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RESEARCH ARTICLE

CLINICAL CONGENITAL ANOPHTHALMIA AND ASSOCIATED SYSTEMIC ANOMALIES: A RETROSPECTIVE CLINICAL STUDY

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ABSTRACT

Purpose: Anophthalmia is a rare congenital ocular malformation defined by the complete absence of the eyeball. It may occur as an isolated finding or systemic and syndromic abnormalities. This study aimed to evaluate the clinical and systemic features of patients with anophthalmia in a tertiary care center.
Materials and Methods: A retrospective review was performed on patients diagnosed with unilateral or bilateral anophthalmia at the Ophthalmology Department of Dokuz Eylul University Hospital between January 2005 and July 2025. Demographic data, ocular findings, and systemic evaluations were analyzed.
Results: Fifteen patients were included, with a mean age of 1.84 ± 2.94 years. Unilateral anophthalmia was found in nine patients and bilateral in six. Systemic anomalies were present in 11 patients (73.3%). Four patients (26.6%) had syndromic diagnoses, including CHARGE, Goldenhar, and Fryns syndromes. The most common non-syndromic anomalies were congenital heart defects and craniofacial malformations. A history of consanguinity was observed in six patients (40%).
Conclusion: The high frequency of systemic and syndromic associations, particularly in bilateral cases, emphasizes the importance of a multidisciplinary approach. Early neuroimaging, systemic screening, and genetic counseling are essential for optimal diagnosis and management.

Keywords: Anophthalmia, congenital ocular malformation, systemic anomalies, syndromic diagnosis, neuroimaging, consanguinity

INTRODUCTION

Anophthalmia, a rare congenital condition characterized by the complete absence of ocular tissues, is one of the most severe anomalies affecting eye development (1). The term congenital anophthalmia is used when there is no detectable ocular tissue; however, histology has shown, in some cases, the presence of neuroectoderm remnants (2). Therefore, the term "clinical congenital anophthalmia" seems to be more appropriate, as it identifies a phenotypic range between microphthalmia and anophthalmia (3). It is reported to occur in 0.6–4.2/100,000 newborn infants, may be unilateral or bilateral, and other anomalies in the fellow eye may

be present if the condition is unilateral (2, 4). These associated ocular findings have been reported to be present in up to 47.4% of affected patients, with the predominant anomalies being coloboma, dermoids, sclerocornea, glaucoma, lens, and optic nerve abnormalities (5). Additionally, anophthalmia can occur in isolation or as part of a syndrome and is often accompanied by other systemic abnormalities involving the central nervous system, craniofacial, cardiac, and genitourinary systems (4-6). This study aims to analyze the clinical and systemic features of patients diagnosed with clinical congenital anophthalmia in a tertiary care center over a 20-year period, highlighting the prevalence and spectrum of ocular and systemic anomalies in the context of limited data in the existing literature, particularly regarding Türkiye-specific findings, and detailed systemic evaluation.

MATERIALS AND METHODS

This retrospective observational study was conducted in a tertiary care center, and the institutional ethics committee approved the study (Approval number: 2025/32-02). Medical records of patients diagnosed with unilateral or bilateral clinical congenital anophthalmia between January 2005 and July 2025 were reviewed. Clinical congenital anophthalmia was defined as the complete absence of the ocular globe within the orbit at birth, with no ocular structures visible on macroscopic clinical examination (7). The qualifier '*clinical'* notes that no globe or ocular structures are visible on examination. Yet, residual neuroectodermal tissue may still be found on imaging or histopathology, distinguishing it from *true* anophthalmia, in which ocular tissue is entirely absent. The inclusion criteria included a confirmed clinical diagnosis of congenital clinical anophthalmia, availability of detailed medical records, and at least one year of clinical follow-up. Demographic data, ocular findings, systemic anomalies, syndromic diagnoses, prenatal consultation records, neonatal unit records, and outpatient clinic records were documented. Systemic evaluations, where available, included cranial Magnetic Resonance Imaging, echocardiography, and renal ultrasonography. All data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to summarize the demographic and clinical characteristics of the study population. Continuous variables, including age at initial examination and maternal age, were reported as mean ± standard deviation. Categorical variables, such as sex, laterality of anophthalmia, parental consanguinity, presence of systemic anomalies, and syndromic diagnoses, were expressed as frequencies and percentages.

