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Risk factors for ischemic stroke and transient ischemic attack in patients under age 50

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Abstract To analyze risk factors for ischemic stroke and transient ischemic attack (TIA) in young adults under the age of 50. To make recommendations for additional research and practical consequences. From 97 patients with ischemic stroke or TIA under the age of 50, classical cardiovascular risk factors, coagulation disorders, history of migraine, use of oral contraceptives, cardiac abnormalities on ECG and echocardiography, and the results of duplex ultrasound were retrospectively analyzed. Literature was reviewed and compared to the results. 56.4% of the patients had hypertension, 12.1% increased total cholesterol, 20% hypertriglyceridemia, 31.5% an increased LDL-level, 32.6% a decreased HDL-level and 7.2% a disturbed glucose tolerance. Thrombophilia investigation was abnormal in 21 patients and auto-immune serology was abnormal in 15 patients. Ten of these patients were already known with a systemic disease associated with an increased risk for ischemic stroke (i.e. systemic lupus erythematosus). The ECG was abnormal in 16.7% of the cases, the echocardiography in 12.1% and duplex ultrasound of the carotid arteries was in 31.8% of the cases abnormal. Conventional cardiovascular risk factors are not only important in patients over the age of 50 with ischemic stroke or TIA, but also in this younger population under the age of 50. Thrombophilia investigation and/ or autoimmune serology should be restricted to patients without conventional cardiovascular risk factors and a history or other clinical symptoms associated with hypercoagulability and/ or autoimmune diseases.

Keywords Young stroke · Thrombophilia · Cardiovascular risk factors · Echocardiography · Duplex ultrasound

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Introduction

Stroke is the most important cause of disablement in the western world. In the Netherlands it is the third cause of lost Disability-Adjusted Life-Years (DALY's)—after coronary disease and anxiety diseases [1]. About 10% of all strokes occur in patients <50 years of age. Risk factors in these young stroke patients differ from those found in older people [2]. Etiology of ischemic stroke in young adults remains uncertain [3, 4] and multiple factors have been reported as risk factors like traditional vascular risk factors [5, 6], thrombophilia [6–18], migraine [6, 19–22], auto-immune disorders [23–27] and cardiac anomalies [6, 28–35].

The present study aimed to determine classical risk factors and prevalence of thrombophilic risk factors and autoimmune serology in patients under the age of 50 with transient ischemic attack (TIA) or ischemic stroke. Furthermore the practical consequences of these investigations are discussed.

Patients and methods

Population

This retrospective study included a series of 97 patients under the age of 50, diagnosed with ischemic stroke or TIA

(after history taking, physical examination and brain imaging studies), admitted to the neurology department of the Radboud University Nijmegen Medical Centre between September 2004 and January 2008. Medical records of these patients were reviewed. The data of these patients were retrospectively analyzed and compared with literature.

Risk factors

The following data were collected: gender, age, type of event, smoking, use of oral contraceptives, cardiovascular history (previous stroke or TIA, myocardial infarction, venous thromboembolism, hypertension, hypercholesterolemia or pre-eclampsia/HELLP-syndrome/spontaneous abortion), positive family history for cardiovascular disease (first-degree female family members <65 years and first-degree male family members <55 years), migraine, diabetes, blood pressure (hypertension was classified as a blood pressure >140/90 mmHg or treatment with antihypertensive medication) ECG, echocardiography and duplex ultrasound of the extra cranial arteries.

Cardiac imaging

ECGs were analyzed. Almost all patients underwent two-dimensional transthoracic echocardiography (TTE). Potential cardiac sources of embolism were: patent foramen ovale (PFO), atrial septal aneurysm (ASA), mitral stenosis, mitral insufficiency, atrial fibrillation, endured myocardial infarction, endocarditis, intracardial thrombus, atrial myxoma, prosthetic valve, non-ischemic dilating cardiomyopathy and left ventricular akinesis.

Carotid ultrasound

The results of duplex ultrasound of the extra cranial arteries were divided in four categories: normal, non-significant atherosclerotic changes (e.g. slightly increased intima media thickness without significant haemodynamic changes), significant atherosclerotic changes (i.e. vascular stenosis with luminal reduction ≥50%) and other significant vascular damage (i.e. dissection).

