Ocular involvement in congenital erythropoietic porphyria (Gunther’s disease): cytopathological evaluation of conjunctival and corneal changes

EDITOR.—The porphyrias are a group of rare inherited disorders caused by specific enzymatic defects of the haem biosynthetic pathway. Congenital erythropoietic porphyria (CEP) is an extremely rare autosomal recessively inherited disorder of the haem synthesis pathway first described by Gunther in 1911. Clinical symptoms are caused by a homozygous defect of the enzyme uroporphyrinogen III synthase which leads to severe anaemia and the accumulation of the biologically inactive type I porphyrins, particularly uroporphyrin I and coproporphyrin I, mainly in bones, erythrocytes, skin, and teeth. Excessive amounts of uroporphyrin and other porphyrin metabolites deposited in skin induce phototoxic, oxygen dependent damage characterised by subepidermal blistering with severe inflammation and subsequent ulceration and scarring of all light exposed skin areas. The phototoxic damage can lead to severe mutilations of hands, fingers, and face, particularly nose, ears, lips, and eyelids. Since 1874 approximately 130 cases of CEP have been reported worldwide. To date there is no known treatment. The only preventive measure is absolute avoidance of sunlight. To our knowledge, there are currently only four patients living in Germany. There are no family relations among our patients.

CASE REPORTS

Patient 1 was a 38 year old man. Visual acuity was right eye: 0.3, left eye: 0.2. There was scarring of the entire face, bilaterally severely scarred retracted eye lids with incomplete lid closure (Fig 1), loss of eye lashes, scarred conjunctiva with hyperkeratotic plaques, scleral tissue substance defect and a clear cornea. Stabilisation of the ocular surface and visual function with topical supportive measures was carried out. Patient 2 was a 55 year old woman. Visual acuity was right eye: 1.25, left eye: 1.0. There were intact lid closure, comparatively mild conjunctival scarring, and clear cornea. Stabilisation of the ocular surface and visual function with topical supportive measures was carried out. The patient had mutilated hands and fingers.

Patient 4 was a 34 year old man. Visual acuity was right eye: 0.2 (amblyopia), left eye: 1.0. There was intact lid closure, comparatively mild conjunctival scarring, and clear cornea. Stabilisation of the ocular surface and visual function with topical supportive measures was carried out. Because of the clinical similarity to xero derma pigmentosum which is known to be associated with a predisposition to malignant changes of light exposed cells and because the cell alterations of the ocular surface in CEP have not yet been characterised, we aimed to rule out malignant conjunctival or corneal cell changes by cytopathological evaluation of brush smears obtained from the ocular surface, a sensitive and easy method.

We believe that supportive topical measures are the only recommendable treatment.

In summary, phototoxic alterations of the eyelids, the conjunctiva and the sclera represent the underlying pathological mechanism leading to ocular complications in CEP. Scarring of the eyelids may result in lagophthalmos with severe keratopathy and further aggravation of light induced damage to conjunctiva and sclera. The risk of development of neoplastic conjunctival or corneal cell changes appears to be low.

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Bitot’s spots and vitamin A deficiency in a child from the UK

EDITOR,—Prolonged nutritional deficiency of vitamin A results in xerophthalmia. Bitot’s spots are an early manifestation of this condition.1 While xerophthalmia is responsible for 70% of childhood blindness in developing countries it is rare in the Western world.2 We report a case of a British, vegetarian girl who developed Bitot’s spots.

CASE REPORT
A 7 year old, indigenous, British, white girl presented with triangular white, foamy lesions in the temporal paralimbal areas of both eyes (Fig 1). She had no visual complaints and denied night blindness or any systemic problem. She had been a vegetarian for 2 years, and preferred processed, frozen food to fresh fruit or vegetables. On examination her unaided Snellen visual acuity was 6/6 and her tear film healthy with a normal tear break up time and no mucous filaments. Funduscopy was normal. Vitamin A levels were depressed at 0.35 μmol/l (normal range 0.4–1.1 μmol/l). Electroretinography was normal.