RESULTS

A total of 15 patients diagnosed with clinical congenital anophthalmia were included in this study. Of these, 9 (60%) were female, and 6 (40%) were male. The mean age at our first examination at our clinic was 1.84 ± 2.94 years. The mean and median follow-up durations of the patients were 6.62 ± 5.83 years (range: 2.4-14.1) and 6.13 years, respectively. Nine patients (60%) had unilateral anophthalmia, whereas six patients (40%) presented bilateral anophthalmia. Among the unilateral cases, the right eye was affected in seven patients, while only two had involvement of the left eye. Three children were prematurely born, six children had consanguineous parents (40%), and maternal age ranged from 22 to 36 years (median 27 years). Prenatal detection of anophthalmia was achieved in one case. Evaluation of the contralateral eye in 9 patients with unilateral anophthalmia revealed the following abnormalities: sclerocornea and retinal detachment (n=1), retinopathy of prematurity (n=1), nystagmus (n=2), and congenital cataract (n=1). No additional ocular pathology was identified in the remaining four patients. Additional systemic anomalies were identified in 11 patients (73.3%). Syndromic diagnosis was confirmed in 4 (26.6%) patients. Among these, two patients were diagnosed with oculo-auriculo-vertebral spectrum (OAVS), also known as Goldenhar syndrome. Additional syndromic diagnoses included Fryns syndrome (n = 1) and CHARGE (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth/development, Genital abnormalities, and Ear anomalies) syndrome (n = 1). The demographic and clinical characteristics of all patients are summarized in Table 1. Additionally, a summary of the Demographic and Clinical Characteristics of All Patients is presented in Table 2.

In patients without an identified syndrome, a total of 39 systemic anomalies were observed. Congenital cardiac anomalies were documented in 10 patients. These included tetralogy of Fallot (n=1), peripheral pulmonary artery stenosis (n=2), patent foramen ovale (n=1), patent ductus arteriosus (n=1), tricuspid

Table 1. Demographic and clinical characteristics of patients are summarized.

Case Number	Gender (M/F)	Age at first examination	Laterality (R/L/B)	Associated Ocular Pathologies	Associated Systemic Pathologies	Prenatal history	Consanguinity
1	F	2 months	R	-	-	-	-
2	F	5 months	R	Nystagmus	-	Prematurity (35 weeks)	-
3	F	1 month	L	Congenital cataract	-	-	-
4	M	3 years	R	Nystagmus	Craniosynostosis, Maxillofacial deformity, Renal agenesis, Microtia, Skin tag, Cleft lip, cleft palate, and Inguinal hernia	-	+ (Married to the uncle's grandson)
5	F	3 months	B	-	ASD PDA	Prematurity	+
6	F	7 months	R	Retinopathy of prematurity	Cleft lip, Clinodactyly, syndactyly, Choanal atresia	Prematurity Eclampsia	-
7	M	10 years	L	-	Fenestrated septum pellucidum	-	-
8	M	10 days	B	-	Peripheral pulmonary artery stenosis, Patent foramen ovale,	-	+ (cousins)
9	F	6 years	R	Sclerocornea Retinal detachment	TOF, Agenesis of the corpus callosum, nasal malformation	-	+ (cousins)
10	M	5 months	B	-	Epilepsy	-	+ (cousins)
11	F	4 months	B	-	Fryns Syndrome, Meningocele, Cleft lip, Bil. Choanal atresia, Cerebellar vermis agenesis	-	-
12	F	3 months	B	-	Goldenhar Syndrome, Choanal atresia, Epilepsy, Tricuspid regurgitation, Pulmonary hypertension, Cerebral atrophy	-	+
13	M	1 month	B	-	Cleft lip and palate, retromicrognathia, low-set ear, Hypospadias, Pulmonary artery stenosis, ASD, Minor aortopulmonary collateral artery, Spina bifida, umbilical hernia	Meconium aspiration, Polyhydramniosis	-
14	F	1 year	R	-	Goldenhar syndrome, Torticollis, ASD	Smoking and alcohol consumption	-
15	M	5 years	R	-	-	-	-

insufficiency (n=1), pulmonary hypertension (n=1), atrial septal defect (n=2), and minor aortopulmonary collateral artery (n=1). Orofacial and craniofacial anomalies, particularly affecting the ears, nose, and oral cavity, were found in 10 patients. These included cleft lip and/or palate (n=5), retrognathia/micrognathia (n=1), low-set ears (n=1), nasal anomaly (n=1), ear hypoplasia (n=1), and preauricular skin tag (n=1). Central nervous system (CNS) anomalies were identified in 8 cases (53.3%). These included agenesis of the corpus callosum (n=1), agenesis of the cerebellar vermis (n=1), and neural tube defects such as spina bifida and meningocele (n=2). Other CNS-related anomalies

Table 2. Summary of demographic and clinical characteristics of all patients.

