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Diabetic retinopathy is a neurodegenerative disorder

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ABSTRACT

Since 1875, controversy has ensued over whether ocular diabetic complications are primarily vasculopathic or neuropathic in nature. Here, we discuss the historical context by which diabetic retinopathy (DR) came to be considered a primary vasculopathy, in contrast to more recent data suggesting the importance of diabetic retinal neurodegeneration (DRN) as the primary manifestation of ocular diabetic damage. Unsurprisingly, DRN parallels other diabetic complications related to neuropathy. In general, there are three possible relationships between microvascular DR and DRN: i) microvasculopathy causes neurodegeneration; ii) neurodegeneration causes microvasculopathy or iii) they are mutually independent. The authors' group has recently produced experimental data showing that DRN precedes even the earliest manifestations of DR microvasculopathy. In combination with earlier studies showing that focal implicit time delays predicted future development of DR microvasculopathy in the same location, relationships i) and iii) are unlikely. As such, ii) is the most likely relationship: DRN is a cause of DR. Granted, additional studies are needed to confirm this hypothesis and elucidate the mechanism of diabetes-induced neurodegeneration. We conclude this review by proposing experimental approaches to test the hypothesis that DRN causes DR. If confirmed, this new paradigm may lead to earlier detection of ocular diabetic damage and earlier treatment of early DR, thereby preventing visual loss in people with diabetes.

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1. Introduction

Since 1875, controversy has ensued over whether ocular diabetic complications are primarily vasculopathic or neuropathic in nature. Traditionally, diabetic retinopathy (DR) has been assumed to be and has been taught as a primary vasculopathy (American Academy of Ophthalmology, 2014). More recently, however, as diabetic retinal neurodegeneration (DRN) has been studied extensively, it is now widely recognized that diabetes causes both a vasculopathy and a neuropathy. This leaves open the question whether vasculopathy precedes neuropathy or vice versa. Although there exists only circumstantial, but no conclusive, evidence, that neuropathy precedes vasculopathy, we invite you to consider the hypothesis that DR is a primary neurodegenerative disorder; in other words, DR begins as a neuropathy, which subsequently causes the classically described phenotype of diabetic microvascular retinopathy (Friedenwald & Day, 1950; Early Treatment Diabetic Retinopathy Study Group, 1991).

1.1. History of retinal vasculopathy and neurodegeneration

Diabetes mellitus (DM) was recognized as a systemic disease in antiquity, with many symptoms described in detail, especially by Aretaeus of Cappadocia. However, at that time, diabetes was a rare disease, and patients typically did not survive to the point at which ocular complications developed. In 1688, Blancardi, an anatomist in Amsterdam, published a study of practical anatomy that contains the first reference to a person with diabetes suffering from visual loss. He described (translated from Latin): "*A young girl suffered from diabetes for almost a year. Before her death, she suffered from blindness in both eyes, and she could see the light of neither sun nor candle. Her skull was opened, and we discovered a fluid filled region, [. . .] which prevented the light from entering the optic nerve*" (Blancardi, 1688).

Many centuries passed before there was further documentation of visual loss from diabetes. In 1875, Leber, then practicing in Göttingen, Germany, published a crucial study on ocular complications

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from diabetes: *Über die Erkrankungen des Auges bei Diabetes mellitus* (Leber, 1875), and wrote (translated from German): "*What is more likely than the hypothesis that similar processes, foci of capillary hemorrhages and fatty degeneration and vessel changes, that we suspect in the retina, analogous to the exhaustively studied histological findings in [nephritis], sometimes also occur in the optic nerve, the chiasma, and the optical tract, even further in the brain and possibly even in the optical centers of the brain.*" Leber thus ascribed the changes in DR to a *primary vasculopathy*. That same year, Dickinson, then practicing in London, wrote in his treatise on nephropathies the following (Dickinson, 1875): "*[. . .] the inference that diabetes is produced by substantial and constant changes in the nervous centers, none the less significant because, as with many other diseases of these structures, they are such as ordinarily to elude the naked eye. They are such indeed as to link symptoms with lesions as closely with natural as artificial glycosuria, and to give diabetes a definite place among the diseases of the nervous system.*" Therefore, as early as 1875, debate existed between experts on diabetes (i.e., Leber and Dickinson) as to whether diabetic complications reflected a primary vasculopathy or a primary neuropathy.

1.2. Diabetes as a primary retinal vasculopathy

In 1879, MacKenzie, then practicing at Moorfields in London, was the first to describe retinal microaneurysms in DR. Familiar with both Leber's and Dickinson's work, he wrote the following: "*I cannot help differing from his conclusions, however, for Dr. Dickinson regards the peri-vascular extravasations and erosions of nervous structures as the cause of the symptoms in diabetes. To my mind the whole evidence points to the changes in the nervous system as well as those in the retina and other organs, being due to an altered condition of the blood. [. . .] the alterations in the nervous centers and in the eyes would appear to be coincident, rather than the latter sequential to the former*" (MacKenzie, 1879). MacKenzie concluded that DR is a primary vasculopathy, although without substantial scientific evidence. Going forward, this conclusion was cited by landmark authors of studies on DR, such as Ballantyne and Loewenstein in 1943 (Ballantyne & Loewenstein, 1943), Friedenwald in 1950 (Friedenwald & Day, 1950), and Cogan in 1961 (Cogan, Toussaint, & Kuwabara, 1961). All of these authors endorsed the primary *vasculopathy* hypothesis for DR, largely based on MacKenzie's treatise. And thus today, most textbooks categorize DR under *Vascular Diseases* of the retina (American Academy of Ophthalmology, 2014; Archer, 1999; Ryan, 2013).