The patient was referred to a paediatric dietician who enabled her to find a more nutritious diet that she found acceptable. The Bitot’s spots had visibly lessened by 6 weeks and disappeared by 3 months.

COMMENT
This case illustrates that the manifestations of vitamin A deficiency can occur in children in the Western world because of poor dietary education. In the UK xerophthalmia is more usually associated with alcoholism/hepatic cirrhosis, or refugee status. A loss of goblet cells in xerophthalmia alters the protective mucous layer resulting in an overlying accumulation of Gram positive bacilli and keratin debris on the paralimbal conjunctiva. A rapid response to vitamin A replacement is usual with goblet cells reappearing within 2 weeks’ and resolution within 3 months.3

The World Health Organization (WHO) categorised the ocular manifestations of vitamin A deficiency as XN night blindness, X1A conjunctival xerosis, X1B Bitot’s spot, X2 corneal xerosis, X3A corneal ulceration or keratomalacia involving one third or less of the cornea, X5 corneal scar, and XF xerophthalmia fundus.1 While this describes the usual pattern of progression of the disease, a study of 114 cases of Bitot’s spots found over 80% had no concurrent clinical night blindness as in this patient.1 Formal night blindness testing was not undertaken in this case as clinical history of poor night vision is believed to be a sensitive test in vitamin A deficiency.4

The condition improved after dietary change although the definitive treatment is one or two doses of vitamin A (200 000 IU). Those that do not respond are frequently over the age of about 6 years and may have normal vitamin A levels and possible previous deficiency.5

Bitot’s spots are an important clinical sign that should prompt a careful dietary history which may enable patients to avert the devastating consequences of xerophthalmia.6

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Localised chronic eyelid disease resulting from long term hydroxyurea therapy

EDITOR,—Hydroxyurea is an antineoplastic agent used in the treatment of various myeloproliferative conditions and severe psoriasis. Documented skin manifestations from long term therapy with hydroxyurea include ichthyosis, a dermatomyositis-like eruption on the dorsal hands, facial erythema, and accelerated development of premalignant and malignant skin lesions.7,8 Our patient is the first described case of a cutaneous manifestation of long term hydroxyurea therapy affecting only the eyelids.

CASE REPORT
A 61 year old man receiving long term hydroxyurea (1–1.5 g daily) for chronic granulocytic leukaemia presented complaining of chronic discomfort in the right eye accompanied by an area of erythema, dryness, and flakiness of the skin on the temporal aspect of the right lower lid. Examination of the right eyelid revealed a marked blepharitic-type reaction with associated lid skin changes. There was an associated temporal conjunctival injection (Fig 1). Visual acuity was 6/6 bilaterally. Following cessation of hydroxyurea therapy, there was a rapid improvement of the clinical findings and complete resolution by 4 months (Fig 2).

COMMENT
The skin manifestations of hydroxyurea therapy are rare and occur after long term high dose therapy. They have been speculated to result from a cumulative toxicity of hydroxyurea on the basal layer of the epidermis due to inhibition of DNA synthesis.9,10 Although the exact incidence of skin complications from hydroxyurea is unknown, Kennedy et al10 reported seven patients with dermatological complications out of 20 patients with chronic myeloid leukaemia on hydroxyurea therapy, other reports being in the form of sporadic cases.11

The rapid resolution of the condition on stopping hydroxyurea treatment should alert ophthalmologists to this possible link in any patients who develop lid problems which do not respond to usual management strategies while on such treatment.

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Continuous renewal of the corneal systemic chemotherapy
Limbal stem cell deficiency arising from cytopathic corneal epitheliopathy and that a histological finding confirmed the diagnosis of LSCD. This latter finding confirmed the diagnosis of LSCD. Because of total LSCD, epithelialisation was not complete despite amniotic membrane transplantation, and a keratolimbal allograft together with a repeat AMT was performed 3 weeks later. Immunosuppression was achieved with systemic cyclosporin 300 mg daily and topical preservative-free methylprednisolone. Complete epithelial healing occurred within 2 weeks (Fig 1D) and 7 weeks later BCVA was 6/8 right eye 6/10 left eye.