Laboratory assays

The following laboratory data were evaluated: total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, glucose, protein C, free protein S and antithrombin activity, factor V Leiden, factor II mutation (prothrombin G202010A mutation), homocysteine, lupus anticoagulant and anticardiolipin antibodies (IgG and IgM), antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA).

Reference values were 70–150% for protein C, 65–130% and 55–115% respectively for men and women for free protein S, >80% for antithrombin, <15 μmol/l for homocysteine, <6.5 mmol/l for total cholesterol, <2.00 mmol/l for triglycerides, >1.10 mmol/l for HDL and <3.50 mmol/l for LDL cholesterol. The normal values for fasting blood sugar and non-fasting blood sugar were <6.1 and <7.8 mmol/l.

Results

Cardiovascular risk factors

Of the 97 patients, 49 had an ischemic stroke and 48 had a TIA. Mean age of the study population was 41.3 ± 7.7 years (range 17.04–49.97 years) and 57 (58.8%) were females. The presence of the classical atherosclerotic risk factors are presented in Table 1. The most common cardiovascular risk factor was hypertension (56.4%), followed by a positive cardiovascular medical history (47.9%), a positive family history (44.4%) and smoking (40.0%). 32.6% of the patients had a decreased HDL-level. LDL was elevated in 31.5%. 73.2% of the patients had two or more cardiovascular risk factors. Only 8.5% had no cardiovascular risk factor.

Cardiac imaging

ECGs showed hardly any abnormalities (Table 2). Disturbed repolarisation was the most common abnormality (7.7%). In our population five patients had a PFO (6.4%) and also five patients (6.4%) had mitral insufficiency (Table 2). One patient had a congenital anomaly consisting of a pulmonary artery aplasia and hypoplastic right ventricle.

Gynaecological history

14% (8) of the women had a history of one or two spontaneous abortions. Three of them had a history of pre-eclampsia. 42.9% of the women used oral contraceptives (Table 1).

Migraine

In our study group, 20.2% of the patients had a history of migraine. The combination of migraine and the use of oral contraception occurred in 9.3%, the combination of migraine and PFO in 3.1%. Sixty percentage of the patients with PFO were familiar with migraine.

Table 1 Demographic data and risk factors

	All ($n = 97$)	Males	Females
Nonmodifiable risk factors			
Age, y	41.3 ± 7.7 (17.04–49.97)[a]	43.0 ± 7.2 (17.04–49.97)[a]	40.1 ± 7.8 (19.25–49.89)[a]
Gender	–	40 (41.2)	57 (58.8)
Ischemic stroke (N)	*49 (50.5)*	19 (38.8)	30 (61.2)
TIA (N)	48 (49.5)	21 (43.8)	27 (56.2)
		Number scored (%)	Positive result (%)
Cardiovascular family history	–	90 (92.8)	40 (44.4)
Well-documented and modifiable risk factors			
Cardiovascular history	–	94 (96.9)	45 (47.9)
Cigarette smoking	–	95 (97.9)	38 (40)
Hypertension	–	94 (96.9)	53 (56.4)
Hypercholesterolemia	–	91 (93.8)	11 (12.1)
Hypertriglyceridemia	–	90 (92.8)	18 (20.0)
Increased LDL	–	89 (91.8)	28 (31.5)
Decreased HDL	–	89 (91.8)	29 (32.6)
Glucose >7.8	–	97 (100)	7 (7.2)
Glucose >6.1	–	97 (100)	19 (19.6)
Cardiovascular risk factors[b]	–	–	–
0	–	82 (84.5)	7 (8.5)
1	–	82 (84.5)	15 (18.3)
2	–	82 (84.5)	21 (25.6)
3	–	82 (84.5)	16 (19.5)
4	–	82 (84.5)	14 (17.1)
5	–	82 (84.5)	8 (9.8)
6	–	82(84.5)	1 (1.2)
Less well-documented, potentially modifiable risk factors			
History of migraine	–	94 (96.9)	19 (20.2)
Oral contraceptive use	–	96 (99.0)/56 (98.2)	24 (25.0)/24 (42.9)

Data are expressed as mean ± SD or *n*(%)

TIA transient ischemic attack; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein

[a] Range

[b] Smoking, hypertension, high glucose level, high total cholesterol, high triglycerides, high LDL, low HDL, significant changes of duplex ultrasound, positive cardiovascular history

Carotid ultrasound

The results of the duplex ultrasound are shown in Table 2. 20% of the patients had non-significant and 11.8% had significant atherosclerotic changes or dissection.

