Cryptogenic Stroke: An Approach Towards Discovery of its Possible Hidden Causes

Thesis

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Dedication

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List of Abbreviations

Abb.	Full term
ACA	Anticardiolipin antibody
AF	Atrial fibrillation
AICD	Automatic implantable cardiac defibrillators
ANA	Anti nuclear antibody
ANCA	Anti neutrophil cytoplasmic antibody
APC	Activated protein C
ApL	Antiphospholipids antibodies.
APS	Antiphospholipid syndromes
ASA	Atrial Septal Aneurysm
ASD	Atrial septal defect
ATE	Arterial thrombotic events
ATIII	Anti-thrombin III
CADASIL	Cerebral autosomal Dominant arteriopathy with subcortical infarctions and leukoencephalopathy.
CARASIL	Cerebral autosomal Recessive arteriopathy with subcortical infarctions and leukoencephalopathy.
CE	Cardioembolic
CRP	C-reactive protein
CS	Cryptogenic Stroke
CT	Computed tomography
DAPT	Dual Antiplatelets Therapy
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte Sedimentation rate
ESUS	Embolic stroke of unknown source
FD	Fabry Disease
FV Leiden	Factor five leiden
Gb3	Globotriaosyl ceramide
GLA	Alpha Galactosidase A enzyme
HbA1c	haemoglobin A1c
HCY	Homocysteine
HDL	High density lipoprotein
HHcy	Hyperhomocysteinemia

List of Abbreviations Cont...

Abb.	Full term
ICMs	Insertable cardiac monitors
ILR	Implantable loop recorder
INR	International normalized ratio
ISHD	Ischemic heart disease
LAA	Large artery atherosclerosis
LAC	Lupus anticoagulant
LDL	Low density lipoprotein
MCA	Middle cerebral artery
MCOT	Mobile cardiac outpatient monitoring
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MTHFR	Methylenetetrahydrofolate reductase
NIHSS	National Institutes of Health Stroke Scale
NOACs	New oral anticoagulants
NT-proBNP	N-terminal pro-brain natriuretic peptide
OAC	Oral anticoagulants
pAF	Paroxysmal AF
PC	Protein C
PFO	Patent Foramen Ovale
PPM	Permenant pace maker
PS	Protein S
RCVS	Reversible cerebral vasoconstriction syndromes
RLS	Right to Left shunting
RoPE	Risk of paradoxical embolization
SVO	Small vessel occlusion
TCD	Transcranial doppler
TEE	Transesophageal Echocardiography
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VTE	Venous throbotic events
	vWF Von Willebrand factor

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INTRODUCTION

Ischemic stroke is among the leading causes of death and disability **(Go et al., 2013).** The cause remains unexplained after routine evaluation in 20 to 40% of cases, resulting in the classification, by exclusion, of cryptogenic stroke (CS) **(Amarenco et al., 2009).**

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria is the most widely used stroke classification to classify stroke etiology into five subtypes: large artery atherosclerosis (LAA), cardioembolic stroke (CE), small artery occlusion (SAO), other determined etiology and undetermined etiology. The classification is mainly based on electrocardiogram, echocardiogram, cervical doppler and Magnetic resonance imaging (MRI) **(Adams et al., 1993).**

CS is defined as cerebral ischemia of obscure origin. The cause of CS remains undetermined because the event is transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown. CS is more frequent in younger than older patients and it was found that when it is properly investigated the most frequent causes would be cardiac embolism, followed by vasculopathy, and coagulopathy according to **Finsterer (2010).**

The term cryptogenic ischemic stroke (or stroke of undetermined pathogenesis) encompasses ischemic strokes without specific cause detected after adequate diagnostic workup.

CS is, thus, a diagnosis done by exclusion. Strokes may remain cryptogenic if diagnostic evaluation is incomplete for one or another reason or in the presence of multiple competitive causes, such as atrial fibrillation (AF) and atherosclerotic stenosis in an ipsilateral relevant artery. Choosing the particular diagnostic investigation should always be balanced between the cost and potential yield, considering patient characteristics and the effect on treatment decisions **(Putaala and Tatlisumak, 2014).**

The cryptogenic category is even larger among younger patients reflecting major challenges in defining their pathogenesis and interpreting causally relevant findings. Up to 40% of patients aged <50 years remained without elusive cause for their stroke in a large multicenter survey **(Yesilot et al., 2013).**

Recurrence rate and prognosis of CS is under debate. There is paucity of data to guide secondary prevention after CS. Current guidelines either did not give statements specifically on CS or recommended antiplatelet therapy **(Furie et al., 2011).**

Amid these limited data on secondary prevention, clinical and subclinical recurrence risk after cryptogenic stroke remains significant. Even the young patients with stroke of undetermined pathogenesis experience recurrent events, with an annual rate of ≈1%. These figures suggest an active pathology underlying most cryptogenic strokes and justifies the use of advanced and often expensive diagnostic equipment targeting to improve the secondary prevention of these patients **(Putaala et al., 2010).**

Aim of the Work

To unleash some of the possible cardiac causes including arrythmias and non-cardiac causes of cryptogenic stroke including inherited and acquired thrombophilia.