COMMENT
The diagnosis of partial (right eye) and total (left eye) LSCD secondary to hydroxyurea treatment was made on the basis of the clinical presentation, and findings from IC and subsequently histopathology. This was confirmed therapeutically by the ultimate success of keratolimbal allograft, which resulted in the rapid and complete re-epithelialisation of the left cornea.

We suggest that the diagnosis of LSCD should not be overlooked in cases of idiopathic corneal epitheliopathy and that a history of the use of drugs known to affect cell cycling—for example, cytotoxic chemotherapy, be specifically sought. If possible, IC should be undertaken and diagnostic tool to detect LSCD and to help formulate therapeutic strategies. Once drug toxicity is suspected, cessation or switching to other non-toxic alternatives is advised. Like radiation induced LSCD, medical therapy to correlate the clinical course of a patient with bilateral epithelial pathology arising from systemic hydroxyurea treatment with cytological and histological evidence of LSCD. We describe an unrecognised cause of both reversible and irreversible LSCD in these two eyes, respectively, and suggest that all cases of persistent corneal epithelial failure be investigated for limbic stem cell dysfunction.

CASE REPORT
A 68 year old man gave a 6 week history of bilateral keratitis prior to referral. He complained of decreased visual acuity with pain, severe photophobia, itching, and redness particularly affecting the left eye. The referring ophthalmologist had treated him with Viroptic (trifluridine, Glaxo-Wellcome Inc, NC, USA) for 3 weeks and Tobradex (tobramycin, dexamethasone, Alcon Laboratories Inc, Fort Worth, TX, USA) for 2 weeks. He had a medical history of chronic myelocytic leukaemia for which he had been treated with hydroxyurea (Roxane, Columbus, OH, USA) at 1500 mg per day for the previous 2 years. He had no other significant ophthalmic or past medical history.

At presentation, the best corrected visual acuity (BCVA) was 6/20 right eye and 6/22 left eye. Slit lamp examination of the both eyes revealed a severe diffuse punctate keratopathy with an irregular corneal epithelium and numerous areas of epithelial breakdown, but no macroepithelial lesions were seen. The fluorescein tear clearance test showed delayed tear clearance but no aqueous tear deficiency. Treatment was commenced with preservative-free 1% methylprednisolone (BPEI pharma) daily for 10 days and Refresh (polyvinyl alcohol, porcine, Allergan, Irvine, CA, USA) ointment three times daily to both eyes. No improvement was noted after 2 months, while punctate epithelial erosions increased and BCVA decreased to 6/22 in the right eye and counting fingers at 2 metres in the left eye. A severe persistent epithelial defect on the right cornea highlighted by fluorescein staining was observed (Fig 1A) and a 4 × 1 mm macroepithelial defect of the left cornea. A provisional diagnosis of bilateral corneal epitheliopathy secondary to chemotherapy was made. Impression cytology (IC) revealed focal LSCD localised to the temporal and inferior portion of the right cornea by exhibiting conjunctival goblet cells and mucous on the cornea and diffuse squamous metaplasia of the left cornea with partial loss of the limbal landmark area.

On the basis of the corneal pathology, and in conjunction with the oncology service, interferon injections were substituted for hydroxyurea as the leukaemia was well controlled. Two weeks later a dramatic decrease in the epithelial keratitis was noted. The right ocular surface was smooth and epithelialised as evidenced by negative fluorescein and rose bengal staining, and the BCVA returned to 6/8. The left eye became less painful with regression of the epithelial defect, but severe superficial punctate keratopathy (SPK) still persisted, and the BCVA remained at counting fingers at 2 metres. Five weeks later, interferon intolerance led to reintroduction of hydroxyurea. Examination 18 days later revealed a mild corneal epithelial change of the right temporal cornea although the corneal epithelium remained largely intact. An epithelial defect on the left cornea measuring 6 × 4 mm was apparent (Fig 1B). Despite topical antibiotics for 5 days, and preservative-free artificial tears for 2 months, the epithelial defect still persisted on the left eye with a BCVA of counting fingers at 2 metres. Pannus formation on the inferonasal temporal portion of the left cornea led to the diagnosis of LSCD and amniotic membrane transplantation was performed. Histological examination of the corneal pannus revealed positive PAS staining indicating the presence of goblet cell mucin on the corneal epithelium (Fig 1C). This latter finding confirmed the diagnosis of LSCD. Because of total LSCD, epithelialisation was not complete despite amniotic membrane transplantation, and a keratolimbal allograft together with a repeat AMT was performed 3 weeks later. Immunosuppression was achieved with systemic cyclosporin 300 mg daily and topical preservative-free methylprednisolone. Complete epithelial healing occurred within 2 weeks (Fig 1D) and 7 weeks later BCVA was 6/8 right eye 6/10 left eye.
support and prevent additional attrition of the remaining corneal epithelial cells should be taken to see if the process can be reversed. Once LSCD becomes persistent and irreversible, AMT can help restore the corneal surface if LSCD is partial, but requires additional transplanted limbal epithelial stem cells if LSCD is total. In this case, we chose to use an allogeneic source as the right eye of the patient we described was also limbal deficient.

