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CORRESPONDENCE

Sir,

Reversible corneal epitheliopathy caused by vitamin B12 and folate deficiency in a vegan with a genetic mutation: a new disease

A 27-year-old woman complained of decreased vision, photophobia and monocular diplopia. She has been a vegan for 7 years. Her best-corrected visual acuity was 20/60 OD and 20/20 OS. The corneas displayed a diffuse epithelial punctate keratopathy with intraepithelial cyst-like relucent lesions (Figures 1a and b). Superficial keratectomy was performed; despite an initial improvement in vision, the lesions reappeared.

Epithelial biopsy detected clusters of degenerating cells (either dyskeratotic or apoptotic; Figure 2a, inset). There were myriad cytoplasmic vacuoles and isolated, swollen, lighter-staining cells beneath the surface parakeratotic layer (Figure 2b). Electron microscopy disclosed cytoplasmic vacuoles among basilar and suprabasilar cells, above which were more electron-lucent cells (Figure 2c). The vacuoles had a floccular content and a two-layered, limiting membrane with an occasional, preserved projecting crista (Figure 2d), establishing that they were degenerating mitochondria.

The patient was referred to a metabolic geneticist and found to have elevated serum homocysteine levels to 60.7 μmol/l (normal <10). Serum folate levels were decreased to 2.9 ng/ml (normal >4 ng/ml) and vitamin B12 levels to 190 pg/ml (normal >211). DNA mutation analysis revealed a homozygous mutation for the C677T of the methylenetetrahydrofolate gene. The patient's diet was supplemented with B12 (1 mg) and folic acid (1 mg). After 6 months, serum levels of homocysteine, vitamin B12, and folate had normalized and the epithelial lesions and symptoms had resolved (Figures 1c and d).

In our patient, methylenetetrahydrofolate deficiency was compounded by nutritional deficits of folate and vitamin B12, which resulted in the emergence of a corneal epitheliopathy due to a mitochondriopathy that was reversible with dietary supplements.[1,2] Vitamin A deficiency, on the other hand, causes bundling of cytoplasmic tonofilaments to form keratofibrils, increases the numbers of desmosomes, and leads to disappearance of surface microplicae, features absent in our case.[3] In cytosol and mitochondria, vitamin B12 is modified by a series of reactions into cobalamine.[4] Cobalamine is a coenzyme necessary for methionine synthase, which is involved in homocysteine metabolism, and methylmalonyl-CoA mutase, which is involved in the catabolism of branched chain amino acids.[4,5] The patient's strict veganism together with methylenetetrahydrofolate deficiency resulted in critically low levels of cobalamine, abolition of the normal breakdown of homocysteine (reflected in the abnormally elevated plasma levels of homocysteine), and interference in the catabolism of branched chain amino acids (hence the mitochondrial abnormalities). This case exemplifies a model of how an endogenous genetic predisposition interacted with an exogenous dietary insufficiency to create a previously unreported corneal entity.

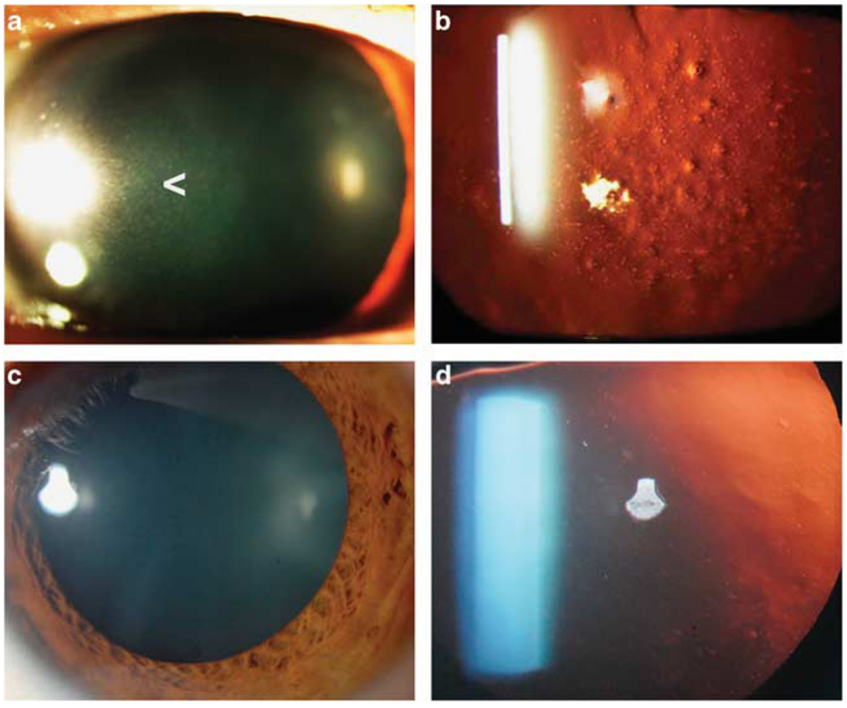

Figure 1 Clinical features of corneal epithelium before and after vitamin supplementation. (a) Diffuse illumination slit-lamp photograph of corneal epithelial lesions that caused diffuse superficial corneal haze (arrowhead). (b) Retroillumination image of intraepithelial cyst-like lesions scattered throughout the visual axis. (c) Resolution of corneal haze after vitamin supplementation. (d) The cyst-like lesions disappeared after vitamin supplementation.

