EXTENDED REPORT

Increase of carotid artery stiffness and decrease of baroreflex sensitivity in exfoliation syndrome and glaucoma

Z Visontai, B Merisch, M Kollai, G Holló

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See end of article for authors' affiliations

Correspondence to: Gábor Holló, MD, PhD, DSc, 1083, Budapest, Tömö u 25–29, Hungary; hg@szem1.sote.hu

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Aim: To investigate the distensibility of the common carotid artery (CCA), baroreflex sensitivity (BRS) and its relation to plasma homocysteine concentration in exfoliation syndrome or exfoliation glaucoma (XFS/XFG).

Methods: Homocysteine concentrations were measured in 30 XFS/XFG patients and 18 age matched controls. In 21 patients and 17 controls the end diastolic diameter of the CCA and pulsatile distension were measured and BRS was calculated.

Results: There was no significant difference between the groups in sex distribution, age, heart rate, blood pressure, systemic diseases, or medication. In XFS/XFG patients homocysteine concentration was significantly elevated (unpaired *t* test, $p=0.023$), and CCA stiffness was higher ($p<0.05$), while strain, cross sectional compliance coefficient, distensibility, and BRS were significantly reduced compared to the controls (Mann-Whitney U test, $p\leq 0.013$ for each parameter). In XFS/XFG patients a positive correlation was found between age and plasma homocysteine level (Pearson's correlation, $r=0.490$, $p=0.007$), and a negative correlation between age and BRS (Kendall's correlation $r=-0.374$, $p=0.021$), as well as between homocysteine concentration and BRS (Kendall's correlation $r=-0.377$, $p=0.024$). No correlation was seen between these variables in the control group.

Conclusions: These results suggest a pathological large artery function as well as altered parasympathetic vascular control in XFS/XFG which increases with age and with higher homocysteine concentration.

Exfoliation syndrome (XFS) is an elastosis-like systemic condition characterised by excessive ocular and extraocular synthesis, together with progressive accumulation of a fibrillar extracellular material called exfoliation material.^{1–4} In certain countries, in the population over 60 years of age, XFS is common⁵; and in many cases it leads to the development of exfoliation glaucoma (XFG), which is one of the leading causes of glaucoma related visual impairment.^{5–6} XFS and XFG can clinically present as either a unilateral or a bilateral eye disease.⁵ In clinically unilateral cases, however, accumulation of the exfoliation material can be histologically detected in the clinically unaffected eye,^{3–4} and manifestation of XFS and XFG in the unaffected fellow eye increases with the length of follow up.^{3–5–7}

In both XFS and XFG, exfoliation material has in addition consistently been detected systemically, including in the vessel wall, myocardium, smooth and striated muscle cells, skin, and visceral organs.^{3–5–7} Although systemic clinical consequences of synthesis and accumulation of exfoliation material in XFS have not been clearly identified, the probability of clinically significant alterations is high. This is especially true for the cardiovascular system. Some plausible reasons for this are: iris vasculopathy is a well known feature of XFS^{8–11}; production of exfoliation material is considered elastosis^{1–2}; exfoliation material is present in the vessel wall, and pericytes in the whole body^{3–4–7–11}; and, lastly, in XFS and XFG plasma total homocysteine concentration is elevated,^{12–15} which can lead to a variety of vascular diseases including stroke, myocardial infarction, and venous occlusions.^{16–18} Despite these arguments however, the true association between different systemic vascular diseases and XFS/XFG remains controversial, since published results in this field are inconsistent. Association between XFS and cardiovascular and cerebrovascular morbidity has indeed been found in some studies,^{19–21} but in others^{22–25} such an association was not detected. Recently, an association

between XFS and aortic aneurysm has been proposed.²⁶ However, this association was not supported by the results of another similar study,²⁷ despite the fact that both aortic aneurysm and XFS can be explained by elastosis.^{1–2–27}

A decade ago, our group was the first to study functional changes in systemic macrocirculation and microcirculation in XFS/XFG. We found a mild parasympathetic cardiovascular neuropathy²⁸ as well as a decrease of cutaneous capillary blood flow and diminished cutaneous flow reactions to cold and warmth provocation.²⁹ These results suggested that systemic vasoregulation is altered in XFS/XFG.

