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LETTER

Letter to the editor: partial central retinal artery occlusion offers a unique insight into the ischemic penumbra

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Kurimoto and colleagues recently reported three cases of unilateral visual loss associated with striking ischemic changes in the posterior retina and impressive visual recovery following treatment.[1] The presenting signs included an indistinct foveal cherry-red spot and a circle of cotton-wool spots (CWSs) surrounding the optic disc. Fundus fluorescein angiography (FFA) revealed a marked delay in the arm-retina circulation time, together with "areas of occlusion of the retinal arterioles" that corresponded to the location of the CWSs.

The authors recognized that this was a variant of central retinal artery occlusion (CRAO), but they confessed to being unclear as to the processes underlying this distinctive clinical picture.[1] They surmised that the central retinal artery (CRA) had been incompletely obstructed and that multiple arterioles closer to the capillary network had also been occluded. Thus, the polymorphous CWSs were regarded as "retinal microinfarctions" involving the nerve-fiber layer (NFL), a view that is in line with widely received wisdom in this regard. If this was truly the case, however, simultaneous occlusions of a dozen or more arterioles of differing sizes must have contributed to the fundus appearance, which is unlikely. Kurimoto and colleagues will need to set aside some of the current orthodoxy in the field of ocular vascular occlusive disorders to appreciate the pathophysiological processes at play in their patients.

Clinical features of partial CRAO

In their epic textbook published in 1971,[2] Wise, Dollery, and Henkind allude to a relatively rare form of CRAO in which the degree of arterial closure is such that retinal cells "waver back and forth at critical survival and functional levels." The fundus signs include mild retinal haze together with scattered, more opaque "cotton-wool-like patches," and the retinal veins appear somewhat darker than usual. Regarding the clinical course, "the critical zone is so narrow that usually in a matter of several days there is … improvement in blood flow and resolution, with varying degrees of residual defect." Alternatively, the occlusion might progress, resulting in inner retinal infarction.[2]

The remarkable fundus appearance developing after such "partial CRAO" was first illustrated in 1978 as part of a detailed description of seven patients who attended Moorfields Eye Hospital during a 4-year period.[3,4] At the same time, a mechanistic theory was proposed that sought to explain all the clinical signs in terms of a solitary

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arterial occlusive event. The features of partial CRAO, as they were reported in 1978, are as follows.

1. Sudden onset of a relative or absolute central scotoma and other visual field loss, with reduction of visual acuity to between 6/12 and 6/36.
2. A heterogenous pattern of grey translucency in the macula (here referred to as "oncotic swelling"), resulting in a somewhat ill-defined cherry-red spot, but sparing the temporal parapapillary retina.
3. Large circumpapillary CWSs and smaller opaque deposits.
4. A markedly delayed dye transit through the inner retinal circulation on FFA (indicating generalised "panretinal hypoperfusion"), together with minor disruption of the blood–retinal barrier and dye masking corresponding to the location of the CWSs.
5. Retinal venous cyanosis (signifying increased O_2 extraction during hemoglobin's slow passage through the inner retina).
6. A relative afferent pupillary defect (RAPD).
7. A reduction in the electroretinographic b-wave.
8. An underlying diagnosis of systemic hypertension, arterial embolism, or giant-cell arteritis (GCA).
9. Reversal of some of the visual field loss and improvement in acuity within 2–3 weeks.
10. A variable degree of optic atrophy by 6 weeks post-CRAO and a persistent RAPD, both indicating an element of irreversible ischemic damage.[3,4]

The term "oncotic swelling" is here intended to include not only irreversible cell membrane failure (signifying anoxic inner retinal necrosis) but also a breakdown of ion and water homeostasis that remains reversible; this might be the result of a period of ischemic anoxia not exceeding the survival time of the retinal tissue, or more prolonged, but sublethal, ischemic hypoxia. In these several circumstances, osmotically obligated water enters affected cells and compromises inner retinal transparency to a variable extent.[5,6] Only in the perifoveal region, where the ganglion-cell layer is thickest, does this translucency approach frank opacity.

The vascular occlusion is presumed to entail either (1) incomplete closure of the main trunk of the CRA, or (2) complete closure of the CRA during its intraorbital course and presence of decidedly competent collaterals that probably anastomose with the CRA via the pia mater of the optic nerve.[7] The possibility that stenosis of an upstream artery (whether the ophthalmic or internal carotid) might give rise to the same, or a similar, fundus appearance has also been entertained.[2,5] On FFA, however, increased disparity in the timing of dye arrival in the CRA branches, compared with the choroid and optic disc vessels, suggests an occlusion along the course of the CRA with no interference with the posterior ciliary arterial (PCA) supply. This early filling disparity is all the more obvious if there is a cilioretinal artery present, with rapid filling of the capillaries within the cilioretinal arterial territory (as in figure 2 from Oji and McLeod's report).[4]

Peripapillary and periarterial sparing

After partial CRAO, tissue perfusion in the immediate vicinity of the optic disc, though much reduced, may nevertheless be sufficient to maintain tissue viability and transparency (so-called benign oligemia). This is because, provided some measure of circulation is continuing, the arterio-venous perfusion pressure across the retinal microcirculation will be greatest near the optic disc, which is also where arterio-venous circuits are shortest.[4,5] However, with increasing distance away from the disc, inner retinal perfusion will gradually fail, the tissue pO_2 profile will slope inexorably downward, and oncotic swelling of the hypoxic/anoxic retina will become apparent once water begins to enter the cells.

Relative to average pO_2 values in the macula, the pO_2 levels within the branches of the CRA will be considerably higher, and diffusion of O_2 across the walls of these vessels will spare the tissues immediately surrounding the arteries from oncotic swelling. The Krogh tissue cylinder model of O_2 diffusion into the parenchyma (where the O_2 is consumed) has been used to illustrate the physiological principles involved.[6] At this much-reduced blood flow rate, however, the radius of the cylinder of oxygenated tissue around the artery will taper dramatically along its length compared with normal circulatory conditions.

As with peripapillary and cilioretinal sparing, the periarterial sparing can be observed with the ophthalmoscope and this sparing was felt to account for the somewhat irregular pattern of macular translucency described in 1978.[4] Although not reported as such, periarterial sparing is readily discernible in the fundus photographs of two of Kurimoto et al's patients (cases 1 and 2).[1] Similar sparing is also a potential feature of panretinal hypoperfusion in eyes with so-called nonischemic central retinal vein occlusion (CRVO). In this instance, however, the subtle changes are usually given the designation "perivenular macular whitening," and are believed to involve the deeper inner retinal lamellae preferentially.[6,8,9]

In 1980, Hayreh and Weingeist reported a "Christmas tree pattern of normal-looking retina around arterioles" in the eye of a single animal (monkey 45) amongst 63 undergoing clamping of the CRA in the orbit.[10] The periarterial

sparing was observed after 90 minutes of CRAO, at which time-point the posterior retina in all the other animals studied showed uniform oncotic swelling and a cherry-red spot. In monkey 45, the arrival and transit of dye on FFA (undertaken prior to CRA unclamping after 102 minutes) was by far the most rapid of all the eyes studied; nevertheless, the time to complete filling of the retinal veins was all of 60 seconds. Evidently, the singular retinal appearance in monkey 45 reflected the incompleteness of the circulatory arrest that had been induced in this particular animal (whether due to less than effective CRA clamping or unusually competent pial collaterals).

