Biomarkers of ischemic stroke: current status

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Abstract

Many patients with acute stroke are not assessed by a stroke specialist. For those assessed in hospital, interpretation of brain imaging appearances can be difficult, as computerized tomography is often normal after early onset of ischemia and may remain normal in patients with mild ischemic strokes. Magnetic Resonance Imaging (MRI) may not be feasible in acutely ill patients because they have a contraindication to MRI, or MRI may not be immediately available. A number of blood biomarkers of ischemic stroke have been identified and show promise to aid in ischemic stroke. Many relate to the underlying pathophysiology of ischemic stroke, including ischemia of central nervous system tissue, acute thrombosis and inflammatory response. Though many candidate biomarkers have been identified, none are currently used in clinical practice. *(J Thai Stroke Soc 2015; 14: 56-61.)*

Keywords: stroke, biomarker, blood, prediction

Introduction

At presence, the diagnosis of ischemic stroke relies on clinical evaluation in combination with neuroimaging. Physicians are very good at diagnosing stroke, therefore the use of a blood test to diagnose stroke is generally limited to specific scenarios where time and/or imaging resources are limited. In a pre-hospital setting where early neuroimaging is not available, a blood test could guide the evaluation and diagnosis of acute ischemic stroke.[1] Though a computerized tomography (CT) scan will likely be required prior to initiation of thrombolysis, a blood test that rapidly identifies ischemic stroke could speed patient transfer to centers and physicians able to perform evaluation for thrombolysis. Additionally, in a minority of stroke patients the diagnosis of ischemic stroke remains unclear in spite of clinical assessment and imaging. In such a situation, a blood test could add confidence to a physician's diagnosis of stroke.[2]

Role of biomarkers in clinical application

In ischemic stroke, studies have evaluated biomarkers to distinguish ischemic stroke from stroke mimics, determine stroke etiology, predict stroke severity and outcomes including early neurological deterioration and hemorrhagic complications, and identify patients who may benefit from specific therapies including decompressive hemicraniectomy and arterial recanalization (Table 1).[3-5]

Table 1 *Potential clinical application.*

Biomarkers for the diagnosis of ischemic stroke
Biomarkers of ischemic stroke etiology
Biomarkers of final infarct volume and outcome
Biomarkers to predict early neurological deterioration
Biomarkers for decompressive hemicraniectomy
Biomarkers of hemorrhagic transformation
Biomarkers of arterial recanalization
Biomarkers for stroke prevention therapy
Biomarkers of ischemic penumbra

Biomarkers can be categorized by their pathophysiological role in stroke (Table 2).[3] Brain injury biomarkers are limited by several factors. They are not specific to ischemic stroke, as many disease processes can damage brain tissue. The blood brain barrier (BBB) restricts release of these biomarkers into systemic circulation. As a result, biomarker levels may not correlate with infarct volume or stroke severity.[6] Molecules involved in acute thrombosis have also been associated with ischemic stroke. There are a number of proteins associated with ischemic stroke, which as yet do not have a clear pathophysiological role in the disease, including PARK7, nucleotide diphosphate kinase A (NDKA), and B-type neurotrophic growth factor (Table 3).

Table 2 *Category of biomarkers.*

Category	Markers
Markers of CNS tissue injury	S100B, GFAP, NSE, NMDA-R Ab, MBP
Markers of tissue inflammation	CRP, IL-6, TNF-α, VCAM-1, ICAM-1, MMP2, MMP9, Lp-PLA2, ApoC-I ApoC-III
Markers of coagulation and thrombosis	Fibrinogen, D-dimer, vWF
Other markers	Plasma DNA, PARK7, NDKA, B-type neurotrophic growth factor

Table 3 *Biomarkers in application.*

Application	Marker
Diagnosis	S100B, GFAP, NSE, NMDA-R Ab, MBP, CRP, VCAM-1, MMP2, MMP9, ApoC-I ApoC-III, D-dimer, vWF, PARK7, NDKA, B-type neurotrophic growth factor
Stroke severity	S100B, NSE, NMDA-R Ab, MBP, TNF-α, ICAM-1, MMP2, MMP9
Infarct volume	S100B, NSE, MBP, IL-6, TNF-α, VCAM-1, ICAM-1, MMP2, MMP9, plasma DNA
Hemorrhagic transformation	S100B, MMP2, MMP9
Early neurological deterioration	IL-6, TNF-α, ICAM-1
Cardioembolic stroke	D-dimer
Stroke risk	CRP, Lp-PLA2, fibrinogen
Stroke outcome	Plasma DNA

