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Imaging Findings in Patients with Clinical Anophthalmos

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PURPOSE: To review the intracranial and facial imaging features in children with congenital anophthalmos. **METHODS:** We retrospectively studied eight children with anophthalmos with respect to intraorbital, intracranial, and craniofacial anomalies (six had CT examinations, including the face, orbits, and brain, and four had MR imaging, including the orbits and brain). **RESULTS:** Three patients had primary bilateral anophthalmos on CT (n = 1) and MR (n = 3) studies. In these patients, MR images showed hypoplasia of the optic chiasm and posterior visual pathways (n = 3), agenesis (n = 1) or dysgenesis of the corpus callosum (n = 2), and a mass in the tuber cinereum region (n = 1). One patient had incontinentia pigmenti. Five patients had unilateral anophthalmos on CT (n = 5) and MR (n = 1) studies. One of these patients had a contralateral congenital cystic eye and one had contralateral severe microphthalmia and absent optic chiasm. All had craniofacial anomalies that consisted of midline facial clefts (n = 2) and concomitant hemifacial hypoplasia (n = 2). One had a craniosynostosis. All five had normal-appearing brains. **CONCLUSION:** Patients with bilateral anophthalmos represent a distinct group from those with unilateral anophthalmos. In our patients, bilateral anophthalmos was associated with absence of the optic chiasm, diminished size of the posterior optic pathways, and agenesis or dysgenesis of the corpus callosum. Patients with unilateral anophthalmos had severe craniofacial anomalies. Imaging of the face is helpful in patients with unilateral anophthalmos.

Index terms: Eyes, abnormalities and anomalies; Pediatric neuroradiology

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Anophthalmos, or congenital absence of an eye or eyes, is a rare anomaly that occurs as a result of insults to the developing eye(s) during the first 8 weeks of life (1). Mann (2) classified anophthalmos into three distinct types. *Primary* anophthalmos is usually bilateral and sporadic and occurs when the optic primordia does not develop. *Secondary* anophthalmos is an extremely rare and lethal anomaly that occurs when the entire anterior neural tube fails to develop. *Consecutive* or *degenerative* anophthalmos occurs when the optic vesicle(s) forms but subsequently degenerates. Anophthalmos may be difficult to differentiate, both clinically and by imaging, from severe microphthalmos. Histo-

logic examination of the orbital contents is helpful in confirming the presence or absence of neuroectodermal derivatives. Degenerative anophthalmos and severe microphthalmos contain neuroectodermal tissues and therefore may be considered as similar entities. The absence of neuroectoderm is, however, typical of primary and secondary anophthalmos (1, 3, 4). *Clinical anophthalmos* is an all-encompassing term used to describe the clinical and radiologic absence of a globe (5, 6). Although these terms do not address the presence or absence of neuroectoderm, they seem sufficient, because the treatment is similar for all forms of anophthalmos. We review the computed tomographic (CT) and magnetic resonance (MR) imaging studies obtained in eight patients with clinical anophthalmos to determine the prevalence and type of brain and facial malformations present.

Materials and Methods

CT (n = 6) and MR (n = 4) imaging studies and clinical data in eight children (three boys and five girls; 30 days to 10 years old) with bilateral (n = 3) or unilateral (n = 5)

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Clinical and imaging findings in eight patients with anophthalmos

Case	Age/Sex	Type of Study	Side	Abnormalities					
				Other Eye	Corpus Callosum	Visual Pathway	Other Brain Areas	Craniofacial	Systemic
1	6 y/F	MR	Bilateral	+	-	+	+	-	-
2	11 mo/M	CT/MR	Bilateral	+	+	+	+	-	-
3	10 y/F	MR	Bilateral	+	+	+	+	-	+
4	30 d/F	CT	L	+	-	+	-	+	-
5	48 d/F	CT	R	-	-	-	-	±	-
6	6 mo/F	CT/MR	L	-	-	+	-	+	-
7	60 d/M	CT	L	-	-	-	-	+	-
8	6 mo/M	CT	R	+	-	-	-	+	-

Note.—+ indicates present, -, absent.

