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Vascular Considerations in Glaucoma Patients of African and European Descent

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Abstract

Glaucoma is the leading cause of blindness in individuals of African descent (AD). While open angle glaucoma (OAG) disproportionately affects individuals of AD compared to persons of European descent (ED); the physiological mechanisms behind this disparity are largely unknown. The more rapid progression and greater severity of the disease in persons of AD further raises the concern for identifying these underlying differences in disease pathophysiology between AD and ED glaucoma patients. Ocular structural differences between AD and ED patients, including larger optic disc area, cup:disc ratio and thinner corneas have been found. AD individuals are also disproportionately affected by systemic vascular diseases including: hypertension, cardiovascular disease, stroke and diabetes mellitus. Abnormal ocular blood flow has been implicated as a risk factor for glaucoma, and pilot research is beginning to identify localized ocular vascular differences between AD and ED OAG patients. Given the known systemic vascular deficits and the relationship between glaucoma and ocular blood flow, exploring these concepts in terms of glaucoma risk factors may have a significant impact in elucidating the mechanisms behind the disease disparity in the AD population.

Keywords

glaucoma; blood flow; African descent; race

INTRODUCTION

Glaucoma is a multifactorial disease that results in progressive death of retinal ganglion cells and loss of visual fields. Studies have shown that open angle glaucoma (OAG) disproportionately affects people of African descent (AD) over those of European descent (ED) and is a leading cause of blindness in persons of AD (Hyman et al. 2001; Congdon et al. 2004; Friedman et al. 2004). Furthermore, it has a younger age of onset, progresses more rapidly and occurs with greater severity in the AD population (Wilensky et al. 1978; Martin

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et al 1985; Wilson et al. 1985; Sommer et al. 1991; Tielsch et al 1991; Racette et al. 2003; Racette et al. 2010). Glaucoma has been noted to affect up to six times more people of AD than those of ED (Congdon et al 2004; Friedman et al. 2004). Moreover, the Ocular Hypertensive Treatment study described African-American race as a baseline factor that predicted increased risk of developing OAG (Gordon et al. 2002). Disparities in occurrence and progression between AD and ED groups have heightened interest in the mechanisms driving the observed disparity in OAG.

While etiology of OAG has yet to be fully described, elevated intra-ocular pressure (IOP) has been identified as a significant and currently only treatable risk factor. However, many patients develop glaucoma progression despite reduced IOP, while others do not develop glaucoma despite elevated IOP (Heijl et al. 2002). This suggests other factors are involved in OAG onset and progression (Harris et al. 2008), including compromised vascular health. Several large population-based studies have shown that decreased ocular perfusion pressure (OPP) has been linked to OAG prevalence, incidence and progression (Tielsch et al. 1995; Quigley et al 2001; Bonomi et al. 2000; Leske et al. 2002; Moore et al. 2008). Multiple small prospective studies have shown that blood flow deficiencies in retinal, choroidal, and retrobulbar circulations are associated with OAG (Yin et al. 1997; Galassi et al 1998; Chung et al. 1999). Specifically, studies have revealed an association of visual field defects with decreased blood flow velocities and increased resistivity indices of the ophthalmic and short posterior ciliary arteries (Galassi et al. 2003; Martinez et al 2005). These data indicate the potential importance of investigating ocular vascular differences between patients of AD and ED as a potential mechanism to explain glaucoma disease disparity.

Just as ED and AD patients differ in glaucoma development and progression, these two groups also differ in number of systemic vascular complications. Systemic vascular abnormalities, such as arterial hypertension, optic disc hemorrhage, and aging of the vasculature may contribute to and be indicative of ocular vascular compromise (Harris et al. 2008; Moore et al. 2008). People of AD have been reported to have higher rates of arterial hypertension (Racette et al. 2003), which may explain their increased rates of stroke (Sacco et al. 1998) and cardiovascular disease (CVD) (Farquhar et al. 1990; Ferdinand 2008). Those of AD have also been reported to have higher rates of diabetes, which is known to have vascular complications (Sample et al. 2009).

The possible relationship between systemic and localized vascular pathology and glaucoma onset and progression in persons of AD may be a contributory mechanism to the observed disease disparity. This paper will review functional, structural and vascular differences of ocular and systemic parameters between persons of AD and ED to better elucidate possible racial differences in glaucoma pathogenesis. We hope this will allow clinicians and researchers to consider and better understand the possible driving forces behind the disproportionate OAG vision loss experienced by persons of AD.

