CASE REPORT

Congenital cystic eye with optic nerve

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SUMMARY

Congenital cystic eye (CCE) is a rare condition caused by failure of invagination of the optic vesicle resulting in a persistent cyst replacing the eye. An associated optic nerve attached to the cyst is a rarely reported phenomenon that has been sparsely described histologically, with no immunohistochemistry reported previously. The authors present a case of CCE with optic nerve tissue inserting into the cyst, and present the histological and immunohistochemical findings.

BACKGROUND

Congenital cystic eye was first described as such by Mann¹ in 1939; however, Harlan² reported a case of 'congenital cyst of the orbit with anophthalmos' in 1893. In the report, he described a 'tumour about half as large as a small hen's egg filling the orbit and projecting beyond it'. He recognised the clinical distinction of this condition in his case, and also in three previous cases, as filling the orbit rather than being associated with the lower lid. He was possibly the first to detail the histological findings describing a peculiar atypical cerebral tissue with collections of nuclei resembling neuroglia.

Including the present case, there have been 46 reported cases of congenital cystic eye. Duke-Elder reported a case of congenital cystic eye in 1963, and, at the time, believed that there were 15 previously reported cases. In 2007, Chaudhry *et al* identified another 20 cases and reported 2 new cases. Since then, there have been another 7 reported cases.^{3–8}

Congenital cystic eye represents an arrest of invagination of the primary optic vesicle, occurring between the 2 and 7 mm stage of fetal development. This results in a persisting cyst at birth, which replaces the eye.^{1–8} Arrested development occurring later in the 7–4 mm embryonic stage results in the more common microphthalmos with coloboma.⁴

We present a case of congenital cystic eye in which detailed histological and immunohistochemical analysis revealed neural tissue within the optic nerve attached to the congenital cyst. Detection and analysis of vestigial optic nerve structures in previous reports have been based on neuroimaging alone with histopathological analysis rarely reported.^{5–10} Immunohistochemistry of optic nerve structures associated with congenital cystic eyes has not previously been reported.

CASE PRESENTATION

A 3-day-old baby girl with a swollen right eye since birth was referred by the paediatric team (figure 1A).

She was otherwise healthy with no significant ocular or family history.

Imaging showed that the right globe was absent (anophthalmos) and was replaced by a reasonably well-circumscribed, heterogeneous cystic mass extending posteriorly into the orbit, containing a 4 mm focus of dense calcification (figure 1B–D). The diagnosis of congenital right anophthalmos with cyst (congenital cystic eye) was made clinically and radiologically. Following observation and periodic assessment, surgery was carried out in January 2012 (baby's age 21 months). This involved removal of the intact cyst (figure 1E) and replacement of orbital volume with a bioceramic implant.

INVESTIGATIONS

The resected specimen was received unfixed and a calotte was taken followed by prolonged fixation in 10% neutral buffered formalin. The optic nerve margin was inked and a transverse section of the margin was blocked. Following fixation, the entire globe was processed and embedded using a prolonged impregnation regime. Following embedding in Paraplast, the cystic structure was sectioned at multiple levels (100) and stained using routine H&E staining (figure 1F). Immunohistochemistry was also performed on selected sections using antibodies for neuron specific enolase (NSE), synaptophysin (SYN), chromogranin, neurofilament protein (NF), glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA). The microscopic sections were scanned using an Aperio scanner and the images captured using imagescope V11.1.2.760.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses to consider include microphthalmos with cyst, cystic teratoma, ectopic brain tissue, encephalocoele, optic nerve meningocele and lymphangioma. The condition is rarely diagnosed until surgical exploration and histopathological analysis confirm the absence of a microphthalmic globe.¹¹

TREATMENT

Following observation and periodic assessment, surgery was carried out in January 2012 (baby's age 21 months). This involved removal of the intact cyst (figure 1E) and replacement of orbital volume with a bioceramic implant.