anophthalmos were reviewed retrospectively with special attention to intracranial and craniofacial abnormalities (see Table). Because this report represents a multiinstitutional study, imaging protocols varied for each patient. Of the six patients who were studied with CT, four had 3-mm-thick contiguous sections obtained in the axial projection from the mandibular symphysis to the vertex. In one case, 3-mm-thick contiguous axial sections were obtained throughout the orbits, and the brain was studied using 5-mm-thick axial sections. In three patients, three-dimensional reformations of the face were done. For those who had MR imaging, a minimum of sagittal, coronal, and axial 5-mm-thick T1-weighted (600/15/1 [repetition time/echo time/excitations]) and axial T2-weighted (4000/19,93/1) images were obtained of the orbits and brain. In two instances, axial and coronal 3-mm-thick T1-weighted images were obtained through the orbital and sellar regions. No patients received contrast material for either CT or MR imaging. Pathologic findings were available in only one patient, who had congenital cystic eye and contralateral anophthalmos.

Results

Three patients (two girls and one boy) had bilateral anophthalmos, and all three had MR imaging studies. The globes were not present, and in their place amorphous soft tissues of intermediate T1 signal intensity (similar to muscle) and low T2 signal intensity were present (Fig 1A). Very thin linear structures in the region of the optic nerves were also present, which perhaps represented remnants of the sheath. All six orbits were shallow and had reduced lateral diameters. The extraocular muscles were partially seen in all three patients and the lateral and medial recti had an almost parallel orientation with respect to each other. MR imaging showed intracranial abnormalities in all three patients, with an absence of the optic chiasm (Figs 1B, 2, and 3). In all three patients, the

posterior optic pathways, defined as the white matter tracts in the temporooccipital regions, were subjectively judged to be reduced in size and volume but of normal signal intensity, indicating normal maturation of myelin at these levels (Fig 1A). The corpus callosum was judged to be thin (dysgenetic) but present in two cases (Figs 1 and 2). In one patient who had bilateral anophthalmos and incontinentia pigmenti, the corpus callosum was absent (Fig 3). Incontinentia pigmenti is a neurocutaneous disorder characterized by skin lesions (vesicles, verrucae, and pigmented and atrophic scars) and by hemorrhagic cerebral infarctions, microcephaly, optic nerve atrophy, hydrocephalus, polymicrogyria, and other congenital developmental brain and skull anomalies. One patient had a small mass of high T1 and relatively low T2 signal intensity in the tuber cinereum region that was believed to be a small lipoma, dermoid, or teratoma (Fig 2). Abnormally everted temporal lobes and enlarged temporal horns were seen in two patients and thought to be associated with hypoplasia of the hippocampal formations caused by dysgenesis of the corpus callosum (Fig 3). Myelination was judged to be adequate for age in these three patients despite the hypoplasia of the posterior white matter tracts.

Five patients (three girls and two boys) had unilateral anophthalmos. One of these patients had both MR imaging and CT; the other four had CT only. In four patients, one globe was completely absent while the contralateral one was considered normal. On the side of the anophthalmos, the optic nerve was not seen and the extraocular muscles were variably present (Figs 4–7). In all cases, the abnormal orbits contained amorphous tissues of intermediate density on

