Peripheral Vascular Endothelial Dysfunction in Glaucomatocyclitic Crisis: A Preliminary Study

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PURPOSE. Glaucomatocyclitic crisis (GCC) is a syndrome of recurrent unilateral increased intraocular pressure associated with mild cyclitis and few clinical symptoms. This study was undertaken to assess brachial artery endothelium-dependent flow-mediated vasodilation (FMD) as an indicator of vascular endothelial dysfunction, to describe the association between GCC and endothelial dysfunction excluding age effects.

METHODS. This prospective study was conducted from January 2007 to April 2009 and included 12 patients with GCC and 15 age-matched normal control subjects. Detailed clinical parameters were reviewed, including highly sensitive C-reactive protein (hs-CRP), homocysteine, anti-SSA, anti-cardiolipin antibodies, and HLA type. Brachial artery FMD and endothelium-independent, nitroglycerin-mediated vasodilation (NMD) were studied by using high-resolution, two-dimensional (2-D) ultrasonic imaging.

RESULTS. Twelve patients with GCC were evaluated. The mean age of the patients was 36.3 years including 5 (41.6%) women and 7 (58.4%) men. There were no significant differences between patients with GCC and control subjects with regard to basal data, including body mass index, smoking, blood pressure, complete blood count, and routine blood biochemistries. Homocysteine and hs-CRP were within normal limits. Two (16.7%) patients were positive for HLA-B27, anti-SSA, and anti-cardiolipin antibodies. The nitroglycerin-mediated vasodilation in the patients with GCC was not significantly different from that of the control group. The FMD was much lower in the GCC group than in the control groups (mean 4.81% vs. 7.89%, that of the control group. The FMD was much lower in the patients with GCC than in the control groups (mean 4.81% vs. 7.89%, P < 0.01).

CONCLUSIONS. The significantly lower FMD in patients with GCC implies peripheral vascular endothelial dysfunction. However, in the 16.7% positive for the HLA-B27, anti-SSA, and anti-cardiolipin antibodies, these parameters are associated with GCC and abnormal FMD. (Invest Ophthalmol Vis Sci. 2010;51:272–276) DOI:10.1167/iovs.09-3849

Glaucomatocyclitic crisis (GCC), or Posner-Schlossman syndrome (PSS),1 is a syndrome of recurrent unilateral increased intraocular pressure (IOP) associated with mild cyclitis and few clinical symptoms. IOP may reach 40 mm Hg or more, and spontaneous remission usually occurs.1 In the acute phase of GCC, episodic changes in the trabecular meshwork lead to impairment of outflow facility and result in an elevation of IOP. It is most often classified as secondary inflammatory glaucoma.1,2

The etiology of GCC has remained elusive. Several factors have been postulated to contribute to the development of GCC, including autonomic defect,3 allergic conditions, a variation of developmental glaucoma, viral infection,4–7 and DNA oxidative damage of the trabecular meshwork.8 The vascular theory considers glaucomatous optic neuropathy to be a consequence of insufficient ocular blood supply, which can be a consequence of vascular endothelial dysfunction.9–11

The brachial artery flow-mediated vasodilation (FMD) measurement by high-resolution ultrasonography is a broadly applicable, noninvasive method that is used for the examination of endothelial function.12 FMD is designated as an endotheliumpendent process that reflects the relaxation of a conduit artery when exposed to the increased flow and shear stress induced by the release of nitric oxide.12,13

Several studies have shown impaired vascular endothelial function in glaucoma,9,10 but data from patients with GCC have not been reported. We assessed brachial artery endothelium-dependent FMD as an indicator of vascular endothelial function to describe the association between GCC and endothelial dysfunction.

