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Original Article

Ankle-brachial index and peripheral artery disease are not related to restless legs syndrome

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ABSTRACT

Objective: Our aim was to investigate the relationship between impaired peripheral arterial circulation as measured by ankle-brachial index (ABI) and restless legs syndrome (RLS) in the general population.
Methods: Data are derived from three independent, German population-based, prospective studies: the control sample of BiDirect ($N = 966$), the second follow-up of SHIP ($N = 2333$), and a subsample of SHIP-Trend ($N = 1269$). RLS was assessed with questions based on the RLS minimal criteria. ABI was measured with an automated method in BiDirect and with Doppler ultrasound in both SHIP studies. An ABI score below 0.9 was indicative of peripheral arterial disease (PAD). Co-morbidities, medications and behavioural factors were self-reported. Additional measurements included body mass index and haemoglobin from blood serum. For BiDirect, a follow-up with identical methodology was performed after a median of 2.5 years.
Results: In cross-sectional analyses, decreased ABI was not significantly associated with RLS as outcome in multivariable logistic regression models adjusted for several potential confounders (BiDirect: odds ratio (OR) = 1.07 for a −0.1 change in ABI, 95% confidence interval (CI): 0.81−1.42, $p = 0.62$; SHIP-2: OR = 0.99, CI: 0.85−1.16, $p = 0.94$; SHIP-Trend: OR = 0.99, CI: 0.87−1.13, $p = 0.88$). Similar non-significant results were achieved using PAD (instead of ABI) as an independent variable. In BiDirect, baseline ABI was not a significant predictor of incident RLS in longitudinal analysis (OR = 0.77, CI: 0.53−1.12, $p = 0.17$).
Conclusion: Results from three independent studies suggest that reduced ABI is not a risk factor for RLS in the general population.

1. Introduction

Restless legs syndrome (RLS) is a frequent neurological disorder characterized by an urge to move the lower limbs often accompanied by unpleasant sensations. Dopaminergic dysfunction of the central nervous system has a prominent role in the development of RLS. Karl-Axel Ekbom, who gave the modern clinical description of RLS in 1945, believed that the disorder was caused by local vasoconstriction of the extremities, and he treated some of his patients with short-acting nitroglycerine tablets [1]. Several, more recent case reports support the notion that vasodilators may effectively relieve RLS symptoms [2–4]. Near-infrared light applied on the legs and feet has a similar therapeutic effect, probably due to vasodilation [5,6].

Microvascular circulation is the blood flow through the smallest vessels embedded within organ tissues. Its main role is the steady exchange of blood gases and nutrients between the blood and tissues. Altered microvascular circulation induces local hypoxaemia in the skin and muscle tissue of the legs in RLS patients [7–11]. Peripheral hypoxia was observed during the emergence of RLS symptoms, which strongly correlated with RLS severity [11].

As opposed to the capillary system, the role of larger arteries is to circulate blood to the organs, smoothing out the pulsatile pressure caused by the intermittent ventricular ejections. Even though larger arteries are controlled by regulatory mechanisms different to

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microvessels, capillary blood flow is also dependent on the macrocirculation. Consequently, reduced blood flow in the larger arteries may also induce local hypoxia in the lower extremities and thus could be a risk factor for RLS. Still, to our knowledge, the integrity of macrovascular circulation has not been investigated in RLS patients.

Ankle-brachial index (ABI) is a standard measure of the arterial blood flow of the lower extremities and the non-invasive gold standard for detecting peripheral artery disease (PAD) [12]. Decreased ABI carries an increased risk of incident coronary events, stroke and mortality in the general population [13–15]. Several studies suggest that reduced ABI is also predictive of compromised microcirculatory flow and tissue hypoxia in patients with PAD and in healthy individuals [16–18]. Our objective was to assess and compare ABI in subjects with RLS vs without RLS, and to investigate the potential relationship between RLS and PAD in three independently conducted population-based studies.

2. Methods

2.1. Study population

Analyses are based on three independent German population-based studies.

BiDirect is an observational cohort study with the primary aim of exploring the mutual relationship between depression and (subclinical) arteriosclerosis [19]. The BiDirect study incorporates three distinct groups of study subjects: (1) patients with acute clinically diagnosed depression ($N = 1004$), (2) patients with established cardiovascular disease (CVD) ($N = 348$), and (3) a control sample randomly drawn from the general population ($N = 966$). The first wave of data collection was conducted between 2010 and 2013, and a follow-up with identical methodology was performed after a median (range) of 2.5 (1.2–4.8) years. Here we report results only for the group of controls at baseline (except for the longitudinal analysis). The response to invitation at baseline in this group was 41.5%, and 81.9% of these individuals ($N = 791$) participated in the follow-up.