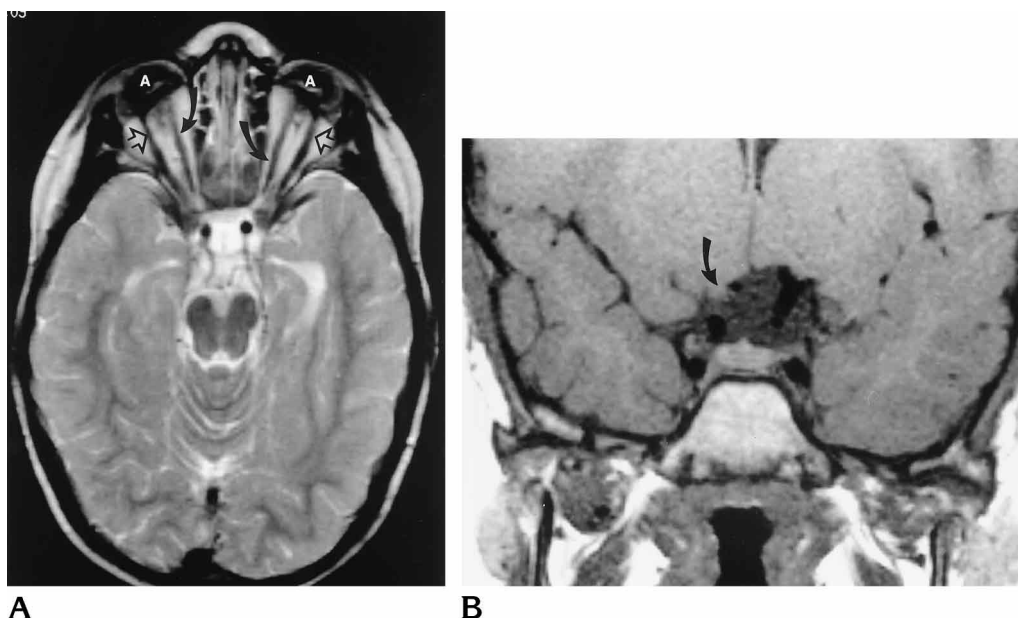


Fig 1. Case 1: Bilateral anophthalmos with absent optic chiasm.

A, Axial T2-weighted (3500/93/1) MR image shows residual disorganized tissue (A) in both orbits. These tissues are hypointense, suggesting fibrosis, not hyperintense as one would expect with microphthalmos, in which there is normal (but reduced volume) of vitreous. The medial (*curved arrows*) and lateral (*open arrows*) recti are thin and approximate each other medially because of lack of support. Between the muscles there is a fine linear hypointensity that could be related to very small optic nerves. The orbital volumes are diminished. The white matter in the temporooccipital regions (along the expected course of the optic radiations) is diminished in volume. The temporal horns of the lateral ventricles are prominent.

B, Coronal T1-weighted (500/15/3) MR image at level of adenohypophysis shows absent optic chiasm with questionable residual optic tract (*arrow*) on right.

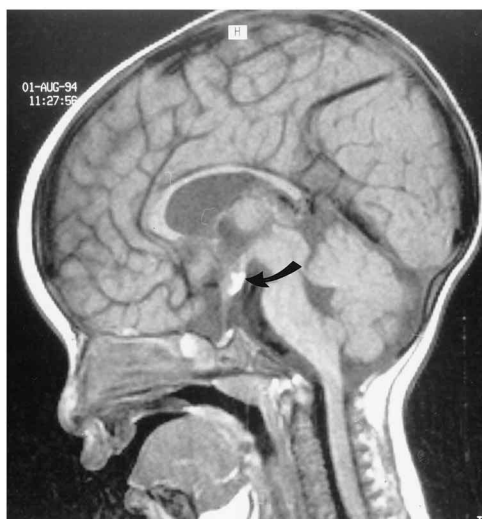


Fig 2. Case 2: Small suprasellar mass in bilateral anophthalmos. Midsagittal T1-weighted (500/15/2) MR image shows absent optic chiasm and hyperintense lesion (*arrow*) at level of tuber cinereum, which could be a lipoma, a dermoid, or a teratoma (no histologic findings were available). The corpus callosum is thin.

CT scans and, in one case, of intermediate T1 signal intensity and low T2 signal intensity on MR images. All the involved orbits were judged to be small in both longitudinal and lateral dimensions. The superior orbital fissures were present and the optic canals were small but also present. In one instance, the optic chiasm was absent. The corpus callosum was present in all five of the patients with unilateral anophthalmos, but its size could not be adequately estimated in those who were examined only by CT.

The size and volume of the posterior optic pathways were judged to be reduced in the patient who had MR imaging, but they were not estimated in patients who had only CT, because of the inherent limitations of that technique. Of the five patients with unilateral anophthalmos, three had well-defined craniofacial syndromes and two had a mild hemifacial hypoplasia ipsilateral to the anophthalmos. One patient had a median cleft syndrome involving predominantly the maxilla and nose (low type), contralateral lambdoid synostosis, and ipsilateral hemifacial hypoplasia (Fig 6). One patient had a median cleft syndrome involving predominantly the na-

Fig 3. Case 3: Anophthalmos and agenesis of the corpus callosum.

A, Axial T1-weighted (500/15/2) MR image shows bilaterally absent eyes with very small amount of residual intraorbital tissues (*white arrows*). The optic nerves (*black arrows*) are very small and only partially seen. The temporal horn (*T*) of the right lateral ventricle is dilated and in the absence of hydrocephalus is probably related to adjacent hippocampal hypoplasia associated with agenesis of the corpus callosum.

