LETTERS TO THE EDITOR

Ochroconis gallopava endophthalmitis in fludarabine treated chronic lymphocytic leukaemia

EDITOR,—Disseminated fungal infection is an important cause of morbidity and mortality in immunocompromised patients, often due to candida and aspergillus species. Endogenous endophthalmitis is a recognised complication.[1] We present, to our knowledge, the first reported case of endogenous intraocular infection with the emerging pathogen *Ochroconis gallopava*, acquired following treatment for chronic lymphocytic leukaemia (CLL).

CASE REPORT

A 69 year old man presented with a 4 day history of painless loss of vision in the left eye after receiving four courses of fludarabine (25 mg/m^2 over 5 days) for CLL. Standard infection prophylaxis following myelosuppression included oral fluconazole 50 mg once daily. His neutropenia improved (7.96×10^9/l) but profound lymphopenia persisted (0.11×10^9/l).

Visual acuity was right eye 6/6+4 and left eye hand movements. The right eye was normal throughout. Anterior uveitis, hypopyon, lens opacity, and vitritis compromised left funduscopy. A lymphoproliferative or infective aetiology was suspected. Anterior chamber paracentesis revealed leucocytes but no intact cells or organisms. Culture was negative. After 2 days of topical steroids vision improved to 1/60. A large preretinal grey/white mass at the posterior pole became evident with keratic precipitates on the posterior vitreous face. Systemic examination and investigations failed to demonstrate any focus of candidiasis. Oral fluconazole was increased to 400 mg daily. Intravitreal amphotericin B 0.005 mg in 0.1 ml saline was administered following vitreous biopsy. Microscopy revealed a filamentous fungus. An isolate was sent to the Mycology Reference Laboratory for identification. Intravitreal amphotericin B treatment was repeated twice at three daily intervals with initial visual improvement (2/60) but fell to hand movements with the development of a retinal "abscess" and infiltration surrounding the optic nerve. The

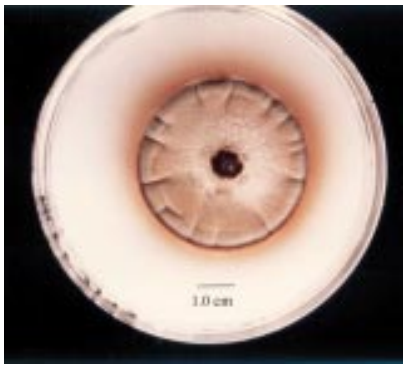

Figure 1 Colonial morphology of Ochroconis gallopava after 10 days' incubation at 30°C on glucose peptone agar. The colony is a dark reddish brown colour with a diffusible pigment.

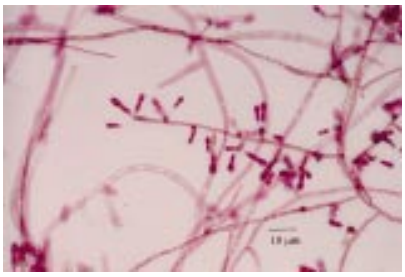

Figure 2 The microscopic morphology of Ochroconis gallopava stained with lactofuscin. Pale brown, two celled conidia are produced on narrow cylindrical denticles.

isolate was reported as the saprophytic mould *Ochroconis gallopava*. The specimen was included in the National Collection of Pathogenic Fungi (No 7195) (Figs 1 and 2) The minimum inhibitory concentration (MIC) for amphotericin was 0.5 mg/l and itraconazole <0.125 mg/l. Fluconazole was changed to intravenous amphotericin (0.6 mg/kg) but stopped after 14 days owing to deteriorating renal function. Though no neurological involvement was suspected clinically, concern over meningitic spread remained. Oral itraconazole 200 mg twice daily commenced. Evisceration was refused. Following informed consent an intravitreal injection of high dose amphotericin (0.02 mg in 0.1 ml) was performed. Visual acuity deteriorated to no perception of light. Dense lens opacity precluded further fundal examination. General debilitation ensued. The patient died 2 months later after congestive cardiac failure and sepsis from heel ulcers. A post mortem was not performed.