The "Christmas tree pattern" revealed in monkey 45, and in the macular retina of patients with partial CRAO, shows that periarterial sparing takes place all the way down the retinal arterial tree to the "arteriae afferentes" of His;[1,4,6,10] these are the small arterial branches that come off medium-sized arteries at right angles and interdigitate with the venae efferentes.[11] These interdigitating vessels, and the precapillary arterioles, capillaries and postcapillary venules that connect them, constitute a series of "microvascular units" for the purpose of studying O_2 movement within the inner retina.[6] The transarterial O_2 diffusion underpinning periarterial sparing from oncotic swelling is likewise responsible for the evolution of the retinal periarterial capillary-free zone during embryonic development, as His discovered in 1880. The term "perivenular macular whitening" points to the fact that, by the time the red blood cells reach the venae efferentes, 100% of the O_2 that they were originally carrying has probably been extracted.

Blockage of retrograde axoplasmic transport

The other distinctive fundus feature after partial CRAO – a circumpapillary ring of CWSs – can also be attributed to sustained panretinal hypoperfusion resulting from a solitary (albeit incomplete) obstacle to blood flow through the retinal circulation.[3–6] To understand the genesis of these lesions, however, it should first be noted that, after complete CRAO, pale optic disc swelling or a narrow ring of NFL opacity at the edge of the disc will often develop within 24 hours of the occlusion.[12] These papillary signs can be attributed to obstruction of retrograde axoplasmic transportation within the optic nerve head at the prelaminar interface between the territories of the CRA and the PCAs, a proposition that has been supported experimentally.[13] Intra-axonal organelles, especially mitochondria, aggregate as a consequence of this "damming-up" process and cause incident light to be largely reflected, thus rendering the formerly transparent tissue opaque.

The modest amount of axoplasmic debris accumulating at the optic disc after complete CRAO is thought to reflect the relatively meager cargoes of mitochondria trafficking back and forth within myelinated segments of the retinal ganglion-cell axons.[14] Within unmyelinated intraocular segments of the same axons, however, an extraordinary number of mitochondria move to and fro.[15] It would appear, therefore, that organelle short-circuiting takes place by virtue of directional transport reversal (from orthograde to retrograde) in the prelaminar region such that only a small proportion of the mitochondria leaving the ganglion-cell somata take the long route to the lateral geniculate body before being transported back to the ganglion-cell layer.

Large volumes of axoplasmic debris accumulate in the peripapillary NFL as a result of retrograde transport obstruction following partial CRAO (since tissue occupying the near field of supply of the CRA is spared from ischemic damage), and this manifests clinically as circumpapillary CWSs.[3–6] The circular pattern of axoplasmic debris deposition within the NFL has been described as "annulate" to avoid any possible confusion with the "circinate" retinopathies wherein lipid exudates accumulate in the outer plexiform layer surrounding microaneurysms or other sources of plasma leakage.[5]

Interpreting the clinical signs requires a careful distinction to be made between tissue translucency and frank opacity on ophthalmoscopy. Translucency indicates water imbibition by cells and their processes (including axons) – "oncotic swelling" – whereas opacity signifies organelle aggregation within axon terminals. As noted, the exception to this rule is the oncotic swelling of ganglion cells in the vicinity of the fovea where these large cells are several cells thick. This semi-opacification is perhaps unsurprising given that the term "cytoid body" (the light microscopic depiction of axon terminals or Cajal's end bulbs in the NFL) refers to a structure of similar size and appearance to a ganglion-cell soma, including a "pseudonucleus" made up of whorls of mitochondrial membranes.

Variability in the size, shape, and distribution of CWSs among different eyes with partial CRAO is the norm, as is evident when the three cases reported by Kurimoto and colleagues are compared.[1] At first glance the CWSs may appear to be "scattered" after partial CRAO, but the dispersal of these lesions in the posterior retina conforms to a basic pattern that can be readily understood in terms of O_2 delivery to, and axoplasmic hold-up within, the NFL. The CRA branches

supplying the ganglion-cell axons are located within or immediately beneath the NFL and their geometry is largely dictated by NFL topography. Thus, the NFL is thickest in the superotemporal and inferotemporal peripapillary regions (because arcuate bundles of nerve fibers give the fovea a wide berth) and these regions also contain the greatest concentration of microvascular components, including an additional layer of capillaries (the radial peripapillary capillary net).[2] After partial CRAO, then:

1. The amount of axoplasmic debris deposited is greatest superotemporally and inferotemporally, while that on the nasal side is much less in volume and is located closer to the optic disc; indeed, in many cases, the axoplasm travels no further into the retina than the disc margin on the nasal side.[4] Thus, peripapillary sparing occurs on the temporal side of the disc for the most part, and the radial peripapillary capillaries are not specifically implicated in CWS formation – they simply supply the thickest part of the NFL which also harbors the greatest potential for axoplasmic debris accumulation.
2. As a result of periarterial sparing, axoplasmic debris is not deposited over the main CRA branches unless the artery is located beneath a particularly thick part of the NFL. However, CWSs are frequently seen overlying the retinal veins, which are hypoxemic.
3. Transarterial O_2 diffusion, by maintaining axonal flow within oxygenated cylinders of NFL tissue surrounding the vessels, causes retrograde axonal transport obstruction to be "deferred" along the course of the CRA branches as they run away from the optic disc.[4] Deposition of axoplasmic debris then takes place where the trajectory of the axon bundles veers away from the route of these vessels. Typically, a CWS develops in the crook of an arterial bifurcation (as seen in case 1 from Kurimoto and colleagues' series).[1]
4. Minuscule axoplasmic deposits may also be discernible alongside the major vascular arcades, even as far away from the optic disc as the temporal macular region. Here, they may reflect obstruction of continuing axoplasmic transportation in a single axon bundle. Case 2 from Kurimoto and colleagues' series is an excellent example.[1]

Deposition of opaque axoplasmic material may thus be apparent within an area of oncotic swelling (rather than marking the boundary of ischemia), a phenomenon called "embedding."[5] Embedding of CWSs can be observed in several other circumstances where inner retinal infarction is incomplete, for example, in some cases of CRVO with cilioretinal infarction.[8,14]