B, Midsagittal T1-weighted (500/15/2) MR image shows absent corpus callosum and optic chiasm. The posterior white matter tracts were also hypoplastic (not shown). This patient had incontinua pigmenti.

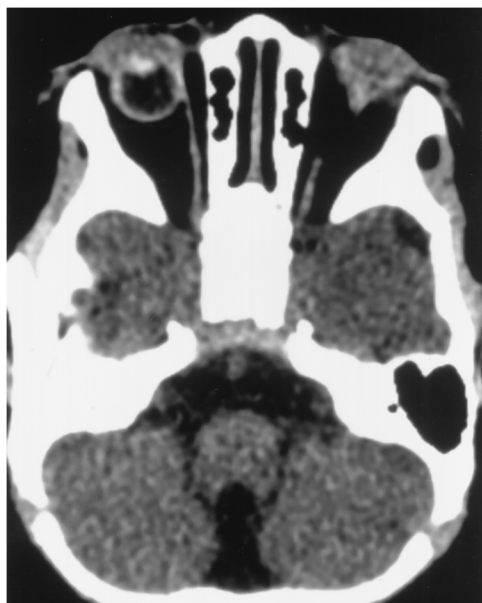
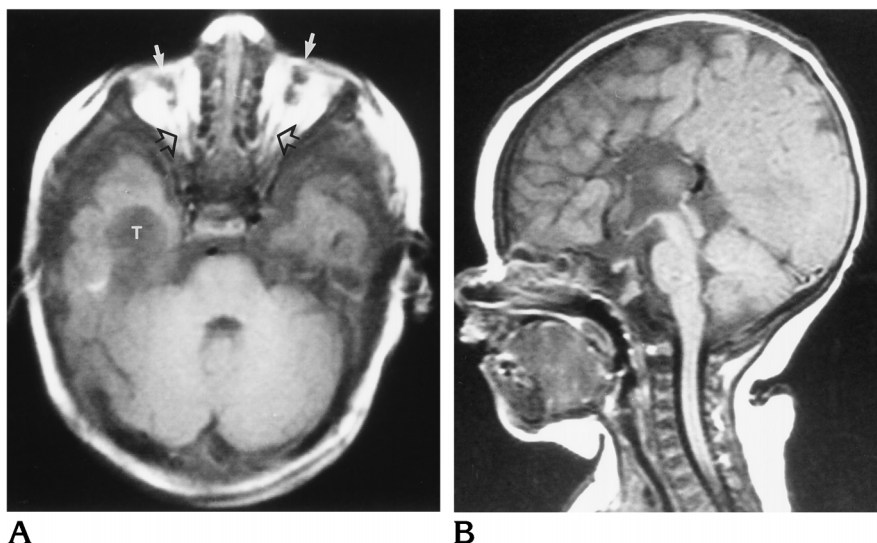


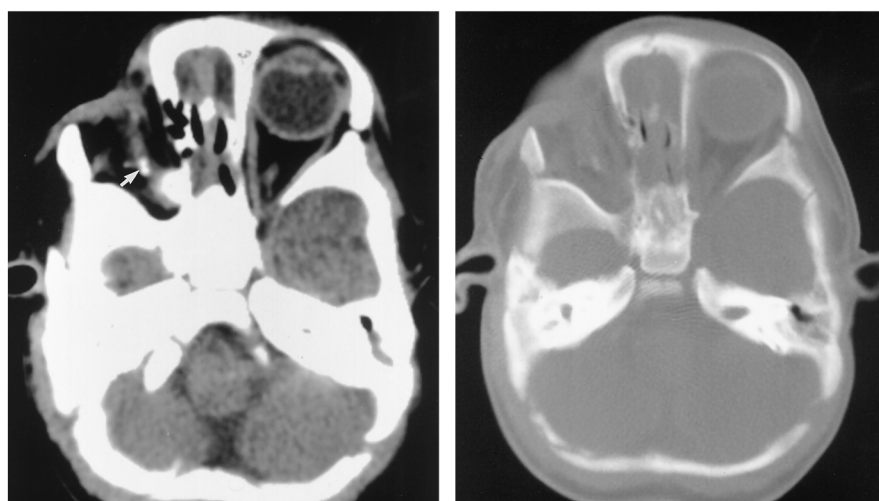
Fig 4. Case 6: Anophthalmos and microphthalmos. Axial CT scan shows disorganized residual tissues in left orbit compatible with anophthalmos and a small (microphthalmic) right eye. Note lack of recognizable structures in orbit with anophthalmos. The lateral diameter of the orbits is reduced. The brain was normal.