COMMENT

In our case of endophthalmitis vitreous biopsy was able to confirm the presence of fungal mycelium with isolation of *Ochroconis gallopava* in pure culture. Dematiaceous (dark pigmented) fungi are increasingly reported as potential pathogens in transplant recipients and patients immunocompromised following chemotherapy.[2] These thermophilic fungi have been isolated from self heated waste piles, thermal soils, and chicken litter. The species *O gallopava* has caused significant mortality through encephalitis in turkey poults and chickens.[3] A neurotropic potential is well recognised from the literature on avian disease and studied with animal models.[4] Since 1990, eight cases of invasive systemic infection have been described in the world literature with brain abscesses as common sequelae and exceedingly high mortality.[2 5 6] Six were transplant recipients, one had T cell CLL, and one large cell lymphoma. Neutropenia has not been a major predisposing factor to infection. More important is a long standing T cell mediated immunosuppression, in this case secondary to the underlying leukaemia and fludarabine. This nucleoside analogue, with good response rates in CLL, is the agent of choice when alkylating agents fail but results in myelosuppression with a more prolonged suppression of cell mediated immunity.

Infection occurred despite prophylaxis with fluconazole, an observation previously documented.[5] Fluconazole has excellent penetration into the cerebrospinal fluid and diffusion into ocular tissue.[7] However, it appears to lack in vitro activity against *O gallopava* with a MIC of >100 mg/l.[8] Successful treatment of cerebral abcess has been reported using systemic amphotericin B and itraconazole.[9] In our case renal function deteriorated on treatment and repeated intraocular injections were poorly tolerated.

Although rare, invasive infections with *O gallopava* are aggressive and it is important that clinicians and laboratory personnel are aware of the significance of this organism in lymphopenic individuals who, even on fungal prophylaxis, may be at increased risk.

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Vancomycin and ceftazidime incompatibility upon intravitreal injection

EDITOR,—The recommended treatment of endophthalmitis includes intravitreal injection of broad spectrum antibiotics. Vancomycin is the drug of choice for Gram positive bacteria, while Gram negative coverage can be obtained by either amikacin or ceftazidime. Owing to potential retinal toxicity with amikacin, the option of its substitution by ceftazidime seemed very attractive.[1–7]

Fiscella,[8] and the pharmacological handbooks have already described physical incompatibility of vancomycin and ceftazidime.[9 10] We encountered this phenomenon in two cases of post-traumatic endophthalmitis, which were treated with intravitreal vancomycin and ceftazidime. Immediately upon injection the antibiotics were seen to form yellow-white precipitates along the needle tract.

CASE REPORTS

Case 1

A 17 year old male was treated for post-traumatic endophthalmitis. Following anterior chamber and vitreous tap and cultures, intravitreal ceftazidime 2.2 mg/0.1 ml and vancomycin 1 mg/0.1 ml were slowly injected, as well as subconjunctival injection ceftazidime 100 mg/0.5 ml and vancomycin 25 mg/0.25 ml. This was done using different needles and syringes for each drug. Immediately upon injection dense yellow-white precipitates were observed along the needle tract in the vitreous cavity.

The subconjunctival vancomycin (25 mg/0.25 ml) and ceftazidime (100 mg/0.5 ml) were injected separately at different sites of the lower conjunctiva. Some of both diffused over the conjunctival surface and immediately whitish precipitates formed, which were washed away from the ocular surface.

Postoperatively indirect ophthalmoscopy revealed yellow-white precipitates along the needle tract through which the ceftazidime and the vancomycin were injected.

The vitreous precipitates were observed to dissolve gradually with a complete clearing of the vitreous cavity over a period of 2 months, with a final visual acuity of 1.0 (20/20).

Case 2

A 44 year old man was treated for late post-traumatic endophthalmitis. Anterior chamber and vitreous tap for stains and cultures were performed. Intravitreal ceftazidime 2.2 mg/0.1 ml and vancomycin 1 mg/0.1 ml were slowly injected via different syringes and needles, through the same port. Immediately upon intravitreal injection of the antibiotics, a dense yellow-white material was observed along the needle tract in the vitreous cavity.

Subconjunctival vancomycin and ceftazidime were injected, and again there was instant precipitation over the ocular surface.

On the first postoperative day a white precipitate could be seen in the vitreous cavity along the injection tract of the antibiotics. During follow up the vitreous opacities gradually disappeared over a period of 2 months, with complete resolution. Best corrected visual acuity stabilised at 0.67 (20/30).

In our laboratory we tried to simulate the precipitates formed by vancomycin and ceftazidime. Into the vitreous cavity of a fresh pig's eyes we injected vancomycin and ceftazidime, through one port, with two different syringes, in doses exactly as we had used on the patients. Instant precipitation of the substances occurred (Figs 1 and 2). On a glass slide we put a drop of vancomycin and a drop of ceftazidime and mixed the two: one can see

Figure 1 On a slide: clear drops of vancomycin and ceftazidime, and the central opaque drop of the mixed antibiotics in which precipitation occurred.