Even though MacKenzie seemed to establish DR as a primary vasculopathy, descriptions of early neuropathy remained a recurring theme in the literature henceforth. For example, Edmunds et al., wrote in 1883 "[. . .] *that the optic nerves were not the only part of the nervous system affected. The changes found in the [optic] nerve appear to us to be too great to be secondary*" (Edmunds & Lawford, 1883). In 1904, Orlandini wrote (translated from Italian): "*Histological examination of the retina in de-pancreatised animals showed [. . .] two types of alterations: alteration of nervous tissue (especially (above all) ganglion cells and nerve fibers), and of blood vessels*" (Orlandini, 1904). Finally, in 1927, Lo Russo described pathologic changes in cadaveric human diabetic retinas, including nerve fiber layer (NFL) and ganglion cell layer (GCL) thinning, as well as cavitation of the inner retina (Lo Russo, 1927).

1.3. Renewed interest in diabetic retinal neurodegeneration (DRN)

In 1961, Wolter at the University of Michigan rediscovered DRN as an important event in the course of DR, via studies of donor eyes of people with diabetes (Wolter, 1961). He detected atrophy of ganglion cells (GCs) and degeneration of the inner nuclear layer (INL) in the donor eyes' retinas: (page 1138): "*[. . .] since it is possible that the nerve damage is primary and a cause of the vascular changes [. . .] The first change to occur in the retina in diabetes [. . .], is the swelling and degeneration of retinal neurons [. . .]*)." His work, which actually identified DR as a primary neuropathy, was later expanded by Barber and Gardner, initially at The Pennsylvania State University (Barber, 2003; Barber et al., 1998; Lieth, Gardner, Barber, Antonetti, & Penn State Retina Research, 2000). Gardner later continued this work at the University of Michigan. Previously, in 1962 at Ohio State, Bloodworth had described degeneration of the inner plexiform (IPL) and GCL in a histological study of 295 postmortem human eyes. He specifically identified pyknosis and fragmentation of GCL nuclei, features which are now recognized as typical characteristics of apoptosis (Bloodworth, 1962). Interestingly, he described a lack of spatial correlation between GCL and vascular lesions.

2. Retinal neurodegeneration: functional and structural aspects

Early findings on DRN work led to a plethora of studies on neuroretinal pathophysiology in diabetes. We now know that diabetes induces neural apoptosis of ganglion, amacrine, and Müller cells, as well as increased expression of glial fibrillary acidic protein (GFAP) in Müller cells, activation of microglia (Barber, 2003) possibly caused by chronic glutamate toxicity (Barber, 2003; Carrasco et al., 2007), inflammatory glial activation (Simo, Hernandez, & European Consortium for the Early Treatment of Diabetic, 2012; Zeng, Green, & Tso, 2008), and increased expression of other neurotrophic factors, including basic fibroblast growth factor and ciliary neurotrophic factor (Feng et al., 2009). Altered glutamate metabolism have been noted recently in diabetic retinas (Lieth et al., 1998; Mizutani, Gerhardinger, & Lorenzi, 1998).

These retinal abnormalities lead to functional changes, which have been well studied and typically precede clinical DR, in some cases occurring prior to the diagnosis of diabetes. Functional changes include deficits in the pattern electroretinogram (pattern ERG) (Falsini et al., 1989), increased implicit times in the multifocal ERG (mfERG) (Han, Adams, Bearse, & Schneck, 2004; Han, Bearse, et al., 2004; Pardue et al., 2014; Aung, Kim, Olson, Thule, & Pardue, 2013), changes in oscillatory potentials (Simonsen, 1980), abnormal dark adaptation (Drasdo, Chiti, Owens, & North, 2002), abnormal contrast sensitivity (Dosso et al., 1998; Sokol et al., 1985), abnormal color vision, and altered microperimetric and perimetric psychophysical testing (Han, Adams, et al., 2004; Realini, Lai, & Barber, 2004; van Dijk et al., 2011). Typically, central visual acuity is not affected in early DR and is normal before the vascular lesions of clinical DR develop (Adams & Bearse, 2012). We have demonstrated in a study, discussed more in detail below, that people with no or minimal DR have an average progressive neuroretinal (NFL, GCL, and IPL) thickness loss of 0.54 μm per year due to DRN (Sohn et al., 2016). While seemingly small, to put this in perspective, in a large study of patients with glaucoma, the average decline in neuroretinal thickness between early (<6 dB perimetric loss) and severe glaucoma (>12 dB loss) is 6–16 μm (Bogunovic et al., 2015). If DRN were to progress linearly at a rate of 0.54 μm per year over 10 years, it would result in a neuroretinal loss of 5.4 μm, the same magnitude as severe glaucomatous damage. Of note, this would occur irrespective of the presence of microvascular DR. While patients with glaucoma receive treatment and regular perimetric examinations to anticipate and prevent visual loss (Kirkizlar et al., 2013), such studies are not employed routinely for people with diabetes.

2.1. In vivo quantification of structural changes due to DRN

Immunohistochemistry has identified structural changes indicative of neurodegeneration: a reduction in optic nerve axons