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Letter to the Editor

Cotton Wool Spots Should not be Regarded as Retinal Nerve Fibre Layer Infarcts

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Retinal cotton wool spots (CWSs) occur in a variety of disorders including systemic hypertension, diabetic retinopathy, stenosis of the carotid artery, central and branch retinal artery or vein occlusion, Purtscher´s traumatic retinal angiopathy, pancreatic diseases, and inflammatory retinal diseases, even AIDS. In a case of temporal arteritis recently reported in this journal [10], the retinal CWSs were described as "localized accumulations of axoplasmic debris within retinal ganglion cell axons" owing to "focal ischaemia from terminal arteriolar occlusion". Although this latter conception is the received wisdom in the literature generally and was attributed to McLeod in the article, it should be noted that McLeod has repeatedly emphasized that CWSs should not be automatically considered to be retinal microinfarts and he has provided an extensive critique to substantiate this view [5].

The dense white swelling of the retinal nerve fibre layer in a CWS is due to a local aggregation of distended axon terminals, each filled with mitochondria and other organelles (so-called "cytoid bodies"). Although CWSs often appear to be discrete fundus lesions, an equivalent ophthalmoscopic appearance is also seen along those edges of inner retinal infarcts that are crossed by ganglion cell axons. Based on this distribution of opaque marginal swelling, McLeod inferred that a CWS reflects obstruction of either orthograde or retrograde axoplasmic transport in the unmyelinated axons [2, 3].

This proposal was confirmed experimentally by injecting tritiated leucine into the vitreous at the same time as occluding branch retinal arterioles.(4,6) Label became concentrated in swollen axon-terminals on the peripheral aspect of the inner retinal infarcts but was absent from the axon terminals on the disc side of the infarcts. The accumulation of 3H-leucine and organelles thus reflected interruption of orthograde axoplasmic transport. However, when tritiated leucine was injected intravitreally prior to arteriolar occlusion (thus allowing label to be incorporated into proteins by the retinal ganglion cells and to be transported to the lateral geniculate body), 3H-leucine also accumulated in the axon terminals on the disc side of the infarcts. Concurrent obstruction of retrograde axonal flow was thus demonstrated. Since infarcted retina is phagocytosed much more quickly than axoplasmic debris, CWSs may persist as "boundary sentinels" on the peripheral aspect and/or on the disc side of inner retinal territories earlier manifesting clinical signs of infarction [5],

For terminal retinal arteriolar occlusion to give rise to a CWS, coexisting impairment of collateral flow owing to generalized retinal hypoperfusion or vasoconstriction must be inferred (because terminal arterioles are not end arterioles), as must combined obstruction of orthograde and retrograde axoplasmic transport [5]. If the arterial inflow to the entire inner retina is obstructed (causing grey oncotic swelling and a cherry red spot at the fovea), only retrograde transport obstruction in ganglion cell axons is manifested [3]. Pale swelling of the optic disc or a ring of white axoplasmic debris at the disc margin thus forms where the central retinal and posterior ciliary arterial circulations abut one another and intermingle to an extent in the optic nerve head. (The similar opaque swelling of the optic disc in arteritic ischaemic optic neuropathy results from posterior ciliary artery occlusion and axoplasmic debris accumulation from blockade of orthograde axoplasmic transport at the lamina cribrosa; here, the chalky white swelling or "CWS of the disc" is believed to be a sentinel of infarction in the retrolaminar optic nerve [3, 7].)

If the retinal circulation is only partially interrupted ("panretinal hypoperfusion"), the peripapillary inner retina remains viable and only the more peripheral retina shows features of oncotic necrosis. Evidence of an associated grey matter penumbra includes increased oxygen extraction (manifested as retinal venous cyanosis) and considerable functional recovery following early restoration of central arterial circulation [5, 8]. In such cases, the obstruction to retrograde axoplasmic transport is deferred from the disc into the retina, with formation of an annulus of polymorphous CWSs at the ischemic penumbral interface (beyond which the inner retina shows a modest degree of oncotic swelling and incomplete cherry red spot formation).

CWSs are said to occur in a significant proportion (perhaps one-third) of eyes affected by temporal arteritis,(1) but their pathogenesis is unclear. Because the inflammatory pathology of the arterial walls only affects ocular arteries in their extraocular course, the CWSs have been tentatively attributed to secondary microembolic occlusion of terminal retinal arterioles. [1]. However, in some cases of temporal arteritis the CWSs represent "penumbral sentinels" from panreti-

nal hypoperfusion and retrograde axoplasmic transport blockade, or "boundary sentinels" of inner retinal infarction from cilioretinal arterial occlusion and orthograde transport obstruction [7-9]. In such cases, therefore, intraocular axoplasmic transport obstruction and CWS formation can be attributed to extraocular arteritic occlusion without the need to infer secondary retinal embolisation.

The relative contributions of focal (embolic) ischaemia, panretinal hypoperfusion and cilioretinal infarction to retinal CWS formation in temporal arteritis is unknown. However, panretinal hypoperfusion appears to be the cause of the CWSs reported and illustrated in the recently published case given the associated clinical features [10]. Moreover, the fundus pathology may also modified by associated neuroprotective influences in temporal arteritis since occlusion of the orbital arteries is a gradually progressive process.

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