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COMMENT

PAMM—Punchy Acronyms May Mislead

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In numerous recent articles, including in *Eye*,[1] the discovery of 'paracentral acute middle maculopathy' (PAMM) has been inadvertently ascribed to Sarraf *et al*,[2] who reported six cases in 2013. The placoid, para-foveal, middle-retinal infarction identified by high-resolution optical coherence tomography (OCT) has been attributed to isolated 'ischaemia of the deep capillary plexus (DCP)' which has no correlate on fundus fluorescein angiography (FFA) but is thought to be amenable to detection by OCT angiography.[1] An analogy has been drawn between PAMM and another 'ischaemic microvasculopathy'—namely, retinal cotton-wool spot (CWS) formation—which is purported to result from focal 'ischaemia of the superficial capillary plexus (SCP)'. Furthermore, PAMM is said to be exhibited in some cases of central retinal artery occlusion (CRAO) and central vein occlusion (CRVO), just like CWS formation.

In reality, however, these views regarding PAMM threaten to draw a veil of confusion over retinal ischaemic pathophysiology comparable to that enshrouding CWS formation for the past half-century. Retinal CWSs do not represent nerve-fibre layer (NFL) infarcts following pre-capillary arteriolar occlusion and 'ischaemia of the SCP', nor is selective 'ischaemia of the DCP' likely to follow occlusion of even the smallest macular artery. These arteries and the pre-capillary arterioles arising are confined to the superficial inner retina (ie, NFL and ganglion-cell layers) and do not feed into specific capillary plexuses.

The characteristic *en face* topography of the middle-retinal infarction associated with partial CRAO was first illustrated nearly 40 years ago in the predecessor to the *Eye* journal, and was described as 'mild ischaemic swelling' with 'peri-arterial sparing'.[3] The delayed and retarded dye transit on FFA and the associated retinal venous hypoxaemia were felt to indicate exaggerated extraction of oxygen from the residual trickle of blood circulating through the inner retina ('misery perfusion'). Equally subtle fundoscopic signs were then reported in 2002/2003 in eyes with pan-retinal hypoperfusion from acute CRVO, and were labelled 'macular peri-venous whitening' (MPvW). The characteristic depth distribution of retinal infarction in MPvW and PAMM was eventually realised by Michel Paques' group in Paris.[4] They demonstrated segments of hyper-reflectivity and subsequent atrophy of the para-foveal middle retina on OCT, sparing the superficial inner retina, well ahead of the inauguration of the term 'PAMM'.[2]

There is every reason to believe that the pathophysiological basis of MPvW (and its focal version—PAMM) remains the same as that postulated in 1978. Misery perfusion implies disproportionate extraction of oxygen from the proximal (or arterial) part of the inner retinal circulation and passage of deoxygenated blood through its distal (or venous) part. The accelerated reduction in intravascular haemoglobin oxygen saturation results in the evolution of three oxygenation-based tissue micro-compartments within the macular inner retina ('normoxic', 'hypoxic', and 'anoxic'), the distribution of which varies according to the severity of ischaemia. Of note, in a recently-introduced severity grading system for such 'hypoperfusion maculopathy', the oxygenation status of the superficial inner retina determines the ranking, whether normoxia (grade 1), ischaemic hypoxia (grade 2), or ischaemic anoxia (grade 3).[5]

The peri-venous middle-retinal infarction seen in eyes with hypoperfusion maculopathy grades 1 and 2 illustrates the general principle that oxygen delivery to parenchymal cells is not confined to the capillary microcirculation but is dependent on the oxygen tension within the nearest blood vessel(s), whether artery, capillary, or vein. Thus, MPvW represents 'anoxic corner' formation at the distal end of Krogh tissue cylinders reflecting countercurrent flow through the interdigitating second-order arteries and veins that radiate towards the fovea.[5] The localisation of ischaemic anoxia and infarction to

the middle retina in MPvW and PAMM, sparing the superficial inner retina, does not indicate selective impairment of perfusion through the DCP. Rather, it reflects the DCP's 'subsidiarity' (ie, its late embryological development from the SCP by angiogenesis) and, consequently, a heightened vulnerability of middle-retinal neurons to more generalised ischaemia. That is to say, although the DCP is not strictly a 'venular' capillary bed under normal physiological conditions, it becomes increasingly so with progressive reductions in inner retinal perfusion because an increasing fraction of the available oxygen is extracted from the arteries, arterioles, and capillaries that occupy the superficial inner retina. Other contributory factors may include the relative hypermetabolism of the horizontal cells and plexiform layers supplied by the DCP, and potential oxygenation of the innermost inner retina from the vitreous.[5]

As mentioned earlier, the superficial inner retina overlying, and the middle-retinal tissues adjacent to, the middle-retinal infarction seen in MPvW and PAMM are not necessarily free from ischaemic abnormality despite their transparency on fundoscopy and their hyporeflectivity on OCT. Rather, they may constitute part of a hypoxic tissue micro-compartment (or 'ischaemic penumbra') that would require employment of a 'hypoxia marker' for detection and will likely recover its neural function on subsequent reperfusion.[5] As for the current scramble to be in the vanguard of discovery of 'deep capillary ischaemia' by OCT angiography, it should be noted that localised vascular attenuation may be the consequence, and not the cause, of the retinal parenchymal changes seen in PAMM, as also applies in the case of CWS formation.

Conflict of interest

The author declares no conflict of interest.

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