MATERIALS AND METHODS

PubMed and Google Scholar searches were conducted through May 7, 2013 with the following keywords: glaucoma, African descent, ocular blood flow, diabetes, cardiovascular

disease, stroke and ocular perfusion pressure. References from all relevant articles found were also reviewed to capture all pertinent articles.

VISUAL FIELD DIFFERENCES

Data from the prospective African Descent and Glaucoma Evaluation Study (ADAGES) showed that individuals of AD perform significantly worse than people of ED on all tests of visual function. Despite a younger average age, patients of AD in this study displayed worse mean deviation and pattern standard deviation and more abnormal points on total and pattern deviation plots compared to their ED counterparts. (Racette et al. 2010). In a retrospective analysis of black and white glaucoma patients, Wilson et al. noted that visual field loss and disc damage were worse in eyes of black patients at initial diagnosis. They also noted greater progression of visual field loss and disk damage in black patients (Wilson et al. 1985). Furthermore, it has been suggested that the association between age and visual field defects is stronger in persons of AD over persons of ED (Quigley et al. 1996). It is highly important to examine why persons of AD have worse visual outcomes compared to their ED counterparts despite similar IOP and available treatment options. Racette et al. hypothesize that the lower visual field performance noted in patients of AD could be due to multiple factors including detection of early visual field loss, lack of ancestry specific normative databases for various visual field tests, genetic diversity, genetic drift, environmental and/or socioeconomic factors; the importance of long term follow-up of patients in this study was emphasized by the authors. (Racette et al. 2010). While these studies indicate a disparity in visual field within AD patients, there is not an investigated mechanism to explain these outcomes. In this paper we will review literature concerning ocular and systemic vascular differences, as well as structural differences in persons of AD and ED in an attempt to explore possible mechanisms other than IOP that may be contributing to this disparity in visual outcome.

OCULAR STRUCTURAL DIFFERENCES AND INTRAOCULAR PRESSURE

Several ocular structural differences in AD and ED OAG patients have been discussed in literature. Studies have shown differences in optic disc structure between AD and ED groups. Significantly, larger optic disc area (Girkin et al. 2010), cup:disc ratio (C/D ratio) (Beck et al. 1985; Martin et al 1985; Chi et al. 1989; Higginbotham et al. 2004) and deeper maximum cup depth in those of AD (Beck et al. 1985; Mikelberg et al. 1995; Girkin et al. 2003; Racette et al. 2003; Girkin et al. 2005;) were found. In fact, the Barbados Eye Study reported C/D ratio to be positively linked with IOP (Leske et al. 1997). OAG patients of AD also tend to have thinner corneas (Racette et al. 2005; Haseltine et al. 2012), a known risk factor for OAG.

Currently, there is inconsistency in data regarding differences in IOP between individuals of AD and ED. Some studies attribute the increased prevalence and incidence of OAG in persons of AD to elevated IOP (Leske et al. 2002; Shimmyo et al. 2003; Girkin et al. 2005; Racette et al. 2005). In black patients in the Barbados Eye Study, Leske et al. identified a 25-fold increase in adjusted relative risk of OAG in patients with IOP greater than 25 mmHg over those with IOP less than or equal to 17mmHg (Leske et al. 2002). However, more

recent studies which have examined AD and ED OAG patient groups have reported no overall differences for mean IOP between AD and ED individuals (Sample et al. 2009; Siesky et al. 2013). It is worth noting that analyses from the Barbados, Rotterdam, and Baltimore studies demonstrated that hypertension is associated with increased IOP and thus may explain group differences in IOP data (Hennis et al. 2003; Racette et al. 2003; Wu and Leske 1997). While these differences in IOP and structure have been reported, there is no clear indication of their role in explaining glaucoma disparity within patients of AD.

OCULAR PERFUSION PRESSURE AND SYSTEMIC BLOOD PRESSURE

Studies have demonstrated a significantly higher incidence of arterial hypertension in persons of AD compared to ED (Wu and Leske 1997; Racette et al. 2003; Hennis et al. 2003; Sample et al. 2009; Siesky et al. 2013). In fact, Hall et al. reported people of AD have the highest prevalence of hypertension among any race regardless of geographic location (Hall et al. 1997). However, despite the reported higher frequency of systemic hypertension among people of AD, Sample et al. did not find differences in IOP between racial groups (Sample et al. 2009). Leske et al. presented predictors of OAG progression from the Barbados Eye Study, which consisted predominately of patients of AD, including lower systolic blood pressure (SBP) and systolic OPP (Leske et al. 2007). Importantly, lower OPP more than doubled the risk of developing OAG (Leske et al. 2008). Furthermore, the Rotterdam Eye study reported patients with an OPP less than 50 mmHg had four times the risk of developing OAG as those with 80mmHg (Hulsman et al. 2007).

