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Original research article

Association between hemostatic markers, serum lipid fractions and progression of cerebral small vessel disease: A 2-year follow-up study

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ABSTRACT

Introduction: Little is known if hemostatic markers and serum lipid fractions can predict further radiological progression beyond vascular risk factors in cerebral small vessel disease (SVD). We investigated whether they are associated with SVD radiological progression and if they are related to different SVD clinical manifestations.

Methods: A single-center, prospective, cohort study with 2 years of radiological follow-up was performed in consecutive patients with different SVD manifestations. The study group consisted of 123 patients: 49 with lacunar stroke (LS), 48 with vascular dementia (VaD) and 26 with vascular parkinsonism (VaP). We assessed SVD progression by a visual SVD scale. We determined the relationship between serum or plasma concentrations of tissue factor (TF), thrombomodulin, beta-thromboglobulin (BTG), fibrinogen, D-dimer and total cholesterol, HDL-C, LDL-C, triglycerides and SVD progression by logistic regression analysis.

Results: 34.9% patients had SVD radiological progression: 43% had isolated WMLs progression, 23.2% had new lacunes, 34.8% had both WMLs progression and new lacunes. Fibrinogen [OR 1.02 (95% CI 1.006–1.011] was significantly associated with risk of new lacunes or WMLs progression regardless of the clinical SVD manifestation. While low HDL [OR 0.96 (0.93–1)] and TF [OR 1.07 (0.99–1.1)] were marginally associated with new lacunes, BTG [OR 1.005 (0.99–1.01)] was associated with WMLs progression.

Conclusion: We found a relationship between fibrinogen and risk of radiological progression of SVD regardless of the clinical SVD manifestation. In addition, lower HDL and increased TF predicted development of new lacunes, and higher BTG was associated with risk of WMLs progression.

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1. Introduction

Cerebral small vessel disease (SVD) is one of the most important and common vascular diseases of the brain caused by lacunar infarcts (LI) and white matter lesions (WMLs). It refers to different but pathogenetically linked processes and mechanisms: atherosclerosis, arteriolosclerosis, lipohyalinosis but also it results from increased permeability of the blood-brain-barrier (BBB) [1]. Features of SVD probably develop over many years before becoming clinically evident, hence SVD can cause several different types of distinct or overlapping clinical presentations such as progressive cognitive decline or vascular dementia (VaD), physical disabilities e.g. vascular parkinsonism (VaP), but also it often results in sudden onset lacunar stroke (LS) [2]. Recently the number of lesions attributable to SVD has expanded. The main imaging features of SVD are now recognized all to be inter-related and visible on conventional magnetic resonance imaging (MRI). They include acute LIs or hemorrhages, lacunes (which reflect old infarcts), WMLs, visible perivascular spaces (PVS), microbleeds (MCBs), and brain atrophy [2]. Lacunes and WMLs are the hallmarks of SVD, they often coexist, but in some patients one type of imaging appearance may predominate. Whether they share similar or different pathogenesis and risk factors is a matter of debate. Population-based studies revealed that age-related WMLs are present in MRI in over 95% of elderly individuals aged between 60 and 90 years [3]. The Leukoaraiosis and Disability Study (LADIS) found WMLs progression in 74% of participants over 3 years particularly in those with confluent lesions at baseline [4]. Progression of SVD is associated with risk of stroke, cognitive decline, gait abnormalities and disability, and therefore it is important to identify associated factors especially those that could be treatable. The relationships of traditional risk factors with SVD are still not completely understood and atherothrombotic risk factors are not consistently common in patients with different SVD manifestations. In a systematic review of 16 studies comparing risk factors between patients with different stroke etiology, hypertension and diabetes were more frequent in patients with LS than in large vessel strokes [5]. Most community-based studies consistently showed that age, hypertension and smoking were associated with WMLs, however they failed to find an association with diabetes [6]. The majority of studies demonstrated that older age and hypertension predicted WMLs progression, however studies on association between diabetes, cholesterol levels or statin use gave conflicting results [4,7].

Although the clinical and radiological course of SVD was evaluated in many studies especially focusing on patients with LS or asymptomatic SVD patients, the prognosis of SVD and predictors of radiological progression, especially in chronic SVD manifestations e.g. VaP or VaD are not well known and have been rarely studied [8]. Variability in clinical and radiological presentations of SVD may be attributable to burden of traditional vascular risk factors leading to endothelial dysfunction, but also may be due to other hemodynamic or hemostatic factors, however their significance in the pathogenesis and prognosis of SVD is not clear. Given the spectrum of SVD pathological pathways – from BBB dysfunction to atherosclerosis it is likely that several components of fibrinolytic or inflammatory-atherothrombotic cascade are involved. Studies investigating association between different biochemical compounds e.g. serum lipid fractions and hemostatic markers and risk of LS or SVD radiological burden gave conflicting results [9]. Previous studies have suggested that the blood viscosity measured in LS was higher than in other stroke subtypes and that increasing triglycerides concentration and decreased LDL cholesterol were associated with WMLs in elderly population [10,11]. However, little is known if they can predict further radiological progression in SVD and add predictive capacity beyond vascular risk factors. We hypothesized that specific markers involved in fibrinolytic process and lipid metabolism are linked to risk of SVD radiological progression and examined if they are related to different SVD clinical manifestations: LS, VaD or VaP.

2. Materials and methods

A single-center, prospective cohort study, with 2 years of radiological follow-up was performed as a part of SHEF-SVD Study (Significance of HEmodynamic and hemostatic Factors in the course of different manifestations of Cerebral Small Vessel Disease) [12]. The study group consisted of 132 patients (54 with LS, 50 with VaD, 28 with VaP) considered to be caused by sporadic SVD of whom 7 patients died and 2 withdrawn a consent during follow-up. Finally 123 patients were analyzed: 49 with LS (39.8%), 48 with VaD (39%) and 26 with VaP (21.1%) (Fig. 1). Baseline demographic data, clinical and radiological characteristics of patients who were excluded from final analysis were comparable to those of the included patients. The patients were recruited from Neurological Outpatient Department and prospectively enrolled to the study between December 2011 and June 2014. The MRI examination was performed at baseline and repeated at the end of the 2-year follow-up with the aim of assessing possible progression of WMLs and development of new lacunes or other lesions. Given the nature of this study, the aim of research is hypothesis-generating rather than confirmatory. The study protocol and methods have been thoroughly described elsewhere [12].

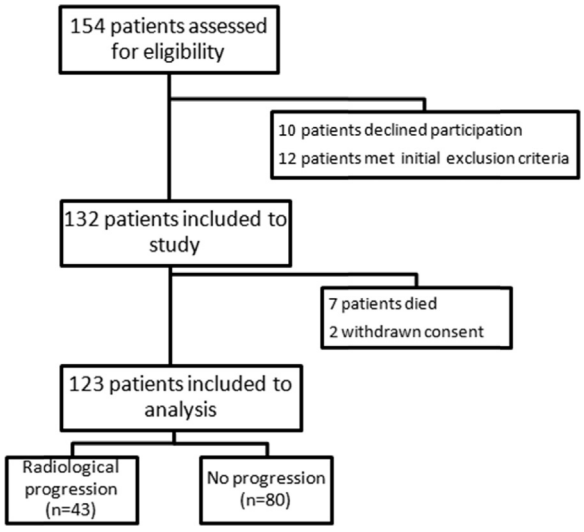

Fig. 1 – A flowchart of study design.

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