PostScript

LETTERS

High β-trace protein concentration in the fluid of an orbital cyst associated with bilateral colobomatous microphthalmos

Bilateral colobomatous microphthalmos with orbital cyst is a rare congenital anomaly.[1–3] It arises between the sixth to seventh weeks of gestation, is usually isolated, and can be either unilateral or bilateral. Association with systemic anomalies may occur, and the involvement of chromosomes 3, 5, 13, 18 and 22 has been reported.[3]

Here, we describe a newborn presenting with bilateral colobomatous microphthalmos with a right orbital cyst. After excision of the cyst, histopathology of the cyst wall was performed and several biochemical parameters of its fluid content were evaluated.

Case report

A newborn presented with bilateral microphthalmos. She was the product of a pregnancy complicated by vitamin A deficiency, documented from at least week 16 to week 24 of gestation, after previous gastric bypass surgery in her 32-year-old mother.

Clinical examination of the newborn showed bilateral microphthalmos. At the right side, a small eye was displaced upwards by a large cyst (fig 1A, B). The cornea with a diameter of 3 mm was diffusely cloudy. A circular pupil and some pupillary membrane remnants were observed. At the left side, microphthalmos was much less pronounced. Some retinal blood vessels were observed in both eyes on fundoscopy.

Ultrasonography confirmed bilateral microphthalmos with chorioretinal coloboma and a right-sided adjacent orbital cyst. Magnetic resonance imaging disclosed the exact location and extent of the cyst (fig 1E, F).

Subsequent management was to keep the cyst for as long as necessary to ensure adequate socket size. However, progressive right lower eyelid inversion led to conjunctival maceration. Excision of the cyst with ligation of the connecting stalk was performed, saving the right microphthalmic eye itself (fig 1C, D).

Histopathologically, the cyst wall was composed of two layers (fig 2A, B). The outer layer contained dense fibrous tissue with some normal blood vessels, resembling normal sclera. The inner layer was one of dysplastic retinal tissue, which consisted of cylindrical, neuroectodermal-like cells with an eosinophylic cytoplasm showing some nuclear stratification. Immunohistochemistry showed no reactivity against cytokeratins 5, 6, 7 and 20. Consequently, the epithelium was not of an adenomatous type. The cylindrical cells of the inner layer stained diffusely and intensely for CD56 (neural cell adhesion molecule), confirming their neuroectodermal origin.

Electrophoresis of cyst fluid produced a pattern almost identical to cerebrospinal fluid (CSF) (fig 2C). β-Trace protein (EC 5.3.99.2), a highly sensitive and specific CSF marker, and cystatin C were quantified with a Behring Nephelometer II (Dade Behring, Germany). β-Trace protein concentration was 32.7 mg/l, whereas cystatin C concentration was 2.4 mg/l. The concentration of hyaluronic acid was less than 2 mg/l. Additionally, total protein concentration was 780 mg/l as measured by a pyrogallol red method (table 1).

Comment

Gastric bypass as treatment for morbid obesity has been shown to carry a considerable risk of nutritional deficiencies, which may lead to retinal dysfunction.[4] In this case, ocular development occurred in the context of a documented vitamin A deficiency during the initial weeks of pregnancy. Such deficiency is also known to disrupt ocular development in both animals and humans.[5 6]

Little is known about the exact nature and origin of the fluid in an orbital cyst associated with microphthalmos. In order to identify the origin of the cyst, several of its parameters were evaluated. The cyst fluid sample produced an electrophoretic pattern identical to a CSF sample, including a typical band of prealbumin. To further corroborate this finding, we assessed the β-trace protein content of the cyst fluid. β-Trace protein, aka prostaglandin D_2 (PGD_2) synthase, is bifunctional, acting as a PGD_2-producing enzyme and as an intercellular transporter of retinoids or other lipophilic substances.[7] This enzyme is produced mainly in the epithelial cells of the choroidal plexus, in the leptomeninges, and to a lesser extent in oligodendrocytes, after which it is secreted into the CSF. It was introduced by Felgenhauer *et al* as a marker for liquorrhoea because its concentration in normal CSF is 35-fold higher than in serum.[8] Nephelometric β-trace protein detection is rapid and highly valid for the diagnosis of a CSF leak (sensitivity ranging from 93% to 100%, specificity of 100%, negative predictive value 0.971, positive predictive value 1).[9 10] The concentration of β-trace protein in the cyst fluid was found to be far above the upper reference limit for CSF. It is as yet unclear what the exact role of this protein may be in the cyst fluid. But it is hypothesised that neuroectodermal cells lining the cyst wall shed β-trace protein in the cyst cavity.

In conclusion, the histopathological findings, the CSF-like electrophoresis and the high concentration of β-trace protein in the cyst fluid are strong arguments in favour of a neuroectodermal origin of the orbital cyst associated with colobomatous microphthalmos.

