Inherited Thrombophilia in Paediatric Ischemic Stroke

Thesis

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By
Maha Zakariya Ramadan Mohammed
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Under Supervision of

Prof. Mohsen Saleh El Alfy
Professor of pediatrics
Faculty of Medicine - Ain Shams University

Prof. Hoda Yahya Tomoum
Professor of Pediatrics
Faculty of Medicine- Ain Shams University

Prof. Yasser Abdel Azeem Abbas
Professor of Radiodiagnosis
Faculty of Medicine- Ain Shams University

Prof. Rasha Hussein Aly
Professor of Pediatrics
Faculty of Medicine – Ain Shams University

Dr. Rania Hamed Shatla
Associate Professor of Pediatrics
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

ACA	Anterior cerebral artery
ACCP	American College of Chest Physicians
ADC	Apparent diffusion coefficient
AHA	American heart association
AIS	Arterial ischemic stroke
ANA	Antinuclear antibodies
AT III	Antithrombin III
BG	Basal ganglia
BP	Blood pressure
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CRP	C reactive protein
CSF	Cerebrospinal fluid
CSVT	Cerebral sinovenous thrombosis
CT	Computed tomography
CTA	Computed tomography angiography
DNA	Deoxyribonucleic acid
DRVV	Dilute Russell viper venom
DWI	Diffusion-weighted image
ECG	Electrocardiogram

EDTA	Ethylene diamine tetra-acetic acid
EEG	Electroencephalogram
ELISA	Enzyme-Linked Immunosorbent Assay
ESR	Erythrocyte sedimentation rate
FPIA	Fluorescence polarization immunoassay
HCY	Homocysteine
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICA	Internal carotid artery
ICP	Intracranial pressure
IPSS	International Pediatric Stroke Study
IQR	Inter quartile range
ISCVT	International Study on Cerebral Venous and Dural Sinuses Thrombosis
ISTH	International Society of Thrombosis and hemostasis
IV	Intravenous
KFT	Kidney function tests
LDL	Low density lipoprotein
LFT	Liver function tests
LMWH	Low molecular weight heparin
LOD-PAP-Test	Lactate oxidase – p –aminophenazone test
MCA	Middle cerebral artery

MELAS	Mitochondrial encephalo-myopathy with lactic acidemia and stroke
MRA	Magnetic resonance arteriography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
MTHFR	Methylenetetrahydrofolate reductase
NS	Normal saline
OR	Odd's ratio
PCA	Posterior cerebral artery
PCR	Polymerase chain reaction
PT	Prothrombin
RCP	Royal College of Physicians
SBP	Systolic blood pressure
SD	Standard deviation
SSS	Superior sagittal sinus
TG	Triglycerides
TIA	Transient ischemic attack
TLC	Total leukocytic count
tPA	Tissue plasminogen activator
UFH	Unfractionated heparin
VIPS	Vascular effects of Infection in Pediatric Stroke

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ABSTRACT

Background: Pediatric stroke, though not common but is a cause of subsequent morbidity, with resultant major medical and financial burden. Diverse risk factors can predispose to pediatric stroke including thrombophilia. Thrombophilia screening is currently recommended for any pediatric patient with arterial or venous stroke.

Objectives: To explore the risk factors, clinical features, and neuroimaging findings and to investigate the role of thrombophilia in a cohort of children with arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT).

Subjects and Methods: The study included pediatric patients with clinical and neuroimaging evidences of stroke recruited from the Pediatric Neurology Outpatient Clinic (Ain Shams University) over a period of 18 months. Patient with sickle cell disease, cardiac diseases, CNS infection or hemorrhagic stroke were excluded.

Results: 31 patients were diagnosed with stroke; 25 had AIS and five patients had CSVT. As regards thrombophilia mutations; 12 patients were heterozygous for MTHFR C677T variant, two patients were homozygous for the same variant, while two patients were heterozygous for factor V Leiden mutation and another two were heterozygous for both

MTHFR C677T variant and factor V Leiden mutation. None of the patients carried the factor II G20210A variant.

Conclusion: Multiple risk factors can predispose to pediatric stroke. Heterozygous MTHFR C677T was prevalent among pediatric patients with stroke in Egypt.

Key words: pediatric, stroke, risk factors, thrombophilia.

INTRODUCTION

Pediatric stroke is defined as any neurological event including a seizure associated with an acute infarction shown by magnetic resonance imaging (***Dlamini & Kirkham 2009***).

Stroke in children is not a common condition with incidence rates ranging from 2 to 8 per 100,000 in children up to 14 years (***Mekitarian Filho & Carvalho 2009***). Nevertheless, stroke and cerebrovascular disorders are important causes of morbidity and mortality among children; they are amongst the top ten causes of childhood death (***Pappachan & Kirkham 2008***).

It is evident from numerous studies that the frequency of inherited prothrombotic factors is increasing in pediatric stroke, nevertheless, thrombophilia alone as a risk factor does not fully explain stroke in a child as it represents only a mild risk factor (***Zadro & Herak 2012***).

Approximately 20-50% of the pediatric patients with stroke have prothrombotic disorders ***(Balcerzyk et al. 2011***). Various prothrombotic risk factors have been investigated in pediatric stroke including elevated homocysteine, lipoprotein (a), antithrombin III, protein C, protein S deficiency, Factor V Leiden and Factor II G20210A ***(Zadro & Herak 2012)***.

A pilot study on Egyptian children with pediatric stroke was conducted on 2012 and showed that methylenetetrahydrofolate reductase MTHFR polymorphism was present in 50% of patients; 25% of the patients with methylenetetrahydrofolate reductase demonstrated combined thrombophilic abnormalities. 15% of patients manifested heterozygous factor V Leiden mutation, whereas a heterozygous prothrombin mutation was present in only (5%). Low protein S was detected in 10% patients (***Shatla et al. 2012***).

The American heart association (AHA) pediatric stroke guidelines suggested that "although the risk of stroke from most prothrombotic states is relatively low, the risk tends to increase when prothrombotic disorder occurs in children with other risk factors". Thus, it is reasonable to evaluate for the more common prothrombotic states even when another stroke risk factor has been identified (***Roach et al. 2008***).

Although multiple types of genetic and acquired thrombophilia are established as independent risk factors for incident AIS, data supporting significant prognostic impact upon recurrence risk are limited to a few individual traits such as elevated lipoprotein (a), protein C deficiency, and the presence of multiple risk factors ***(Strater et al. 2002; Bernard et al. 2011***).