CWSs as sentinels of an ischemic penumbra

As demonstrated in cases 1 and 2 from Kurimoto et al's case series,[1] some of the circumpapillary CWSs may be very large, with a "width" well in excess of 300 μm; (for the absence of doubt, the width of a CWS refers to its linear dimension along the axis of the axons). In practice, 300 μm is the maximum width of axoplasmic debris seen bordering a retinal infarct, but the width of the CWSs associated with partial CRAO may be upwards of 1500 μm.[5]

This suggests that the boundary between viable retina and necrotic retina is not well delineated. As with the ischemic lesions developing after cerebrovascular occlusions, the unaffected retinal tissues and anoxic tissues are separated by an intermediate zone of progressively increasing hypoxia – the "ischemic penumbra."[16,17] As axoplasmic transportation (which depends on local O_2 delivery along the course of the axons) gradually fails, therefore, axoplasmic debris is deposited over a greater meridional distance (and presumably at varying depths) within the NFL.[5]

The circumpapillary CWSs evolving after partial CRAO are thus "sentinels" of this hypoxic penumbral zone in the retina. As well as being unusually wide, the CWSs tend not to show "striations" or have a "zig-zag" internal structure; these are commonly recognizable features of "boundary sentinels" (the accumulations of axoplasmic debris where ganglion-cell axons cross the peripheral and/or disc-side margins of retinal infarcts).[5,12,18,19] Along such margins, or wherever the interface between normal NFL and damaged NFL is abrupt, Cajal's end bulbs become very tightly packed inside the glial compartments formed by linear arrays of Muller cells. As a result, the mass of swollen axon terminals (each up to ten times the axon's normal diameter) will compress the retinal lamellae underlying the NFL and will bulge into the vitreous cavity.[5] This retinal "compartment syndrome" is not a feature of penumbral sentinels or is less of a feature of these overly wide CWSs.

Absent dye filling within CWSs

The absence of fluorescein dye from the location of the circumpapillary CWSs, as described and illustrated by Kurimoto and colleagues,[1] is primarily due to masking of the background fluorescence by the NFL opacification.[4] There might also be an element of focal microcirculatory nonperfusion within CWSs,[20,21] but such capillary closure appears to result from the retinal "compartment syndrome" discussed above.[5,22] That is to say, a rise in tissue pressure (from massive axonal swelling within the confines of relatively unyielding

Muller cell partitions) squeezes the capillaries shut, and they may remain closed thereafter despite restoration of tissue perfusion elsewhere and removal of Cajal's end bulbs by phagocytosis.

A similar "tissue pressure" mechanism is believed to account for the perifoveal vascular closure that often remains evident on FFA when the retinal circulation otherwise reopens some time after complete CRAO.[21,23] In this instance, the tissue swelling derives from oncotic necrosis of the ganglion-cell layer which, as noted, is several cells thick at this location. Although arterioles abutting the area of capillary closure on FFA are blunted, this obviously is not the result of multiple discrete occlusions of individual vessels. By the same token, where focal capillary closure accompanies CWS formation, it is almost certainly the consequence, not the cause, of the CWS lesion. It represents "secondary amplification" of the pathological changes within CWSs that derive from an altogether separate vascular occlusive event.

As noted, the extent to which Cajal's end bulbs are packed together while forming penumbral sentinels is unlikely to result in focal capillary closure, so such closure will seldom contribute to the FFA signs at the location of CWSs. The fact that the localized absence of dye corresponds very precisely with the site and shape of the CWSs indicates that this is simply a consequence of dye masking.[4] It does not signify that closure of the arterioles feeding these "areas of occluded capillaries" is responsible for CWS formation, as Kurimoto and colleagues suggested;[1] quite the contrary. An ischemic lesion of over 600 μm width, resulting from occlusion of a branch retinal artery, would be expected to take the form of a "bracketed infarct";[5] that is to say, an area of grey oncotic swelling sandwiched between opaque axoplasmic deposits of 2–300 μm width, as illustrated elsewhere.[24]

Instead of a scattering of "NFL infarcts" resulting from multiple retinal arteriolar occlusions, therefore, it is the combined influence of peripapillary, periarterial and, in some eyes, cilioretinal sparing from the effects of severe oligemia throughout the CRA territory that yields the fascinating clinical picture of axoplasmic transport obstruction after partial CRAO.[3–6] The developing fundus changes can be readily understood – but only provided they are viewed while keeping axonal flow in mind and eschewing overly narrow thinking in terms of "retinal microinfarction."

As noted earlier, the precise configuration of the CWSs resulting from partial CRAO differs in every patient, unlike the instantly recognizable oncotic swelling and cherry-red spot formation after complete CRAO. The changes developing after partial CRAO depend on: (1) the degree of panretinal hypoperfusion, (2) the specific anatomical arrangement of the CRA branches within the affected eye, and (3) any recent history of sublethal ischemic or hypoxic events that may result in "ischemic preconditioning" whereby tissue susceptibility to renewed ischemic challenges is decreased and the damaging effects attenuated.[5] The third patient from Kurimoto et al's series had such a prehistory and relatively inconspicuous fundus signs, so this may well be a case in point.[1] Thus, the variation in the clinical picture, and the relative rarity of this critical degree of retinal hypoperfusion, may explain why partial CRAO tends not to be recognized as such.

A window on the ischemic penumbra

Sustained oligemia to a degree falling just short of that producing ischemic anoxia and cell death will generate a variety of physiological responses intended to ensure that the affected tissues remain viable. The immediate "vascular response" is one of autoregulatory vasodilatation that minimizes flow resistance in the affected microcirculation, prolongs the transit time and thus allows the amount of O_2 extracted from the blood to increase. After partial CRAO, the transit time of dye through the retinal circulation on FFA is greatly extended and retinal venous hypoxemia attests to the increased "O_2 extraction fraction" (OEF).[4–6] Case 2 from Kurimoto et al's series demonstrates the retinal venous cyanosis particularly well.[1]

Once the maximum OEF (100%) has been attained, the reduced supply of O_2 is such that anaerobic metabolism is called into play, and other "metabolic responses" are required in order to assure tissue viability. After a period of temporary shutdown of all but vegetative cell functions (in the case of neurons this is called "electrical silence")[16], conservation of the residual energy supply requires an ongoing reduction in tissue O_2 consumption ("hypometabolism").