METHODS

Participants

This prospective study was conducted from January 2007 to April 2009, and included 12 consecutive patients with GCC who were younger than 50 years (to diminish aging effects on endothelium) and were receiving treatment at the glaucoma clinic of Chang Gung Memorial Hospital. A presumptive diagnosis of GCC was made based on the following findings: (1) a history or record of unilateral recurrent transient episodes of elevated IOP; (2) a few keratic precipitates accumulating in the lower half of the cornea; (3) minimal flare and/or a few inflammatory cells in the anterior chamber; and (4) open iridocorneal angle without peripheral anterior synechia.14 Exclusion criteria included a history of ocular trauma, ocular laser treatment, or ophthalmic surgery before the diagnosis of glaucoma. Patients with systemic diseases such as hypertension, congestive heart failure, hypercholesterolemia, diabetes mellitus, cerebral vascular accident, or coronary

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artery disease were also excluded. Thus, none of the patients was currently taking systemic medications such as antihypertension drugs, cholesterol-lowering agents, aspirin, or nitrates, and none were receiving hormone replacement therapy. No subjects had migraine or Raynaud phenomenon. Most of the patients with GCC were being treated with topical IOP-lowering agents, oral carbonic anhydrase inhibitors, and topical corticosteroids.

The 15 age-matched normal control subjects who were undergoing routine medical examinations in the same hospital had normal physical and ocular examination results and no history of cardiovascular disease. None of the control subjects were taking systemic medications. The patient records were reviewed for demographic data, medical and ocular history, best corrected Snellen visual acuity (BCVA), highest IOP, and anterior and posterior segment findings. These two groups were referred to the vascular laboratory for vascular ultrasound after acute glaucomatous stage. All patients provided informed consent to the study procedures, which were reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital (98-1121B). The study conformed to the tenets of the Declaration of Helsinki.

**Blood Biochemical, Inflammation Markers, and Autoimmune Antibodies Measurements**

Venous blood samples were collected after 12 hours of overnight fasting. Fasting blood glucose levels (normal range, 70–105 mg/dL) were measured by the glucose oxidase method (AU640; Olympus, Tokyo, Japan). Serum cholesterol (desired range, <240 mg/dL), triglyceride (desired range, <150 mg/dL), creatinine (normal range: female, 0.6–1.2 mg/dL; male, 0.4–1.4 mg/dL), alanine aminotransferase (normal range, 0–36 U/L), and uric acid (normal range, <8.0 mg/dL) levels were measured enzymatically.

The presence of other autoantibodies, such as anti-nuclear antibody (ANA, normal <1:80), anti-cardiolipin antibody (positive >20 GPL U/mL), and anti-SSA antibody (positive >130 AU/mL) was determined and analyzed. The level of the nonspecific marker of immune system activation and inflammation, highly sensitive C-reactive protein (hs-CRP) (<1 mg/L, low risk; 1–3, mg/L average; and >5 mg/L, high risk), were determined by a high-sensitivity commercial assay (Daichi Pure Chemicals Co. Ltd., Tokyo, Japan; analyzer model 7600-210, Hitachi, Tokyo, Japan). Homocysteine (normal <12 μmol/L), protein C (normal, 70%–140%), and protein S (normal, 60%–140%), were also analyzed.

**Measurement of Vascular Endothelial Function**

All study subjects were referred to the vascular laboratory in the morning after fasting overnight for at least 8 hours after an acute glaucomatous episode. Tobacco, caffeinated beverages, and any medications including topical drugs were prohibited before examination. Brachial artery FMD was studied by high-resolution two-dimensional (2-D) ultrasonic imaging, as described previously. Two-dimensional images of the left brachial artery and pulsed Doppler flow velocity signals were obtained with an 7.5-MHz linear array transducer (model L7600; Acuson, Mountain View, CA). Imaging was performed in a dimly lit, quiet, temperature-controlled room. Patients rested supine for at least 10 minutes before the first scan and remained supine until the final recording was acquired with electrocardiogram continuous monitoring. Blood pressure was obtained from the right arm before imaging. Images were obtained approximately 3 to 5 cm above the antecubital fossa. Baseline 2-D images and pulsed Doppler blood flow velocity were acquired.