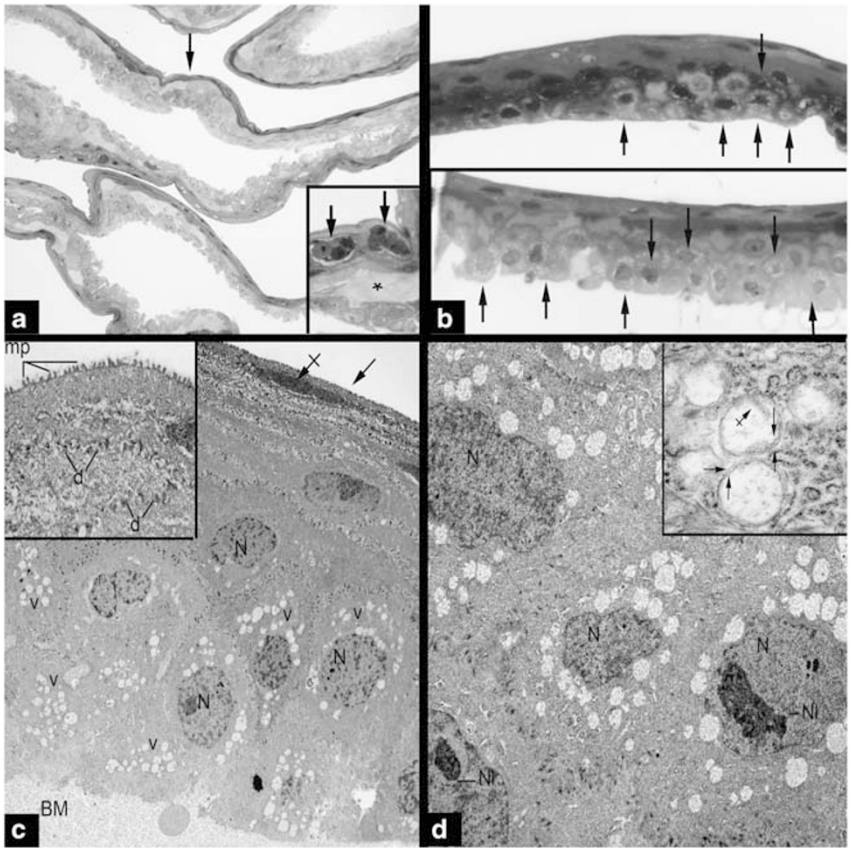

Figure 2 Pathological features of corneal epithelial biopsies. (a) An undulating strip of corneal epithelium displays two to three layers of parakeratotic, hyperstaining surface cells (pre-keratinization, arrows). The inset shows small clusters of dyskeratotic or apoptotic cells and a clear cell (asterisk; 1 μ plastic section, toluidine blue, $\times$80, inset $\times$120). (b) High-power fields from each of the two biopsies showing basilar and suprabasilar (wing), frequently pale cells with cytoplasmic vacuoles that often indent the nuclei (arrows; 1 μ sections, toludine blue, $\times$180). (c) Electron micrograph of a full-thickness portion of epithelium with degenerative changes consisting of myriad basilar and suprabasilar cell vacuoles, apical surface cells with dissolution of their cell membranes (arrow), and fragmentation of their nuclei (crossed arrow). The inset displays preservation of surface microplicae in another region and subjacent desmosomes (designated 'd'). BM, a portion of included Bowman s membrane; N, nuclei of basilar and suprabasilar cells ($\times$2600). (d) The numerous cytoplasmic vacuoles contain a fibrillo-flocculent material. The inset demonstrates a double membrane (arrows) delimiting the vacuoles, indicating that they are distorted mitochondria, as does a crista (crossed arrow) projecting centrally. Profiles of rough endoplasmic reticulum envelop the mitochondria. N, nuclei of suprabasilar cells; Nl nucleolus. ($\times$4600, $\times$25000 inset).

Conflict of interest
The authors declare no conflict of interest.

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Author contributions
UVJ, FAJ designed the study; UVJ, FAJ, RJ conducted the study; UVJ, FAJ, JS, FRZ, NM, RJ collected, managed, analyzed and interpreted the data; UVJ, FAJ, JS, FAZ, NM, RJ prepared, reviewed and approved the manuscript.