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Orbital entomophthoramycosis in an infant: recovery following surgical debridement, combination antifungal therapy and use of hyperbaric oxygen

Editor—Entomophthoramycosis is a rare granulomatous disease caused by the fungus Conidiobolus coronatus (class Zygomycetes), and usually manifests as chronic, indolent, and localized infection of the rhinopharyngeal region. While immunodeficiency may predispose to dissemination of infection, the condition usually presents in immunocompetent individuals. Standard treatment includes single or combination antifungal therapy and surgical debridement.

We report orbital entomophthoramycosis due to Conidiobolus coronatus in an infant with congenital nasolacrimal duct obstruction, which resolved following excision of granulomatous tissue, administration of antifungal and immunomodulating drugs, and use of hyperbaric oxygen.

CASE REPORT

A 5 month old infant girl presented with a swelling near the left eye. From the age of 2 months, she had received various topical and oral antibiotics for suspected bacterial dacryocystitis. Examination revealed a thriving infant weighing 7 kg, with redness and swelling over the left lacrimal sac and the nasolacrimal duct, the orbital swelling continued to increase despite broad spectrum, topical and systemic antifungal therapy. Computed tomography (CT) of the orbit demonstrated a solid mass in the region of the left lacrimal sac (Fig 1). Microscopic examination of a biopsy revealed fungal hyphae, and subsequent culture on Sabouraud’s agar led to identification of the fungus Conidiobolus coronatus (Fig 2). There was no evidence of underlying immunodeficiency.

Intravenous fluconazole (6 mg/kg/day) and co-amoxiclav (100 mg/kg/day) were commenced, but due to lack of sustained improvement, they were replaced with intravenous amphotericin B (1 mg/kg/day) and clocaxillin (200 mg/kg/day). Despite this change, the child’s condition deteriorated with extension of the granuloma into surrounding tissue (Fig 3). One month after admission, all visible tumour, including adhesions to overlying skin, was excised. A drain was left in situ to facilitate daily amphotericin irrigation. Within a week, however, new indurated areas appeared in the nasal part of the upper eyelid, and proptosis with downward and outward displacement of the eyeball was observed. Biopsy showed persistence of fungal elements, and CT of the orbit demonstrated extension of the tumour towards the orbital apex. Chest x ray revealed a right upper lobe opacity, which was suspected to be metastatic fungal infection. Antibiotic was discontinued at this stage and oral fluconazole (loading dose 28 mg/kg/day; maintenance 10 mg/kg/day) was administered for 10 days, but without benefit.

Therapy with high dose intravenous fluco- nazole (12 mg/kg/day), liposomal amphotericin B (Ambisome) (7 mg/kg/day), and oral potassium iodide (20 mg/kg/day) was then initiated. Subcutaneous granulocyte-colony stimulating factor (5 µg/kg/day) was added to the treatment regimen. Hyperbaric oxygen therapy was commenced 10 days later and consisted of 90 minute sessions of exposure to 100% oxygen for 15 weeks. In total, 40 sessions were administered over 6 weeks. In the hyperbaric chamber, the child was sedated intravenously with a 4–8 ml solution of ketamine and midazolam, and a Bain circuit was used to administer the pure oxygen. Intense redness over affected areas was observed during treatment sessions.