Characteristics	n (%) or Mean ± SD
Total patients	15
Female / Male	9 (60%) / 6 (40%)
Mean age at first examination (years)	1.84 ± 2.94
Laterality	Unilateral: 9 (60%) / Bilateral: 6 (40%)
Right eye involvement (unilateral)	7 (77.8%)
Left eye involvement (unilateral)	2 (22.2%)
Premature birth	3 (20%)
Consanguinity	6 (40%)
Prenatal diagnosis	1 (6.7%)
Syndromic cases	4 (26.6%)
Isolated cases	11 (73.4%)
Patients with systemic anomalies	11 (73.3%)
Cardiac anomalies	10 (66.7%)
Craniofacial/orofacial anomalies	10 (66.7%)
CNS anomalies	8 (53.3%)
Musculoskeletal anomalies	4 (26.7%)
Genitourinary anomalies	2 (13.3%)
Gastrointestinal anomalies	2 (13.3%)
Respiratory anomalies	3 (20%)

observed included septum pellucidum fenestration, cerebral atrophy, and epilepsy (n = 4). Musculoskeletal abnormalities were identified in four cases, including syndactyly (n = 1), clinodactyly (n = 1), craniosynostosis (n = 1), and torticollis (n = 1). Genitourinary anomalies were observed in two patients, including hypospadias and renal agenesis. Gastrointestinal and abdominal wall anomalies were present in two cases, including umbilical hernia and inguinal hernia. Respiratory anomalies were observed in three patients, all of whom had choanal atresia.

All bilateral cases of clinical congenital anophthalmia were associated with systemic abnormalities (100%), whereas among the nine unilateral cases, only five presented with additional systemic pathologies (55.6%). Comparison of unilateral and bilateral anophthalmia cases is summarized in Table 3.

DISCUSSION

The present findings provide additional support for the well-documented association between clinical congenital anophthalmia and multisystem congenital anomalies. The rate of syndromic diagnoses in our cohort was consistent with previous literature, which estimates syndromic forms of anophthalmia in up to one-third of cases (3). The identification of OAVS, CHARGE, and Fryns syndromes, as well as multiple systemic diseases, in our sample confirms the phenotypic diversity and underscores the need for comprehensive, systematic evaluation. Among the unilateral cases, the right eye was affected in 7 patients, while only 2 had left-eye involvement. Additionally, the predominance of right-eye involvement in unilateral cases has also been observed in both human and animal studies, possibly reflecting the influence of developmental genes governing embryonic laterality (6, 8).

In our study, all bilateral cases were associated with systemic anomalies, whereas only 5 out of 9 unilateral cases (approximately 55.6%) had systemic involvement. This observation suggests that bilateral anophthalmia may represent a more severe disruption of early ocular morphogenesis, reflecting broader embryologic defects with multisystem involvement. These findings align with previous literature, which reports that bilateral cases are significantly more common in children with systemic anomalies, suggesting that laterality may serve as a useful clinical indicator for multisystem involvement (6). Consanguinity was slightly more common among unilateral cases in our study; however, syndromic diagnoses, such as CHARGE and OAVS, were identified in both groups. This finding is consistent with the previously described genetic heterogeneity in anophthalmia and microphthalmia cohorts (6, 9). Importantly, unilateral cases frequently demonstrated contralateral ocular pathology, including sclerocornea, retinal detachment, and congenital cataract, underscoring the importance of detailed ophthalmological evaluation even in the clinically unaffected eye.

Cardiovascular anomalies were present in 66.6% of the cohort, making them the most frequent systemic anomaly group, along with orofacial anomalies, in this study. Documented findings ranged from major malformations such as tetralogy of Fallot and pulmonary artery stenosis to milder anomalies like atrial septal defects and patent foramen ovale. The shared embryological origin of ocular and cardiac tissues may partially explain the frequent association between ocular and cardiac malformations. In particular, both systems depend on neural crest cells and morphogenic pathways involving genes such as SHH, CHD7, and PAX6 (9). These genes play essential roles in optic vesicle morphogenesis and

Table 3. Comparison of unilateral and bilateral anophthalmia cases

Characteristics	Unilateral (n=9)	Bilateral (n=6)
Gender (F/M)	6/3	3/3
Mean age at first examination (years)	2.92±0.13	0.23±0.15
Consaguity	4 (44.4%)	2 (33.3%)
Contralateral Ocular Findings	Sclerocornea+RD (1), ROP (1), Nystagmus (2), Congenital cataract (1)	Not applicable
Associated Systemic Pathologies	5 (55.6%)	6 (100%)
Syndromic diagnosis	2 (OAVS, Fryns)	2 (OAVS, CHARGE)
Cardiac anomalies	5	5
Craniofacial/orofacial anomalies	5	5
CNS anomalies	4	4
Musculoskeletal anomalies	3	1
Genitourinary anomalies	2	0
Gastrointestinal/abdominal wall anomalies	2	0
Respiratory anomalies	1	2

cardiac neural crest development. Their disruption has been linked to syndromes such as CHARGE, which is characterized by ocular anomalies and congenital heart disease (10).