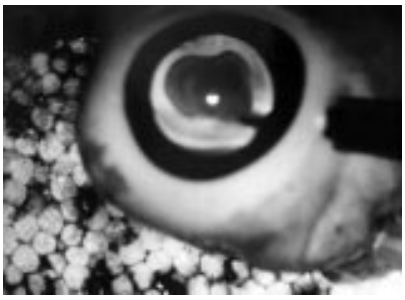

Figure 2 Opacification after injection of vancomycin and ceftazidime into the vitreous cavity of a fresh pig's eye.

that the mixture is opaque compared with the clear liquids on either side.

COMMENT

We encountered two similar cases of endophthalmitis following perforating trauma, which were treated with intravitreal injection of vancomycin and ceftazidime.

Vancomycin was chosen for its broad spectrum Gram positive coverage, and ceftazidime for the broad spectrum Gram negative coverage it provides.

Recent reports describe retinal toxicity due to aminoglycosides, including amikacin.[1] This has led some authors to recommend the use of ceftazidime as an alternative to amikacin.[4 6] However, the Endophthalmitis Vitrectomy Study Group prefers the continued use of amikacin.[1] The reasons are that even though amikacin is potentially more retinotoxic than ceftazidime, it has a concentration dependent bactericidal effect, is not dependent on the inoculum size for its effect, and is synergistic with vancomycin.[5]

The theoretical advantages of ceftazidime lie in its lower potential for retinal toxicity, and better efficacy in acidic and hypoxic environments (such as endophthalmitis) compared with amikacin.

From the pharmacological literature it is clear that vancomycin and ceftazidime are incompatible.[6 8] Vancomycin and ceftazidime precipitate when mixed. This is thought to be due to the alkaline pH of vancomycin (pH 5–7.5) compared with ceftazidime (pH 2.5–4.5) and the presence of bicarbonate in most ceftazidime preparations, even though precipitation also occurred in preparations that did not contain bicarbonate.[9]

Most authors who recommend the combination of intravitreal vancomycin and ceftazidime were unaware of its physical incompatibility. Those who were aware thought the clinical consequences of the incompatibility minor.[6] Fiscella stated the possibility of the formation of microprecipitates, and the unknown pharmacological consequences of this combination.[8] From our experience, the precipitates that form after the injection of vancomycin and ceftazidime clear completely without adverse sequelae within 2 months. It is unclear whether the antibiotic properties of these drugs after precipitation in terms of bioavailability, efficacy, and toxicity, have not been compromised.

Further studies to evaluate those properties should be conducted. Meanwhile we have stopped using the combination of vancomycin and ceftazidime for intravitreal injection, until conclusions can be drawn.

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Acute zonal occult outer retinopathy

EDITOR,—Acute zonal occult outer retinopathy (AZOOR) is a clinical syndrome described as acute zonal loss of outer retinal function associated with photopsia, minimal or no fundal findings initially, full field ERG abnormalities, and visual field loss.[1]

Most patients previously reported with AZOOR show abnormal full field flash electroretinogram (ERG).[1 2]

The diagnosis of the patient reported here is consistent with AZOOR. However, she showed a normal full field flash ERG and, interestingly, an abnormal multifocal ERG.

CASE REPORT

A 33 year old white myopic female presented in Italy in September 1996 with the sudden appearance of a dark spot in the visual field of the right eye associated with photopsia. She was first seen at Princess Alexandra Eye Pavilion, Edinburgh, in November 1996 with the same complaint. She had no systemic problems and was taking no medications. Vision was 6/5 N5 in each eye with correction. She

Table 1 Electophysiological finding from full field ERG recording (μV) along with confidence intervals. Although some disparity is evident between eyes, both responses fall within normal limits

	Normal range	1st measurement		2nd measurement	
		Right	Left	Right	Left
Rod response	39–390	205	265	233	272
Cone response	80–240	164	268	178	292
Maximum response	260–740	336	402	364	411

