

Commentary

On the cause of serous detachments and acute central serous chorioretinopathy

Serous detachments, with bullous elevation of the retina, occur in a variety of disorders including central serous chorioretinopathy (CSC), age related macular degeneration, lupus erythematosus, choroidal ischaemic disorders such as accelerated hypertension and pre-eclampsia, systemic corticosteroid usage, over some choroidal tumours, and in inflammatory disorders such as Harada's disease. There is little mystery about the appearance of fluid when it overlies a large area of leaky retinal pigment epithelium (RPE), which itself overlies exudative choroidal inflammation or vasculopathy. However, the development and persistence of elevated detachment is rather curious in disorders such as CSC where the region of leakage is very small relative to the area of retina that is detached. Under these conditions, the question of pathophysiological interest is not so much 'why does fluid enter?' but 'why does fluid persist?'

To form a serous detachment, there must be a driving force for fluid entering the subretinal space (for example, a pressure gradient from the choroid acting through an RPE defect) that overcomes retinal adhesive force. But how and why is the detachment maintained? Animal experiments have shown that fluid does not ordinarily persist in the subretinal space (SRS), since it is rapidly transported across the RPE by active and facilitated ionic transport.^{1–3} Hydrostatic and osmotic forces also drive fluid towards the choroid,^{4, 5} but are less powerful in a normal eye because they are blocked by the tight junctional barrier of the RPE. It is not surprising, therefore, that when the RPE barrier is damaged (for example, by laser or by an RPE toxin such as sodium iodate), fluid actually leaves the subretinal space faster.^{6, 7} Removal of the barrier allows a more rapid passive egress of subretinal fluid.

Why, then, do some serous detachments (as in CSC) extend far beyond a focal site of leakage? Traditional teaching had often described acute CSC as a disease 'caused by' the leak (which is visible on fluorescein angiography)—that is, caused by a small defect in the tight junctional barrier of the RPE. However, the experimental data indicate that a serous detachment will not form unless there are conditions that drive fluid against the normal gradients into the subretinal space and that also limit its subsequent removal by active and passive transport. In fact, one can argue that a necessary condition for serous detachment to extend significantly beyond the leak is an intact tight junctional RPE barrier under the elevated retina (except directly over the areas of leakage), since fluid would otherwise leave under hydrostatic and osmotic pressure.⁸ A diminished capacity for absorption of subretinal fluid in CSC would explain why subretinal fluid under a large retinal detachment can absorb within 24 hours after placement of a scleral buckle, yet the fluid under the serous detachment in CSC may require weeks to absorb even after the leakage has been stopped by photocoagulation.

Could the reason that some detachments spread far beyond the leakage sites be unusually aggressive leakage into the SRS, rather than less aggressive fluid absorption? Several lines of reasoning suggest that this is unlikely and that compromised or subnormal fluid absorption across

the RPE is necessary to the pathogenesis of such detachments. This statement does not mean that the primary disease is necessarily within the RPE; it simply means that one correlate of the disease process (which may well be choroidal and ischaemic) is diminished fluid absorption. Firstly, bullous detachments can form within hours in rabbit eyes in which the RPE and choroid have been damaged pharmacologically (with *n*-ethylmaleimide) or by photodynamically induced ischaemia (using rose bengal).^{9, 10} Fluorescein angiography shows vigorous leakage throughout the base of these detachments, but the serous elevation does not extend much beyond the area of leakage. When the RPE leak is much smaller, as it usually is in CSC, there must proportionally be less fluid entering and even less pressure that would extend a detachment (in the absence of other facilitating abnormalities). Secondly, the area of detachment over small photodynamic injuries in the cat expand after pretreatment (and presumed injury) of the surrounding RPE with intense light.¹¹ Thirdly, fluid that enters experimental detachments has been found to have an initial protein concentration only 60 to 70% of serum levels.^{9, 10} This indicates that the fluid is a transudate—that is, partly filtered, and fluid pressure from the source does not reach the subretinal space unmodulated. It seems unlikely that the pressure head of leakage in CSC would be an order of magnitude greater than that which occurs in inflammatory and ischaemic disorders that do not cause extensive elevated detachment.

The high protein content of serous detachments has at times been put forth itself as an explanation (by oncotic pressure) for why subretinal fluid forms and persists in CSC. However, if albumin (serum) or even larger molecules are introduced into the SRS experimentally, all of the fluid will absorb within hours even though protein or protein size molecules may remain in the SRS.^{6, 7, 12} Furthermore, retina is sufficiently permeable to water and ions that subretinal fluid equilibrates rapidly and continuously with the vitreous to neutralise osmotic gradients.¹³ Even albumin can cross the retina at a modest rate, and proteinaceous fluid within the SRS loses roughly 5% of its protein concentration per hour into the vitreous.¹³ In other words, protein will diffuse continuously out of the subretinal space of serous detachments, and a high subretinal protein content will be maintained only if there is continued entry of new fluid with protein. It is this continued influx, and the presence of a reduced absorptive capacity of the surrounding RPE, that maintains the detachment.