OUTCOME AND FOLLOW-UP

There was a thick layer of fibrous connective tissue forming a cystic capsule mimicking a scleral layer, but without the density and organisation of true scleral tissue.

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Figure 1 (A) Patient at 1 month of age with right congenital cystic eye (CCE) visible as a blue-tinged orbital swelling displacing the normal right lower lid upwards. The left eye was normal. (B) Well-circumscribed, heterogeneous, cystic mass in the right orbit, which is hypointense to cerebrospinal fluid on coronal T2-weighted MRI. (C) Axial CT image demonstrating a calcific area within the cyst. The lacrimal gland, orbital bones, extraocular muscle cone and optic chiasm had normal appearances. (D) An axial CT image at a different anatomical level showed a normal medial rectus muscle, lateral rectus muscle and optic nerve-like structure merging with the wall of the cyst. (E) Macroscopic appearance of CCE immediately after surgical removal. Arrow denotes area of insertion of optic nerve. (F) Aperio scan of a complete transverse section through the CCE (24 mm×18 mm), with the optic nerve attached posteriorly (arrow). An area of dystrophic calcification is seen within the cavity (arrowhead) corresponding to the radiological findings.

The lumen contained benign glial tissue that resembled the appearances seen in long-standing retinal detachment with proliferative retinopathy (figure 2). There were also areas of retinal differentiation represented by disorganised retinal tissue, similar to that seen in some types of retinal dysplasia, with very poorly formed, large rosette-like structures. These were unlike Homer-Wright rosettes, Flexner-Wintersteiner rosettes, fleurettes or the pseudorosettes seen in retinoblastoma. There was no mitotic activity.

There was no division between the anterior and posterior chambers, no vitreous or aqueous humour and no corneal tissue was present. Some disorganised retinal pigment epithelium was present but no lens or fully developed retinal tissue was present. No normal uveal tract tissue was identifiable. The iris was not present. Some of the pigmented tissue possibly represented abnormal ciliary body-type tissue but no normal structures were present. Optic nerve tissue inserted into the capsule of the

Figure 2 (A) Gliotic tissue within congenital cystic eye (H&E, ×200). (B) Glial fibrillary acidic protein (GFAP) highlighting glial tissue within congenital cystic eye (CCE) (×100). (C) Disorganised retinal tissue in congenital cystic eye (H&E, ×100). (D) Synaptophysin highlighting retinal cells within CCE (×200).

Figure 3 (A) Transverse section of optic nerve showing relationship to retinal vessels (H&E, $\times 40$). (B) Transverse section of optic nerve showing central retinal vein (H&E, $\times 200$). (C) Longitudinal section of optic nerve attaching to the glial tissue in the CCE (H&E, $\times 40$). (D) Longitudinal section of optic nerve showing central retinal vessel (H&E, $\times 100$). (E) Optic nerve immunohistochemistry for glial fibrillary acidic protein (GFAP) ($\times 100$). (F) Meningeal tissue adjacent to optic nerve positive for epithelial membrane antigen (EMA, $\times 100$).

congenital cystic eye but this was distorted, partly atrophic, and surrounded by the fibrous connective tissue (figure 3A–D). A normal optic nerve head was not present.

The skeletal muscle was attached to the outside of the congenital cystic eye, representing some development of extraocular muscles. A small amount of stratified squamous epithelium was present on the anterior surface.

Immunohistochemistry was performed using standard techniques. The tissue within the cystic eye was positive for GFAP but negative for chromogranin and neurofilament protein. Nerves were present in the surrounding fibrous connective tissue capsule ('sclera') and were positive for neurofilament protein. The cells corresponding to the attempted differentiation towards retinal tissue were positive for SYN. The optic nerve showed a positive reaction with GFAP. Using EMA, a reduced layer of meningeal tissue adjacent to the optic nerve was demonstrated.