Table 1 Comparison of concentration of several biochemical parameters between cyst fluid, cerebrospinal fluid and serum

	Cyst fluid	Cerebrospinal fluid (reference range)	Serum (reference range)
β-Trace protein (mg/l)	32.7	5.4–23.8	0.2–0.72
Cystatin C (mg/l)	2.4	1.2–4.2	0.53–0.95
Hyaluronic acid (mg/dl)	<2	<0.1	<0.1
Total protein concentration (mg/l)	780	150–450	60 000–80 000

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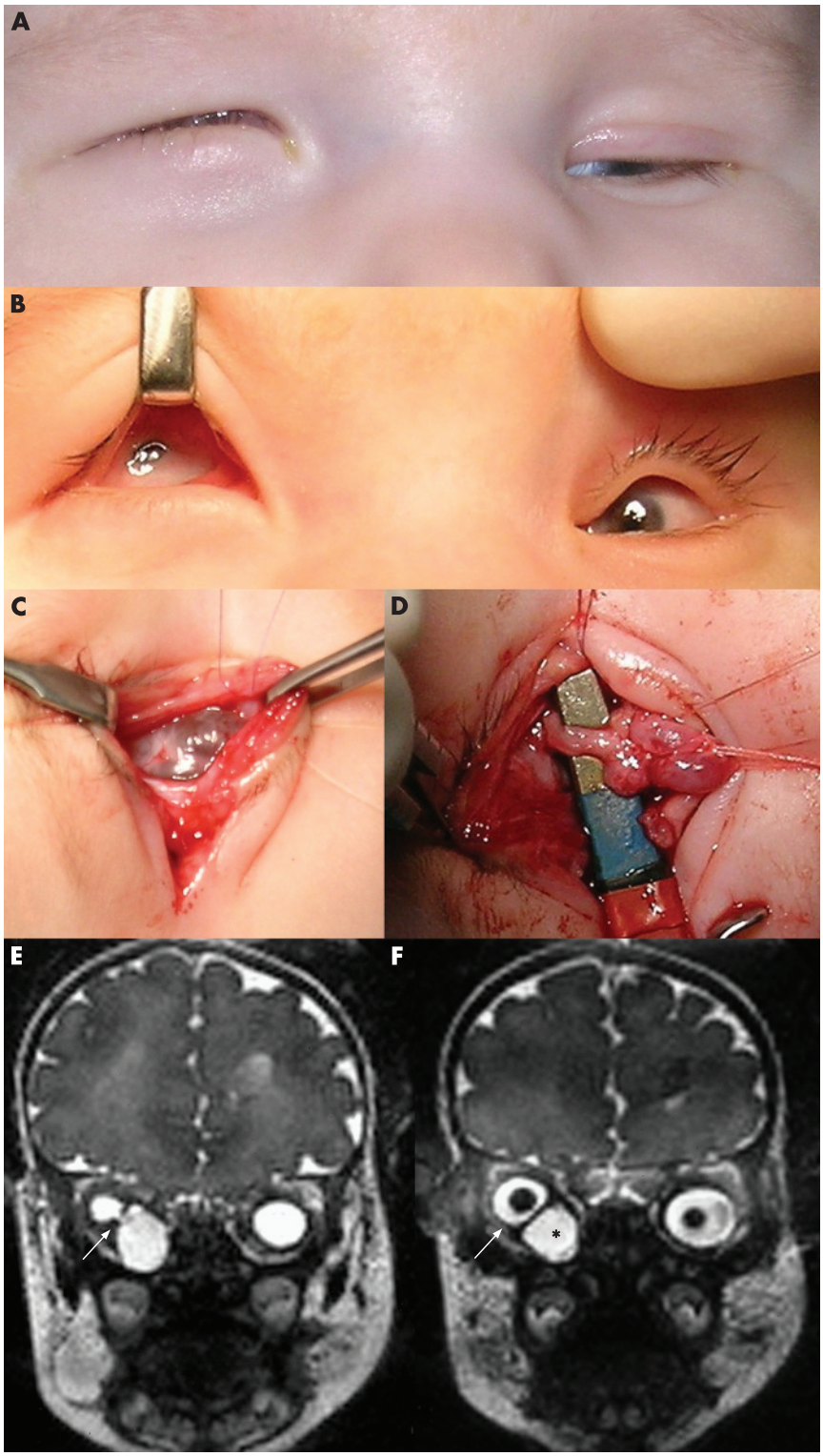

Figure 1 (A) External appearance of newborn with bilateral colobomatous microphthalmos with right orbital cyst. Note the bluish bulge in the right lower eyelid; (B) preoperative presentation of both eyes; (C) peroperative dissection of right orbital cyst; (D) intraoperative view of connective stalk between cyst and right microphthalmic eye; (E, F) Orbital T_2-weighted magnetic resonance imaging shows bilateral microphthalmos and large cyst in right orbit; (E) coronal view, demonstrating a connective stalk between microphthalmic eyeball and cyst (arrow); (F) coronal view, showing hyperintense cystic mass (black asterisk) causing superotemporal displacement of right microphthalmic eye (arrow).

