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Full Length Article

Thrombophilia testing in young patients with ischemic stroke

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ABSTRACT

Introduction: The possible significance of thrombophilia in ischemic stroke remains controversial. We aimed to study inherited and acquired thrombophilias as risk factors for ischemic stroke, transient ischemic attack (TIA) and amaurosis fugax in young patients.

Materials and methods: We included patients aged 18 to 50 years with ischemic stroke, TIA or amaurosis fugax referred to thrombophilia investigation at Aarhus University Hospital, Denmark from 1 January 2004 to 31 December 2012 (N = 685). Clinical information was obtained from the Danish Stroke Registry and medical records. Thrombophilia investigation results were obtained from the laboratory information system. Absolute thrombophilia prevalences and associated odds ratios (OR) with 95% confidence intervals (95% CI) were reported for ischemic stroke (N = 377) and TIA or amaurosis fugax (N = 308). Thrombophilia prevalences for the general population were obtained from published data.

Results: No strong associations were found between thrombophilia and ischemic stroke, but patients with persistent presence of lupus anticoagulant (3%) had an OR at 2.66 (95% CI 0.84–9.15) for ischemic stroke. A significantly higher risk of TIA/amaurosis fugax was found for factor V Leiden heterozygote (12%) (OR: 1.99 (95% CI 1.14–3.28)). No other inherited or acquired thrombophilia was associated with ischemic stroke, TIA or amaurosis fugax.

Conclusions: In young patients, thrombophilia did not infer an increased risk of ischemic stroke. Only factor V Leiden heterozygote patients had an increased risk of TIA/amaurosis fugax, and persistent presence of lupus anticoagulant was likely associated with ischemic stroke. We suggest the testing restricted to investigation of persistent presence of lupus anticoagulant.

1. Introduction

Ischemic stroke is a leading cause of death and disability globally [1,2,3]. One in thousand aged less than 50 years experiences an ischemic stroke [1,4]. This accounts for ten percent of all ischemic strokes [5,6]. In these young patients, cryptogenic stroke with an unknown cause is more common than in the elderly, and the role of atherosclerotic risk factors has been inconsistently reported [1,5–8].

Thrombophilias are defined as an inherited or acquired abnormality of haemostasis predisposing to thrombosis [9]. Thrombophilias are associated with an increased risk of venous thrombosis, but their relation to arterial ischemic stroke is less established [4,6,10–12].

Lupus anticoagulant may predispose to arterial ischemic stroke [11–13]. However, the available literature has important shortcomings by studying patients with systemic erythematosus and by methodological differences across laboratory protocols [11]. The significance of asymptomatic antiphospholipid antibodies as independent risk factor for ischemic stroke is unclear [14]. Patent foramen ovale (PFO) has been reported to be associated with cryptogenic stroke, especially in younger patients [11]. The inherited thrombophilias Prothrombin 20210G:A variant and Factor V Leiden are found more prevalent in young ischemic stroke patients with PFO as compared to patients without [15].

Transient ischemic attack (TIA) and amaurosis fugax are clinical conditions with shared aetiology that both increase the risk of ischemic stroke [16–18].

The aim of the present study was to investigate the role of inherited and acquired thrombophilias as risk factors for ischemic stroke, TIA and amaurosis fugax in young patients.

2. Materials and methods

2.1. Study population and setting

In the present study, we included patients aged 18 to 50 years with the diagnosis of ischemic stroke, TIA or amaurosis fugax referred to thrombophilia investigation at Centre of Haemophilia and Thrombosis, Department of Clinical Biochemistry, Aarhus University Hospital, Denmark, from 1 January 2004 to 31 December 2012 (n = 685).

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Extraction of laboratory data was finalised 31st December 2012, which was six months before collection of clinical data was begun in order to allow at least 6 months follow-up and to ensure that all patients had completed the investigation. Referrals were neurological departments and outpatient clinics, and medical departments treating patients with ischemic stroke and TIA in The Central Denmark Region. We grouped patients with a history of TIA or amaurosis fugax together due to their shared aetiology and role as risk factors for ischemic stroke [16]. Both the Danish Data Protection Agency and the Danish Health and Medicines Authority approved the study.

2.2. Data sources

In 2001, The Danish Stroke Registry was established as a clinical quality database covering all Danish hospitals treating adult patients in the acute stage of ischemic stroke [19]. Registration to The Danish Stroke Registry was mandatory during the entire study period [19]. The validity of The Danish Stroke Registry is high with a sensitivity of 97% and a positive predictive value of 90% [19]. Stroke severity in the initial stage of admission was evaluated by attending physicians using The Scandinavian Stroke Scale [8,19].