The restoration and maintenance of energy homeostasis (ie, the process of matching O_2 utilization to O_2 delivery) is achieved through activation of hypoxia-inducible factor-1 (HIF-1) which senses, and adapts affected cells to, the low pO_2 levels.[6] The O_2 requirements of the hypoxic tissues diminish through suppression of protein synthesis; for example, the density of energy-expensive ion pumps in the cell membranes may be greatly reduced. However, various proteins with neuroprotective and angiogenic properties, such as vascular endothelial growth factor (VEGF), are overexpressed. In time, these molecules will stimulate arteriogenesis (dilatation and remodelling of collateral arterial conduits), venogenesis (collateral vein formation in the case of venous

occlusions), or angiogenesis (new vessel proliferation from pre-existing vessels, mostly veins).[11,25]

A new "steady state" is thus arrived at whereby the hypoxia-tolerant cells constituting the ischemic penumbra may survive indefinitely provided there is no further deterioration (or restoration) of tissue perfusion or an imposed increase in metabolic load. The range of pO_2 values that defines this zone of hypoxia tolerance is very narrow, but the volume of penumbral tissue generated is potentially quite extensive. This is because the induced hypometabolism reduces the slope of the tissue pO_2 profile (since less O_2 is being consumed), so O_2 will diffuse over longer distances before the pO_2 threshold for irreversible anoxic damage is reached.[6]

After partial CRAO, the translucency of the macular retina resulting from water imbibition in the face of profound oligemia is not uniform. As blood enters the arteriae afferentes, the "O_2 head pressure" (arterial pO_2) is sufficient to maintain the viability and transparency of periarterial cells, but all the available O_2 will have been extracted by the time the blood enters the venae efferentes. The "whitening" (actually oncotic swelling) around these small macular veins probably encompasses both reversible and irreversible disruption of ion and water homeostasis from severe hypoxemia at this point within each microvascular unit. Once the blood reaches the larger veins, however, it will mix with blood from elsewhere with a somewhat higher O_2 saturation.

Uncertainty surrounds the ophthalmoscopic manifestation of the ischemic penumbra – is penumbral tissue transparent or translucent? The perivenular macular whitening seen soon after the onset of CRVO may be informative in this respect; the subtle oncotic swelling surrounding the small macular veins tends to recede after 2 or 3 days despite continuance, or even worsening, of panretinal hypoperfusion.[9,14] This suggests that, once hypoxia tolerance has been induced genomically through HIF-1 action, the hypometabolic retinal tissue may begin to regain its transparency and improve its function.

On the other hand, long-term paracentral micro-scotomata often attest to an irreversible necrotic component of the perivenular macular whitening associated with such "oligemic CRVO."[14] A much larger number of ganglion-cells are undoubtedly lost as a result of partial CRAO (either from oncotic ganglion-cell necrosis or loss secondary to disruption of ganglion-cell axons). Although panretinal hypoperfusion implies an ischemic assault on the inner retina generally, with consequent incomplete optic atrophy, this atrophy isn't necessarily uniform given that NFL "grooves" sometimes appear. These may correspond to the previous location of major accumulations of axoplasmic debris, as illustrated in figure 1 from Kurimoto et al's article,[1] and may represent "secondary amplification" of the CWS pathology. As revealed by histopathological studies, however, long-term *survival* of certain ganglion-cell axons within ischemic retina often relates to their location in a "mantle" around arteries ("periarterial sparing") or immediately beneath the internal limiting membrane of the retina ("vitreo-retinal sparing").[5]

Choroido-retinal sparing and the penumbra obscura

The topography of the ischemic penumbra developing after partial CRAO is further complicated by the fact that the PCA supply to the outer retina is capable of maintaining the viability of the full thickness of the peripheral retina.[10,26] This "choroido-retinal sparing" reflects the gradual reduction in the density of rod photoreceptors with increasing eccentricity from the fovea,[27] when set against the relatively uniform O_2 head pressure throughout the choroid (courtesy of a very low OEF and arteriovenous O_2 shunting).[6]

While cone photoreceptors dominate the foveal and immediate perifoveal region, the highest density of rods is to be found in the "rod ring," an elliptical zone around the fovea at the eccentricity of the optic disc (ie, somewhere between 10° and 20° eccentricity from the fovea). A 50% fall in rod density from this maximum value is observed at approximately 50° eccentricity from the fovea.[27] Beyond a certain distance from the fovea, therefore, choroid-derived O_2 will penetrate the "metabolic O_2 barrier" represented by the energy-expensive photoreceptors and will begin to provide an alternative energy resource for the inner retina after CRAO (whether after partial or complete CRAO).[6] This inner retinal oxygenation by the choroid will then progressively increase with increasing eccentricity until the full thickness of the retina is spared from oncotic necrosis.

Courtesy of the pO_2 gradients arising within the inner retina as a result of choroido-retinal sparing, an annular mid-peripheral ischemic penumbra can be confidently predicted.[6] It will comprise an elliptical zone of hypoxic inner retinal tissue interposed between (1) the area of inner retina centered on the fovea wherein choroid-derived O_2 is excluded (especially at night) because the O_2 is completely consumed by the photoreceptor inner segments and, (2) the area of thin peripheral retina wherein the choroid is capable of oxygenating the entire thickness of the inner, as well as the outer, retina. This annular penumbra is located at the outer limit of oncotic swelling in the posterior pole after CRAO. Unlike the macular penumbra with its axoplasmic

sentinels and heterogenous oncotic swelling, it cannot be distinguished ophthalmoscopically (hence the term "penumbra obscura").

The ischemic penumbra evolving after partial CRAO thus has two components – a homogenous annular penumbra obscura in the mid-periphery and a heterogenous macular penumbra. Given that the natural history of partial CRAO is generally one of early circulatory reinstatement (and HIF-1 downregulation), angiogenesis is not a threat. After complete CRAO, however, the penumbral component of the pathology will solely comprise the penumbra obscura. Should the CRA fail to be recanalized, then cilioretinal arteriogenesis may be induced, either within the optic nerve head or on the pia mater of the nerve if the site of CRAO is in the orbit; cilioretinal optic disc collaterals have been reported to develop in 18% of eyes with complete CRAO.[28] In the event that the CRA circulation fails to be reperfused by CRA recanalization or by collateral arterial flow, however, angiogenic sequelae may then arise reflecting the persistence of the penumbra obscura.[6] According to one prospective study, rubeosis iridis is the fate of 15%–20% of eyes with CRAO,[29] particularly those with "extreme prolongation of the arteriovenous transit time" on FFA.[30]

The "ischemic penumbra" is thus an appropriate modern-day expression denoting the "hypoxic extravascular retinal tissue" that secretes a "vessel growth-promoting factor" after retinal vascular occlusions, as Michaelson deduced over 60 years ago.[11,31] Traditionally, a neovascular response has been thought unlikely after CRAO (because necrotic inner retina is incapable of secreting VEGF), and this view still prevails in some quarters. In theory at least, combined CRAO and PCA occlusion, as seen most frequently in GCA, will affect the location and extent of the penumbra obscura.

Proof of an annular midperipheral penumbra arising as a consequence of choroido-retinal sparing requires study of an eye with CRAO that was enucleated for rubeotic glaucoma. Alternatively, experimental CRA clamping maintained for >2 days before euthanizing would allow time for HIF-1 induction. Enduring penumbral tissue could then be identified using, for example, hypoxia tracers such as fluoromisonidazole[32] and/or in situ hybridization to locate sites of VEGF synthesis.[33] An in vivo indicator of a retinal ischemic penumbra, perhaps a fluorescent tagged hypoxia marker, would be very helpful clinically, for example in targeting scatter laser photocoagulation to the ischemic penumbra rather than necrotic or well-oxygenated retina.