To induce hyperemia, a 5.6-in-wide blood pressure cuff was inflated to 250 mm Hg at the forearm. Arterial occlusion was maintained for 5 minutes with the transducer positioned carefully in an identical position by a micrometer-adjustable stereotactic probe holder. The cuff then was deflated rapidly, and pulsed Doppler velocity signals were recorded 5 to 10 seconds after deflation. At 60 seconds after cuff deflation, 2-D images of the brachial artery were recorded for 10 seconds. After the patient rested for another 10 minutes, nitroglycerin spray (400 μg) was administered. Brachial artery scans were performed again at the same location 4 minutes after the nitroglycerin spray. The FMD was expressed as the percentage of maximum vessel diameter change induced by hyperemia. Similarly, nitroglycerin-mediated vasodilation (NMD) was expressed as the percentage change in diameter response to nitroglycerin sublingual spray. The intraobserver and interobserver coefficient of variation for baseline arterial diameter measurement was 1.6% and 2.1%, respectively (n = 15).

**Statistical Analysis**

Data are expressed as the mean (range) for continuous variables and as a percentage for categorical variables. Continuous variables were compared among the GCC and control groups by the nonparametric Mann-Whitney test; P < 0.05 was considered statistically significant. The post hoc power was also calculated because of the small sample size.

**Results**

**Clinical Findings**

Twelve patients with GCC were evaluated. The mean age of the patients was 36.3 years (range, 18–50 years). This patient population was predominately male, including five (41.6%) women and seven (58.4%) men. In the control group, the mean age at diagnosis was 38.3 years (range, 19–50 years). The group consisted of 4 (26.7%) women and 11 (73.3%) men. All control patients were asymptomatic (Table 1).

There were no significant differences between these two groups in basal data, including body mass index, smoking, blood pressure, complete blood count, and routine blood biochemistries (Table 1). The best corrected visual acuity was 20/20 among all patients with GCC, but with elevated IOP (mean 45.8 mm Hg) and variable cupping area (mean area, 45.8%; Table 2). IOP was controlled in all patients with GCC within 1 week (Table 2).

**Activities of Inflammation, Autoimmune Markers, and Antibodies**

The indicators of atherosclerosis, homocysteine, and the acute phase protein increasing during systemic inflammation, hs-CRP, were all within normal limits. Moreover, the major physiological anticoagulant, protein C and protein S were normal. One patient (8.3%) in the GCC group was ANA positive (1:80), two patients (16.7%) in the GCC group were HLA-B27 positive, and two patients were anti-cardiolipin and anti-SSA antibody positive (Table 2).

**Impaired Endothelial Functions**

The mean FMD was 4.81% and 7.89% in the GCC and control groups, respectively (P < 0.01; Fig. 1). The post hoc power calculation was 0.84 for FMD (α = 0.05). Meanwhile, the mean NMD was 16.33% in the GCC group and 16.35% in the control group (P = 0.57; Table 1).

**Discussion**

GCC is considered to be an inflammatory glaucoma. Its detailed mechanism and etiology have remained unknown. Elevated IOP of GCC is believed to result from an increase in aqueous humor outflow resistance at the level of the trabecular meshwork. Malfunction of the trabecular meshwork in open angle glaucoma is associated with the expression of markers for inflammation, cellular senescence, oxidative damage, and decreased cellularity. Moreover, either nonarteritic anterior ischemic optic neuropathy or impaired ocular blood
flow is associated with glaucoma.11 15 However, endothelial dysfunction may precede vascular involvement. We elucidated the role of endothelial dysfunction in the prediction of vascular involvement in patients with GCC and tried to determine relation of the pathophysiology to autoimmune disease.

Relation of the Inflammation of GCC to Elevated hs-CRP and Hyperhomocysteinemia

There is a high prevalence of cytomegalovirus infection in eyes presenting with GCC, which may warrant a more judicious use of steroids until a viral etiology can be excluded.5–7 Measurement of hs-CRP, an inflammatory biomarker, independently predicts future vascular events and improves global classification of risk of cardiovascular diseases.16 Whether elevation of some other environmental or infectious stimulus or even directly effects platelet aggregation or coagulation is still undetermined.16 In this study, the normal white counts and hs-CRP levels (Table 1) implied that GCC may not be an active or systemic inflammation, even though local infection cannot be completely ruled out. Homocysteine is a highly reactive amino acid and is known to produce endothelial cell injury in both experimental animal and cell culture studies.17 The pathophysiological consequences of such endothelial injury may include impaired release of nitric oxide, associated with significant alterations in vascular function.

