Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome

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Area of interest (study setting): Specific aims:Transient triggers and chronic riskfactors (case-crossover and casecontrol)(1) To investigate frequency and strength of association between transient physical andpsychological triggers and early-onset...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON43346

Source
ToetsingOnline

Brief title
SECRETO

Condition

- Cardiac arrhythmias
- Cardiac and vascular disorders congenital
- Central nervous system vascular disorders

Synonym
infarction, ischemic stroke

Research involving
Human

Sponsors and support

Primary sponsor: Helsinki University Central Hospital
Source(s) of monetary or material Support: Hospital District of Helsinki and Uusimaa in Finland - Academy of Finland - The Finnish medical foundation

Intervention

Keyword: Cryptogenic, Etiology, Stroke, Young

Outcome measures

Primary outcome

Etiology (TOAST)

Mortality

New vascular events

Secondary outcome

Risk factors

Other outcome (hypertension, diabetes)

Study description

Background summary

In 60% of all strokes in young adults the cause remains unknown and are called cryptogenic.
To prevent, treat and prescribe secundary preventive medication or give advice, it is essential that the cause (etiology) is known.
An underdiagnosed but possibly relevant finding in young adults is an open foramen ovale between the two heart atria. This can be detected with transcranial Doppler of the heart in combination with transthoracal echocardiography. If and how this plays a role in causing strokes is not known.
With this study we look for new etiologies by looking at risk factors and triggers and we closely investigate the heart by more structured and extensive echo cardiography.

Study objective

Area of interest (study setting):	Specific aims:
Transient triggers and chronic risk factors (case-crossover and casecontrol)	(1) To investigate frequency and strength of association between transient physical and psychological triggers and early-onset CIS. (2) To look for frequency and characteristics of preceding infections, their potential hazard periods, and impact on the risk for early-onset CIS. (3) To estimate the strength of association of well-documented chronic vascular risk factors and anthropometric measures and early-onset CIS, and (4) Similarly analyze measurable less well-documented risk factors (eg migraine with aura, stress, short or long sleep duration, snoring).
Advanced cardiac imaging (case-only and case-control)	(1) To develop a step-by-step performance protocol for standardization of transthoracic and transesophageal echocardiography for better accuracy in the evaluation of potential cardiac sources of embolism. (2) To identify high-risk cardiac features (case-control study) focusing on patent foramen ovale (PFO) characteristics, and left atrial and left atrial appendage dimensions, as well as their functional parameters.
Thrombosis/hemostasis, biomarkers (case-control); see Appendices I and II.	(1) To investigate the role of modestly and often transiently elevated antiphospholipid antibodies in early-onset CIS. Blood samples outside of the acute/subacute period after index stroke are essential for this analysis. (4) To study whether activation of intrinsic coagulation factors and thrombosis initiator activity (eg high vWF or low ADAMTS13) is associated with early-onset CIS. (5) To explore whether plasma biomarkers of inflammation, atherogenesis, endothelial function, thrombosis, platelet activation, hemodynamic stress, and renal dysfunction may hint of underlying mechanisms of early-onset CIS.
Genetics (case-control)	(1) To assess to what extent routinely tested genetic thrombophilia with uncertain causality (factor V and II mutations, deficiency of antithrombin, protein C or

protein S)
increase the risk of early-onset CIS.
(2) To test association of potentially relevant candidate genes, e.g. genes encoding
endothelial function, platelet glycoprotein receptors, thrombosis activation and regulation, inflammatory response regulation (however, the decision whether to study
candidate genes may be dependent on the results of more sophisticated genetic approaches).
(3) To find new genetic loci and ultimately susceptibility genes for young-onset ischemic
stroke using genome-wide association study (GWAS) and next generation sequencing techniques (whole exome or whole genome sequencing, depending on funding opportunities). For GWAS, this cohort will be meta-analyzed with existing
young-onset stroke cohorts to increase power to detect significant loci.

Prognosis (follow-up of patients)
(1) To describe long-term risks of recurrent ischemic cerebrovascular events (primary
outcome), composite of noncerebrovascular arterial or venous thrombotic events, or
cerebral venous thrombosis, death from any cause, and new-onset atrial fibrillation
(secondary outcomes).
(2) To assess functional neurological, neuropsychosocial, and vocational outcomes.
(3) To find predictors of outcomes based on patient phenotype*e.g. considering PFO
status, neuroimaging subtype, thrombosis/hemostasis or biomarker profile*and genotype established in previous studies.
(4) To define use of secondary preventive measures in this patient population, evaluate
compliance to medication and its effectiveness with propensity score matching method.
(5) To describe the change in the patient phenotype and risk factor profile during followup
and assess whether the causal stroke etiology will be revealed at the time of recurrence.

Study design

Case-control

Study burden and risks

Very low risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Ischemic stroke
Age 18 - 49 years
Hospitalized due to first-ever imaging postive ischemic stroke without cause found after complete and timely minimum diagnostic testing

Exclusion criteria

Baseline mandatory minimum tests not obtained in the first week following stroke onset, including:
a. Brain MRI
b. Routine blood tests, including complete blood count with differential, CRP, fasting glucose, creatinine, aPTT, INR, total cholesterol, LDL-cholesterol, HDL-cholesterol, HbA1C, and hemoglobin electrophoresis in individuals of African origin
Other baseline mandatory minimum tests not obtained within the first two weeks following stroke onset, including:
a. Imaging of cervicocephalic arteries by CTA, MRA, or DSA
b. Transesophageal (highly recommended) and/or transthoracic echocardiography (N.B. Early screening of venous thrombosis in the lower extremities is highly recommended in patients with established right-to-left shunt)
c. 24-hour Holter monitoring (or continuous in-hospital ECG monitoring for at least 24 h)
d. Screening for thrombophilia, including anticardiolipin antibodies, lupus anticoagulant, anti-β2-
glycoprotein antibodies, factor V mutation (or aPC resistency ruled out), factor II mutation, homocysteine, antithrombin III, protein C, and protein S. It is highly recommended to retest any abnormal finding >12 weeks from the initial testing or >4 weeks after cessation of anticoagulation at any later time point.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2016
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO Date:	18-07-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT01934725
CCMO	NL58600.091.16