Changes in Cell Mediated Immunity In Patients With Acute Cerebrovascular Stroke

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In Internal Medicine
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تغيرات الجهاز المناعي الخلوي المصاحبة للجلطة الدماغية الحادة

رسالة توطئة للحصول على درجة الماجستير **في أمراض الباطنة العامة**

مقدمة من

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Summary and Conclusion

It is now increasingly clear that human stroke results in multi-organ systemic disease, rather than in solely a brain lesion. While acute stroke patients may survive the initial brain insult, many have subsequent complications over time. Infection is the most common of these complications and the chief cause of morbidity and mortality in the stroke survivor. The role of aberrant systemic immune function in post-stroke infection has only been demonstrated in many clinical studies **(Patricia et al., 2007).**

This study was carried out on 30 hypertensive atherosclerotic patients (15 patients with acute ischemic stroke and 15 non stroke patients), and 15 totally healthy individuals as a control group. Those patients were selected from Ain Shams University internal medicine inpatient department.

This study was aiming to follow up the changes in cell mediated immunity in acute cerebrovascular stroke in comparison to atherosclerotic patients with no previous vasculo-occlusive disorders.

In conclusion, we found that atherosclerosis is an inflammatory process which is characterized by predominance of Th1 response with increased circulating levels of Th1 cytokines including IFN-gamma. But after acute ischemic brain injury, reversal of Th1/Th2 ratio occurs with decrease in Th1, which leads to immune-depression, protecting brain antigens from recognition by immune cells which helps in neuroprotection after the acute insult. But that immune-depression leads also to increased host liability to infections which restores the Th1 dominance and worsens stroke prognosis.

List of Abbreviations

4-HNE	4-hydroxynonenal
APC	Antigen presenting cell
AF	Atrial fibrillation
BBB	Blood brain barrier
CD	Cluster of differentiation
CFU	Colony form unit
CTA	Computed tomography angiogram
CT	Computerized tomography
CHD	Coronary heart disease
CRP	C-reactive protein
DC	Dentritic cells
ER	endoplasmic reticulum
FDA	Federal drug association
Flt3	Fms-like tyrosine kinase 3
Foxp3	forkhead box P3 transcription factor
GM-CSF	granulocyte-macrophage colony stimulating factor
HDL-C	High density lipoproteins cholesterol
HLA antigens	human leukocyte-associated antigens
ITAMs	immunoreceptor tyrosine activation motifs
Ig	immunuglobulin
IFN- γ	Interferon gamma
IL	interleukin
INR	International normalized ratio
JNK	jun N-terminal kinase
Lp-PLA2	lipoprotein-associated phospholipase A2
LDL-C	Low density lipoproteins cholesterol
Lck	lymphocyte-specific protein tyrosine kinase
LMP	lysosomal membrane permeabilization
MRI	magnetic resonance imaging
MHC	Major histocompatibility complex

List of Abbreviations (Cont.)

MCA	Middle cerebral artery
mAbs	monoclonal antibodies
MCP	monocyte chemoattractant protein
NK	Natural killers
nNOS	Neuronal form nitric oxide synthase
NO	Nitric oxide
Fyn	Proto-oncogene tyrosine-protein kinase
rtPA	Recombinant tissue plasminogen activator
RORC	Related orphan receptor C
Stat	Signal transducers and activators of transcription
SMCs	Smooth muscle cells
TCR	T cell receptor
Tc	T cytotoxic
Th	T helper
Treg	T regulatory
TLRs	Toll Like Receptors
GATA-3	Transcription factor GATA-3
t-bet	Transcriptional factor-bet
TGF	Transcriptional growth factor
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
VCAM	vascular cell adhesion molecule
VLDL	Very low density lipoproteins
ZAP-70	zeta-associated protein-70

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الملخص العربي

لقد أصبح من الواضح على نحو متزايد أن إصابة الإنسان بالجلطة الدماغية ينتج عنه اعتلال العديد من أنظمة الجسم المختلفة وليس مقتصر على إصابة المخ فقط. في الوقت الذي يمر الوضع المرضي لمرضى الجلطة الدماغية الحادة بسلام في بعض الحالات, يعاني الكثير منهم من مضاعفات عديدة مع مرور الوقت.وتعتبر الإصابة بالعدوى من أهم هذه المضاعفات والسبب الر ئيسي للإعتلال والوفيات في هؤلاء المرضى. وقد تم طرح الدور الغير واضح للوظيفة الجهازية المناعية في الإصابة بالعدوى في مرضى الجلطة الدماغية في عدد غير قليل من الدراسات الإكلينيكية.

تمت هذه الدراسة علي ٣٠ مريضا بمرض ارتفاع ضغط الدم وتصلب الشرايين (١٥ منهم مصابين بالجلطة الدماغية الحادة و١٥ غير مصابين بالجلطة الدماغية) و ١٥ شخص اصحاء وتم اختيار هؤلاء المرضي في مستشفيات جامعة عين شمس من المرضى المقيمين بالأقسام الداخلية لتلقي العلاج.