As OPP is partially dependent on SBP, the relationship between each of these parameters and the development and/or progression of OAG is complex and results presented throughout the literature are varied. Many studies have found a positive correlation with SBP and IOP in patients with OAG (Dielmans et al. 1995; Tielsch et al. 1995; Bonomi et al. 2000; Klein et al. 2005; Yip et al. 2007). Deokule and Weinreb reported that each 10 mm Hg baseline SBP increase led to a mean 0.23 mm Hg to 0.31 mm Hg rise in IOP in OAG patients. They reported such a positive correlation to be present in all races, as such a relationship was found in studies that specifically investigated ED patients, AD patients and patients of Asian descent (Deokule and Weinreb 2008). In OAG patients, each 10 mm Hg DBP increase from baseline led to a 0.19 to 0.6 mm Hg IOP increase (Deokule and Weinreb 2008). However, they suggested that blood pressure may be more strongly correlated with OHT than with OAG. Each 10 mm Hg SBP increase (OR = 1.20) and DBP increase (OR = 1.38) was associated with 20-30% increase in OHT prevalence. On the other hand, each 10 mm Hg increase in SBP and DBP had an odds ratio for OAG of 1.08 to 1.12 and 1.00 to 1.09, respectively. They suggested perhaps there is a SBP threshold that must be met to affect OAG prevalence (Deokule and Weinreb 2008).

SYSTEMIC VASCULAR DIFFERENCES IN AD VS ED

Cardiovascular Disease and Stroke

Cardiovascular disease occurs in higher rates in persons of AD. According to the American Heart Association, the death rate per 100,000 persons for cardiovascular disease was 28.7 for white males, 39.0 for black males, 20.1 for white females, and 27.7 for black females

(Roger et al. 2012). In addition to having higher rates, people of AD also have an earlier onset and higher severity of cardiovascular disease. This is significantly affected by risk factors such as obesity, smoking, and a sedentary lifestyle (Ferdinand 2008). Siesky et al. also reported significantly higher heart rates in OAG patients of AD compared to ED (Siesky et al. 2013). Increased heart rate, in addition to arterial hypertension, is considered a risk factor for cardiovascular disease (Chambless et al. 2003, McGruder et al. 2004).

A difference between AD and ED populations also exists in stroke rates. People of AD have a 2.5-fold increase in stroke incidence compared to ED (Sacco et. al 1998; Howard et al. 2013). Howard et al. suggest that the disparity may be attributed to higher SBP and DBP, as well as poorer control of arterial blood pressure. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, after a 4.5 year follow up, Howard et al. reported a 10-mm Hg difference in SBP was associated with an 8% increase in stroke risk in whites but a 24% increase in stroke risk in for blacks (Howard et al. 2013). As both hypotension and hypertension have been associated with OAG (Weinreb and Harris, 2009), uncontrolled blood pressure may be a contributing factor to insufficient ocular perfusion in AD and ED OAG patients.

Atherosclerosis

Endothelial dysfunction and atherosclerosis also contribute to dysfunctional vascular regulation. Atherosclerosis, a chronic and progressive disease that affects many vascular beds, including the ocular circulation (Davies 1990), is the result of deposited lipids, inflammatory cells, and connective tissue within arterial walls. Buildup eventually leads to plaque formation and obstruction of flow (Davies et al. 2004). Endothelial cell dysfunction has been described as the first detectable change in atherosclerotic vessels (Behrendt & Ganz 2002). Many of the risk factors that account for the racial disparity of cardiovascular disease are also risk factors for atherosclerosis, including smoking, hypertension, diabetes, dietary patterns, and physical inactivity (Luscher et al. 1993, Agyemang et al. 2009). A higher risk of cardiovascular disease, a known risk factor of OAG (Higginbotham et al. 2004), may also be present within the ocular vasculature and may contribute to the difference in OAG risk between AD and ED persons.

Diabetes Mellitus

Evidence has also shown that individuals of AD differ from those of ED with respect to diabetes mellitus (DM). ADAGES reported their AD group to have higher prevalence of DM, that, although was not significant, approached significance ($p=0.10$) (Girkin et al. 2010). Moreover, although cardiovascular disease is not specific to diabetes, it is more prevalent among patients with type 1 or type 2 DM than among those without DM (Krolewski et al. 1987; Laing et al. 2003). Dysfunction of vascular regulation has also been shown in patients with DM (Triggle and Ding 2010), which may be apparent within the eye's vascular system. Both diabetic and glaucoma patients have been shown to have dysfunction in endothelial factors responsible for maintaining vascular tone (Shoshani et al. 2012).