Clinical information was obtained from The Danish Stroke Registry and through systematic review of medical records. The individual retrieving the clinical data was blinded to thrombophilia status. All patients were diagnosed by the attending physician at the time of event based on the recommendations from World Health Organisation, i.e. a condition with a presumed vascular aetiology leading to rapid progression of symptoms of loss of neurological function lasting >24 h or causing death [19]. We included only patients diagnosed with stroke of ischemic origin. TIA was defined as brief episodes (<24 h) of neurological dysfunction resulting from focal cerebral ischemia without permanent cerebral infarction [17]. Amaurosis fugax was defined as transient (<24 h) monocular visual loss attributed to ischemia or vascular insufficiency and no overt ophthalmological disease [18].

Investigation and diagnosis of PFO was performed by a transesophageal echocardiogram or transthoracic echocardiogram at a cardiac department in relation to diagnosing after the event. In the present study PFO was registered as present or non-present without further staging. High cholesterol and hypertension was defined as a registered diagnosis in the Danish Stroke Registry, in medical records or if the patient received lipid lowering agents or antihypertensive treatment before or during the index admission for the ischemic event.

Information on any consecutive cerebral ischemic event was obtained through review of medical records in the follow-up period from the event date until 1 September 2014 with a median follow-up time at 5.5 years (range 0.8–10.6 years).

Data on thrombophilia investigations were obtained from the laboratory information system LABKA I (1st January 2004 to 16th May 2008) and LABKA II (17th May 2008 until end of study period 31st December 2012).

2.3. Thrombophilia investigations

Standard coagulation analyses and thrombophilia analyses were performed at Centre of Haemophilia and Thrombosis, Department of Clinical Biochemistry, Aarhus University Hospital, Denmark, except the genotype analyses, which were performed at Department of Molecular Medicine and Department of Clinical Biochemistry, Aarhus University Hospital, Denmark. Thrombophilia investigations were performed in proper timely distance from the acute event to avoid false positive results due acute phase response (mean time of 2 months). Confirmatory testing was performed for all positive thrombophilia results, apart from genotype analyses. The thrombophilias included in our investigations have changed over time, wherefore not all patients have had all tests done.

Tubes containing 3.2% sodium citrate (Terumo, Lueven, Belgium) were utilised for analyses of international normalised ratio (INR), prothrombin time, activated partial thromboplastin time (APTT), thrombin time, coagulation factor VIII:Clot, von Willebrand factor (antigen), fibrin D-Dimer, fibrinogen (functional), natural anticoagulants, and lupus anticoagulant. 3.5 ml silicone coated tubes containing clot activator and gel for serum separation (BD, Plymouth, UK) were used for β-2-glycoprotein antibodies. DNA for genotype analysis and plasma homocysteine was isolated from EDTA anticoagulated blood (Terumo, Leuven, Belgium). The plasma homocysteine were sampled after a minimal stasis. The patients were not fasting at the time of collection.

Supplementary Table 1 provides an overview of the methods, assays, reference intervals, and clinical decision limits for standard and specialised coagulation analyses used in the present study. All patients were retested in case of suspected deficiency of the natural anticoagulants at the first investigation. Presence of antiphospholipid antibodies was always re-tested for confirmation with at least 12 weeks in-between.

Factor V Leiden G169A and Prothrombin G20210A gene polymorphisms were detected by ABI 7500 Fast Real-Time PCR System (Thermo Fisher Scientific, New York, USA).

2.4. Statistical analysis

The absolute distributions of inherited and acquired thrombophilias were reported including their associations to ischemic stroke (N = 377), TIA or amaurosis fugax (N = 308) by odds ratios (OR) with 95% confidence intervals (95% CI). The present findings were compared to data published on thrombophilia distributions on large cohorts of the general Western population [13,20–24]. Chi-square test and Fisher's exact test were used; the latter when the number in each cell was

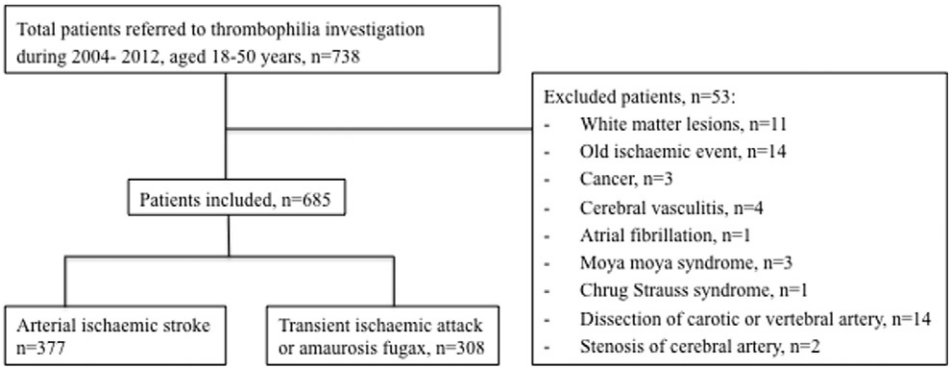

Fig. 1. Flowchart of the study population.