Recently a non-invasive, high precision, automated ultrasound wall tracking system has been introduced which enables researchers to measure arterial elasticity.^{30–34} In a previous study using this technique we were able to identify increased arterial stiffness and decreased baroreflex function in juvenile and primary open angle glaucoma.³⁵ In the present study, in order to investigate systemic arterial function in XFS/XFG, using the ultrasound wall tracking system we measured end diastolic diameter and pulsatile distension of the common carotid artery, and calculated baroreflex sensitivity (BRS) in XFS/XFG patients and in normal control subjects of similar age. In addition, we tried to identify possible relations between BRS, age, and plasma homocysteine concentration in the two groups of subjects.

METHODS

The research protocol was approved by the institutional review board for human research of Semmelweis University, and informed consent was obtained from all participants before blood sampling and ultrasound examination. Thirty

Abbreviations: BRS, baroreflex sensitivity; CC, compliance coefficient; CCA, common carotid artery; DC, distensibility coefficient; MTHFR, 5,10-methylenetetrahydrofolate reductase; WTS, wall track system; XFG, exfoliation glaucoma; XFS, exfoliation syndrome

Table 1 Clinical characteristics of XFS/XFG patients and control subjects

	XFS/XFG (n = 30)	Controls (n = 18)	p Value
Age (years) (SD)	68.5 (7.0)	65.2 (6.8)	0.120*
range	54–84	55–77	
Sex (male/female)	9/21	5/13	0.869†
HR (bpm)	65.9 (10.8)	68.3 (9.7)	0.471*
SBP _B (mm Hg)	147.3 (19.5)	141.9 (15.8)	0.363*
DBP _B (mm Hg)	77.7 (11.1)	76.8 (11.2)	0.808*
ΔP _B (mm Hg)	69.6 (12.8)	65.1 (11.6)	0.262*
Systemic conditions			
Arterial hypertension	19	13	0.53†
Diabetes mellitus	4	4	0.45†
Stroke	3	1	1.00‡
Elevated serum cholesterol	5	3	1.00‡
Atherosclerosis	2	2	0.62‡
Smoking	1	0	1.0‡
Systemic medication			
Anticoagulant therapy/thrombocyte aggregation blocking	6	4	1.00‡
β blockers	3	4	0.40‡
Calcium antagonists	0	2	0.14‡
Diuretics	0	1	0.38‡
α1 blockers	0	1	0.38‡

HR, heart rate; SBP_B, brachial systolic blood pressure; DBP_B, brachial diastolic blood pressure; ΔP_B, brachial pulse pressure.

Unpaired *t* test; † χ^2 test; ‡Fischer's exact test.

consecutive XFS/XFG patients (25 with XFG and five with XFS) with no other active eye disease, and 18 control subjects with no clinical sign of XFS/XFG or other eye disease were involved in the study, which was carried out between April and June 2005. Before the measurements each participant underwent a detailed ophthalmological assessment which included slit lamp examination with pupil dilation, tonometry, automated perimetry, stereoscopic evaluation of the ocular fundus, and gonioscopy. Demographic and medical data on the participants are shown in table 1.

Of the 25 XFG patients, two had previously had cataract surgery, two argon laser trabeculoplasty, four trabeculectomy, and three both cataract surgery and trabeculectomy. Topical intraocular pressure lowering medication in this group at the time of the investigation consisted of β receptor blockers (*n* = 5), prostaglandin F_{2α} analogues (*n* = 9), and carbonic anhydrase inhibitors (*n* = 1). In each case, both topical and systemic medication was stopped for 24 hours before the ultrasonography. Blood samples for the purpose of plasma homocysteine concentration measurement were collected in EDTA tubes, in the morning after 12 hours of fasting; the samples were sent straightaway to the nearby central laboratory, where they were prepared and analysed immediately. Total plasma homocysteine concentration was measured by fluorescence polarisation immunoassay using the IMx system (Abbott Laboratories, North Chicago, IL, USA); the technique gives intraclass and interclass coefficient of variation <5%, normal range: 5.9–16.0 μmol/l. All participants underwent this blood sampling for plasma homocysteine concentration measurement; and 21 of the XFS/XFG patients and 17 of the control subjects attended the scheduled ultrasonography visit. In order to clarify the background of the elevation of plasma homocysteine concentration in the XFS/XFG group, in these patients plasma folic acid concentration was measured with Roche Modular Analytics technique and the single point mutation at position 667 of the human 5,10-methylenetetrahydrofolate reductase (MTHFR) gene was determined by using the Genosign MTHFR C677T kit (Nebotrade, Hungary).

