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Vascular function and ocular involvement in sarcoidosis

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ABSTRACT

Ocular involvement occurs in sarcoidosis (Sar) patients mainly in the form of uveitis. This study was designed to determine if uveitis in Sar patients is associated with vascular impairment. We enrolled 82 Sar patients and 77, age and sex matched, control subjects (Cl). Sar patients were divided into those with ocular sarcoidosis (OS) and those without ocular sarcoidosis (WOS). Endothelial function was evaluated by flow-mediated dilation (FMD). Pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of arterial wave reflections. Although there was no significant difference in sex, age and mean arterial pressure, patients with OS compared to WOS patients and Cl subjects had impaired FMD ($p < 0.001$), increased AIx ($p = 0.02$) and increased PWV ($p = 0.001$). Interestingly, impaired FMD in Sar patients was independently, from possible covariates (age, sex, smoking habits, arterial hypertension, dyslipidemia), associated with increased odds of ocular involvement (odds ratio = 1.69, $p = 0.001$). More precisely ROC curve analysis revealed that FMD had a significant diagnostic ability for the detection of OS (AUC = 0.77, $p < 0.001$) with a sensitivity of 79% and a specificity of 68% for an FMD value below 6.00%. To conclude in the present study we have shown that ocular involvement in Sar patients is associated with impaired endothelial function and increased arterial stiffness. These results strengthen the vascular theory which considers uveitis a consequence of vascular dysfunction in Sar patients and reveals a possible clinical importance of the use of endothelial function tests.

Introduction

Sarcoidosis is a chronic multisystemic granulomatus disease attributed to an exaggerated cellular immune response against a variety of antigens or self-antigens, which is directly characterized by non-caseating epitheloid granulomas in affected organs (Newman et al., 1997). Sarcoidosis except for lungs and lymph nodes, can also affect heart, liver, nervous system, skin, muscles, and eyes (Barnard and Newman, 2001; Kul et al., 2014). Microvascular disease, endothelial dysfunction and arterial wall properties have gained interest lately, as they are implicated in the pathophysiology of the disease and they can partially explain the clinical presentation of the patients (Mavrogeni et al., 2014).

Although its mortality rate is low, sarcoidosis adversely affects the cardiovascular system. Myocardial lesions are observed in 20–30% of patients (Barnard and Newman, 2001) while endothelial function and arterial wall properties are markedly impaired in this population in parallel with the severity and duration of the disease (Siasos et al., 2011a).

Importantly, the chronic nature of the disease can be disabling both physically and mentally (Saligan et al., 2010). Ocular disease may be the initial manifestation in sarcoidosis or may evolve during the disease course (Demirci and Christianson, 2011; Bernard et al., 2013). The overall ocular involvement (mostly in the form of uveitis) is present in 25%–50% of patients with systemic sarcoidosis and among all the cases of uveitis sarcoidosis is responsible for around 5% (Rothova, 2000). The most common type of sarcoidosis associated uveitis is anterior uveitis, affecting mainly younger ages. In contrast, posterior type and panuveitis affect middle and older ages (Rothova, 2000). Unfortunately, sarcoid uveitis is considered a major cause of visual loss in Europe (Rothova et al., 1996).

Abbreviations: AIx, augmentation index; FMD, flow mediated dilation; OS, ocular sarcoidosis; PWV, pulse wave velocity; WOS, without any manifestations of ocular sarcoidosis.

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As arterial wall properties and endothelial function are impaired in other ocular and inflammatory diseases (Siasos et al., 2011b; Palenski et al., 2013) and as there are no data concerning the association and the progression of sarcoid uveitis with endothelial function and arterial wall properties we examined the association of endothelial dysfunction and arterial stiffness in the incidence of uveitis in a population of sarcoidosis patients and the potential clinical implications.