DISCUSSION

Congenital cystic eye is usually unilateral; however, two bilateral cases have been reported.^{9 11} The cause is unknown and there is no gender preference. The condition is not hereditary and insults during pregnancy and childbirth do not appear to be precursors. Unlike microphthalmos and anophthalmos, there is no known associated chromosomal abnormality; however, one case associated with Turner syndrome and one associated with Orbeli syndrome (13q deletion syndrome) has been reported.^{5 7}

The diagnosis of congenital cystic eye is based on clinical examination, imaging, surgical findings and histopathology. Differential diagnoses to consider include microphthalmos with cyst, cystic teratoma, ectopic brain tissue, encephalocele, optic nerve meningocele and lymphangioma. The condition is rarely diagnosed until surgical exploration and histopathological analysis confirm the absence of a microphthalmic globe.¹¹ Imaging techniques are helpful for diagnostic purposes, planning surgery and detecting the presence of associated intracranial abnormalities.

The composition of the cyst depends on whether the failure of invagination is complete, in which case only primitive ocular tissues are present, or partial, in which case dysplastic ocular structures may be found.⁸ No vision is possible with a congenital cystic eye. Occasionally, rudimentary forms of iris, lens or cornea are present; however, these dysplastic structures are more commonly seen in association with microphthalmia.¹⁰ Gross examination of resected specimens reveals a cystic structure reported as being up to 60 mm in diameter, which may be filled with a clear yellow, serosanguinous or dark tan fluid.⁷ The cyst may be surrounded by normal extraocular muscles, abnormal muscles or scattered fascicles of skeletal muscle, or there may be no evidence of extraocular musculature at all.^{2 8 11 12}

In the cyst's most primitive and common form, the outermost layer is composed of loose fibroadipose tissue with variable smooth muscle or skeletal muscle and peripheral nerve tissue. There may be calcification and glandular structures in this layer. Infiltrates of plasma cells, lymphocytes and neutrophils may be

Table 1 Reports of congenital cystic eye with optic nerve findings

Original report	Cyst size (mm)	Sex	Eye	Optic nerve findings	Optic nerve histology	Intracranial abnormalities	Systemic abnormalities	Histopathology of ocular structures	IHC (immunohistochemistry)
Baghdassarian <i>et al</i> ¹⁰	45×35×25	M	L	Optic nerve-like structure continuous with cyst	Connective tissue septae and astrocytes	No	No	Dysplastic retina rudimentary lens underdeveloped iris	—
Sacks and Lindenberg ⁹		F	OU (both eyes)	Intracranial optic stalk remanent	Only efferent fibres No anterior pathways	Yes	Yes	No normal ocular tissue	—
Tsitouridis <i>et al</i> ⁷	60	M	L	Extraconal optic nerve and chiasm	—	Yes	Yes	Primitive retinal elements	—
Singer <i>et al</i> ⁶	—	F	L	Optic nerve merged with posterior aspect of cyst	—	Yes	No	Primitive retinal elements	—
Robb <i>et al</i> ¹²	34×19×14	M	R	Optic nerve-like structure at posterior cyst	Septate connective tissue in the neuroglial tissue resembling optic nerve	No	No	Primitive retinal elements	GFAP SYN
Raina <i>et al</i> 2002	35×25×20	F	R	Optic nerve stalk—partially developed	—	No	No	Disorganised retinal and choroidal tissue	—
Gangadhar <i>et al</i> ³	—	M	R	Rudimentary ONH (optic nerve head) communicating with intracranial space	—	Yes	No	Primitive retinal elements	—
Gupta <i>et al</i> ⁴	—	M	L	Optic nerve stalk continuous to chiasm	—	Yes		Primitive retinal elements	—
Helveston <i>et al</i> ¹⁴	25×15×12	M	L	Optic nerve stalk	Surrounded by collagenous tissue	No	No	Primitive retinal elements Dysplastic cornea	—
Kavanagh <i>et al</i> ⁵	—	F	R	Optic nerve—primitive	Primitive optic nerve with surrounding channels	Yes	Yes	Primitive retinal elements	GFAP NSE NF
Mansour and Li ³	25×30	F	R	Optic nerve tract—rudimentary	—	Yes	Yes	Primitive retinal elements	GFAP S-100