After complete CRAO, the inner retinal infarct in the posterior pole and the putative annular midperipheral penumbra have the same spatial relationship to one another as the brain infarct and surrounding cortical ischemic penumbra evolving after occlusion of the middle cerebral artery (MCA). The central "core" of infarction after MCA occlusion includes the territory of end-arterial branches of the MCA that supply the deep nuclei of the cerebral hemisphere; these tissues cannot survive more than 1–2 hours of ischemic anoxia.

However, blood flow derived from the anterior and/or posterior cerebral arteries, delivered via leptomeningeal (ie, pial) arterial anastomoses, provides a collateral supply to the MCA territory in the cerebral cortex. Marginal perfusion of the cortical tissue immediately surrounding the infarct core then results in a contiguous ischemic penumbra.[16,17] The analogy goes much deeper than the merely topographic, however, because the choroid is the ocular equivalent of the pia-arachnoid layer covering the brain; and, like the MCA, the CRA within the retina has a proximal end-arterial component and a distal component that does not meet the criteria for an end-artery by virtue of choroido-retinal sparing.

Reinstatement of the retinal circulation

As demonstrated by cases 2 and 3 from Kurimoto et al's series,[1] reperfusion of the CRA territory is accompanied by an increase in venous hemoglobin O_2 saturation; the cyanotic veins resume their former appearance which reflects an OEF of 50% or so. Typically, signs of oncotic swelling fade before the axoplasmic debris is phagocytosed.[5] In consequence, the circumpapillary CWSs will appear to be "isolated" for some weeks before they eventually disappear (as is evident when figure 2A and 2E in Kurimoto et al's report are compared).[1] Recovery of retinal transparency in areas of oncotic swelling may involve both phagocytosis of necrotic material and re-establishment of ion and water homeostasis within surviving cells.

As already noted, there is anecdotal evidence that HIF-1 action per se may improve visual function as hypoxia tolerance is being established. However, it is generally acknowledged that restoration of CRA circulation is a prerequisite for significant visual recovery after CRAO. Reversal of hypoxia within penumbral retinal tissue is the mechanism by which most of that recovery phase of the natural history of the CRAO will take place, albeit there is some evidence that this visual recovery capability is relatively short-lived, perhaps a matter of a few days or a couple of weeks.[23]

After partial CRAO, the macular retina comprises a complex mix of adequately oxygenated, penumbral and necrotic tissue with remarkable retention of central vision and capability for reversal of visual loss. Substantial improvement in vision

was reported in the 1978 case series, and this was confirmed by Kurimoto and colleagues in their recent article.[1,3,4] In the author's experience, however, circulatory restitution occurs spontaneously, so the treatment regimens administered to their patients by Kurimoto and colleagues cannot be assumed to have contributed to CRA reperfusion or to visual gain. A modicum of visual functional recovery may also accompany restoration of inner retinal perfusion after complete CRAO lasting well in excess of the survival time of the inner retina ("the idling retina").[34] Of more significance to patients with little or no potential for visual recovery, however, is the freedom that CRA reperfusion grants from the threat of intraocular neovascularization (through reversal of HIF-1 induction).

Therapeutic rationale in CRAO

The clinical course of partial CRAO reveals a fundamental difference between the ischemic penumbra developing in the retina and that evolving within the cerebral cortex. After cerebrovascular occlusions (both in patients and experimentally), the initially viable penumbral tissue begins to "self-destruct" within a few hours of the arterial occlusion and becomes progressively (if not entirely) incorporated into the central core of infarction thereby.

This second phase of damage is thought to be due to tissue hypermetabolism induced by waves of membrane depolarization and repolarization, resulting in apoptotic cell death starting near the edge of the infarct core. As such, the cerebral ischemic penumbra is regarded as a "dynamic region that undergoes change in both time and space."[35] The penumbral conversion to umbra (infarction) is accompanied by a reduction in the OEF because dead tissue does not extract O_2 from the blood (or, to be pedantic, the gentle slope of the pO_2 profile across necrotic tissue is determined solely by Krogh's diffusion coefficient).[6]

No such penumbral transformation, or a much reduced version of it, occurs within the retinal penumbra unless perfusion deteriorates further.[2] After partial CRAO, the fundus signs and visual deficit often persist largely unaltered for several days, and no change in the cyanosis within the retinal veins is seen until the circulation is reinstated (at which point the OEF decreases).[4] The clinical course reported by Kurimoto and colleagues is in keeping with these observations,[1] as is the long-term persistence of penumbral tissue after CRVO (as demonstrated by in situ hybridization for VEGF message). Thus, the enduring retinal penumbra retains its angiogenic, arteriogenic and venogenic potential.

The difference in penumbral behavior between brain and retina in the immediate aftermath of a vascular occlusion probably reflects the reduced volume and compactness of the affected retina compared with cerebral cortex, and better means of dealing with electrolyte overload deriving from an adjacent infarct.[6] After all, the retinal ischemic penumbra is essentially two-dimensional whereas its cerebral counterpart is three-dimensional. Emergency therapy to re-establish the cerebral circulation (such as intravenous tissue-type plasminogen activator) is directed at "salvaging" penumbral tissue that will otherwise undergo conversion to infarction within a matter of hours. Irreversible anoxic damage in the "core" is taken as read.

Therapeutic CRA recanalization, say using local intra-arterial fibrinolysis, is primarily directed toward restoring inner retinal perfusion within the survival time of the tissue; that is to say, retinal tissue is to be rescued from the immediate danger of oncotic necrosis (as distinct from salvaging the penumbra). The retinal survival time is a somewhat unknown quantity, however, as it depends not only on the inherent capability of the tissue to reverse the various processes along the oncotic pathway to necrosis,[10] but also on the degree of oligemia and whether or not HIF-1 has already been activated (and hypometabolism and neuroprotection induced) by recent sublethal ischemic or hypoxic events.

If the survival time of retinal tissues rendered anoxic by severe oligemia has already been exceeded, expediting penumbral reversal by fibrinolytic treatment is unlikely to confer an advantage vision-wise over that deriving from spontaneous reinstatement of the CRA circulation, provided this occurs within a week or so. A meta-analysis of the results of intra-arterial fibrinolysis for CRAO, performed in this department 11 years ago, came to the conclusion that such interventions had not been shown to be useful.[36] As noted earlier, however, CRA recanalization grants the eye freedom from the risk of rubeosis iridis irrespective of any change in vision. Whether this potential benefit could possibly justify intervention depends on whether or not the attempted fibrinolysis results in CRA recanalization in a significant proportion of eyes in which CRA reperfusion (by recanalization or arteriogenesis) was not going to happen anyway within a few weeks of the occlusion. Watchful waiting is recommended.

Classification of CRAOs

Eyes with CRAO can be classified according to the following.

