

Helicobacter pylori and idiopathic central serous chorioretinopathy

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Summary

Idiopathic central serous chorioretinopathy (ICSC) is a disease that typically affects middle-aged adults and involves the sensory retina, the retinal pigment epithelium (RPE) and the choroid. Patients usually have mild visual loss. ICSC generally resolves without therapy, although the disease can become chronic with ensuing RPE decompensation. Some patients, particularly older adults, can also develop choroidal subretinal neovascularisations (CNV), which may lead to a severe loss in visual acuity. Although the aetiopathogenesis of the disease is still incompletely understood, a correlation with psychophysical stress supports the idea that the disease may be “adrenergically con-

ditioned”, leading to the development of one or several defects in the RPE, with subsequent focal leakage of serous fluid and its retention in the subretinal space. An association between ICSC and the *Helicobacter pylori* (HP) infection has also been recently documented, suggesting that this organism may possibly be involved in the development of some cases of ICSC. Pathogenetic mechanisms that may explain the contribution of HP in the development of ICSC are postulated.

Key words: idiopathic central serous chorioretinopathy; Helicobacter pylori; macula; retina

Introduction

Idiopathic central serous chorioretinopathy (ICSC) is classically described as a condition with an acute presentation, characterized by a serous detachment of the neurosensory retina in the macular region, preferentially affecting young men (85%) between 25 and 45 years of age. One eye is predominantly affected as a bilateral and symmetrical presentation of the disease is reported to develop in only 10% of patients. Recurrences have been documented in 50% or more of cases [1]. Many individuals with ICSC have no previous medical and family history and no systemic symptoms or signs. On the contrary, if the detachment spreads into the central macular area, the patient may typically develop metamorphopsia together with a central positive scotoma, micropsia and impaired colour vision. Alterations in colour vision are detectable on standard testing (e.g. Ishihara plates, Lanthony 15-Hue Desaturated Test) and the central visual defect may be demonstrated by using an Amsler grid test or a microperimetric examination. Additional retinal findings, which may be studied very precisely with fluorescein and indocyanine green (ICG) angiography, Optical Coherence Tomography images [2] and/or three-dimensional confocal angiography [3], include reti-

nal pigment epithelium (RPE) detachment, RPE atrophic tracks, capillary teleangiectasis, retinal or choroidal neovascularisations and intraretinal or subretinal depositions [1, 4].

Most cases of ICSC spontaneously resolve with recovery of visual function. In a small percentage of subjects, however, a chronic or progressive disease with widespread decompensation of the retinal pigment epithelium (RPE) and severe vision loss may develop [2]. There is no current effective treatment for the disease although ICG angiography-guided photodynamic therapy utilizing verteporfin has been reported by some authors to be beneficial in the treatment of the chronic variant of the disorder [5, 6] and of subfoveal choroidal neovascularisations [7, 8]. An ICG dye-enhanced subthreshold micropulsed diode laser photocoagulation has also recently been proposed as a possible approach to the management of chronic ICSC with persistent central serous neuroepithelial detachment [9].

The precise pathophysiology of ICSC is still poorly understood. The disease is thought to be due to the development of one or more areas of RPE defects with subsequent focal leakage leading to serous fluid retention in the subretinal space [1].

It is theorised that damage to the RPE active fluid transport mechanisms, which normally dehydrate the subretinal space, may also play a contributing role [1]. Cigarette smoking, uncontrolled systemic hypertension, pregnancy, allergic respiratory disease, antibiotic or alcohol use [10], sildenafil citrate [11] or systemic corticosteroid therapy [12, 13], sympathomimetic agents [14], antiphospholipid antibodies [15], retinitis pigmentosa [16], psoriasis [17], endogenous mineralocorticoid dysfunction [18] have been reported as potentially associated risk factors for the disease. ICSC has been described as case reports in patients with a benign tumour of the adrenal gland [19], cryoglobulinaemia [20], systemic lupus erythematosus [21] or after bone marrow transplantation [22]. A psychosomatic origin has also been hypothesized for ICSC, particularly in highly motivated, eager individuals with a type A personality [23].

Kitaya and associates observed choroidal hyperpermeability, vessel congestion and small, localized hypofluorescence areas surrounding regions of fluorescein leakage by simultaneously utilizing fluorescein and ICG angiography in combination with confocal scanning laser ophthalmoscopy (Heidelberg® Retina Angiograph) [24]. The authors suggested that the hypofluorescence of non-perfused areas, representing filling delays of the choroidal arteries and choriocapillaries, might result from focal occlusion of the choriocapillary vessels. Prunte and Flammer reported a similar interpretation some years before [25].

Considering that the antifibrinolytic agent, plasminogen activator inhibitor 1, has been reported to be elevated in ICSC patients [26] and that this disease has been documented to be associated with the use of sympathomimetic medications [14], the focal occlusion of the choroidal microcirculation with secondary ischaemia might result from impaired fibrinolysis and choroidal vasoconstriction [24]. A reduced choroidal blood flow in the foveal region, demonstrated using laser Doppler flowmetry, supports the theory of a choroidal microcirculatory occlusion ensuing in patients with ICSC [24]. However, it should be noted that almost all ICSC subjects show a diffuse and bilateral choroidal hyperfluorescence on ICG but it is still unclear why one eye only is usually affected or much more affected than the other. In fact, the choroidal vascular hyperpermeability, from which ICSC generally develops [1], may probably be the correct explanation for the hyperfluorescence seen on ICG angiograms but not for the asymmetric manifestation of the disease. Differences between both eyes might be found in the increase of choroidal tissue hydrostatic pressure (which, superseding that of the retina, reduces or stops the solute flow across the RPE [1]) or in the serous detachment itself ("blow-out" of the RPE according to Carvalho-Recchia et al [12]) as well as in the different degrees of RPE alterations. Nevertheless, there is no doubt that the main reasons underlying the asymmetrical presentation of ICSC need further and extensive investigations in the future.