Homocysteine-related endothelial dysfunction may be involved in the initiation and progression of atherosclerosis and/or thrombosis.17–19 Moreover, hyperhomocysteinemia is present in patients with nonarteritic anterior ischemic optic neuropathy and central retinal artery occlusion.20 Patients with

Table 2. Clinical Features of Patients with GCC

<table>
<thead>
<tr>
<th>No.</th>
<th>IOP (mm Hg)</th>
<th>Cupping (%)</th>
<th>Glaucoma Therapy</th>
<th>Protein S (60%–140%)</th>
<th>Protein C (70%–140%)</th>
<th>HLA-B27</th>
<th>Autoantibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>20</td>
<td>A, B, C, P</td>
<td>91.0</td>
<td>105.0</td>
<td>–</td>
<td>Anti-cardiolipin (+), anti-SSA (+)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>30</td>
<td>A, B, C, P</td>
<td>72.0</td>
<td>77.2</td>
<td>–</td>
<td>Anti-cardiolipin (+)</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>70</td>
<td>B, C, P</td>
<td>97.2</td>
<td>135.6</td>
<td>–</td>
<td>Anti-SSA (+)</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>50</td>
<td>A, B, C, P</td>
<td>85.0</td>
<td>135.9</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>70</td>
<td>A, B, C, P</td>
<td>102.0</td>
<td>99.3</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>50</td>
<td>A, C, P</td>
<td>104.0</td>
<td>170.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>40</td>
<td>A, C, P</td>
<td>91.0</td>
<td>120.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>30</td>
<td>A, C, P</td>
<td>90.0</td>
<td>98.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>60</td>
<td>A, C, P</td>
<td>94.0</td>
<td>128.8</td>
<td>–</td>
<td>–</td>
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<tr>
<td>10</td>
<td>48</td>
<td>40</td>
<td>A, C, P</td>
<td>86.0</td>
<td>106.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>45</td>
<td>A, C, P</td>
<td>115.2</td>
<td>96.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>45</td>
<td>A, C, P</td>
<td>92.0</td>
<td>100.8</td>
<td>ANA+</td>
<td>–</td>
</tr>
</tbody>
</table>

BVCA in all patients was 20/20; in all, IOP had been controlled to <20 mm Hg within 1 week. A, acetazolamide (250 mg) tablets; ANA, anti-nuclear antibody (normal limit, <1.80); B, topical 0.15% brimonidine; C, topical 2% carteolol; IOP, the highest IOP (mm Hg) of the affected eye; normal anti-cardiolipin, <20 GPL U/mL; anti-SSA, <130 AU/mL; P, topical 1% prednisolone suspension.
GCC in our study did not have hyperhomocysteinemia but had a lower level of the protein (mean, 12.5 μmol/L vs. 9.2 μmol/L, \( P < 0.05 \)). The normal homocysteine level implies that supplementation with folic acid or vitamin B12 may be not necessary.

**Relation of GCC to Autoimmune Diseases with High Incidence of HLA-B27, Anti-SSA, and Anti-cardiolipin Antibodies**

Our results demonstrated a relatively high incidence of HLA-B27, positive anti-cardiolipin, and anti-SSA antibodies (each in 16.7%) of patients. Moreover, one (8.3%) patient with GCC was ANA positive.

