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A novel hypothesis for the pathogenesis of glaucomatous disc hemorrhage

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ABSTRACT

Disc hemorrhage is known to be associated with glaucoma development and progression. Several hypotheses have been proposed to explain the pathogenesis of disc hemorrhage in glaucoma, including mechanical and ischemic theories. However, no theory has yet provided a clear explanation of cellular-level events and related histologic findings. Moreover, research has yet to elucidate why glaucomatous disc hemorrhage occurs around the optic disc and at the margin of the retinal nerve fiber layer defect. Understanding the pathogenic mechanism of disc hemorrhage will facilitate interpretation of its clinical importance, and provide better insight into clinical practice. In this review, we sought to provide a plausible hypothesis for the development of glaucomatous disc hemorrhage that could explain the aforementioned characteristic features. We suggest a new and detailed mechanism for disc hemorrhage. Critical microscopic events are also discussed in relation to reactive gliosis in glaucoma. With proliferative reactive gliosis, fibrous glial scar forms, and we suggest that the traction force induced by glial scar formation might disrupt capillary at the border between the healthy and damaged retinal nerve fiber layer, and develop splinter-shaped peripapillary hemorrhage. In addition to glial scar formation, remodeling and deformation of lamina cribrosa beams would insult the capillary surrounding the pore of the lamina cribrosa, and lead to development of round blotch-shaped cup hemorrhage. Histopathologic confirmation of these findings should be explored in future investigations.

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Abbreviations

BM	basement membrane
CNS	central nervous system
DH	disc hemorrhage
ECM	extracellular matrix
ET	endothelin
GFAP	glial fibrillary acidic protein
ILM	internal limiting membrane
IOP	intraocular pressure
LC	lamina cribrosa
MMP	matrix metalloproteinase
NTG	normal tension glaucoma
OCT	optical coherence tomography
ONH	optic nerve head
POAG	primary open-angle glaucoma
PACG	primary angle-closure glaucoma
RNFL	retinal nerve fiber layer
TGF	transforming growth factor
TIMP	tissue inhibitor of matrix metalloproteinase

1. Introduction

Since its initial description by Bjerrum, optic disc hemorrhage (DH) has been a topic of concern because of its strong association to glaucoma development and progression (Bengtsson, 1990; Budenz et al., 2006; Chung et al., 2015; De Moraes et al., 2013; De Moraes et al., 2009; Diehl et al., 1990; Drance et al., 1977, 2001; Drance, 1989; Ernest et al., 2013; Ishida et al., 2000; Siegner and Netland, 1996; Sonnsjo et al., 2002). However, the pathogenesis of DH has not been elucidated in the past 100 years. The low prevalence of this condition makes investigation more difficult, in addition to its transient nature (Diehl et al., 1990; Healey et al., 1998; Heijl, 1986; Kim et al., 2015; Suh and Park, 2011; Tomidokoro et al., 2009; Yamamoto et al., 2004).

DH was initially considered a precursor for glaucomatous damage because detection of DH was followed by diagnosis or progression of glaucoma (Begg et al., 1971; Bengtsson, 1990; Budenz et al., 2006; Diehl et al., 1990; Drance and Begg, 1970; Drance et al., 1977; Healey et al., 1998; Ishida et al., 2000; Shihab et al., 1982; Sonnsjo et al., 2002; Tuulonen et al., 1987). However, recurrent hemorrhage does not always correlate with faster progression of glaucoma as compared to a single episode (Park et al., 2015b; Rasker et al., 1997). And it has been suggested that DH does not appear to be a discrete event leading to subsequent progression, but rather a result of glaucomatous changes (Chung et al., 2015; Gracitelli et al., 2014; Park et al., 2015b).

Whether DH is the primary or secondary event, a good hypothesis for the DH development mechanism should successfully explain its characteristics and distinctive features. Despite a few suggestions, no single theory has explained the specific cellular and molecular mechanisms of DH's occurrence at the border of the retinal nerve fiber layer (RNFL) defect and the optic disc margin (Airaksinen et al., 1981; Gloster, 1981; Jonas and Xu, 1994; Nitta et al., 2011; Sonnsjo et al., 2002; Sugiyama et al., 1997, 1999b).

We present a new hypothesis on the pathogenesis of DH. This review does not address glaucoma pathogenesis, but instead explores how hemorrhages develop, as they are observed in all types of glaucoma including primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG). Features of DH will be briefly summarized with previous theories of DH development. Our hypothesis is closely associated with reactive gliosis in glaucoma. Moreover, we divide DH into two subtypes because different pathogenic mechanisms may exist for the two.

Our purpose is to achieve a better understanding of the pathogenic mechanism of DH so as to facilitate interpretation of its clinical importance.

2. Clinical features of DH

2.1. Prevalence

The prevalence of DH is different among study groups. In population studies, the prevalence of DH in normal subjects is between 0.0 and 1.08% (Healey et al., 1998; Kitazawa et al., 1986; Tomidokoro et al., 2009; Wang et al., 2006). In glaucoma patients, the number differs by the type of glaucoma, between 1.45 and 36.9% (Diehl et al., 1990; Healey et al., 1998; Jonas and Xu, 1994; Kim et al.,

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