The earliest signs of recovery, with reduction in proptosis and softening of the tissue mass appeared 5 days after starting combination antifungal therapy, and this trend was maintained during treatment with hyperbaric oxygen. CT of the orbit performed at the end of 6 weeks confirmed resolution of the fungal mass and chest x ray showed resolution of the pulmonary lesion. Intravenous antifungal therapy was continued for another 15 weeks, and oral fluconazole and potassium iodide for a further 10 weeks.

Three years later, there has been no evidence of recurrence of the fungal granuloma, the only sequela of the orbital infection being a small angle exotropia of the left eye and epiphora (Fig 4).
COMMENT
Infection with *Conidiobolus coronatus* characteristically begins in the inferior nasal turbinates and extends to the perinasal tissues, producing nodular, subcutaneous masses and occasionally, severe disfigurement.1 Rarely, pulmonary and systemic infection may be encountered.2 Ours is the first report of orbital infection with *C. coronatus*, and our patient appears to be the youngest case of entomophthoramycosis on record.3

*C. coronatus* is ubiquitous in nature and is commonly present as a saprophyte in soil and on decaying vegetation. The majority of reports of human infection come from the tropical rain forest areas of Africa;3 however, this is the first report from Oman which experiences an arid climate. The pathogenesis of infection is unclear, but rarity of the disease indicates low intrinsic pathogenicity. The portal of entry of spores is believed to be by inhalation or direct inoculation. The child’s home, with open roofed hall, was located close to a small area containing humid and rotting vegetation. We suspect that prolonged antibiotic treatment disturbed the normal immunity in our patient, allowing fungal spores which had been inhaled or had entered her conjunctiva, to germinate and become established.

Diagnosis is made by demonstrating distinctive non-septate hyphae with surrounding eosinophilic sheath (Splendore-Hoeplli phenomenon) in tissue sections. Vascular invasion and thrombosis as well as tissue infarction are notably absent. Culture of the fungus allows identification of the species; however, as hyphal elements of zygomycetes are prone to physical damage, specimens must be directly inoculated onto culture media avoiding excessive grading.3 Despite being recognised as a common laboratory contaminant, *C. coronatus* is infrequently isolated in the clinical laboratory,1,3 and in human infections, reliable culture identification of the fungus is made in less than 50% of the cases.4 Although spontaneous resolution is known, the fungal granuloma is more likely to persist and extend without effective treatment.4,5 Surgery, which includes removal of infected tissue and reconstructive procedures, is seldom curative. A wide variety of antifungal drugs, singly or in combination, have been reported to be effective, including ketoconazole, itraconazole, fluconazole, sulfamethoxazole, potassium iodide, and amphotericin B.1,3,5,10 Susceptibility testing for fungi responsible for entomophthoramycosis is not standardised and is an unreliable guide to choice of therapeutic agent.1 Several authors have reported a beneficial effect of hyperbaric oxygen in rhinocerebral mucormycosis,1,5,10 and there has been one report of successful use in the therapy of *Conidiobolus* infection.12 Hyperbaric oxygen is believed to accelerate the healing process by enhancing vasodilatation, thereby improving perfusion of compromised infected tissue and augmenting immune responses. Our patient was successfully managed by employing more than one form of treatment. Progressive development of the child’s own immune system also, no doubt, contributed to resolution. It can only be conjectured whether one or more of these factors, acting independently or synergistically, was instrumental in her final recovery.

In conclusion, a healthy child with congenital lacrimal duct stenosis treated with prolonged courses of broad spectrum antibiotics, developed extensive and invasive candidiasis and invasive orbital entomophthoramycosis by the fungus *C. coronatus*. Addition of hyperbaric oxygen to standard therapy (combination antifungal therapy and surgery) yielded recovery. Although rare, the possibility of fungal superinfection should dissuade clinicians from indiscriminate use of antibiotics in the management of congenital nasolacrimal duct obstruction.

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Limbal stem cell deficiency arising from systemic chemotherapy

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