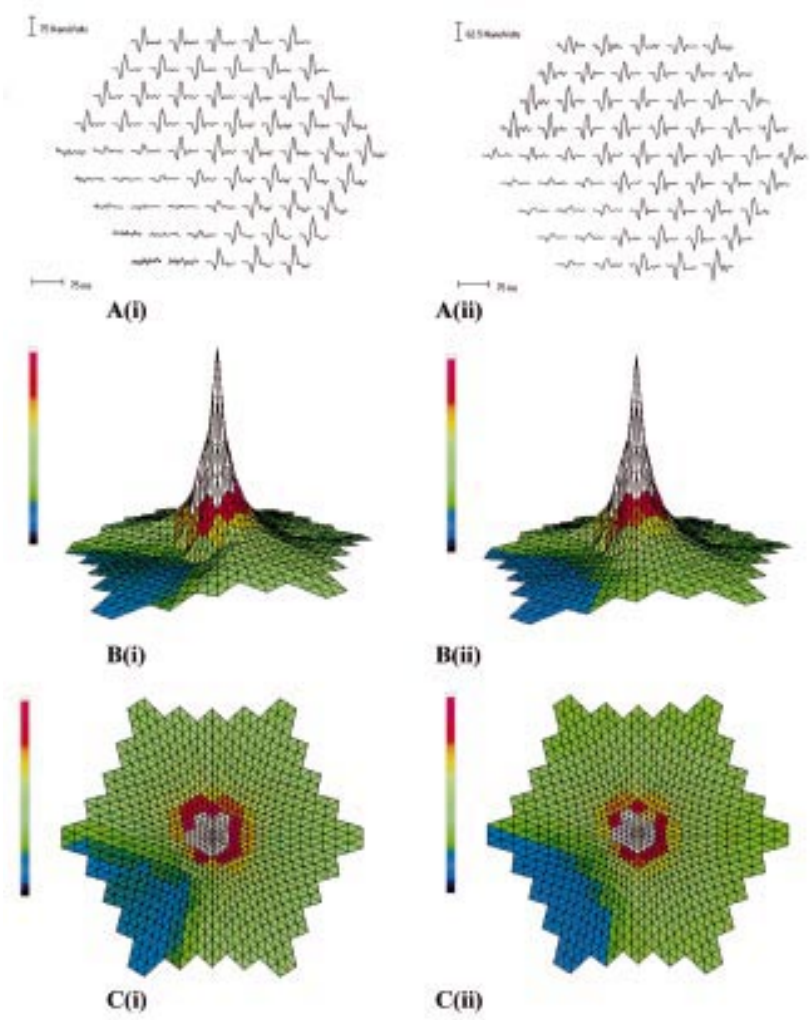

Figure 1 Multifocal ERG maps showing records of initial and subsequent measurements performed after 5 month interval. (A(i), A(ii)) multifocal waveforms indicate reduction in inferior nasal response. (B(i), B(ii)) Topographical maps of retinal function (scalar product plot, see Sutter et al [3]), and (C(i), C(ii)) plan view topographical maps.

has no afferent pupillary defect. There was no inflammation in the anterior chamber or the vitreous. The right fundus showed retinal pigment epithelial atrophy superiorly. Neurological examination was normal. Visual field test showed inferonasal scotoma in the right eye. Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICG) done in Italy showed peripheral "hyperfluorescent spots" which were interpreted as choriocapillaris in the same eye. Brain magnetic resonance imaging was normal.

COMMENT

The system used for the multifocal ERG recording was similar to the commercially available VERIS system.[3] However, it was custom built to run on Microsoft/PC platform. Care was taken to assure maximum filter bandwidth as differentiation of the response is known to lead to signal distortion.[4] Ground electrodes were placed on the forehead, reference electrodes were placed on the outer canthi, and active electrodes were placed in the lower lid.[5]

Conventional Ganzfield ERGs were recorded using our custom build system triggering a Ganzfield stimulator.[6] Multifocal and conventional ERGs were repeated after 5 months.

Electrophysiological findings from full field ERG recordings along with confidence ratings are summarised in Table 1. These results indicate that although some disparity is evident between the two eyes, both responses fall within normal limits. The multifocal ERG results are reported as topographical maps of retinal function. The evoked response maps in Figure 1 are a good record of the initial and subsequent recording performed after a 5 month interval. These responses indicate localised dysfunction in the inferonasal field of the right eye. Repeat measurements indicated no significant improvement or deterioration over this short period.

Given the suggested outer retinal dysfunction associated with AZOOR, the electroretinogram, it would appear, is an ideal test for assessing and diagnosing such pathologies as its record is a direct measure of photoreceptor and bipolar cell function.[7] However, if suggestions are correct that AZOOR represents a localised dysfunction in the outer retinal system and since the full field flash ERG represents a global response to a diffuse stimulus, information derived from the full field flash ERG in the investigation of localised retinal pathologies is of limited value.