Determination of arterial elasticity variables and BRS

The diameter of the common carotid artery (CCA) and its changes during the arterial pressure pulse were measured

using ultrasonography. The ultrasound device consisted of a vessel wall echo tracking system called the wall track system (WTS) (Pie Medical, Maastricht, Netherlands) combined with a conventional ultrasound scanner (Scanner 200, 7.5 MHz linear array, Pie Medical, Maastricht, Netherlands). The WTS with the integrated software is a standard device in cardiovascular research, and has been described in detail elsewhere.^{30–31} Carotid artery pressure was measured by applanation tonometry (SPT-301; Millar Instruments, Houston, TX, USA), and the carotid pulse wave recording was calibrated by using diastolic and mean brachial pressure values measured sphygmomanometrically on the right brachial artery. Brachial blood pressure was measured before and after ultrasonography of the CCA, and the mean values were used for the calculation of elasticity variables. Both the carotid tonometric pressure (the exact measure of CCA pressure) and the brachial sphygmomanometric pressure (the pressure conventionally used in earlier investigations) were used to calculate the elasticity parameters of the CCA.

To determine BRS, blood pressure was also monitored non-invasively and continuously beat by beat in the right middle finger, using plethysmography (Finapres 2300, Ohmeda, Helsinki, Finland).^{32–33} Spontaneously occurring fluctuations in the RR interval (time interval from the R-wave to the next R-wave on the electrocardiogram) and systolic blood pressure were used in the calculation.³²

The subjects reported for testing in the early afternoon, 2–3 hours after a light meal. During the day of the study they refrained from consuming coffee, tobacco, or alcohol. They were instrumented for electrocardiographic and arterial blood pressure recordings and were then allowed to rest for 15 minutes in a supine position (air temperature 21°C). This was followed by BRS determination and ultrasonography of the right common carotid artery. A standard limb three lead electrocardiogram was recorded to obtain R-waves that served as a trigger for activation of the WTS algorithm. The ultrasound transducer was kept in the same position throughout the recording period. At least five successful recordings were obtained from the artery during each recording session.

Data analysis

At least 10 cardiac cycles were used for analysis in each subject. Carotid vessel wall strain was defined as the relative

Table 2 Dimensions and elasticity variables of the common carotid artery, and baroreflex sensitivity, for XFS/XFG patients and control subjects

Parameters	XFS/XFG (n = 21)		Controls (n = 17)		p Value*
	Mean (SD)	Quartile range	Mean (SD)	Quartile range	
Strain (%)	3.89 (1.38)	2.91–4.35	5.32 (1.29)	4.39–6.41	0.004
CC _B (mm ² mm Hg ⁻¹)	0.05 (0.02)	0.03–0.06	0.07 (0.04)	0.05–0.08	0.011
CC _C (mm ² mm Hg ⁻¹)	0.05 (0.03)	0.03–0.06	0.07 (0.02)	0.05–0.07	0.005
DC _B (10 ⁻³ mm Hg ⁻¹)	1.11 (0.47)	0.77–1.41	2.01 (1.04)	1.51–1.94	<0.001
DC _C (10 ⁻³ mm Hg ⁻¹)	1.62 (1.19)	0.90–1.85	2.30 (1.13)	1.64–2.41	0.011
Stiffness _B	0.18 (0.07)	0.14–0.22	0.12 (0.04)	0.10–0.16	0.003
Stiffness _C	0.20 (0.11)	0.14–0.23	0.14 (0.03)	0.12–0.16	0.044
BRS (ms mm Hg ⁻¹)	7.23 (5.53)	2.55–10.25	13.15 (8.75)	8.00–14.70	0.013

*Mann-Whitney U test.

Strain, relative change of the carotid artery diameter; CC_B, cross sectional compliance coefficient calculated using brachial blood pressure values; CC_C, cross sectional compliance coefficient calculated using carotid blood pressure values; DC_B, distensibility coefficient calculated using brachial blood pressure values; DC_C, distensibility coefficient calculated using carotid blood pressure values; Stiffness_B, stiffness calculated using brachial blood pressure values; Stiffness_C, stiffness calculated using carotid blood pressure values; BRS, baroreflex sensitivity.