Retinal seeding from anterior segment coccidioidomycosis after vitrectomy

Coccidioidomycosis is usually localised in the eye either to the anterior or to the posterior segment, but only rarely to both.[1–8] We present a case in which the initial infection involved the anterior segment, but was followed by extensive superficial retinal seeding after vitrectomy. Retinal involvement after vitrectomy raises the possibility of the anterior hyaloid face acting as a barrier to spread of the fungus posteriorly. A review of prior cases indicates that, in the absence of vitrectomy, retinal involvement does not occur in anterior segment coccidioidomycosis.

Case report

A 64-year-old man had been treated 3 years previously for iritis and secondary ocular hypertension with topical prednisolone acetate 1% and timolol 0.5%, with alleviation of symptoms. He presented with recurrence of similar symptoms that did not resolve with topical, retroseptal, and systemic corticosteroids and glaucoma drugs. A detailed systemic evaluation was negative.

On examination, the right eye was unremarkable. Visual acuity of the left eye was perception of hand motion at 5 feet. Keratic precipitates and a white mass in the anterior chamber were seen (fig 1A, inset). An iris biopsy and anterior chamber aspiration showed numerous spherules.

After treatment with oral fluconazole, intravenous amphotericin B, pars plana vitrectomy and lensectomy, the vitreous humor, retina and choroid appeared normal, but an infiltrate reformed in the anterior chamber soon after. Tissue plasminogen activator and intracameral amphotericin B were given, followed by another pars plana vitrectomy. At 1 month after the second vitrectomy, the eye was enucleated for intractable pain.

Examination of the eye showed granulomata with spherules on the retinal surface (fig 1B, inset), posterior chamber cornea, iris, ciliary body, and in the vitreous space (fig 1).

Comment

This case shows that retinal seeding may follow vitrectomy for anterior segment coccidioidomycosis. There are only two other reports of vitrectomy for anterior segment coccidioidomycosis.[1 8 9] In each case, the eye was enucleated within weeks of the vitrectomy.[1 9] Pathological sections from both cases were reviewed. One of the cases was subsequently shown to have superficial seeding of the retina after vitrectomy.[9 10] The other was reported from our files and showed a tractional retinal detachment with granulomatous inflammation and adjacent cysts, but with no direct retinal involvement (fig 2B).[1]

The prognosis for anterior segment coccidioidomycosis is poor. Of the 10 histologically proved cases, seven did not have vitrectomy. Four of these seven cases were not enucleated and at least two retained vision.[1 4 11 12] None of these four eyes had evidence of posterior segment involvement after treatment. In contrast, all three eyes that underwent vitrectomy were enucleated within months of the procedure, despite the extended course of the disease before the operation in two of the cases. The histological findings of superficial retinal involvement in our case suggest spread

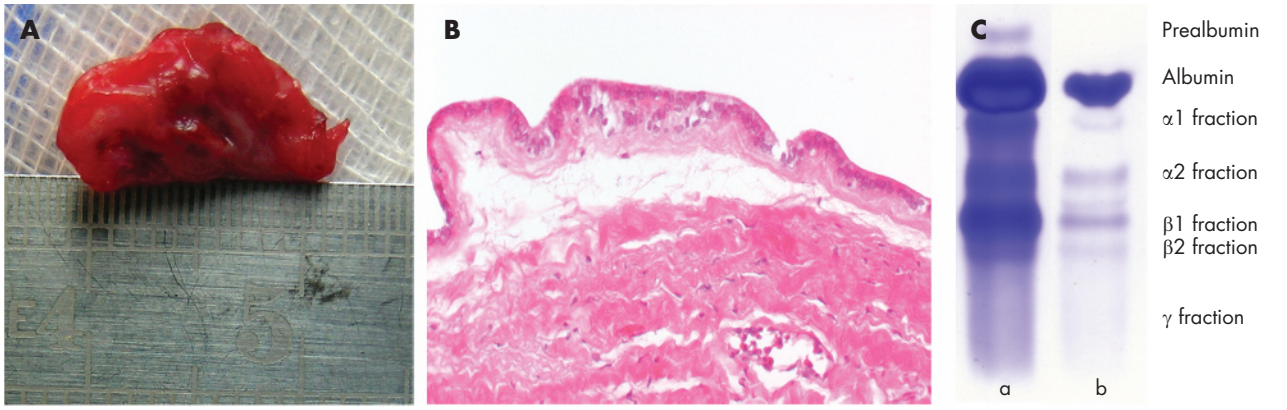

Figure 2 (A) Excised orbital cyst; (B) haematoxylin and eosin-stained section of cyst wall (at magnification ×200), demonstrating the inner layer of neuroectodermal-like cylindrical cells without any organisation, and outer layer of dense fibrous tissue; (C) electrophoresis of (a) cyst fluid and (b) serum sample as negative control.