The recent advances in the application of pseudo random binary sequences (PRBS) to signal averaging has addressed the limitation of local ERG measurements and made them a routine clinical practicality.[3 8–10]

It should be mentioned however that the multifocal technique, in its present form, is not a replacement for either full field electrophysiology or its subjective partner perimetry. It merely complements the arsenal of investigative techniques available to clinicians.

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Linear naevus sebaceous syndrome, optic disc staphyloma, and non-rhegmatogenous retinal detachment

EDITOR,—Linear naevus sebaceous syndrome, with its synonyms Schimmelpenning-Feuerstein-Mims syndrome,[1 2] epidermal naevus syndrome, and Solomon syndrome, is a rare congenital and sporadic disorder without known familial aetiology. It includes deformities and dysplasias of the skin, eyes, brain, skeleton, and heart, such as a linear naevus sebaceous Jadassohn, mental retardation, convulsions, asymmetries of the cranial structures and dilated cerebral ventricles ipsilateral to the naevus.[1–3] Ocular abnormalities described in patients with Schimmelpenning-Feuerstein-Mims syndrome are microphthalmia, colobomas of the eyelids, large optic nerve heads, and congenital teratomas or dermoids of the conjunctiva and cornea.[4–6]

The present study reports on an unusual association of Schimmelpenning-Feuerstein-Mims syndrome with an optic disc staphyloma and non-rhegmatogenous retinal detachment.

CASE REPORT

A 38 year old male patient presented with retinal non-rhegmatogenous detachment extending from the optic disc to the ora serrata in the inferior nasal quadrant of his right eye. With the macula attached, central visual acuity measured 20/33 with a refractive error of −5.0 dioptres. The vitreous was clear with no marked vitreous reaction in the sense of a proliferative vitreoretinopathy. Visual acuity in his left eye was finger counting due to a corneal dermoid extending from the limbus to the centre of the cornea. Ophthalmoscopy of the right eye revealed a staphyloma of the optic nerve head in association with a macrodisc and a pit-like appearance of the nasal region of the optic disc (Fig 1), a parapapillary chorioretinal atrophy at the temporal border of the optic disc, and alterations of the retinal pigment epithelium in the fovea in addition to the retinal detachment. A retinal defect was not found. In the left eye, ophthalmoscopy was not possible owing to the corneal opacification. Sonography of the left eye was unremarkable. General findings included a linear sebaceous naevus and patchy alopecia on the anterior and posterior part of the scalp. There was no family history of consanguinity or birth defects.

After retinal detachment surgery including encircling band, transscleral exodrainage of the subretinal fluid, and exocryocoagulation of the retinal periphery in the region of the retinal detachment, the retina attached in the right eye. A retinal defect was not found during surgery. Five days later, the retina redetached again, extending from the inferonasal intrapapillary region of the optic disc to the ora serrata. Again, the vitreous was unremarkable. A second operation was carried out consisting of pars plana vitrectomy including removal of the posterior vitreous surface, temporary instillation of perfluorocarbon liquid, endodrainage of the subretinal fluid through a planned peripheral small retinotomy, and ocular endotamponade by silicone oil. After instillation of the perfluorcarbon liquid, the subretinal fluid was pressed to the fundus periphery without leaking into the vitreous cavity. Endodrainage of the subretinal fluid became possible first after intentionally performing a small peripheral retinotomy to release the subretinal fluid. Four months later, silicone oil was removed.

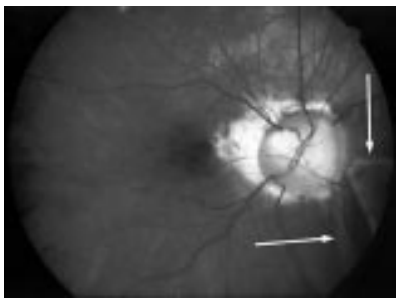

Figure 1 Fundus photograph showing the large optic nerve head (area 13.75 mm²) with optic disc staphyloma, a pit-like appearance of the nasal region of the optic disc, and associated non-rhegmatogenous retinal detachment (white arrows).