Thrombophilic and autoimmune investigations

Not all patients had a complete trombophilia and auto-immune work-up (Table 2). Increased homocysteine was present in 13.6%. The two patients with mildly decreased protein C and the patient with decreased protein S used oral contraceptives. The auto-immune research resulted in a positive ANA in 8.1% and a positive ANCA in 7.4%. Studying the history of the patients, we found that a disorder associated with increased blood coagulation and/or vasculitis in combination with ischemic stroke was present in 17 patients (Table 3). This group represented 1/2 decreased protein C, 1/1 decreased antithrombin, 1/1 positive lupus anticoagulant, 3/6 FVL, 1/3 factor II mutation, 5/7 positive ANA and 2/6 positive ANCA (divided over 10 patients). Two patients in Table 2 were not screened for trombophilia and auto-immune disorders.

Some patients showed more than one abnormality. One patient known with SLE had a positive ANA and lupus anticoagulant; one patient with SLE presented with positive ANA, FVL and factor II mutation; one patient known with M. Crohn had a decreased protein C and antithrombin; a patient with

Table 2 Etiology of ischemic stroke/TIA

	Positive result (%)
Echocardiography ($n = 78$)	
PFO	5 (6.4)
ASA	1 (1.3)
Mitralis stenosis	0
Mitralis insufficience	5 (6.4)
Atrial fibrilation	0
Endured myocardial infarction	2 (2.6)
Endocarditis	0
Intracardial thrombus	0
Atrial myxoma	0
Prosthetic valve	2 (2.6)
Non-ischemic dilating cardiomyopathy	1 (1.3)
Left ventricular akinesis	2 (2.6)
Congenital cardiac anomaly	1 (1.3)
ECG ($n = 91$)	–
Sinus rhythm	91 (100)
Atrial fibrillation	0
Endured myocardial infarction	0
Disturbed repolarisation	7 (7.7)
Left ventricle hypertrophy	1 (1.1)
Left bundle-branch block	1 (1.1)
Congenital cardiac anomaly	2 (2.2)
Thrombophilia	–
Protein C <70 ($n = 82$)	2 (2.4)
Free Protein S: ♂ <65; ♀ <55 ($n = 82$)	1 (1.2)
Antithrombin <80 ($n = 85$)	1 (1.2)
Factor V Leiden[a] ($n = 85$)	6 (7.1)
Factor II mutation[a] ($n = 84$)	3 (3.6)
Homocysteine >15 ($n = 81$)	11 (13.6)
Auto-immune	–
Lupus anticoagulant ($n = 85$)	1 (1.2)
Anticardiolipine IgG ($n = 83$)	2 (2.4)
Anticardiolipine IgM ($n = 83$)	1 (1.2)
ANA ($n = 86$)	7 (8.1)
ANCA ($n = 81$)	6 (7.4)

PFO patent foramen ovale, *ASA* atrial septal aneurysm; [a] Heterozygote

decreased protein C and FVL had a history of pre-eclampsia and two spontaneous abortions; one patient with a blank history showed a positive ANA and anticardiolipin IgG.

None of the patients with a coagulation disorder had a PFO.

Discussion

The results of the present study demonstrate that conventional cardiovascular risk factors are not only an important risk factor in patients over the age of 50 with ischemic stroke/TIA, but also in this younger population under the age of 50.

Almost half of the patients (47.9%) had a positive cardiovascular history. Eight of these patients had a history of spontaneous abortions and/or pre-eclampsia. Also the family history for cardiovascular disease was frequently positive (44.4%). In the Netherlands, 28% of the general population was smoking at that time [36], in our population 40% was smoking. The results of the lipids and glucose values are difficult to compare with results from the literature because of different cut-off values.

58.8% of our population was of the female gender. This is comparable with the literature [37]. The higher proportion of women is possibly due to the nature of risk factors for stroke/TIA at younger age; like pregnancy, migraine en oral contraceptives use. These risk factors tend to occur more frequently in women.

We found a history of migraine in 20.2% of the population. This is analogous to the results of Milhaud et al. [19]. They found migraine in 29.3% of their population, which was younger (<35 years). Furthermore they found 18.2% of the patients with migraine (<45 years) having a PFO. This is analogous to our results (15.8%). Of all women in our study 42.9% used oral contraceptives. This is comparable to the Dutch population between 20 and 45 years old (41%) [38].