sal bridge and frontal bones (high type) with associated ipsilateral hemifacial hypoplasia and absence of the ascending ramus of the mandible (Fig 7). These two patients with midline clefts had hypertelorism, normal-appearing contralateral eyes, and no basal encephaloceles. Two different patients had abnormalities of the contralateral orbits, including microphthalmos and congenital cystic eye. In the patient with contralateral microphthalmos, that eye was normally formed but very small (Fig 4). In

this patient, the face was hypoplastic and asymmetric with the more severe reduction in size ipsilateral to the anophthalmos. In the patient with a contralateral congenital cystic eye, that orbit contained a mass of intermediate density without a recognizable globe in a markedly enlarged orbit. Histologic findings were consistent with a congenital cystic eye. The side of the face ipsilateral to the anophthalmos was hypoplastic. The findings are summarized in the Table.

Discussion

At about 3 to 4 weeks of life, the forebrain develops the optic folds, which invaginate to form the primitive optic vesicles (1). Progressive growth of these vesicles results in their elongation, flattening of their lateral aspects, and constriction of their connections with the forebrain, forming the optic stalks. The optic stalks are the precursors of the optic nerves. Between the fourth and eighth weeks of life, each globe is formed and closes along its embryonic fissure. During this latter stage, ganglion cell projections proceed centrally to decussate through the primitive chiasmatal commissure. Insults early on (1 to 4 weeks of life) result in primary or secondary anophthalmos while insults during the second stage of development (4 to 8 weeks of life) result in degeneration of the elements already formed (degenerative anophthalmos) (1). Lack of properly established connections from the developing globes to the optic pathways results in hypoplasia or absence of related white matter tracts and the lateral geniculate ganglia (4).



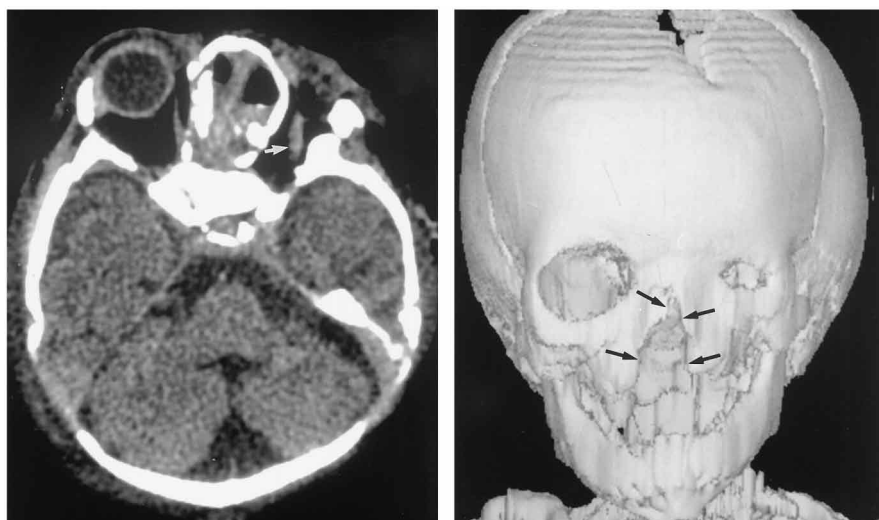
A

B

Fig 5. Case 5: Unilateral anophthalmos.

A, Axial CT scan shows normal left orbit and globe. There is right anophthalmos with disorganized residual tissues anteriorly that are contiguous with sunken eyelids. The dysmorphic right optic nerve contains a focus of calcium (*arrow*). The brain was normal in this patient.

B, Corresponding CT scan with bone window settings shows small right bony orbit with an incompletely formed lateral wall, a thick greater sphenoidal wing, a small middle cranial fossa, and a superiorly displaced petrous bone. Slight facial asymmetry (but no frank microsomia) was present.



A

B

Fig 6. Case 7: Anophthalmos with low median facial cleft syndrome (Sedano type B facies).

A, Axial CT scan shows normal right orbit and left-sided anophthalmos. Note residual and disorganized tissues in anterior aspect of left orbit. The linear soft-tissue structure (*arrow*) is probably one of the extraocular muscles. The left bony orbit is very small. The left side of the face and a portion of that hemicranium are also small. The nasal root is broad and there is hypertelorism.