Given the higher rates of diabetes and vascular complications in persons of AD, a better understanding of the diabetes, ocular vascular dysregulation and their relationship to glaucoma is imperative. Earlier studies have shown a correlation between DM and OAG (Becker 1971, Wilson et al. 1987), whereas more recent studies that exclude IOP as a criterion for OAG (Foster et al. 2002) found no increased OAG risk in diabetics (Quigley et al. 2001, Bonomi et al. 2000, Friedman et al. 2006). Moreover, the Ocular Hypertension Treatment Study reported that early diabetes protects against the development of OAG (Gordon et al. 2002), a finding that has since been questioned (Coleman et al. 2008). However, eyes of diabetic patients have exhibited more cross-linking of collagen through glycation (Goh and Cooper 2008), and it is suggested that such increased stiffness of the cornea and sclera reduces strain at the optic nerve head resulting from IOP-induced stress in the eye wall and thus limits damage (Quigley 2009). Since diabetes may cause vascular dysregulation and have neurotoxic effects that contribute to glaucoma progression (Shoshani et al. 2012), it is important to clarify how diabetes may be involved in patients of AD with OAG.

OCULAR (LOCALIZED) VASCULAR DEFICIENCY

In addition to systemic vascular compromise and low OPP, persons of AD may have other OAG vascular risk related factors including ischemia (Nickells 1996, Kyhn et al. 2009) and vascular dysregulation (Tielsch et al. 1995; Bonomi et al. 2000; Leske et al. 2002) although these have not been specifically investigated in the AD population. A recent retrospective study by Siesky et al. investigated ocular blood flow differences between AD and ED persons with OAG providing some of the first data to support these concepts. Results revealed statistically significant lower retrobulbar blood flow velocities in AD patients compared to ED patients. Reductions in peak systolic velocity in the ophthalmic artery ($p=0.0001$), central retinal artery ($p=0.010$) and nasal and temporal short posterior ciliary arteries ($p<0.0001$ and $p=0.0037$, respectively) were found in those of AD compared to ED. Lower ophthalmic artery end diastolic velocity ($p=0.0008$) was also found in patients of AD. These differences were found despite statistically similar IOP (Siesky et al. 2013). Similarly, a newly published prospective study by Adeyinka et al measured retrobulbar blood flow velocities in African patients with OAG in Nigeria and found reduced peak systolic and end diastolic velocities and increased resistivity in the ophthalmic and central retinal arteries of OAG patients compared to controls (Adeyinka et al 2013). Previous studies have demonstrated a reduction in blood flow velocities in the retrobulbar vessels of glaucoma patients in general (Sergott et al. 1994; Nicolela et al. 1996; Chiou et al. 1999; Akarsu and Bilgili 2004; Abegão Pinto L et al 2012), and lower retrobulbar blood flow within in OAG patients of AD may be a mechanism which contributes to their OAG disease disparity. Importantly, vascular resistance of retrobulbar vessels has been shown to predict visual field progression (Martinez et al. 2005); similarly, constricted blood flow has been associated with visual field loss (Galassi et al. 2003). It is important to note that while these studies on retrobulbar blood flow using color Doppler imaging are of great value, there are limitations to this methodology. These limitations include variability in measured parameters, inter-observer variability, and the inability to precisely measure vessel diameter, and therefore determine volumetric flow (Stalmans et al. 2011).

Despite those limitations, however, these studies suggest that persons of AD may be at a higher risk for vascular deficits contributing to OAG compared to persons of ED and in part may explain the differences in disease onset and progression.

CONCLUSION

Despite increased OAG incidence, prevalence and progression in individuals in AD over ED counterparts, the mechanisms accounting for disparity between the two groups have yet to be elucidated. Non-pressure dependent differences in ocular blood flow between people of AD and ED are beginning to be reported (Siesky et al. 2013) and may help identify the contributing mechanisms to this disease disparity. Persons of AD are known to have higher incidence of hypertension and other systemic vascular diseases, such as CVD, stroke, and diabetes. Many studies have shown an association between systemic vascular health and OAG, yet the exact relationship of these systemic vascular complications to ocular vascular health has not been defined. The mechanisms behind the disparity of OAG disease in persons of AD may involve the ocular vasculature, and further prospective investigation is highly suggested.

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