After a follow up period of an additional 3 months, in which visual acuity increased to 20/33, the retina redetached again necessitating a second pars plana vitrectomy with silicone oil endotamponade. Again, a peripheral, central, or paracentral retinal defect was not detected. After additional 12 months, silicone oil was removed leading to a new retinal redetachment, again starting in the intrapapillary nasal inferior region of the optic nerve head. In the following revitrectomy, no retinal defect was found, neither in the periphery nor in the vicinity of the optic disc where the retinal detachment had started each time. During the first operation, a subconjunctival tumour located at the 12 o'clock position close at the limbus in the right eye was removed. Its histological examination showed ectopic lacrimal gland tissue.

This report suggests that an optic nerve head staphyloma with a macrodisc, pit-like appearance of the nasal disc region, and with associated non-rhegmatogenous retinal detachment may be added to the panoply of features of Schimmelpenning-Feuerstein-Mims syndrome. It confirms recent reports on the association of the linear naevus sebaceous syndrome with large optic nerve heads and retinal or choroidal colobomas.[6 7] With no retinal defect either in the paracentral region or in the fundus periphery detected, the pathogenesis of the retinal detachment starting in the intrapapillary region of the staphylomatous optic nerve head remains unclear. It might be similar to the pathogenesis of non-rhegmatogenous retinal detachments observed in eyes with optic nerve head pits. The association of the linear naevus sebaceous syndrome with the ectopic lacrimal gland tissue at the limbus confirms a recent report on complex limbal choristomas in the linear naevus sebaceous syndrome.[6 7]

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Can leucocoria be the first manifestation of protein C deficiency?

EDITOR,—Protein C is a plasma inhibitor protein that, once activated, inhibits clot formation and enhances fibrinolysis. Protein C deficiency has two forms. The homogeneous form presents in the neonatal period with ecchymotic-necrotic skin lesions and widespread thrombosis in major blood vessels with very low or undetectable protein C activity. Heterozygote individuals have protein C levels of approximately 50% and usually remain asymptomatic until adolescence.[1]

We present a neonate with homozygous protein C deficiency whose initial finding was leucocoria.

CASE REPORT

A 2 day old female infant was referred to Gazi University Hospital Division of Newborn Medicine with bullous haemorrhagic lesions on both heels and left leg and leucocoria of the left eye. At the time of birth she was noted to be completely normal other than the ocular finding. On the second day of life blue-black necrotic lesions appeared on the left leg at the injection site of vitamin K and both heels at the venesection sites. Family history was remarkable for a first degree consanguinity between the parents. Physical examination revealed purpuric necrotic lesions on her left thigh, and both heels, and leucocoria was present on the left eye.

Laboratory findings were as follows: haemoglobin: 16.7 g/dl, platelets: 46 000/mm³, prothrombin time: 24.4 seconds, partial thromboplastin time: 66 seconds, fibrinogen: 41mg/dl, D-dimer: 8 ng/ml, fibrin degradation product <5 ng/ml. Coagulation tests were abnormal and consistent with disseminated intravascular coagulation. Protein C activity: 1.65%, maternal protein C activity: 18.6%, paternal protein C activity: 50.5%. TORCH screen: negative. Abdominal and cranial ultrasound were both within normal limits.

Ophthalmological examination and eye ultrasound revealed leucocoria, and 10×7 mm hyperechogenic structure underneath retina of the left eye consistent with subretinal haemorrhage.

With these findings the patient was diagnosed to have homozygous protein C deficiency and disseminated intravascular coagulation and was treated with fresh frozen plasma, sodium warfarin, and low molecular weight heparin. No other intrauterine infections or reasons were found to explain ocular findings.

COMMENT

Primary causes of leucocoria in children are cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity, retinal detachments, and retinoblastoma. Retinal vascular or vitreal haemorrhages have been infrequently reported to result in leucocoria in infants with protein C deficiency.

Ophthalmological manifestations of protein C deficiency result from retinal arterial or venous occlusions, retinal, preretinal, or vitreous haemorrhages.[2] The lesions may be intrauterine events or occur postnatally.[3] At birth neonates can present with non-reactive pupils, periorbital oedema, and chemosis. To our knowledge earliest leucocoria due to protein C deficiency was reported in a 2 months old infant.[4] However, in our patient leucocoria was present at birth and the skin lesions appeared on the second day of life showing that the infant actually suffered from protein

C deficiency in utero. Therefore, we conclude that leucocoria by itself can be the first manifestation of homozygous protein C deficiency; this should alert the physician to the problem since these infants can also have severe cerebral complications which are preventable if treated on time.

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