Orofacial anomalies, including cleft lip and/or palate, were also a leading group of systemic anomalies in our series and were often part of broader craniofacial syndromes. These anomalies were present both as isolated findings and as part of syndromic diagnoses such as CHARGE syndrome (10). The co-occurrence of orofacial clefts with anophthalmia likely reflects disruptions in neural crest cell migration and early embryonic midline patterning, processes critical to both ocular and facial morphogenesis (3).

Genetic contributors, such as CHD7, SHH, and OTX2, all of which play roles in both craniofacial and ocular development, may explain this frequent overlap (9). For example, mutations in CHD7, commonly associated with CHARGE syndrome, are known to affect the development of the pharyngeal arches, contributing to both cleft palate and ocular anomalies (10). Furthermore, defects in the SHH signaling pathway have been implicated in holoprosencephaly spectrum disorders. These disorders are characterized by midline facial anomalies, including cleft lip and palate, and are often accompanied by severe ocular malformations, such as anophthalmia (9).

Central nervous system anomalies were the second most frequent group of systemic abnormalities after cardiovascular and orofacial anomalies, echoing the embryologic linkage between eye formation and forebrain development. The optic vesicles arise from the diencephalon between the third and fourth weeks of gestation, and disruption in this early developmental stage may affect both ocular and brain structures (11). Structural anomalies such as agenesis of the corpus callosum, cerebellar vermis hypoplasia, and neural tube defects in our sample further support this association. In the National Study of MAC in Scotland (Morrison et al., 2002) (12), the researchers conducted a detailed population-based genetic and clinical investigation of microphthalmia, anophthalmia, and coloboma (MAC) cases born in Scotland between 1981 and 1996. Out of 122 clinically confirmed cases, neurological abnormalities and other major malformations were identified in 40 individuals. Notably, the study found that neurological anomalies were more common in the anophthalmic group compared to the microphthalmic group, regardless of whether they had optic fissure closure defects (OFCD) or non-OFCD. This finding is consistent with previous studies, which have identified neurological abnormalities, particularly midline anomalies, especially when the eyes are more severely affected (13, 14). As noted by Ragge et al.(2), neuroimaging is crucial for identifying subtle anomalies that might otherwise go unnoticed but have significant consequences.

In the study by Stoll et al. (2024), the authors conducted a population-based, retrospective cohort study spanning a 29-year period in northeastern France, analyzing 98 cases of anophthalmia and microphthalmia among 387,067 consecutive pregnancies. Their findings revealed that 88.8% of the cases exhibited additional congenital anomalies,

categorized into chromosomal abnormalities (25.5%), non-chromosomal recognizable conditions (17.3%), and multiple congenital anomalies without a recognizable pattern (45.9%). The most frequently associated anomalies involved the musculoskeletal, cardiovascular, and central nervous systems. Trisomy 13 and 18 were the most common chromosomal findings, while CHARGE syndrome, amniotic band sequence, and VACTERL association (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities) were notable among the non-chromosomal diagnoses.

Interestingly, nearly half of the patients in our study had consanguineous parents, supporting the hypothesis that recessive genetic inheritance may play a significant role in the etiology of bilateral and syndromic cases. Previous population-based studies from the Middle East region have also identified consanguinity as a risk factor for complex congenital anomalies, including ocular defects (15).

Furthermore, anophthalmia was prenatally detected in only one patient diagnosed in 2020. Considering the long study period, prenatal detection was likely not feasible for most earlier cases. This low rate may also reflect system-level limitations in Türkiye, including historically heterogeneous prenatal screening coverage and limited access to targeted fetal orbital imaging. Ultrasonographic evaluation of fetal ocular anomalies has been available since 1991 (16), with orbital assessment possible from approximately 12 weeks' gestation. It plays a key role in the prenatal diagnosis of congenital clinical anophthalmia. Early prenatal detection enables genetic counseling, postnatal management, parental preparation, and multidisciplinary care planning.

Despite the relatively small sample size, this study contributes valuable data to the growing literature on clinical congenital anophthalmia and associated systemic anomalies, particularly from the Turkish population. The retrospective design is a limitation, potentially introducing selection bias, especially as our institution serves as a referral center for complex pediatric ophthalmic cases. As a retrospective review, it is influenced by incomplete documentation and variability in the extent of systemic testing, particularly in earlier years. Our patients didn't undergo genetic testing, limiting our ability to confirm genotype-phenotype correlations. Nonetheless, the high frequency of both syndromic and isolated anomalies observed confirms the importance of thorough systemic screening and genetic counseling in all patients with congenital anophthalmia.

CONCLUSION

In conclusion, this study highlights that clinical congenital anophthalmia is rarely an isolated ocular condition. Given the high prevalence of associated congenital anomalies, a comprehensive multidisciplinary approach, including detailed neuroimaging, genetic consultation, and systemic screening, is essential. Early detection enables timely interventions, optimizes developmental outcomes, and provides more accurate prognostic counseling for affected families.

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