1. The etiology (embolic, thrombotic, arteritic) where this can be determined; this factor has a major influence on the likely duration of CRAO and the possibility of combined CRAO and PCA occlusion.

2. The site of the occlusion, whether at the CRA's origin from the ophthalmic artery, its site of penetration of the dura mater of the optic nerve, at the lamina cribrosa or at the CRA's first bifurcation on the optic disc; this will have a profound influence on the potential for arterial collateral formation,[7] but in practice the occlusion site may be difficult to determine.
3. The presence or absence of inner retinal territories of variable size that connect with the optic disc (usually temporally) and are supplied by one or more cilioretinal arteries branching from the PCAs within the orbit or in the choroid; this aspect is relatively easy to assess both clinically and on FFA. Where cilioretinal sparing involves the maculopapillary bundle and/or the fovea, this can profoundly influence the extent of visual field retention from the outset of CRAO and/or recovery of vision thereafter. As well as the local effect in preserving the territory of the cilioretinal artery, it may foster neural connectivity between the peripheral retina and the optic disc despite macular infarction.
4. The severity of oligemia within the CRA territory, which depends on the degree of CRA closure and the contribution of arterial collaterals. Simple clinical assessment can reveal cattle-trucking (signifying complete circulatory stasis), a Christmas tree pattern of periarterial sparing from oncotic swelling (indicating profound oligemia), and retinal venous cyanosis (demonstrating an increased OEF and survival of hypoxic tissue within the perfused area). Delayed arrival of dye in the inner retina, and a prolonged dye transit time, are useful FFA indices of oligemia, albeit they can be somewhat difficult to quantitate; these parameters are also subject to overestimation because the patient's systemic arterial blood pressure may drop during the actual performance of FFA.
5. The duration of occlusion, based largely on the patient's recollections of the time of onset of amaurosis (or first realization of visual loss) and, if applicable, the time interval before sight improved or recovered. However, there may be a considerable delay between restoration of CRA circulation and visual recovery.
6. The signs of inner retinal ischemia, including the degree and distribution of oncotic swelling (always absent from the peripheral retina and fovea provided the PCA supply is intact), and the amount and distribution of axoplasmic debris accumulating as a result of retrograde transport obstruction. Accumulations of axoplasm at the optic disc usually accompany complete CRAO unless there is associated anterior ischemic optic neuropathy (AION),[12] whereas circumpapillary CWSs result from partial CRAO.

In their quest for an explanation for the fundus picture they observed in their three patients, Kurimoto and colleagues sought guidance from a seemingly authoritative source, but will have found it wanting. Hayreh and Zimmerman had taken a pragmatic approach to categorizing clinical CRAO subtypes when reporting on 260 eyes with symptoms and signs of CRAO.[23,28] In effect, they constructed a short algorithm in which eyes with CRAO secondary to GCA were considered separately (13 eyes), as were those with significant cilioretinal sparing (35 eyes). This was because these factors were felt likely to dominate the outcome (as was subsequently confirmed).

The remaining 212 eyes were then split according to the state of retinal perfusion (informed by FFA) at the time of initial presentation some hours, days or weeks after the acute amaurosis. Two "distinct categories" of CRAO were created on the basis of this initial FFA study, 1) eyes with absolute or very severe circulatory stasis, and 2) those in which the CRA circulation had returned to normal at some point between the onset of CRAO and the performance of FFA. Thus, there was no intermediate FFA category in the Iowa CRAO classification that was equivalent to the severity of oligemia that Kurimoto and colleagues had discovered in their patients while making the correct diagnosis of partial CRAO.[1]

The 41 eyes in which the CRA circulation was fully restored were deemed to have "transient CRAO" according to the Iowa classification, and the duration of CRAO in these eyes was said to vary from "several minutes to many hours."[23] How this period of CRA closure had been determined, and how a CRAO lasting only a few minutes could result in irreversible ischemic damage, was not disclosed. Furthermore, the use of the word "transient" in this context was unfortunate because, by convention, this term is taken to mean rapid onset and complete reversibility of all clinical signs and symptoms (as in "transient ischemic attack").

Those 171 eyes still manifesting absolute or very severe circulatory stasis at presentation were regarded as having a "permanent CRAO."[23,28] No follow-up FFA studies were performed, but spontaneous restoration of the retinal circulation was to be expected sooner rather than later in a sizeable proportion of these eyes.[7] Had such a patient presented for FFA study just after, or even long after, this restitution of CRA circulation, the eye would presumably have fallen into the category of "transient CRAO"; this notwithstanding a duration of CRAO measured in days or weeks rather than minutes or hours. The fact that eyes with "permanent" CRAO regularly go on to become examples of "transient

CRAO" strongly suggests that the terminology used in the Iowa algorithm is inappropriate.

Two "totally different" appearances of the fundus were also noted on presentation in the 212 eyes. Most of the eyes had the "classic signs" of CRAO, specifically a cherry-red spot at the fovea and, frequently (but not invariably – for reasons unexplained), diffuse oncotic swelling in the posterior pole, especially around the fovea.[28] Eyes with this fundus picture included all those with "permanent CRAO" and some of the eyes with "transient CRAO"; the duration of CRAO in all these eyes presumably exceeded the survival time of the inner retina.

Other eyes with restored CRA circulation manifested "multiple scattered patches of retinal opacity (or infarction) all over the posterior pole with or without intervening retina showing whitening or even a faint cherry red spot."[23,28] This description will have resonated with Kurimoto and colleagues. The number of eyes with these features was not disclosed, however, although CWSs were reported in three of the 41 eyes with "transient CRAO" (as well as in five eyes with "permanent CRAO"). Thus, the prevalence of "transient CRAO" with the non-classic CRAO picture (ie, "multiple scattered patches of retinal opacity") may have been as low as three out of 260 eyes (1.1%) overall.

How this clinical picture of "multiple scattered patches" came about following "transient CRAO" was not made clear. Although the "classic" CRAO picture was consistently induced experimentally after 20 minutes of CRA clamping, clamping the CRA for less than 20 minutes had the following outcome as reported in the clinical morphology paper – "multiple retinal opacities, similar to CWSs, were the only finding in the posterior pole."[28] The time taken for reversal of these changes after such "short-term transient CRAO" was not disclosed, but must have been less than the 5 hours taken for full ophthalmoscopic resolution (and no residual damage on histology) after 90 minutes of CRA clamping. Clearly, these were all truly "transient" ischemic events with rapid and complete recovery of ion and water homeostasis. There can be no justification, therefore, for carrying over this "short-term transient CRAO" picture of "multiple retinal opacities" into the clinical sphere in terms of "transient CRAO" with its inherent irreversible tissue damage.