change in carotid diameter from end diastole to peak systole, and was expressed as percentage change. Cross sectional compliance coefficients (CC_C calculated using pulse pressure of the common carotid artery, and CC_B using the brachial artery pulse pressure) were calculated as: $\Delta A/\Delta P$; where ΔA is the change in cross sectional area from end diastole to peak systole in the CCA, and ΔP is the carotid pulse pressure (for CC_C) or brachial pulse pressure (for CC_B). Artery distensibility coefficients (DC_C calculated using pulse pressure measured on the carotid artery, and DC_B calculated with pulse pressure measured on the brachial artery) were calculated using the expression: $2\Delta D/(D \times \Delta P)$; where D is the carotid end diastolic diameter, ΔD is the change in carotid diameter from end diastole to peak systole (distension), and ΔP is the carotid pulse pressure (for DC_C) or brachial pulse pressure (for DC_B). Stiffness, a pressure independent measure of arterial elasticity (Stiff_C calculated using carotid, and Stiff_B using brachial blood pressure values), was calculated as $\ln(SBP/DBP)/(\Delta D/D)$, where SBP and DBP are the systolic and diastolic blood pressure values (carotid or brachial). The coefficients of variation for carotid dimensions and distensibility were <10% for each of our participants.

Statistical analysis

Statistical analysis was performed using the StatSoft program package, Statistica for Windows, Release 5.0 (Statsoft, Tulsa, OK, USA). The unpaired *t* test was used to compare plasma homocysteine concentration, heart rate and systolic, diastolic, and pulse pressure of the brachial artery between the groups. The unpaired *t* test, χ^2 test, or Fisher's exact test (as appropriate) was used to compare the frequencies of sex, systemic medical conditions, and systemic medication between the groups, according to the expected numbers and the table sizes. Because of the non-normal distribution of

strain, cross sectional compliance coefficients, distensibility coefficients, stiffness, and the BRS, the Mann-Whitney U test was used for group comparison. Pearson's correlation coefficients were calculated to investigate the relation between age and plasma total homocysteine concentration, and Kendall's correlation coefficients to investigate the relation between age and BRS, and between plasma homocysteine concentration and BRS. A *p* value <0.05 was considered as statistically significant.

RESULTS

No significant differences were seen between the XFS/XFG group and the controls (table 1), or between the 21 XFS/XFG patients and the 17 control subjects who underwent ultrasonography (detailed data not shown for these subgroups) with respect to age, sex distribution, systemic conditions and medication, heart rate, or systolic, diastolic, and pulse pressure. Total plasma homocysteine concentration was significantly higher (*p* = 0.023) in XFS/XFG patients (11.95 (4.32) μ mol/l, mean (SD) than in the controls (9.14 (3.08) μ mol/l). Three XFS/XFG patients (10%), and none of the control subjects, had hyperhomocysteinaemia (total homocysteine concentration >16.0 μ mol/l). Carotid strain, CC and DC were significantly lower, and stiffness was significantly higher, in XFS/XFG patients than in the controls (table 2).

Corresponding elasticity parameters, calculated by using carotid tonometric pressure and brachial sphygmomanometric pressure, showed similar differences between the groups (table 2). BRS was significantly lower in the XFS/XFG group than in the control group (*p* = 0.013, table 2).

In the XFS/XFG group a significant positive correlation was found between age and plasma total homocysteine concentration (*p* = 0.007), and a significant negative correlation

Table 3 Correlations between age and measured parameters, for XFS/XFG patients and control subjects

	R	p Value
XFS/XFG patients		
Age v Hcy (n = 30)	0.490	0.007*
Age v BRS (n = 21)	-0.374	0.021†
Hcy v BRS (n = 21)	-0.377	0.024†
Controls		
Age v Hcy (n = 18)	0.441	0.076*
Age v BRS (n = 17)	0.336	0.069†
Hcy v BRS (n = 17)	0.183	0.343†

Hcy, plasma homocysteine concentration; BRS, baroreflex sensitivity.

*Pearson's correlation; †Kendall's correlation.

between age and BRS ($p = 0.021$) as well as between plasma total homocysteine concentration and BRS ($p = 0.024$, table 3). In contrast, no correlation was found between these variables in the control group (table 3).

In the XFS/XFG group, plasma folic acid concentration (mean 10.48 (SD 5.23) $\mu\text{g/l}$) was not below the normal range (2.0–9.1 $\mu\text{g/l}$) in any patient, and only one patient had a homozygote mutation of the MTHFR C677T gene.