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Sir,

Hemoglobin AC retinopathy managed with vitrectomy and adjunctive bevacizumab

Since the first report of hemoglobin (Hb) AC retinopathy,[1] few cases have been described and the pathogenesis remains obscure.[2] Significant intraoperative bleeding may make vitrectomy for proliferative retinopathy from sickling hemoglobinopathies challenging.[3]

Case report

A 33-year-old African American male, with idiopathic hypertension and mild renal failure, complained of decreased vision in his right eye for 6 months and floaters in his left eye for 2 years. Right and left visual acuities (VA) were 6/18 and 6/7.5, respectively. Anterior segments were normal. Fundoscopy showed vitreous hemorrhage (VH), right more than left; sclerotic retinal vessels, more so inferiorly (right more than left); and preretinal fibrosis with localized traction retinal detachments in the midperiphery of both eyes (Figures 1a and b). Fluorescein angiography showed neovascularization, capillary dropout and capillary remodeling (Figures 1c and d). Infective and autoimmune laboratory screen was negative. Hematological assessment revealed Hb AC (A = 56.9%, A2 = 2.8%, F = 0.7%, C = 39.6%), no sickling, and a normal blood count with an Hb level of 15.0 g/dl. Blood sugar was normal and creatinine was mildly raised to 1.5 mg/dl.

Scatter photocoagulation was placed in the anterior retina in both eyes. Three weeks later the left VH worsened (Figure 1e). One month later, VA remained at 6/60, due to nonclearing central VH, and possibly macular traction. After receiving 1.25 mg IVB 5 days before surgery, the VH and preretinal fibrosis were removed and the retina attached, with postvitrectomy VA stable at 6/7.5 (Figure 1f).

The right VH worsened 2 months after laser treatment. Because of nonclearing VH and tractional detachment threatening the macula, this eye was vitrectomized 4 months post laser with VA at 6/45. IVB of 1.25 mg was given 5 days before vitrectomy. The VA improved to 6/18, with persistent inferior macular ischemia (similar to presurgery; Figure 2).

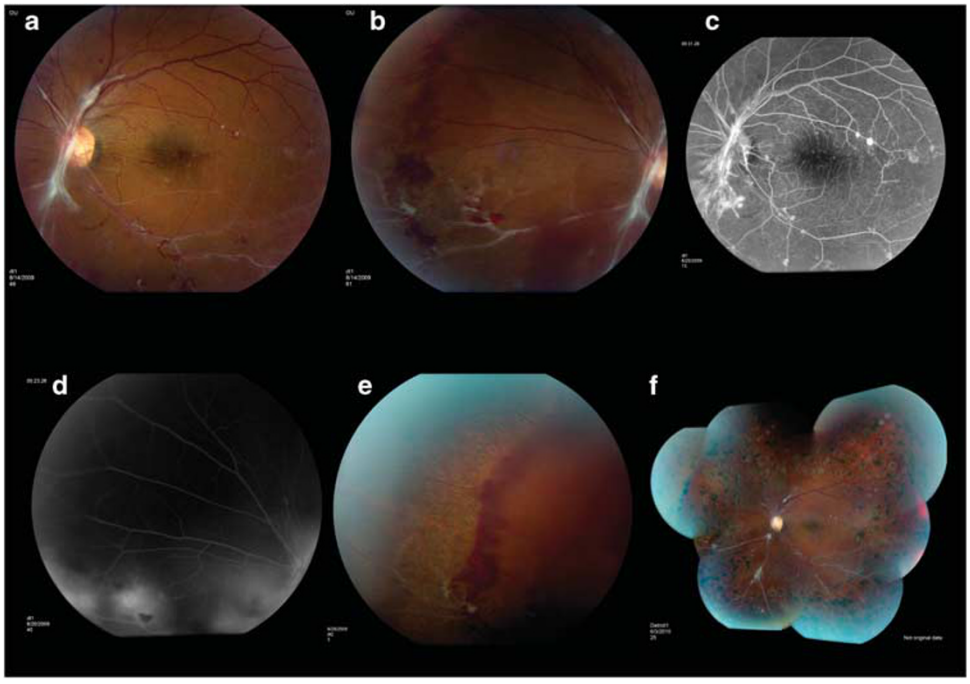

Figure 1 Left eye imaging. (a, b) Pretreatment color photographs show neovascularization, preretinal fibrosis and equatorial hemorrhage. (c, d) Pretreatment fluorescein angiography shows neovascular leakage from the preretinal fibrotic membranes, vascular remodeling of the posterior pole and capillary dropout at the midperiphery. (e) At 3 weeks after scatter laser therapy, color photograph shows a good laser pattern peripheral to preretinal hemorrhage of the superonasal equatorial region. (f) At 8 months post vitrectomy, the retina is fully attached with islands of segmented fibrosis, with visual acuity of 6/7.5.