Materials and methods

Study population

In this case control study we accessed data of 180 consecutive patients with sarcoidosis presenting at the Outpatient Department of Sarcoidosis, Chest Disease Hospital "Sotiria" in Athens. Sarcoidosis diagnosis was biopsy proven by the presence of non-caseating granulomas in various specimens such as lung, lymph nodes, and skin. Based on chest X-ray, biochemical measurements and the absence of clinical signs and symptoms (Iannuzzi et al., 2007), we excluded from the study population those with no active form of the disease. We also excluded those with involvement of the heart or other organs (except eye) to avoid the possible impact of other organ involvement in arterial function. Finally, we included 82 sarcoidosis patients with lung or eye and lung involvement who were under cortisone treatment and free from other immunological or inflammatory disorders and retinal or uveal diseases. Moreover subjects with clinical cardiac symptoms, known or suspected neoplasm, hematological malignancies, chronic kidney disease, diabetes mellitus, immunosuppression, hepatic impairment and recent surgery (within the previous 6 months) were excluded from the study. Eventually, sarcoidosis patients were divided based on a comprehensive ophthalmologic examination, into two groups according to the presence of ocular manifestations in the form of uveitis. The first group consisted of 54 patients without any manifestations of ocular sarcoidosis (WOS) and the second group of 28 patients with ocular sarcoidosis (OS) specifically in the form of sarcoid uveitis. Moreover we recruited 77 control subjects from the Outpatient cardiology department of Hippokration Hospital in Athens, without evidence of cardiovascular or other disease, based on medical history, physical examination and blood tests. History of cigarette use was assessed through an interview preceding the physical examination. We defined as "smoker" the current smokers, who smoked at least one cigarette per day and as "no smoker" those who had never tried a cigarette in their lives or those who had stopped smoking for at least 1 year. Blood pressure and a hematological and biochemical profile were determined. Diabetes was considered present if a patient was treated with insulin or oral agents or had a fasting glucose level $\geq$126 mg/dl. Hypertension was defined by systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, the current use of antihypertensive treatment, or a combination of the three. Hyperlipidemia was defined as total cholesterol level $\geq$200 mg/dl, the current use of lipid-lowering treatment, or both.

The study (complied with the Declaration of Helsinki) was approved by the Institutional Ethics Committee and an informed consent was given by each participant.

Ophthalmic investigations

All patients recruited in the study had an ophthalmological examination (visual acuity measurement, tonometry, slit lamp biomicroscopy, funduscopy, fluorescein angiography and Optical Coherence Tomography were performed where necessary) in the context of sarcoidosis investigation. The diagnosis of uveitis was established following the seven international diagnostic criteria proposed by the first IWOS in 2009 (Table 1, (Herbort et al., 2009)).

Table 1
Diagnostic criteria for ocular sarcoidosis.
Herbort et al. (2009).

1. \Mutton-fat keratic precipitates (large and small) and/or iris nodules at papillary margin (Koeppe) or in stroma (Busacca)
2. Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3. Snowball/string of pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active and atrophic)
5. Nodular and/or segmental peri-phlebitis ($\pm$ candle wax drippings) and/or macroaneurism in an inflamed eye
6. Optic disk nodule(s)/granuloma(s) and or solitary choroidal nodule
7. Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

Evaluation of endothelial function

Endothelial function was evaluated in Hippokration Hospital by estimating the flow mediated dilation in the brachial artery, as previously described (Tousoulis et al., 2005). Briefly, after a 10 minute rest, the right brachial artery was scanned in longitudinal section, 5 cm above the antecubital fossa using a linear array U/S transducer. A pneumatic cuff placed distal to the ultrasound probe was then inflated to suprasystolic pressure on the forearm for 5 min to induce reactive hyperemia. After the release of the ischemia cuff, brachial artery diameter was measured every 15 s for 2 min, and flow mediated dilation (FMD) was defined as the % change of vessel diameter from rest to the diameter 60 s after cuff release. The same examiner throughout the study conducted the examinations. The same observer who was blinded to the image sequence and the disease status of the participants measured images. The repeatability of the technique in our institution for determining FMD was determined according to the Bland–Altman method. The repeatability coefficient, which was calculated as defined by the British Standard Institution, that is, according to the formula: repeatability coefficient $= 2 \times \sqrt{(\Sigma di^2 / N)}$ (where N is the sample size and di the difference between the two measurements in a pair), was 5.0%.

Evaluation of arterial stiffness

a) Carotid-femoral pulse wave velocity (PWV), which is considered to be an index of aortic stiffness (Vlachopoulos et al., 2005) was calculated from measurements of pulse transit time and the distance traveled between 2 recording sites (PWV = distance in meters divided by transit time in seconds) by using a well validated noninvasive device (SphygmoCor, AtCor Medical) (Asmar et al., 1995). Two different pulse waves were obtained at 2 sites (at the base of the neck for the common carotid and over the right femoral artery) with the transducer. Distance was defined as the distance from the suprasternal notch to femoral artery minus the distance from the carotid artery to the suprasternal notch.
b) Augmentation index (AIx) of the central (aortic) pressure waveform was measured as an index of wave reflection (Vlachopoulos et al., 2004). AIx is a composite measure of the magnitude of wave reflection and arterial stiffness, which affects timing of wave reflection. Large values of AIx indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased PWV (owing to increased arterial stiffness) and vice versa. AIx was measured with a validated, commercially available system (SphygmoCor, AtCor Medical) that uses the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse.

Statistical analysis

All variables were tested for normal distribution of the data. Normally distributed data were expressed as means $\pm$ standard deviation and skew variables as median with first and third quartiles. For normally