These arguments suggest that the primary abnormality in acute CSC is diffuse dysfunction of the choroid and RPE, which creates not only a pressure head for fluid leakage (and an opportunity for breaks to appear in the RPE barrier) but which also weakens retinal adhesiveness (a process that depends on RPE metabolism¹⁴) and impairs the outward transport of fluid. Early evidence for this concept came from Japanese studies which showed that the systemic administration of adrenaline (sometimes along with corticosteroids) led over time to the appearance of multifocal serous exudation in animals.^{15, 16} Indeed, CSC is

known to be more prevalent in people under stress and with type A personality,^{17, 18} or in those using systemic corticosteroids.¹⁹ Adrenergic stress could in theory act upon either the choroidal vasculature or the RPE directly through known $\alpha 1$ and β adrenergic receptors.^{20, 21} The relevant point is that extensive areas of the fundus will be involved rather than only a tiny focus of RPE barrier damage. The angiographic leak may well be an epiphenomenon that occurs because a few RPE cells decompensate over a region of blocked choroidal capillaries or inflammation.

In the past few years, angiographic evidence has accumulated which supports this general concept of CSC. Fluorescein angiography often shows multifocal areas of RPE damage that indicate the disease has been widespread and/or recurrent. Some patients develop a chronic syndrome with extensive RPE abnormalities and sometimes with low and chronic subretinal fluid, but our concern here is with earlier disease and bullous elevation over focal leaks. Indocyanine green angiography even in early and acute CSC has consistently shown choroidal vascular abnormalities that extend well beyond the focal site of leakage, including capillary and venous congestion with hyperpermeability in the late stages of the angiogram.²²⁻²⁷ Some authors have described hypoperfusion in the early dye transit and have postulated that ischaemia, leading to vascular damage and leakage, is the primary event.²²⁻²⁴ Others have argued that the hyperperfusion and hyperpermeability are the primary pathological abnormalities.²⁵⁻²⁸ In either case, the end result is vascular leakage and fluid pressure within the choroid, which will passively impede egress from the SRS. To the degree that there is ischaemia or altered haemodynamics, there will probably also be metabolic compromise of the overlying RPE with a weakening of retinal adhesion (that helps fluid to spread) and a diminution of active ionic transport (that allows fluid to persist).

Various theories have been proposed for the pathogenesis of CSC. Gass recognised many years ago that many serous detachments are preceded by a small focal RPE detachment at the site of leakage.²⁹ This is relevant to the manner in which pathologically elevated choroidal pressure initially affects the overlying RPE, but does not argue for or against the concept of underlying diffuse choroidal or systemic disease. Spitznas postulated that the cause of CSC leakage might be a focal imbalance of RPE ionic transport systems, causing RPE cells at the site of leakage to pump fluid in an inward rather than outward direction.³⁰ It seems unlikely that a few cells could transport fluid at such a rapid rate as to overcome normal transport in a wide surrounding area, and this theory does not explain the entry of protein or fluorescein through leaks, or the frequent presence of RPE detachment. Nevertheless, a shift in the balance of inward versus outward transport over a broad area of RPE could be a part of the mechanism by which choroidal dysfunction reduces RPE absorption. My own earlier analysis of CSC had emphasised impaired RPE active transport, although I had noted that choroidal or systemic disease might underlie the RPE abnormality.⁸

This present commentary is not intended to propose a new or different theory of CSC, but to provide a framework in which the balance of forces acting upon the subretinal space can be taken into account. A pressure gradient from choroid to SRS must be present, and there must be gaps in the RPE barrier through which fluid can enter. However, fluid will not spread much beyond these sites of leakage unless retinal adhesiveness is weakened and the surrounding RPE has an intact barrier (to prevent passive absorption of fluid) while fluid absorption is compro-

mised (so that fluid can accumulate). Protein entering the SRS can be sequestered and can be concentrated by fluid absorption, but it does not directly cause or maintain the detachment. Although fluid absorption across the RPE is compromised, the underlying pathology appears often to be choroidal vascular disease. The ultimate prevention and management of CSC will come through understanding the pharmacology and pathophysiology of choroidal and RPE dysfunctions, rather than by attacking an anatomical site of leakage.

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