GFAP, glial fibrillary acid protein; NF, neurofilament protein; —not reported; NSE, neuron specific enolase; SYN, synaptophysin.

present, leading some authors to suggest an inflammatory aetiology.¹¹ The next layer represents the outer layer of the cyst and is composed of dense fibrous connective tissue, which may be vascularised. The cystic cavity is lined by neuroglial tissue within which aggregates of immature retinal tissue, referred to as rosettes, may be found.^{3–4} The cuboidal epithelium in this layer is described as resembling ependymal epithelium, and is thought to be responsible for the fluid within the cyst, although this fluid is biochemically dissimilar to CSF.⁸ Some studies report this fluid to be biochemically similar to serum but this is not universal.¹³ Pigment cell clusters containing melanin may be observed and are thought to represent a primitive retinal pigment epithelium.⁸ Myxoid tissue and calcific bodies are also variably reported within the inner layer.^{8–11}

This case is of interest because an optic nerve attached to the cyst has not been a well-documented feature in previous histopathological reports of congenital cystic eye. The histological presence and extent of development of the optic nerve, as well as immunohistochemical findings, are also poorly described. An optic nerve attached to the cyst would be expected, however, it may not be detected histologically due to a number of reasons. Depending on the timing of surgery, the anterior optic nerve stalk may have undergone complete or partial atrophy, leaving only a vestigial optic nerve stub in the posterior orbit or extending from the chiasm. Detection would also depend on the surgical method, as more anteriorly transected specimens may leave vestigial optic nerve structures in the orbit. The method of specimen preparation is critical, with extensive sectioning increasing the likelihood of detecting optic nerve structures.

The optic nerve has been previously reported as being not present, usually absent, or, if present, composed of astrocytes and devoid of neurons.^{7–8} A summary of all the cases reporting an optic stalk or rudimentary optic nerve is provided in [table 1](#). In the literature, there were 11 cases reporting congenital cysts associated with optic nerve tissue and only 4 of these described optic nerve histology.^{5–9–12–14} Sacks and Lindenberg reported a case of bilateral cystic eye in which the intracranial portion of one optic nerve was a tubular remnant of the optic stalk and the other contained only efferent nerve fibres. The optic nerve remnants were not attached to the posterior aspect of the congenital cystic eyes, but the patient in this case was 35 years of age when the congenital cystic eyes were examined at autopsy. The lateral geniculate body was composed of disorganised but normal nuclei forming normal radiations and a normal calcarine cortex. They reasoned that the anterior visual pathways could not develop in the absence of a formed retina and that the efferent fibres were destined to innervate retinal vascular structures.⁹ Specimens can be further analysed using immunohistochemistry. A positive reaction with GFAP demonstrated a strong expression for astrocytes in the neuroglial tissue. Other reports have found that the primitive retinal tissue reacts with S-100, vimentin and NSE. This specimen did not react with NF; however, the primitive retinal tissue was positive for SYN, demonstrating neuronal tissue within the inner layer.

In conclusion, we present the histopathology and immunohistochemistry of a congenital cystic eye with an optic nerve attached. Immunohistochemical studies in future reports of this

condition would enhance our understanding of early optic nerve development and its arrest.

Learning points

- ▶ Congenital cystic eye (CCE) is a rare condition caused by failure of invagination of the optic vesicle resulting in a persistent cyst replacing the eye.
- ▶ An associated optic nerve attached to the cyst is a rarely reported phenomenon that has been sparsely described histologically, with no immunohistochemistry reported previously.
- ▶ We present a case of CCE with optic nerve tissue inserting into the cyst and present the histological and immunohistochemical findings.
- ▶ Immunohistochemical studies in future reports of this condition would enhance our understanding of early optic nerve development and its arrest.

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