Discussion

A correlation between ICSC and the *Helicobacter pylori* (HP) infection has recently been hypothesized [27, 28]. A case report of ICSC in a 43-year-old man, documented that recurrences of the disease were always associated with the presence of HP (histology of gastric biopsy specimens or ¹³C-urea breath test). Resolution of ICSC and recovery of visual acuity were correlated significantly with successful eradication of the bacterium utilizing the conventional antimicrobial tripletherapy (amoxicillin, clarithromycin, and omeprazole) [27]. However, although indicative of an association, it should be emphasized that in this patient other factors (e.g. stress) may have been involved in the resolution of ICSC independently of any contribution made by the bacterial infection.

In a second prospective pilot study of sixteen subjects affected either by active long-lasting ICSC or by diffuse retinal epitheliopathy, the prevalence of HP infection was found to be significantly higher in subjects with ICSC. This prevalence was also significantly higher when compared to that of an age-matched control population in the same country as that of the participating subjects [28].

This association is still unclear. However, a possible explanation might indirectly arise from other correlations already found, e.g. between the HP infection and the development of atherosclerosis [29]. In fact, although the aetiology of atherosclerosis is considered to be multifactorial, it has been documented that HP-cytotoxin-associated gene-A (CagA) positive strains may contribute to and significantly increase the risk of its development [30]. It has been suggested that anti-CagA antibodies may cross-react with vascular wall antigens, triggering an immunological cascade that causes arterial cell wall damage and leads to the development of atherosclerosis [29]. An inflammatory process has been recognized as a contributing factor in the development of atherosclerosis [31]. In fact, the immunoglobulin-G (IgG) antibody response to the infection by multiple and specific pathogens has been similarly considered to be a risk factor leading to the endothelial dysfunction. This fact may represent an additional mechanism by which pathogens such as HP may contribute to atherogenesis [31].

Moreover, elevated serum titres of anti-heat shock proteins (HSP) antibodies expressed and/or secreted by several pathogens including HP, have

been reported to correlate with a higher risk of coronary heart disease [32]. Purified anti-HSP antibodies are also known to recognize and mediate the lysis of stressed human endothelial cells and macrophages in vitro [32]. It has been proposed that HP infection promotes increased lipid and fibrinogen levels in response to a low grade inflammatory stimulation, causes a raise of anti-HSP antibodies [29], up-regulates the endothelial adhesion molecules, increases the polymorphonuclear leukocyte adhesion [33, 34], binds the von Willebrand factor and consequently induces a IgG-mediated increase of platelet activation and aggregation by interacting with the glycoprotein Ib [29, 34, 35].

It has also been theorized that in the presence of a genetic susceptibility, antigens against HSP may also cross-react with homologous host proteins, like those present on the vascular endothelium [32]. In fact, the capacity of the host to control the pathogen induced inflammatory response is likely to be influenced by genetic factors. In support of this hypothesis, the association, for example, between coronary artery disease (CAD) and several infectious pathogens (such as Chlamydia pneumonia, cytomegalovirus, HP and herpes virus simplex type 1) was found to be modulated by the interleukin (IL)-6/G-174C polymorphism, this interaction being mediated by variations in serum IL-6 levels [33]. However, the authors themselves recommended that caution is needed in the interpretation of these results, since no genotype dif-

ferences were found between cases and controls and the risk of CC homozygotes was not increased as would be expected in presence of an additive effect of the 174C allele [33].

Moreover, it should also be noted that the above mentioned case report [27] did not completely support this theory of a “molecular mimicry”, since it would be expected that although the bacteria is eliminated, remaining auto-antigens may still be present, thus prolonging the disease process. If an auto-inflammatory aetiology, as here suggested, was solely responsible for the development of ICSC in that patient, in addition to the eradication of the bacterium, steroids would probably have been needed to suppress the inflammation. Incidentally, steroids have been documented to be associated with the development of some cases of ICSC [12, 13]. Nevertheless, although infectious interactions and autoimmune mechanisms may not solely explain the pathology of microangiopathies such as CAD or ICSC, which are more likely to represent organ response to multifactorial insults, a contributory mechanism for HP could be hypothesized in both conditions.

Focal occlusion of the choroidal microcirculation may also promote choroidal neovascularisations and the associated serosanguineous complications observed in ICSC [5, 7, 8, 24]. Interactions between HP and vascular endothelial growth factor-A [36] might help to explain the choroidal ischaemia and the secondary activation of host angiogenesis observed in some of these patients.

Conclusion

In conclusion, ICSC may be better understood not as a retinal condition arising from an isolated RPE defect but as one resulting from a more widespread RPE disease. From this standpoint, a generalized involvement of choroidal microcirculation may be responsible for the ICSC pathogenesis and a HP-mediated immune mechanism, similar to that proposed for CAD, might also be encountered in the pathophysiology of ICSC.

Further multiple centre, randomised, case control trials are necessary to confirm the potential contributory role of the HP infection in the pathogenesis of ICSC since diverging results regarding a possible association between infectious

agents and endothelial dysfunction have also been published [37, 38].

Nevertheless, if this hypothesis were to be confirmed in the future, a novel medical and antimicrobial approach to the disease might be possible, especially for a better prevention of its complications.

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