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 homozgyous 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 retractable eye lids with incomplete lid closure (Fig 1), loss of eye lashes, scarred conjunctiva with symblepharon, corneal vascularity and hyperkeratotic plaques in both eyes (Fig 2), with chronic recurrent corneal erosions.

There was corneal surface stabilisation with subsequent improvement of visual function to right eye: 0.5, left eye: 0.2 with topical supportive measures. Patient 2 was a 55 year old woman. Visual acuity was right eye: 0.6, left eye: 0.4. There was scarring of the entire face, bilateral lid closure was almost complete, loss of eye lashes, scarred conjunctiva with hyperkeratotic plaques, scleral tissue defect and a clear cornea. Stabilisation of the ocular surface and visual function with topical supportive measures was carried out.

Patient 3 was a 42 year old man. Visual acuity was right eye: 1.25, left eye: 1.0. There were scarred eye lids with incomplete lid closure in the left eye, scarred conjunctival and scleral alterations with conjunctival hyperkeratotic plaques in the left eye, bilaterally scarred eye lids with symblepharon in both eyes, and a 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 photodynamic 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.

It revealed hyperkeratotic squamous cells, few granulocytes and lymphocytes with inflammatoive activation and degenerative unclear changes. Malignant or dysplastic cell changes of the ocular surface were excluded in all four patients.

Topical lubrication has led to improvement or at least stabilisation of visual function in all four patients. All patients reported subjective improvement of disturbing foreign body sensation with topical treatment.

COMMENT

Alterations of lids, conjunctiva, and sclera, as well as the changes of other light exposed parts of the skin, are directly related to the described toxic effect of sunlight. The corneal changes, on the other hand, have two causes. Firstly, conjunctival scarring causes a disturbance of the mucin layer of the tear film which in turn leads to a dry eye syndrome. Secondly, the dry eye syndrome is further aggravated by severely scarred eyelids with incomplete lid closure leading to lagophthalmos. Inadequate closure of the lids not only results in corneal drying but also leads to increased exposure of the cornea, the conjunctiva and the sclera to sunlight. Overall, in CEP, lagophthalmos seems to be the main cause of severe aggravation of ocular surface symptoms. Our clinical findings are in accordance with reports of CEP patients in the literature. In light and electron microscopy, Ueda et al found a reduced number of keratocytes, leucocytes, a thickened basement membrane of corneal and conjunctival blood vessels, and microfibrillar material in the extracellular space of the conjunctival stroma. There are no reports of malignant cell changes in the literature. The cytopathological evaluation of brush smears obtained from the ocular surface of our patients are compatible with these findings.

Attempts to correct lagophthalmos surgically cannot stop the ongoing scarring of the eyelids. We therefore recommend avoiding surgical treatment of scarred eyelids in CEP.

Hamard et al reported scarring of the eyelids, but not from surgical correction of the eye lids because of impaired postoperative wound healing. We believe that supportive topical measures are the only recommended 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. While xerophthalmia is responsible for 70% of childhood blindness in developing countries it is rare in the Western world.1 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). Electoretinography 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 weeks1 and resolution within 3 months.1

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.6

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.1

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.1

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Localized 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.3,4 Our patient is the first described case of a cutaneous manifestation of long term hydroxyurea therapy affecting only the eyelids.

Figure 1 Triangular white, foamy lesions in the temporal paralimbal areas of both eyes.

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 blepharitis-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.1,2 Although the exact incidence of skin complications from hydroxyurea is unknown, Kennedy et al 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.1,3

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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Limbal stem cell deficiency arising from systemic chemotheraphy

Editor,—Continuous renewal of the corneal epithelium is vital for the preservation of a smooth, transparent, refractile surface necessary for clear vision and ocular comfort. The regeneration of corneal epithelial cells takes place through centripetally migrating transient amplifying cells ultimately derived from stem cells located at the limbus.1,2 Deficiency of these progenitor cells leads to failure of epithelial regeneration and its replacement by invading conjunctival epithelium. This pathological pathway is called limbal stem cell deficiency (LSCD) (see reviews Tseng and Sun3 4). Corneal diseases with LSCD are characterised by conjunctival epithelial ingrowth, vascularisation, chronic inflammation, and fibrous ingrowth. Patients with LSCD often suffer from severe photophobia and profound loss of vision.

Cytotoxic agents such as 5-fluorouracil (FU) and mitomycin C are recognised causes of persistent epithelial defect and LSCD,5 when applied locally. Although a case of epithelial erosion arising from systemic cytotoxic therapy has been reported,6 little is currently understood about the pathophysiology of this effect. We were able to accurately 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 limbal 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 Viropic (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 test7 showed delayed tear clearance but no aeous tear deficiency. Treatment was commenced with preservative-free 1% methylprednisolone (BPEI pharmacy) daily for 10 days and Refresh (polyvinyl alcohol, porcide, Alphalan, 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 epithelial pannus opacity 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 mucins 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 punctuate keratopathy (SPK) was 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 inferior cornea (Fig 1C) and anterior chamber inflammation (Fig 1D) were noted. This 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.

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 as an important 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
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 treatments.

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Infection with _Conidiobolus coronatus_ characteristically begins in the inferior nasal turbinates and extends to the perinasal tissues, typically begins in the inferior nasal turbinates, and occasionally, severe disfigurement. It may be associated with pulmonary and systemic infection. The fungus usually appears as a saprophyte in soil and is ubiquitous in nature. It is an unreliable guide to choice of treatment. Although spontaneous resolution is known, reports of human infection come from the tropical rain forest areas of Africa; however, the first report from Oman which experienced an arid climate. The pathogenesis of infection is unclear, but rarely 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 false septate hyphae with surrounding cosinophilic sheath (Splendore-Hoeppli 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 _zymoseptoria_ are prone to physical damage, specimens must be directly inoculated onto culture media avoiding excessive grinding. Despite being recognised as a common laboratory contaminant, _C. coronatus_ is infrequently isolated in the clinical laboratory, and in human infections, reliable culture identification of the fungus is made in less than 50% of the cases. 

Although spontaneous resolution is known, the fungal granuloma is more likely to persist and extend without effective treatment. Surgical, 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, sulphanmethoxazole, potassium iodide, amphotericin B, and clotrimazole. Susceptibility testing for fungi responsible for entomophthoramycosis is not standardised and is an unreliable guide to choice of therapeutic agent. Several authors have reported a beneficial effect of hyperbaric oxygen in rhinocerebral mucormycosis, and there has been one report of successful use in the therapy of _Conidiobolus_ infection. 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 orbital entomophthoramycosis by the fungus _C. coronatus_. Addition of hyperbaric oxygen to standard therapy (combination antifungal therapy and surgery) aided 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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Figure 4. Photograph of the patient 1 year after successful treatment of orbital entomophthoramycosis.

COMMENT