The first published illustration of "multiple scattered patches of retinal opacity," thought to reflect "transient CRAO," appeared recently.[21] The photograph (figure 19 in Hayreh[21]) shows several of the classic features of "partial CRAO," including circumpapillary CWSs, periarterial sparing from oncotic swelling in the macula and retinal venous cyanosis. Moreover the figure legend mentions a "slightly sluggish" retinal circulation. Thus, the three eyes with "transient CRAO" and CWSs in the fundus[23,28] were almost certainly examples of "partial CRAO." Perhaps the CRA circulation had already improved from an intermediate magnitude of panretinal hypoperfusion in these patients, thus explaining their categorization in the "transient CRAO" group.

The utility of lumping together (in the "transient CRAO" category) eyes with partial CRAO and those with complete CRAO but prior restoration of CRA circulation is highly questionable. The three cases reported by Kurimoto and colleagues[1] underscore the fact that partial CRAO is a well-defined clinical entity that surely merits being recognized in its own right. This is not least because the clinical features of partial CRAO can be appreciated using ophthalmoscopy alone, and its course is characteristic (including the prospect of considerable visual recovery). The favorable outcome of partial CRAO may be equivalent to that seen after complete CRAO with a large area of cilioretinal sparing.

Annulate retinopathy in giant-cell arteritis

One of the seven patients from the original 1978 case series had partial CRAO and outer retinal infarction related to GCA.[3,4,6] This has a significant bearing on the cases of partial CRAO reported by Kurimoto and colleagues.[1] Firstly, the CRA (and the PCAs) are only directly affected by this inflammatory vascular pathology during their course within the orbit (and not within the eye); only the extraocular component of the CRA is truly an artery, its intraocular branches being "arterioles" when considered within the context of the cardiovascular system generally. The association of the partial CRAO picture with GCA supports the hypothesis that the fundus signs derive from occlusion of the main trunk of the CRA and not from multiple occlusions of distal branches within the retina.[4,5] The counter argument is that the CWSs may be due to platelet emboli forming within upstream extraocular vessels and occluding the terminal retinal arterioles downstream. However, this assumes that terminal arteriolar occlusion will indeed result in CWS formation, which is highly questionable.[5]

Second, whether associated with partial CRAO or with complete CRAO, signs of choroidal perfusion delay on FFA should alert the ophthalmologist to the possibility of GCA, especially given the catastrophic potential implications of missing this diagnosis.[21,23,28] In cases 1 and 3 from Kurimoto et al's series,[1] FFA evidence of medial PCA involvement was discovered, with delayed filling of the nasal choroid

and the nasal half of the optic disc. One could therefore argue that a more concerted approach to excluding GCA was indicated in these patients. There was no specific reference to GCA in Kurimoto et al's report (perhaps reflecting the low prevalence of GCA in Japan), and it appears the pulsed steroid treatment regime was not given with this particular diagnosis in mind.

Third, the clinical picture in cases 1 and 3 was considered to represent partial CRAO combined with AION.[1] This conclusion rested in part on an incorrect assumption that central visual field loss and an RAPD cannot be explained by partial CRAO alone. This misapprehension apparently arose because, in case 2, no evidence of PCA involvement was discovered on FFA (and therefore no AION was assumed), and no RAPD was elicited. However, it is impossible to envisage an eye with partial CRAO and no afferent defect. Either the swinging flashlight test was not undertaken properly or the patient had a pre-existing RAPD in the fellow eye.

Eyes with FFA evidence of involvement of both the CRA and a main PCA may have an occlusion (almost always arteritic) involving the joint stem of these vessels from the ophthalmic artery.[21,23] In seeking to determine whether or not both CRAO and AION are present in such eyes, it should be noted that the principal clinical manifestation of AION secondary to PCA occlusion is massive prelaminar axoplasm accumulation (ie, a "cotton-wool spot of the optic disc"). This reflects continuing orthograde axoplasmic transportation in the territory of the CRA and its blockage at the lamina cribrosa proximal to retrolaminar optic nerve infarction.[3,37] Since retinal ischemia attenuates the optic disc manifestations of AION, and pale disc swelling occurs after CRAO alone,[12] any disc changes must be interpreted with caution. Describing arteritic AION in terms of "acute ischemia … of the optic nerve head"[23] does not do justice to the (retrolaminar) location of optic nerve infarction in such cases.

Conclusion

Since the mid-1970s, the ischemic penumbra has been one of the most important concepts in neurology,[16,17] and it also figures very highly on the list of physiological principles underpinning cardiology. However, many of the precepts involved have been known to ophthalmology since Michaelson's studies in the 1940s,[11,31] though these have tended to surround the long-term angiogenic potential of penumbral tissue as opposed to the facility for visual functional recovery after timely penumbral reperfusion.

In 1971, Wise, Dollery, and Henkind[2] explained their thinking about the vaso-occlusive retinopathies in the following terms. After retinal capillary or vein occlusion, "involved retinal cells become hypoxic but not necrotic," and such critically hypoxic retinal cells have the capability to elaborate a vasoproliferative stimulus. However, prompt recanalization of the occluded vein or development of a collateral circulation will restore tissue oxygenation and nutrition, so there will be no vasoproliferative response. After acute retinal arterial occlusion, "cell death prevents the elaboration of a vasoformative stimulus," so no neovascularisation ensues. However, if arterial inflow to the eye slowly diminishes, as in pulseless disease, "some retinal cells die but others remain viable and sufficiently hypoxic to produce a vasoformative stimulant."[2]

Forty years on, and several stumbling blocks remain that jeopardize a conceptual synthesis encompassing both the visual functional outcome of CRAO and its vasoformative sequelae (whether arteriogenic or angiogenic).

1. Foremost amongst these is the unwavering view that complete CRAO results in necrosis throughout the entire inner retina (provided, that is, the duration of occlusion exceeds the survival time of the retinal tissues).[21] This is at odds with the century-old demonstration of choroido-retinal sparing in the peripheral retina after CRAO.[10,26] The development of a mid-peripheral annulus of surviving hypoxic tissue (here called the "penumbra obscura") is the theoretical corollary of such sparing.

   The penumbra obscura is held responsible for (i) permitting limited visual recovery after early CRA flow restitution (for example, reduction in the area and depth of a central scotoma); (ii) inducing the formation of cilioretinal arterial collaterals (thus allowing eventual return of CRA perfusion but no visual recovery); and (iii) stimulating the development of rubeosis iridis in eyes with no CRA flow restitution. The only alternative so far proposed to such an inner retinal source of angiogenic stimulation after CRAO is an outer retinal source in consequence of carotid artery stenosis.[21] To date, however, an outer retinal penumbra has only been demonstrated in eyes with proliferative diabetic retinopathy complicated by retinal detachment.[6]
2. The second obstacle that has to be overcome if an all-embracing portrait of CRAO is to be painted is the view that the CRA inevitably becomes completely occluded whenever its patency is compromised. As earlier noted, there was no room for "partial CRAO" in the Iowa CRAO classification; indeed, the existence of this type of occlusion (defined by its degree rather than its duration) was specifically discounted.