DISCUSSION

Though systemic vascular alterations in XFS and XFG have in the past 15 years been studied both with epidemiological^{20–27} and physiological^{19, 28–29} methods, the exact nature and clinical significance of such alterations have not been identified. In this study we investigated whether arterial distensibility is reduced and spontaneous baroreflex sensitivity is impaired in XFS/XFG, and whether the alteration of parasympathetic vascular control is related to age and plasma total homocysteine concentration. The background of this investigation is the accumulation of exfoliation material in the vessel wall, which suggests several consequences: degenerative vascular changes,^{3–5} the pathological alteration of cutaneous capillary blood flow and its regulation in XFS,²⁹ and the significant elevation of plasma homocysteine concentration,^{12–15} which is generally associated with several vascular pathologies.^{16–18} Each of these pieces of evidence, taken independently, refers to some kind of systemic vascular damage or alteration; but their co-occurrence in XFS/XFG suggests the possibility of a more severe condition.

Our XFS/XFG patients did not differ from the control subjects in age, sex distribution, systemic diseases, and medication, and both topical and systemic medications were stopped for 24 hours before the ultrasonographic measurements. This shows that the observed differences between the groups were not caused by different demographic or medical conditions but, probably, by the presence or absence of exfoliation material in the body. We found a significantly elevated plasma total homocysteine concentration in XFS/XFG compared to the controls, which accords with the published reports on this syndrome.^{12–15} The exclusion of other possible causes (the fact that in the XFS/XFG group no patient had low plasma folic acid concentration, and only one was homozygotic for the MTHFR C677T mutation) suggests that the elevation of plasma homocysteine concentration and the damage to large artery function were related to the production of the exfoliation material. Moreover, we found that in XFS/XFG total plasma homocysteine concentration increased significantly with increasing age, a phenomenon which was not seen in the control group. As far as we know this is the first report on the age dependency of plasma homocysteine concentration in XFS/XFG. Our result suggests that plasma homocysteine level may increase during the age dependent progression of XFS.

Using the high precision, automated ultrasound wall tracking system^{30–34} we found that parameters characterising arterial distensibility (strain, CC, and DC) were significantly lower, and stiffness, a parameter which characterises arterial rigidity, was significantly higher in XFS/XFG than in the control group. These results suggest that the arteries become more rigid as a result of XFS/XFG.

BRS was significantly reduced in XFS/XFG, indicating a pathologically altered parasympathetic cardiac control in this patient group. It is of special interest that in the XFS/XFG group BRS correlated negatively both with age (age range 54–84 years) and plasma total homocysteine concentration, but in the control group (age range 55–77 years) no similar correlation or tendency was seen. Age dependent decrease of BRS has been shown in studies correlating age and BRS in subjects, representing a wide age range (18–70 years of

age).^{28–34} However, over 50 years of age the correlation became undetectable because of an age related increase of vascular rigidity even in normotensive subjects.^{28–34} Our finding that an age dependent decrease of BRS was detectable in XFS/XFG patients over 54 years of age suggests that large vessel function is specifically and progressively damaged in this disease. The positive correlation between age and plasma homocysteine concentration in the XFS/XFG patients suggests that the excessive age related decrease of BRS may be connected to the age related increase of plasma homocysteine level. Mild to moderate elevation of plasma homocysteine concentration leads to several serious vascular diseases like myocardial infarction, stroke, and venous occlusions,^{16–18} which all involve sclerotic changes of the arterial wall and show association with XFS.^{19–21}

It is well documented that in XFS the amount of exfoliation material increases with age, and that the complications of XFS (development of XFG, zonulolysis, etc) appear with increasing frequency also with advancing age.^{3–5, 7} Considering these facts together with the results of our study, it seems possible that an age dependent progression of XFS severity leads to increased excess production of both the exfoliation material and of homocysteine. This process may, in due course, result in a measurable increase of arterial wall rigidity and a decreased baroreflex function.

Our findings, from the functional, physiological point of view, support the previously published epidemiological results on the association between systemic vascular diseases and XFS. To determine the clinical significance of systemic vascular changes in XFS/XFG, further clinical studies may be advantageous. Such studies could focus on the relation between measurable cardiovascular dysfunction and the duration of the XFS (or age, as an easily available marker for disease duration), as well as on plasma homocysteine concentration.

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Authors' affiliations

Z Visontai, G Holló, Department of Ophthalmology, Semmelweis University, Budapest, Hungary

B Merisch, M Kollai, Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary

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None of the authors has any interest in any instrument or technique used in the study.

Ethics approval (see also Methods section): the research protocol was approved by the Institutional Review Board for Human Research of Semmelweis University, and informed consent was obtained from all participants before imaging was performed.

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