In contrast to what is known from literature, a small number of cardiac anomalies was detected by echocardiography. Kittner [3] and Rodes-Cabau et al. [33] described cardiogenic emboli as the most common cause of ischemic stroke in younger persons (15.4%). PFO and atrial septal aneuryms (ASA) are described in literature as the most common cardiac anomaly found in stroke/TIA [28–32]. Cabanes et al. [28] distinguished PFO in 43% and ASA in 28% of the population <55 years old. In our study PFO was detected in only 6.4% and ASA in 1.3% of the patients. This discrepancy can be explained by the difference in technique of echocardiography. Cabanes et al. [28] used—like most of the other investigators [29–32]—transesophageal echocardiography (TEE), instead of TTE. It is suggested that the transesophageal technique is more sensitive in detecting interatrial septum anomalies (PFO, ASA, atrial septal defect), atrial thrombi during atrial fibrillation and mitral valve vegetations like endocarditis [35].

Most of the abnormalities found in thrombophilia- and auto-immune investigations, were detected in patients already known with diseases associated with an increased coagulation before the stroke occurred. Furthermore all patients with decreased protein C and S used oral contraception, which is a known cause of decreased protein C and S [18].

Hankey et al. [8] demonstrated no significant differences between patients with young stroke and controls for protein

Table 3 Disorders associated with increased blood coagulation/vasculitis

	n	Comment
Systemic lupus erythematosus	2	1 with positive ANA and lupus anticoagulant; one with positive ANA, FVL and factor II mutation
Colitis ulcerosa	2	1 with positive ANA; one with positive ANCA
M. Crohn	2	1 with FVL; one with decreased PC and AT
Systemic malignancy	2	1 with Non-Hodgkin lymphoma; one with Hodgkin lymphoma
Rheumatoid arthritis	1	Positive ANA
Syndrome of Sneddon	1	Positive ANCA
Moya Moya syndrome	1	
Henoch-Schönlein	1	
Discoid lupus erythematosus	1	
M. Buerger	1	FVL
Anti-Jo-1-antibodies syndrome	1	Positive ANA
Thrombotic thrombocytopenic purpura	1	[a]
Polycythaemia vera	1	[a]
Total *n*(% of total patient population)	17 (17.5%)	

ANA anti-nuclear antibodies, *FVL* factor V Leiden, *ANCA* anti-neutrophil cytoplasmic antibodies, *PC* protein C, *AT* antithrombin

[a] Two patients were not screened for thrombophilia and auto-immune disorders

C, S and antithrombin levels. Amiri et al. [9] did not find decreased levels of protein C and antithrombin at all. The percentages of protein C and S that Hankey et al detected are in the range with the percentages we found, except for the antithrombin level. We found a decreased antithrombin level in only 1.2% of the patients compared to 5.2% of Amiri et al.

The percentage of our patients with FVL and factor II mutations (7.1 and 3.6%) is in accordance with the results of the literature [8, 10, 14–16]; none of these studies reported significant differences between patients and controls, or just a minimal increased risk. It has to be noted that positive trombophilia screening has no practical consequences for the patient. There is no difference in kind and duration of anticoagulant treatment between patients with or without a thrombophilic factor.

The homocysteine level was increased in 11 patients. Nowadays it is questionable whether it is still useful to investigate homocysteine levels, since large placebo-controlled trials are published concerning the effect of treating hyperhomocysteinemia [39–42]. Patients (with hyperhomocysteinemia) in these studies had a positive vascular history or a myocardial infarction. Vitamin supplementation caused no significant decrease of recurrence hazard of cardiovascular events. Only Saposnik et al. [43] concluded that vitamin supplementation reduces the risk of overall stroke (ischemic and haemorrhagic), but not stroke severity or disability in a population with and without history of cerebrovascular disease.

In our population a few patients with positive antiphospholipid antibodies were found (1.2%). Brey et al. [24] found a prevalence of 26.9% of antiphospholipid antibodies and a prevalence of 14% of anticardiolipin IgG and 0.6% of anticardiolipin IgM. Difference with our population is the fact they only measured all antibodies once, without the corroboration of a second measurement. The patients in our population had a positive test result repeatedly. Munts et al. [2] found a confirmed prevalence of anticardiolipin IgG of 17%. Nencini et al. [25] found prevalences of 18, 9 and 7% for antiphospholipid antibodies, anticardiolipin IgG and IgM.