Experimentally and clinically, the great majority of eyes with "complete CRAO" show a very variable but limited amount of "residual circulation" on FFA; this has been attributed to collateral arterial flow from optic nerve pial anastomoses.[10,21,23,28] In eyes with a given duration of experimental CRAO, the magnitude of this collateral flow was considered to determine the severity of long-term damage to the NFL and the degree of optic atrophy, so its effect was not deemed to be insignificant.[38] It requires no major leap of faith to appreciate that eyes with somewhat more "residual circulation" (either from collaterals or from incomplete luminal closure in the CRA) may have a different fundus appearance from the classic picture of CRAO. In monkey 45, this intermediate level of oligemia, while still severe in magnitude, lead to a "Christmas tree pattern" of periarterial sparing,[10] and this is directly equivalent to the pattern of oncotic swelling seen in the macula of patients with partial CRAO.[4,5] The associated signs of (i) retinal venous cyanosis, and (ii) CWS evolution in an annulate distribution, follow perfectly logically from this severity of ongoing oligemia.

These findings demonstrate beyond all reasonable doubt that the key to the clinical pathology in Kurimoto et al's cases is not a temporary, but rather a partial, arterial occlusion. It is recommended that the Iowa CRAO category of "transient CRAO" be abandoned and that the term "transient" be reserved for "transient ischemic attack" according to existing convention; that is to say, an acute onset of major visual loss affecting one eye, together with rapid and complete reversibility of symptoms and no residual signs of ischemic damage.

3. Another barrier to understanding retinal vascular disorders is the misconception that retinal CWSs represent "NFL infarcts," "inner retinal ischemic spots" or "retinal microinfarctions" in consequence of terminal retinal arteriolar occlusion. It was this mistaken belief that lead directly to the difficulty that Kurimoto and colleagues experienced in explaining the Purtscher-like retinopathy that they had observed in their patients.[1]

   The "focal retinal ischemia" theory of CWS formation first gained traction in the 1960s when the effects of embolization of the porcine retina were reported (but were severally misinterpreted).[39] The semi-opaque patches developing downstream of the embolized vessels were considered to be CWSs, but they were in fact bracketed inner retinal infarcts resulting from cilioretinal or branch arterial occlusion.[5,24] Owing to the paucity of ganglion-cell axons in the pig retina, the "brackets" (ie, the axoplasmic debris accumulating in the NFL) were virtually indistinguishable ophthalmoscopically from the inner retinal infarcts, albeit the histological distinction between these two types of pathological change was clearly recognized.

   The accumulation of mitochondria within the distended axon terminals was wrongly attributed to a reactive hypoxia-induced proliferation of organelles in situ within surviving axon segments at the periphery of the infarct.[39] This mistake arose because the topographical relationships inherent in "bracketing" were not appreciated (that is to say, Cajal's end bulbs only evolve where ganglion-cell axons cross ischemic boundaries and not where the axons run close to, but parallel with, such boundaries).[18,24] The possibility of axoplasmic flow obstruction was discounted for spurious reasons discussed elsewhere.[40]

   When smaller emboli (of 15 μm diameter) were injected into the pig carotid and individual arterioles of smaller caliber were occluded thereby, no patches of inner retinal infarction developed. This was attributed to capillary collateral flow that prevented severe focal ischemia and infarction from appearing.[39] By contrast, an experimental retinopathy with genuine CWS formation (in an annulate distribution) has been observed in primates with severe systemic hypertension.[20,21] In these eyes, "overwhelming evidence" is said to be available proving that the CWSs result from terminal arteriolar occlusion. However, the evidence so far presented (such as focal capillary closure and NFL grooves) fails to discriminate between the cause and consequences of CWS formation.

   No-one now doubts that CWSs comprise discrete accumulations of Cajal's end bulbs (not infarcted tissue), and that these conspicuous lesions can result from obstruction of either orthograde *or* retrograde axoplasmic transport.[18,24] That said we are, of course, witnessing the death throes of the ganglion cells – what Ramon y Cajal called "the agony of the axons" when referring to axon end-bulb formation.[24] Apart from partial CRAO, CWSs or CWS-like lesions develop in a wide variety of retinal vascular disorders, including:

   i. Branch arterial occlusion (and occasionally after branch vein occlusion), wherein axoplasmic material with exactly the same appearance as an isolated CWS collects on the peripheral or on the disc-side of inner retinal infarcts as a result of orthograde or retrograde transport obstruction respectively (or on both sides in the case of a "bracketed infarct").[18,19]

ii. CRVO, wherein CWSs may have a similar distribution to that seen in partial CRAO and reflect panretinal hypoperfusion, retinal venous hypoxemia and retrograde axonal transport block.[5] However, CWSs may otherwise arise through mechanical axonal damage owing to dilatation and tortuosity of the main venous tributaries ("perivenous CWSs"), or they may be sentinels of cilioretinal infarction (and orthograde axoplasmic transport obstruction).[5,14]

iii. Ischemic diabetic retinopathy, wherein retrograde axonal transport in the NFL is typically obstructed just outside the major vascular arcades and nasal to the optic disc (ie, in a C-shaped distribution). The CWSs have an intervascular location that reflects perivenous as well as periarterial sparing (as a result of the prevailing retinal venous hyperoxemia).[5,6,41]

In none of the above circumstances is terminal arteriolar occlusion implicated. What remains at issue, therefore, is not whether all CWSs are due to terminal arteriolar occlusion (which is clearly not the case), but whether *any* CWSs arise in this fashion? Radius and Anderson explained the possible mechanism as follows: "a minute area of ischemia through which axoplasmic transport cannot proceed, so transported material collects around it and buries it to form the cotton-wool spot."[13] The burden of proof of "focal retinal ischemia" now rests with those who continue to adhere to this outdated and discredited theory. Corroboration of this mechanism will require demonstration of both orthograde and retrograde axonal transport obstruction within the same lesion.[5]

Once CWSs are looked at in a wider ischemic context, their role as "sentinels" becomes clear. The three cases illustrated by Kurimoto and colleagues demonstrate retrograde transport block and penumbral sentinel formation in eyes with partial CRAO in exemplary fashion.[1] In another recent report in Clinical Ophthalmology,[42] a solitary parapapillary CWS, interpreted as an "isolated" lesion, was in fact a boundary sentinel signaling orthograde axoplasmic transport block related to cilioretinal arterial occlusion.

Although partial CRAO is a relative rarity compared with "complete CRAO," the Moorfields' 1978 case series[4] and the cases from Kurimoto and colleagues[1] indicate that patients with this diagnosis will present to ophthalmologists from time to time. It is clear, however, that difficulties are likely to be experienced in interpreting the signs despite the fact that the configuration of all the fundus features conforms to a reproducible pattern and one that has been widely communicated.[4–6] Partial CRAO offers an exciting opportunity to delve into the physiology and pathology of the ocular vasculature and the oxygenation of retinal neurons. It is an opportunity not to be squandered.

Disclosure

The author declares no conflicts of interest in this work.

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