The Study of Health in Pomerania (SHIP) is a population-based cohort project with two main objectives: (1) to assess prevalence and incidence of common risk factors, subclinical disorders and clinical diseases, and (2) to investigate their complex associations. The study region for SHIP is West Pomerania, a region in the northeast of Germany. In 1996, 6267 adults aged 20–79 years were invited for the first cohort (SHIP-0) and 4308 (68.7%) participated. This study employed data from the 2333 subjects (54.2%) who participated in the second follow-up examinations 10 years later (SHIP-2) [20].

SHIP-TREND is an independent cohort conducted in the same region sampled between 2008 and 2012. A total of 4420 individuals aged 20–79 years participated out of 8826 invited subjects (50.1%). Within this cohort, 1269 participants (28.7%) agreed to undergo an optional one-night polysomnography in addition to the standard examination protocol; they were included in the analyses of this report.

2.1.1. Ethical approval

All studies were approved by the respective local ethics committees and followed the Declaration of Helsinki. All participants provided written informed consent for participation in the study.

2.1.2. Data collection

Interviews were carried out by trained and certified interviewers. Only those tools that are pertinent to the current analyses are detailed below, more detailed study protocols have been previously published [19,20].

Information about age, gender, history of diabetes, cardiovascular diseases, renal disease, stroke, hypertension, physical activity, and smoking status was collected during the interviews [21]. In BiDirect, physical activity was assessed with the short form of the International Physical Activity Questionnaire [22], which yields high, moderate, and low activity categories. The first two categories were pooled together for the purpose of the present analyses. In the SHIP studies, subjects engaging in physical training during summer or winter less than 1 h/week were classified as being physically inactive. Smokers were categorized as non-smokers, former smokers, and current smokers. Participants were asked to bring packages of their current medication, and the obtained data were classified according to their therapeutic and chemical properties based on ATC Codes (Anatomic Therapeutic Chemical/Defined Daily Dose Classification System) [23]. Subjects reporting a physician-made diagnosis of diabetes or receiving medical treatment for diabetes were classified as diabetic. Hypertension was defined either as reporting a diagnosis of hypertension or a measured systolic blood pressure $\geq$140 mmHg or a diastolic blood pressure $\geq$90 mmHg or taking antihypertensive medication. Weight and height were measured with shoes and heavier clothes removed.

2.1.3. RLS assessment

RLS was assessed identically in all studies, using a short questionnaire that had previously been validated against physician's classification [24] and has already been used in prior reports [25–30]. In addition, the questionnaire is currently undergoing a validation against physician's diagnosis within a subset of BiDirect participants. Based on interviews with 57 subjects, the tool has a sensitivity of 85.2% and a specificity of 83.3% (unpublished results). The questions followed the minimal criteria published by the International Restless Legs Syndrome Study Group. Participants were only classified as RLS positive if they answered all symptom questions with “Yes”. The frequency of RLS symptoms was also assessed with a single question (“How often do these symptoms occur?”) with the following answer categories: “Daily,” “three to six times a week,” “Once or twice a week,” “One to three times a month,” and “Less than once a month.” In BiDirect, participants also had to specify the number of years elapsed since the onset of RLS symptoms, and they were asked if they had ever been diagnosed with RLS by a physician. Participants with RLS symptoms in the SHIP studies were asked whether symptoms were strong enough to take medications for it. In SHIP-Trend, RLS assessment was restricted to those who participated in the sleep laboratory examination ($N = 1269$).

During the follow-up of the BiDirect study, RLS was assessed identically as it was done during baseline. RLS incidence was defined as reporting no RLS at baseline and having positive RLS status at follow-up. Subjects without RLS at both assessments were classified as having no RLS. Participants evaluated as RLS-positive cases at baseline were excluded from the denominator when calculating incidence of RLS.

2.1.4. ABI measurements

The ABI is calculated as a ratio of systolic blood pressure measured at the ankle to that measured on the upper arm. Decreased ABI values relate to impaired arterial blood flow in the lower extremities.

All observers were trained in assessing ABI using the respective device according to the instructions of the manufacturers and standard operating procedures. In BiDirect, trained study nurses measured the ABI using the ‘Vascular Explorer’ device (Enverdis GmbH, Jena, Germany). Blood pressure was measured simultaneously on both the arm (brachial artery) and ankle (posterior