Acute anterior uveitis is the most common form of intraocular inflammation, and approximately 50% of cases are associated with the HLA-B27 allele.\(^{21,22}\) HLA-Bw54 was found to be associated with 41% of cases of GCC in one series of 22 patients.\(^{25}\) However, HLA allele distributions can vary dramatically from one ethnic group to another. Typically, HLA-B27-associated uveitis is characterized by recurrent alternating acute unilateral episodes. The diagnosis of B27-associated uveitis is usually favorable, but some studies have reported up to 11% of patients becoming legally blind.\(^{24}\)

The anti-SSA antibody is a clinically important anti-nuclear antibody in patients with connective tissue diseases. It is found in 60% of patients with Sjögren syndrome and in 30% of patients with systemic lupus erythematosus.\(^{25,26}\) The antiphospholipid syndrome is an acquired autoimmune syndrome characterized by arterial and/or venous thrombosis and/or pregnancy morbidity in association with the prolonged presence of serum autoantibodies, including the so-called lupus anticoagulant and anti-cardiolipin antibodies.\(^{27,28}\) Antiphospholipid syndrome correlates closely with atherosclerosis, and the correlation with a type of anti-cardiolipin antibody may be predictive of more accelerated atherosclerosis. Our patients with GCC were without obvious thrombosis events, but 16.7% were positive for anti-SSA and anti-cardiolipin antibodies.\(^{29}\)

**Association of GCC with Endothelial Dysfunction**

FMD uses high-frequency ultrasonographic imaging of the brachial artery to assess endothelium-dependent FMD.\(^{29,30}\) Actually, vascular endothelial dysfunction plays an important role in the increased risk of cardiovascular diseases with aging patients.\(^{30}\) The physiology of brachial artery FMD is a response of ischemic/hypoxic challenge followed by anatomic vasodilatation that implies a compensatory increase in the blood flow to repair the transient damage induced by the noxious physiologic challenge. Hyperemia induced by transient ischemia of the forearm increases the shear stress on the brachial artery vessel wall, which provokes endothelial nitric oxide release and subsequently causes vasodilation.\(^{13}\) Brachial FMD can be measured also during ischemic handgrip exercise to see whether there is increased vasodilation.\(^{31}\) In addition, it has been shown that isometric handgrip exercise training improves FMD in hypertensive patients along with medication.\(^{32}\) FMD can be used as an indicator for clinical follow-up and response to medical treatment.\(^{12,13}\) We excluded the patients with GCC who were older than 50 years to avoid age-induced FMD. Therefore, the much lower FMD in younger patients with GCC implies endothelial dysfunction in the GCC group compared with the control groups (mean, 4.81% vs. 7.89%, \( P < 0.01 \); Table 1), but a normal response to non-endothelium-dependent NMD after an acute glaucomatous episode remained (Fig. 1).

Direct evidence of local ocular endothelial dysfunction is difficult to obtain.\(^{29,30}\) The impairment of endothelial function of the brachial artery in patients with GCC observed in this study indicated a systemic rather than a local vascular effect, even after an acute glaucomatous episode and excluding the factor of older age. Again, whether such a dysfunction exists in ocular circulation and its relationship to the progression of the disease remain uncertain.

Improvement of endothelial dysfunction may inhibit flare-ups of GCC. Conventional cardiovascular therapies such as angiotensin-converting enzyme inhibitors, statins, insulin-sensitizing agents, and estrogens have been shown to alleviate endothelial dysfunction, often independent of their effects on systemic disease processes.\(^{33}\) Strategies to reverse endothelial dysfunction include dietary supplementation with L-arginine and nifedipine to preserve, at least partly, endothelial integrity in patients with hypertension by enhancing the number and activity of endothelial progenitor cells.\(^ {34,35}\)

Our results imply that FMD impairment is found in patients with GCC. Differences in homocysteine and hs-CRP levels were not statistically significant between these two groups, but the higher rate of polymorphism of HLA-B27 and the autoimmune antibodies (anti-SSA, ANA, and anti-cardiolipin) are related to GCC. Based on the findings in this study, it is recommended that patients with GCC be evaluated with blood tests to determine HLA-B27, anti-SSA, and anti-cardiolipin status; in addition, brachial artery ultrasonography is recommended for finding the likely presence of abnormal endothelial response to the physiological challenge of artificially induced ischemic hypoxia.

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**References**


