Title: Similarities in the Histological Mouse Model of Early Herpes Simplex Retinopathy with Punctate Inner Choroidopathy and Ebola Virus Disease Retinopathy

Running title: Punctate Inner Choroidopathy Imaging Comparison

Authors: Paul J. Steptoe[1] FRCOphth; Catherine M. Guly[1] MRCP, MRCOphth; Andrew D. Dick[1,2,3] FMedSci, FRCOphth

Affiliations:

1. Princess Alexandra Eye Pavilion, Edinburgh, United Kingdom
2. Bristol Eye Hospital, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom.
3. Bristol Medical School, University of Bristol, Bristol, United Kingdom.
4. Institute of Ophthalmology, University College London, London, United Kingdom.

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Corresponding author:

Mr. Paul Steptoe,
Princess Alexandra Eye Pavilion
Chalmers Street
Edinburgh
United Kingdom
EH3 9HA
Email Address: paul.steptoe@nhs.net
Telephone: +44 (0)7969237935
ORCID ID: 0000-0002-7323-1681

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Correspondence

The term punctate inner choroidopathy (PIC) was first used by Watzke *et al* in 1984 to describe the findings in a group of 10 patients with multifocal, well-circumscribed, usually small choroidal lesions.[1] The underlying aetiology and pathogenesis of PIC remain poorly understood.[2]

We report a case of a 15-year-old Caucasian myopic female diagnosed with bilateral PIC. Multiple, small punctate lesions were present bilaterally at the posterior pole on fundus imaging (Figure 1A). Optical coherence tomography (OCT) through one of these lesions demonstrated a focal photoreceptor loss and a distinctive V-shaped collapse of the overlying retinal layers. (Figure 1A).

Whilst phenotypically different on colour imaging, a near-identical OCT appearance to the PIC lesion seen in Figure 1A was observed in a recent study of retinal lesions secondary to Ebola virus disease (EVD) (Figure 1B).[3] Within which, the authors highlighted the resemblance of this characteristic appearance with the early histological appearance of neuronally transmitted herpes simplex virus (HSV) type 1 retinopathy (Figure 1C) induced by the von Szily model in mice.[4] The neural retina and RPE were also identified as targets in experimental coronavirus retinopathy.[5] Evidence to support the potential for a neurotropic pathogenesis in the white dot syndrome, Acute Posterior Placoid Pigment Epitheliopathy (APMPPE) has also recently been published.[6]

Whilst alternative autoimmune mechanisms leading to this appearance cannot be excluded, given the occurrence of this distinctive phenotypic appearance has been demonstrated in an animal model where the pathophysiological mechanism leading

to its formation (as a consequence of the direct neurotropic transmission of a virus to the outer retina) has been demonstrated,[4] and its clinical appearance in other viral associated retinopathies (with hypothesised neurotropic pathogenesis)[3] has been observed, the potential of a common pathophysiology accounting for the appearance in PIC lesions is a possibility which may provide a potential avenue for future research.

Figure 1.

A) Left image - Scanning laser ophthalmoscope fundus appearance of a 15-year female diagnosed with punctate inner choroidopathy. Greenline denotes the area of the adjacent optical coherence tomography (OCT) line scan. Right – OCT line scan through a retinal lesion demonstrating a focal outer retinal loss and V-shaped collapse of the overlying retinal structures.

B) Left image - Colour fundus photography of an Ebola retinal lesion. Right image - Corresponding OCT with an appearance resembling Figure 1A. Source: Steptoe et al[3] (CC-BY License).

C) Light micrograph of the non-inoculated eye, 6 days following the inoculation of herpes simplex virus type 1 into the contralateral anterior chamber of a mouse eye. Disruption of the outer nuclear layer with the collapse of nuclei into the photoreceptor layer (white arrow) identifies an early focus of HSV retinopathy. Ganglion cells overlying the focus of collapse have marginated chromatin, characteristic of HSV infection (black arrow) (x500). Source: Holland et al[4]

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