تهدف هذه الدراسة إلى متابعة التغيرات التي تحدث في نظام المناعة الذي يقوم على الدور الفعال للخلايا المناعية في مرضى الجلطة الدماغية الحادة وذلك مقارنة بمرضى تصلب الشرايين ممن لم يصابوا بانسداد الشرايين من قبل.

وبتلخيص ما سبق وجد أن عملية تصلب الشرايين هي عملية التهابات تتميز بغلبة المردود المناعي للخلايا الليمفاوية التائية المساعدة ١ مع زيادة في مستوى السيتوكينات التي تنتجها هذه الخلايا والتي تتضمن (الإنترفيرون جاما) . ولكن يحدث انعكاس في نسبة المردود المناعي للخلايا الليمفاو ية التائية المساعدة ١/التائية المساعدة ٢ بعد حدوث نقص حاد في تدفق الدم لخلايا المخ. ومع ذلك يحدث نقص في الخلايا التائية ١ مما ينتج عنه انخفاض في الأداء المناعي للجسم. وهذا من فوائده حماية خلايا المخ من أن تهاجم من قبل الخلايا المناعية

مما يسفر عن حماية الجهاز العصبي ككل. ولكن تزامنا مع هذا الانخفاض في أداء جهاز المناعة يكون المريض أكثر عرضة للإصابة بأنواع العدوى المختلفة مما يؤدي إلى تنشيط وغلبة الخلايا المناعية الليمفاوية التاية المساعدة ١من جديد مؤديا هذا إلى تدهور مردود المرض و سوء عاقبته.

وفي الختام نأحذ مما سبق أن على الأطباء الأخذ في الإعتبار بصورة جدية نظام لحماية مريض الجلطة الدماغية من خطر الإصابة بالعدوى وذلك عن طريق المضادات الحيوية الوقائية والتفكير في أساليب أخرى لعملية تعديل الجهاز المناعي لتحسين الوضع المرضي النهائي لمرضى الجلطة الدماغية.

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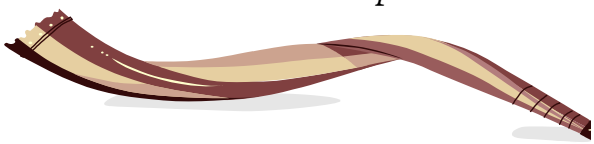
Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.



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Introduction

Stroke is defined as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer, or leading to death with no apparent cause other than of vascular origin. Although this definition includes the hemorrhagic forms of stroke, 80 % of stroke cases occur due to the occlusion of arteries carrying blood to the brain and subsequent ischemia **(Yilmaz and Granger, 2008).**

Acute ischemic stroke is the third leading cause of death in industrialized countries and the most frequent cause of permanent disability in adults worldwide **(Lakhan et al., 2008).**

When the immune system becomes activated, a delicate balance between inflammatory and anti-inflammatory states is maintained by the innate (nonspecific) and adaptive immune systems. Cells of the adaptive immune system include T-cell lymphocytes (helper T cells [generally CD4+] and cytotoxic T cells [generally CD8+] natural killer cells, and B-cell lymphocytes **(Baird, 2006).**

CD4 T helper (Th) cells play critical roles in adaptive immune responses. They recruit and activate other immune cells including B cells, CD8 T cells, macrophages, mast cells, neutrophils, eosinophils and basophils. Based on their functions, their pattern of cytokine secretion and their expression of specific transcription factors, Th cells are differentiated from native CD4 T cells, into four major lineages, Th1, Th2, Th17 and T regulatory (Treg) cells, although other Th lineages may exist **(Zhu and Paul, 2010).**

A Th1 immune response is characterized by the secretion of proinflammatory cytokines (interleukin [IL]-2, IL-12, tumor necrosis factor-α, interferon [IFN]-γ) that promote the cellular immune response. A Th2/Th3 immune response is

characterized by the secretion of cytokines (IL-4, IL-10, transforming growth factor [TGF]-β1) that modulate the cellular immune response **(Gee et al., 2007).**

Shortly after focal cerebral ischaemia, the peripheral immune system is being activated massively. A pronounced increase in T regulatory cells has been reported soon after experimental stroke, resulting presumably in inhibition of CD8+ and CD4+ Th1 cells. The reciprocal systemic Th2 enhancement of the immune response has been suggested to be a beneficial process in neuroprotection and axonal regeneration following acute central nervous system injuries in animal models. However, the price for this protective Th2 inflammatory shift is increased susceptibility to infection, mainly because of impaired cell-mediated immunity **(Theodorou et al., 2008).**

Aim of the Work

This study aims to follow up the changes in cell mediated immunity in acute cerebrovascular stroke in comparison to atherosclerotic patients with no previous vasculo-occlusive disorders.