B, Frontal 3-D CT reformation shows tiny left orbit and midline cleft (*arrows*) involving the maxilla and nose, compatible with a low median cleft syndrome. Note that the left side of the face is small. The brain was normal in this child.

Because primary and secondary anophthalmos occur earlier, they are accompanied by a greater arrest of development of the visual apparatus than is consecutive/degenerative anophthalmos.

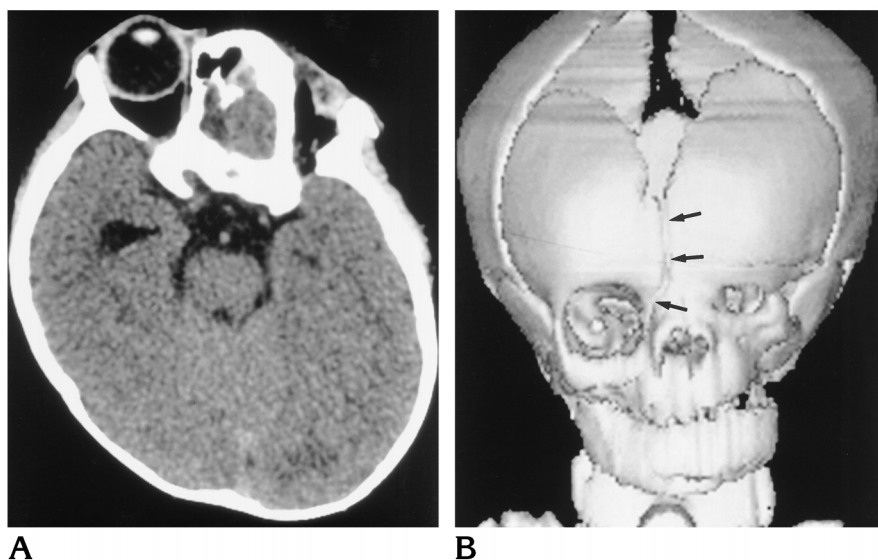
Anophthalmos is a rare congenital anomaly with an annual incidence of only 0.22 per 1000 births (7). Congenital anophthalmos and severe microphthalmos account for blindness in 0.6% to 1.9% of all blind children (7). Hereditary cases have been reported (3, 4, 8). Anophthalmos is known to be associated with several rare trisomy syndromes, the relatively more common trisomy 13, thalidomide embryopathy, and Lenz, Waardenburg, and Meckel syndromes (1, 9–11). Consanguinity is known to predispose to anophthalmos (8). Congenital rubella infection

and maternal vitamin A deficiencies have also been associated with anophthalmos (6). There has been one reported case in which clinical anophthalmos occurred as a result of traumatic amniocentesis presumably due to penetration of the developing globe (12). None of these antecedents were found in our patients. Anophthalmos is also known to be associated with systemic disorders, such as focal dermal hypoplasia syndrome (4). In one of our patients with bilateral anophthalmos, a different systemic disorder with cutaneous manifestations (incontinentia pigmenti) was present. In our study, bilateral anophthalmos tended to be accompanied by intracranial malformations. All three of our patients with bilateral anophthalmos had absence of the optic chiasm and hypoplasia of

Fig 7. Case 6: Anophthalmos with high median cleft syndrome (Sedano type B facies).

A, Axial CT scan shows left anophthalmos with residual intraorbital tissues and very small bony orbit. The right temporal horn of the lateral ventricle is minimally prominent but the brain appeared otherwise normal in this child.

B, Frontal view of 3-D reformation shows cleft (*arrows*) involving the nose and frontal bones, compatible with a high median cleft syndrome. The left orbit is extremely small and there is ipsilateral hemifacial hypoplasia. The left ascending ramus of the mandible is absent and there is a large frontal cranium bifidum, which was clinically occult.



the posterior optic pathways. Two patients had dysgenesis of the corpus callosum, and in one patient this structure was absent. The high rate of intracranial anomalies in our patients with bilateral anophthalmos suggests overall maldevelopment of the forebrain structures and failure of formation or degeneration of the optic vesicles during early gestation. This sequence of anomalies is probably related to the formation of the lamina terminalis, which is a precursor of the forebrain and the corpus callosum (13). This would explain the presence of an anomalous corpus callosum in patients with bilateral anophthalmos.

