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Functional outcome of macular edema in different retinal disorders

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ABSTRACT

Macular edema accompanies many ocular pathologies, affecting visual function and is an important factor in treatment decisions and disease outcome. Though visual acuity is commonly used to evaluate patient vision it does not always provide a complete estimate of their visual abilities or reflect their own visual perception. Furthermore, different pathologies result in macular edema causing a variable effect on visual function, related to the rate of fluid accumulation and accompanying ocular changes. Use of complementary visual function tests, such as retinal contrast sensitivity on microperimetry and reading speed provide additional information that can be used to evaluate patients and assist in treatment choices. Here we explore the effect of macular edema on visual function in different retinal pathologies, namely diabetic retinopathy, retinal vein occlusion and uveitis, examine its influence on the various vision tests and discuss the factors underlying this variable response.

Contents

Abbreviations: BRB, blood-retinal barrier; FFA, fluorescein angiography; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor; RVO, retinal vein occlusion; UCVA, uncorrected visual acuity; BCVA, best corrected visual acuity; LogMAR, logarithmic minimal acuity of resolution; ETDRS, early treatment diabetic retinopathy study; MNREAD, Minnesota Near Reading Test; DME, diabetic macular edema; CSME, clinically significant macular edema; SD-OCT, spectral domain-optical coherence tomography; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; TNF, tumor necrosis factor; Tregs, regulatory T cells; TGF-β, Tumor growth factor beta; ELM, external limiting membrane; IVTA, intravitreal triamcinolone acetate; APMPPE, acute posterior multifocal placoid pigment epitheliopathy; VKH, Vogt-Koyanagi-Harada; SEM, standard error of the mean; PPV, pars plana vitrectomy.

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Macular edema forms part of the clinical presentation of many retinal and ocular pathologies. It has a profound effect on patients' visual function, can result in persistent visual loss and is the focus of treatment whenever it occurs. Treating macular edema has been the objective of many clinical trials and new drug development, with most studies using visual acuity as their endpoint. While this is an easily quantifiable measure of vision in the clinic many patients report that our documented visual acuity does not represent their visual experience in daily life, and in many cases patients with a good recorded visual acuity continue to complain of poor vision. Furthermore, the effect of macular edema appears to be variable in different diseases and patients with similarly thickened macula may have very different complaints.

In this paper we attempt to explore the range of quantifiable visual function tests, including visual acuity, retinal contrast sensitivity using Microperimetry and reading speed, and determine their relationship to the presence of macular edema. We further examine the effect of macular edema in various common ocular pathologies, mainly diabetic retinopathy, retinal vein occlusion and uveitis and discuss why it has a variable effect on visual function in each condition.

1. General pathophysiology of retinal edema

Macular edema is defined as an accumulation of fluid in the outer plexiform and inner nuclear layers around the fovea (Cunha-Vaz and Travassos, 1984). It may be related to a rapid reduction in visual acuity, due to disruption of the retinal intercellular relationship and in most cases is caused by extracellular edema, though intracellular edema may also occur (Augustin et al., 2010). Extracellular edema is related to disruption of the blood-retinal barrier (BRB) in perifoveal capillaries and breakdown of mechanisms that prevent the accumulation of extracellular fluid in the retina including osmotic and hydrostatic gradients and restricted capillary permeability. When the balance between the capillary filtration rate and fluid removal from extracellular retinal tissue by glial and RPE cells is disrupted, the intrinsic balance between osmotic and hydrostatic forces is lost. BRB disruption is influenced by mediators such as vascular endothelial growth factor and nitric oxide, which are elevated in cases of retinal hypoxia and inflammation (Fine et al., 2001; Kaur et al., 2008; Kim et al., 2004). The macular region is more prone to the development of edema due to its unique anatomical structure: high concentration of cells and metabolic activity; a watershed vascular arrangement within the foveal avascular zone that reduces extracellular fluid resorption and an anatomical structure of the outer plexiform layer (Henle's layer) that allows for the accumulation of extracellular fluid. The accumulation of fluid results in expansion of the retinal extracellular space and may manifest either as a diffuse thickening of the macula area or in formation of cystic spaces, mainly in the outer plexiform layer (Henle's layer, Fig. 1A, (Tranos et al., 2004)).

Macular edema is usually diagnosed by visual examination of the retina, when the normal foveal depression and light reflex are obscured. Investigations used to diagnose macula edema include fluorescein angiography (FFA) (Fig. 1B) and optical coherence tomography (OCT), which have allowed the demonstration of retinal structure and pathology (Fig. 1C). The vitreo-macular interface when disturbed particularly by traction can play a role in macular edema formation and lack of response to treatment (Lehpamer et al., 2014). Disruption of the normal vitreoretinal interface can cause stress at the Muller cell end-feet, contributing to the release of inflammatory factors such as basic fibroblastic growth factor, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (Scholl et al., 2010; Reichenbach et al., 2007). Separation of the retina and RPE results in BRB breakdown and lysis of Muller cells that leads to further leakage and edema.

Macular edema represents a common pathologic sequel to a variety of conditions such as uveitis, central or branch retinal vein occlusion (RVO), diabetic retinopathy, intra-ocular surgery, vitreo-macular traction, age related macular degeneration (Ciulla and Rosenfeld, 2009), following cataract extraction, in perifoveal retinal telangiectasis, Coat's disease (Gelman et al., 2014; Lee et al., 1991), choroidal tumors (Mashayekhi et al., 2015; Michael and De Venecia, 1995) or inherited diseases (Hirakawa et al., 1999; Saksens et al., 2015). The involvement of macular edema from such diverse causes reflects on the different mechanisms that result in extracellular fluid accumulation, BRB breakdown, vascular proliferation (Michael and De Venecia, 1995) and retinal traction. Though it accompanies many different diseases its effect on visual function is variable (Tranos et al., 2004), in some cases resulting in a rapid deterioration of vision, while in others visual function is maintained even with a large accumulation of fluid and for long periods of time (Coscas and Gaudric, 1984; Henderly et al., 1986; Kim et al., 2013; Nisic et al., 2014). The relationship between macular edema,