Urbanus et al. [26] found lupus anticoagulant to be a significant risk factor (OR 43.1) for arterial thrombotic event in women under age 50. Antiphospholipid antibodies were present in 17% of the patients. The APASS investigators [27] concluded that the presence of antiphospholipid antibodies does not predict an increased risk for subsequent vascular occlusive events in patients with a non-cardiogenic stroke. And thereby may not offer enough value for decisions on therapy.

In contrast to the literature [29, 30] we did not identify a combination of thrombophilia and PFO in our population. This can be caused by a low prevalence of both parameters in our population. Furthermore the size of our population is too small to demonstrate an association. Belvís [31] and Florez et al. [34] did not find a significant association between patients with and without PFO for coagulation disorders.

A limitation of this study is that it is retrospective, resulting in incomplete data. Strength of the study is that we investigated many possible risk factors for ischemic stroke in one study. Many studies investigated just one or

few risk factors in relation to ischemic stroke. Additional prospective, controlled studies of ischemic stroke/TIA patients under age 50 are needed to better assess the roles of the risk factors in the etiology of ischemic stroke/TIA. A relation between migraine and stroke should be corroborated by further studies.

Conclusion and recommendations

Screening for conventional cardiovascular risk factors remains the most important considering the high percentage of cardiovascular risk factors in patients under age 50. These high frequencies also indicate optimal secondary prevention strategies.

Based on the low laboratory yield of thrombophilia- and auto-immune search, it is not indicated to do this complete laboratory search in all patients under 50, especially not when there is no history related to these diseases. Furthermore in most cases a positive thrombophilic factor has no therapeutic consequences, such as switching of type of anticoagulation or duration of anticoagulation. Thrombophilia and auto-immune research is only indicated in specific cases.

Because of the low number of abnormalities found in TTE, TEE seems preferable instead. Disadvantage of the transesophageal technique is its more invasive nature. Another possibility is the use of TEE in selected young patients, without other risk factors for ischemic stroke.

The ECG should be used to exclude atrial fibrillation. It is cheap and simple.

The use of duplex ultrasound of the extra cranial arteries should be continued. It is a non-invasive test and gives information about the presence of atherosclerosis or dissection in the carotid arteries. Is has a sensitivity of 86% and specificity of 87% [44].

History taking remains important in detecting risk factors. Characteristics of auto-immune diseases could be specifically interrogated.

The recommendation for diagnostic testing for possible etiologies and risk factors of ischemic stroke or transient ischemic attack in patients under age 50 is summarized in Fig. 1. The suggested scheme developed on the basis of the results of this study should be further validated in prospective studies.

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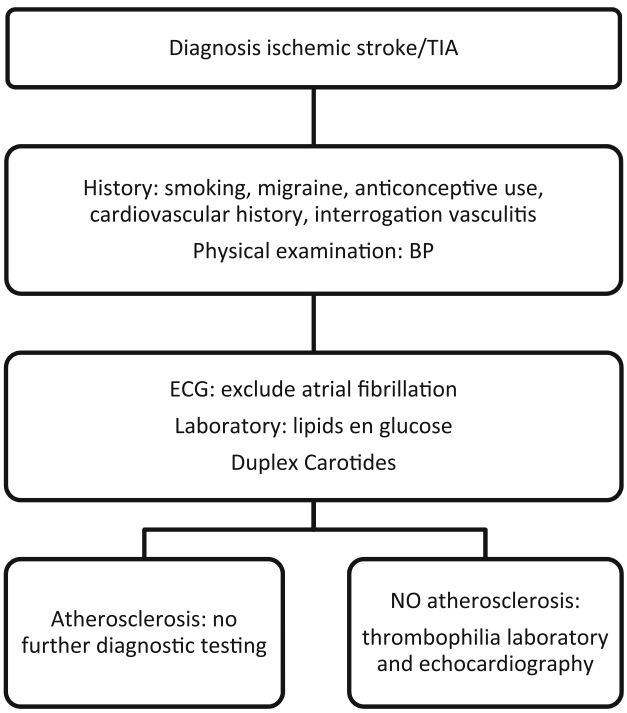

Fig. 1 Recommendation for diagnostic testing in patients with young stroke

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