia ranged from 1.8% to 57.1% in 14 articles. Anophthalmia was mentioned in six studies, with a prevalence range of 1.5% to 42.9% in cases of OAVS.<sup>33</sup>

Saethre–Chotzen syndrome was identified in one of the patients with anophthalmia. This is a rare syndromic craniosynostosis that can also be included in the acrocephalosyndactyly type 3 group, an unusual set of congenital malformation syndromes characterized by coronal craniosynostosis and associated syndactyly, often with other phenotypic abnormalities varying between subjects, such as facial asymmetry, strabismus, ptosis, and characteristic features with prominence of the ear ridge. There is no report in the literature on its association with anophthalmia, as there

Oculocerebrocutaneous syndrome (OCCS), also known as Delleman's syndrome, is a rare congenital anomaly characterized by focal skin defects, orbital anomalies, and malformations of the central nervous system. The diagnosis of Delleman's syndrome is based on the triad of eye, central nervous system, and skin defects and is confirmed by MRI.<sup>34</sup> The case identified here was associated with anophthalmia in the left eye and microphthalmia in the right eye. It also entails changes in the nose, cleft lip and palate, and changes in the shape of the ear.

was in our sample. It is a rare syndrome that affects 1:25,000-50,000 live births.<sup>27</sup>

Anophthalmia, microphthalmia and both associated with nose malformation was detected in, respectively 14,5%, 15% and 5,5%. It was an expressive data in the sample given the rarity of these malformations in the general population. Tessier et al. (2009), in an analysis of arhinia, identified that 40% of patients with nasal alteration have arhinia. Hemiarhinia or lateral proboscis was associated with microphthalmia.<sup>35</sup>

Stallings et al. (2018) published data on population-based birth defects in the United States between 2011 and 2015 focusing on the ear and eye. In this study, a large proportion of anophthalmic and microphthalmic patients had simultaneous occurrence of ear, face, and neck defects.<sup>36</sup> In their survey, approximately 13% of patients with ear changes, annotation, or microtia exhibited concomitant ear changes and anophthalmia/microphthalmia, similar to the current findings of a 10.2% prevalence of ear changes in patients with anophthalmia, microphthalmia, or both.

Amniotic band sequence is a spectrum of asymmetric congenital malformations due to constrictive bands in the shape of a ring in the limbs, head, face, and trunk. The bands produce varying degrees of polymorphism with different clinical findings of skin marks on limb amputation. The incidence of this syndrome ranges from 1:1,200 to 1:15,000 live births. Morphogenesis in clefts is not well defined and is the topic of much debate. The fissures may be due to the swallowing of the bands by the fetus or failure of the migration or degeneration of the neural crest cells that are responsible for the formation of the fissure. It may be associated with multiple defects, including anophthalmia and microphthalmia.<sup>37</sup> The only case found in our sample was

associated with bilateral anophthalmia, amputation of fingers, skin marks, and anomalous implantation of eyebrows and hair.

Dermofocal hypoplasia, also known as Goltz–Gorlin syndrome, is a rare congenital disease characterized by a combination of skin defects and abnormalities in the skeleton and eyes. These patients often have microphthalmia, anophthalmia, coloboma, retinal pigment, and vascular defects as anomalies.<sup>38</sup> It has phenotypic overlap with microphthalmia with linear skin defect syndrome. The most consistent features of the syndrome are microphthalmia with turbid cornea or sclerocornea and linear skin defects restricted to the face and neck. Harmsen et al. (2009), in a study of 13 cases, found two patients with microphthalmia associated with Goltz–Gorlin syndrome, and the phenotype was quite similar to that of the two patients identified in our sample; however, one patient in the current sample had microphthalmia and anophthalmia and microphthalmia only.<sup>39</sup>

The fact that it is a retrospective study that depends on information from medical records and images from previous exams turns out to be a limitation in the study. The HRAC-USP is a reference center for craniofacial anomalies and mainly orofacial clefts, which may have been one of the factors that led to a higher frequency of association of anophthalmia and microphthalmia with clefts, a finding that is rarely found in the current literature.