Unilateral anophthalmos has been reported to occur in association with first and second branchial arch defects, resulting in hemifacial hypoplasia (such as Goldenhar syndrome) (14, 15), which was present in two of our patients with unilateral anophthalmos. Slight facial asymmetry was present in one case but without frank microsomia. The association between first and second branchial arch defects and unilateral anophthalmos reflects the fact that normal development of mesenchyme (which eventually forms the maxilla and mandible) is critical for the induction of optic vesicle(s) and orbital growth, and that abnormalities in its development may result in degenerative anophthalmos (14). Two of our patients had midline facial clefts, hypertelorism, and a broad nasal root compatible with Sedano type B facies. On CT studies, one had a low cleft (involving the maxilla and nose) and one had a high cleft (involving the nose and frontal bones). In both cases,

the side of the face ipsilateral to the anophthalmos was small. The association of the hemifacial microsomia (particularly Goldenhar and Crouzon syndromes) with midline facial clefts is well known (14). One of these patients also had premature closure of one lambdoid suture, which is known to occur in patients with midline facial clefts. Patients with Sedano type B facies are considered to have hypertelorism, a broad nasal root, a midline facial cleft, and commonly (but not always) a frontal cranium bifidum occultum. These patients may also have eye abnormalities that include colobomas, optic nerve dysplasias, microphthalmos, and anophthalmos. In both our patients with midline cleft syndrome, anophthalmos was present.

A different patient had bilateral congenital anophthalmos and a small hyperintense mass (on T1-weighted images) in the region of the tuber cinereum. The differential diagnosis for this lesion includes lipoma, dermoid, and teratoma. Two case reports have described anophthalmos in patients with perisellar mass lesions (16, 17). In one of these cases, a large suprasellar germinoma was present and the authors suggested that compression of the optic pathways by the mass may have resulted in its maldevelopment and led to degenerative anophthalmos (16). In a different case, however, a small teratoma at the level of the mammillary bodies (similar to the mass seen in our patient) was present and its relationship to anophthalmos was uncertain (17). In a third and different case, a giant suprasellar aneurysm was associated with aplasia of one optic nerve and chias-

mal commissure as well as anophthalmos (18). In that patient it was thought that compression by the aneurysm led to lack of advancement of ganglion cells from the optic vesicle into the forebrain anlage of the optic chiasm, leading to aplasia of the optic pathways and subsequent degeneration of the optic vesicle and resulting in unilateral anophthalmos. In our case, the relationship between the small suprasellar mass and anophthalmos is uncertain.

In our patients, anophthalmos was manifested as a lack of globe(s) with the presence of amorphous tissues contained within small bony orbits. In the four patients who had MR imaging, these amorphous tissues were isointense with muscle on T1-weighted images and markedly hypointense on T2-weighted sequences. It is possible that this imaging feature is related to fibrosis. On CT scans, these tissues were of intermediate density. These imaging characteristics readily establish anophthalmos as different from severe microphthalmos, in which one should be able to identify a tiny globe with the normal signal/density characteristics of the vitreous and lens. Despite the lack of pathologic correlation in our patients, we postulate that the presence of optic nerves, even those that were extremely hypoplastic, speak in favor of degenerative anophthalmos or severe microphthalmos rather than primary or secondary anophthalmos. However, because pathologic findings were available in only one of the patients, we cannot corroborate this observation. It is possible that the linear structure present in the course of the intraorbital optic nerves in our patients was related to remnants of the sheath, since the absence of an optic chiasm in these patients would also indicate an absence of the optic nerves. Regardless of the histologic type of anophthalmos, these patients are blind, and enucleation with insertion of prostheses is needed to assure normal growth of the orbits and face. Therefore, to distinguish between different histologic types of anophthalmos may be academic.

In summary, patients with bilateral anophthalmos had intracranial anomalies involving the corpus callosum, optic chiasm, and posterior optic pathways, implying a disorder affecting the development of the rostral neural tube in a more generalized fashion than unilateral an-

ophthalmos. Patients with unilateral anophthalmos had ipsilateral facial anomalies, suggesting an alteration in induction of ocular growth by the abnormal mesenchyme of the first and second branchial arches and subsequent degeneration of the optic vesicle. However, ocular anomalies contralateral to anophthalmos do occur.

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