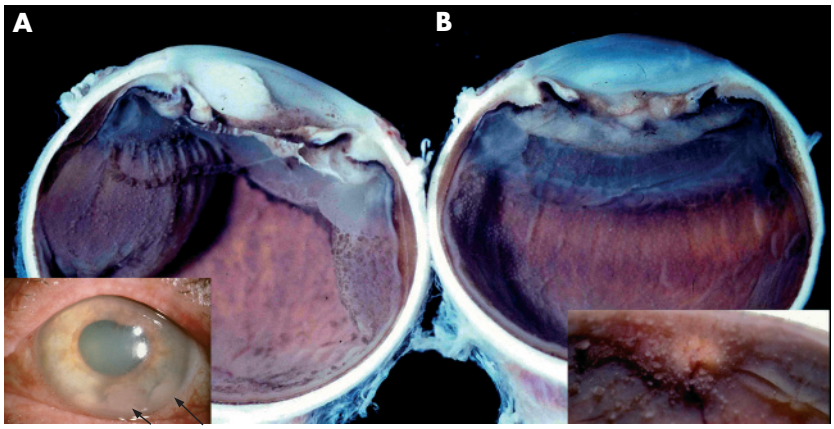

Figure 1 The present case (Mondino–Glasgow–Holland). (A, B) Macrophotograph of the enucleated eye showing multiple rows of superficial granulomata lying on the surface of the retina. The inset in (A) shows hypopyon, iris synechiae and large fluffy masses in the inferior portion of the anterior chamber. The inset in (B) shows numerous granulomata coating the surface of the optic nerve head.

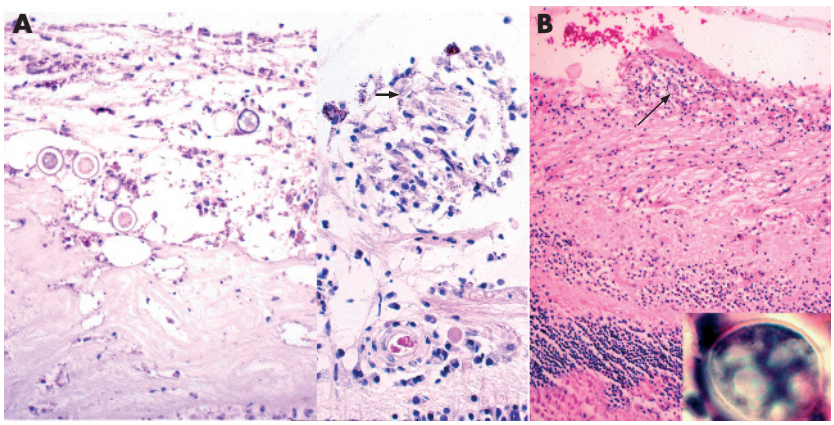

Figure 2 (A) Right, photomicrograph of a retinal surface granuloma with a collapsed spherule, arrow (haematoxylin and eosin, original magnification ×300), left, numerous spherules lying on the extensive anterior fibrous tissue, proliferative vitreoretinopathy (haematoxylin and eosin, original magnification ×300). (B) Photomicrograph from the case published by Stone *et al*.[1] The patient was a 26-year-old man with anterior segment coccidioidomycosis. After vitrectomy, there was evidence of posterior involvement, and the eye was subsequently enucleated. Illustrated is a granuloma on the surface of the retina (haematoxylin and eosin, original magnification ×120). The inset in (B) shows a spherule of coccidioidomycosis (haematoxylin and eosin, original magnification ×400).

from the vitreous. Vitrectomy may be a factor in the dissemination of *Coccidioides immitis* to the posterior segment from infection of anterior tissues. Corticosteroid treatment did not seem to be an important factor, as it was initiated in four of the cases without vitrectomy, of which no evidence of posterior segment involvement was noticed. We hypothesise that vitrectomy disrupts the anterior hyaloid, thereby permitting spherules accumulated between the lens and anterior hyaloid (Berger space) to seed the posterior segment. We are uncertain of the role of vitrectomy in producing disease in the two cases where posterior infection may have followed vitrectomy, but clearly there was no improvement after vitrectomy. Taken together, the findings suggest that the anterior hyaloid may present a barrier to the spread of organisms, and that vitrectomy should be avoided in infection of *C immitis* that is confined to the anterior segment.

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