#### CONCLUSION

When characterizing the anophthalmic sockets and microphthalmic eyes, both have an association with facial malformations and anophthalmia has a greater tendency of association with them than microphthalmia does. Consultation with an ophthalmologist can provide better early rehabilitation for patients with facial malformations and consequently contribute to a better quality of life.

#### **OVERALL CONCLUSION**

When characterizing the anophthalmic and microphthalmic cavities, a strong association was observed with facial malformations that arise at the same time in early embryology development. The prevalence of anophthalmia was higher than that of microphthalmia or both alterations. This is because genetic or environmental factors have early interference effects in development, as well as its greater association with malformations, as patients with anophthalmia had a greater tendency to have other facial anomalies.

Among the most prevalent anomalies, rare clefts and cleft lip and palate were most frequently found. The fact that HRAC is a reference center for such diseases may influence this result. As it is a service of excellence, it is noted that more than half of the patients were surgically approached for rehabilitation using ocular prostheses.

Molecular analysis is not yet a reality that is easily accessible to patients in the Brazilian public service, so few patients underwent such tests, and none of them identified any isolated gene related to the studied malformations.

In summary, there is anophthalmia and microphthalmia with anomalies of high prevalence in the population studied, and they are associated with other facial anomalies. The joint treatment of these malformations is highly important for the better rehabilitation of patients. It is important to correctly describe the disease characteristics as well as prioritize rehabilitation and genetic analysis to better manage the demand for these resources.

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### APPENDIX

#### Annex 1 Opinion substantiated by the Research Ethics Committee.



#### DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CARACTERIZAÇÃO CLÍNICA DE CAVIDADES ANOFTÁLMICAS E MICROFTÁLMICAS EM INDIVÍDUOS COM ANOMALIAS CRANIOFACIAIS Pesquisador: ISABELLA PARIZOTTO PAULA Área Temática: Versão: 1 CAAE: 39342520.6.0000.5441 Instituição Proponente: Hospital de Reabilitação de Anomailas Craniofaciais da USP Patrocinador Principal: Finandamento Próprio

#### DADOS DO PARECER

Número do Parecer: 4.371.477

#### Apresentação do Projeto:

Trata-se de um projeto de Dissertação, de autoria de ISABELLA DE OLIVEIRA LIMA PARIZOTTO PAULA sob orientação de Cristiano Tonello e equipe de pesquisa Nancy Mizue Kokitsu Nakata e Nivaido Alonso. Este estudo caracteriza-se como descritivo transversal retrospectivo e propõe a participação de individuos regulamente matriculados no Hospital de Reabilitação em Anomalias Craniofaciais da Universidade de São Paulo (HRAC-USP) com diagnóstico realizado pela Equipe de Cirurgia Craniofaciais da Universidade de São Paulo (HRAC-USP) com diagnóstico realizado pela Equipe de Cirurgia Craniofaciai e Genética do HRAC-USP de anomalia craniofaciai congênita. A avaliação será realizada por meio de dados secundários como anàlise de prontuário, fotografias e achados de Imagem de Tomografia Computadorizada (TC) e Ressonância Magnética (RNM). Serão selecionados pacientes atendidos pela equipe craniofacial do HRAC no intervaio dos anos 2000 a 2020. Os individuos serão classificados com anofialmia ou microfialmia e serao analisadas as seguintes características: - Lateralidade; - realização de cirurgia reconstrutiva; maiformação craniofaciai associada;- comprometimento de anexos oculares;-aiterações genéticas de acordo com a disponibilidade no prontuário. Os dados obitidos serão tabulados e analisados segundo os principios da estatística descritiva e comparados por meio das médias e desvios-padrão.

Quando possível, as variáveis serão submetidas a testes estatísticos considerados pertinentes pelo estatístico.

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Página 01 de 04



USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRÁNIOFACIAIS DA UNIVERSIDADE DE SÃO PAULO -HRAC/USP



Continuação do Parecer: 4.371.477

#### Objetivo da Pesquisa:

Objetivo Primário: Caracterização clínica de anofalmia/microftalmia em individuos com anomalias craniofaciais. Objetivo Secundário: Availar a prevalencia de maiformações craniotaciais em pacientes com anoitaimia e microftalmia; Caracterizar as maiformações craniofaciais associadas a anoftaimias e microftaimias; Definir um índice de abordagem cirúrgica frente as cavidades anoitámicas e microfiaimicas. Availação dos Riscos e Beneficios: Riscos: Como o projeto envolverá apenas dados secundários, não se aplicam riscos ao paciente. O paciente não serà exposto a nenhum novo exame, questionários ou nenhum tipo de abordagem que possa constrangé-lo. Beneficios: Como a literatura é escassa neste assunto, a caracterização clínica das cavidades anoftálmicas e microftálmicas contribui para melhor diagnóstico e tratamento quando associadas as anomalias craniofaciais. Comentários e Considerações sobre a Pesquisa: Pesquisa descritiva transversal com dados secundários e metodologia adequada a sua proposta. Considerações sobre os Termos de apresentação obrigatória: Os seguintes termos foram apresentados adequadamente: Carta de encaminhamento;

Formulário HRAC; 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.

#### Recomendações:

Não hà.

Enderaço: Rus Silvio Marchione, 3-20 Bairo: Vile Nova Cidade Universităria CEP: 17.012-000 UF: SP Menicipio: BAURU Telefone: (14)3235-8421 Fax: (14)3234-7818 E-mail: cephrac@usp.br

Página 02 de 04



USP - HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRÁNIOFACIAIS DA UNIVERSIDADE DE SÃO PAULO -HRAC/USP



Continuação do Parecer: 4.371.477

#### Conclusões ou Pendências e Lista de Inadequações:

O projeto de pesquisa não apresenta nenhuma irregularidade de ordem ética. Assim, sugiro ao CEP sua aprovação.

#### 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 availação. 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 availação.

Cabe ao pesquisador notificar via Plataforma Brasil o relatório final para availação. 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_P ROJETO 1585344.pdf	19/10/2020 20:55:23		Acelto
Projeto Detalhado / Brochura Investigador	PROJETOCARACTERIZACAOCLINICA CAVANOFEMICROFTEMACF.docx	19/10/2020 20:55:09	ISABELLA PARIZOTTO PAULA	Acelto
Folha de Rosto	folhaderostoalunaisabellaPPaula.pdf	19/10/2020 20:50:56	ISABELLA PARIZOTTO PAULA	Acelto
Outros	FORMCADASTROHRAC2.pdf	19/10/2020 20:49:07	ISABELLA PARIZOTTO PAULA	Acelto
Outros	TERMODECOMPROMISSOCONFIDEN CIALIDADEEAUTORIZACAODEUTILIZ ACAODEDADOSEMPROJETOSDEPES QUISA.pdf	14/08/2020 19:10:56	ISABELLA PARIZOTTO PAULA	Acelto
Outros	TERMODECOMPROMISSODETORNA RPUBLI.pdf	14/08/2020 19:10:12	ISABELLA PARIZOTTO PAULA	Acelto
Solicitação Assinada pelo Pesquisador Responsável	CARTADEENCAMINHAMENTOAOCEP. pdf	14/08/2020 19:08:42	ISABELLA PARIZOTTO PAULA	Acelto
Declaração de Pesquisadores	TERMOCOMPDOPESQRESPONSAVE L.pdf	14/08/2020 19:08:17	ISABELLA PARIZOTTO PAULA	Acelto

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Página CD de Of

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Ausenual				

Situação do Parecer: Aprovado Necessita Apreciação da CONEP: Não

BAURU, 30 de Outubro de 2020

Assinado por: Renata Pacielio Yamashita (Coordenador(a))

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# Annex 2

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS									
We hereby declare that we are aware of the article CLINICAL CHARACTERIZATION OF ANOPHTALMIC AND MICROPHTHALMIC CAVITIES IN INDIVIDUALS WITH CRANIOFACIAL ANOMALIES will be included in Dissertation of the student Isabella de Oliveira Lima Parizotto Paula was not used and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.									
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