Biomarkers for Diagnosis of Ischemic Stroke

Several studies have investigated to develop a blood test to diagnose stroke by using one or several proteins.[5,6] About 60 proteins have been studied as possible biomarkers for the diagnosis of ischemic stroke. In spite of this attempt, a blood based biomarker to diagnose ischemic stroke remains to be established. Some of these proteins have also been associated with hypertension, atherosclerosis, prior stroke, epilepsy, systemic lupus erythematosus and encephalitis. Thus, the specificity of these proteins to patients with acute ischemic stroke remains uncertain. The clinical problem is not whether an ischemic stroke can be distinguished from a healthy control, but whether an ischemic stroke can be distinguished from disease that mimics ischemic stroke such as hemorrhagic stroke, seizure, migraine, syncope or hypoglycemia. Of significant importance is distinguishing ischemic stroke from hemorrhagic stroke, due to the implications in acute thrombolytic therapy. In addition, though ischemic stroke can be identified reasonably well with biomarkers, many non-ischemic stroke patients are also incorrectly predicted to be ischemic stroke. The challenge of developing a biomarker with sufficient sensitivity and specificity for clinical applications is yet to be investigated.[7-10]

Biomarkers of Ischemic Stroke Etiology

A number of biomarkers have been found to distinguish cardioembolic from non-cardioembolic ischemic stroke. Gene expression profiles in blood have also been shown to distinguish cardioembolic from large-vessel ischemic stroke. However, further validation of these profiles in larger cohorts is required. Less is known regarding biomarkers of small vessel ischemic strokes.[11-17]

Biomarkers of Final Infarct Volume and Outcome

Several biomarkers have been associated with infarct volume. However, it should be emphasized that infarct size may not correlate with neurologic outcome, as even small infarcts can cause devastating neurological outcomes when they occur in certain anatomical regions such as the brainstem. Markers to predict outcome would be useful in the management of ischemic stroke patients as potential surrogate measures.[18-20]

Biomarkers of Hemorrhagic Transformation

Several biomarkers have also been associated with an increased risk of hemorrhage following administration of tissue plasminogen activator (tPA), including MMP-9 and S100B. The most evidence exists for elevated levels of MMPs predicting hemorrhagic transformation following ischemic stroke. MMPs are involved in destruction of microvascular integrity by degradation of the basal lamina and extracellular matrix. Levels of MMP-9 predict hemorrhagic transformation in ischemic stroke patients who have and have not been treated with t-PA. Identification of hemorrhagic transformation will become more important once there is a treatment to prevent it, or testing could be performed in time to impact hemorrhagic transformation associated with thrombolysis.[21-26]

Biomarkers of Ischemic Penumbra

No plasma biomarker of human ischemic penumbra has been reported. Glucose tends to be higher and glutamate lower in penumbral tissue. Cells that survive following ischemia express a number of stress response proteins. Such proteins serve as tissue markers of ischemic penumbra in brain. Whether a corresponding biomarker in blood can be identified requires further study.[27-28]

Conclusion

Though many candidate blood based biomarkers for ischemic stroke have been identified, none are currently used in clinical practice. With further well designed study and careful validation, the development of blood biomarkers to improve the care of patients with ischemic stroke may be achieved.

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บทคัดย่อ

ผู้ป่วยโรคหลอดเลือดสมองเฉียบพลันจำนวนมากอาจไม่ได้รับการประเมินโดยผู้เชี่ยวชาญด้านโรคหลอดเลือดสมอง สำหรับผู้ที่ได้รับการประเมินในโรงพยาบาล การแปลความหมายของภาพถ่ายสมองอาจเป็นเรื่องยาก เช่น เอกซเรย์คอมพิวเตอร์มักจะเป็นปกติหลังจาก ที่เริ่มมีอาการของการขาดเลือด และอาจยังคงปกติในผู้ป่วยที่มีสมองขาดเลือดเล็กน้อย การทำภาพถ่ายคลื่นแม่เหล็กไฟฟ้าอาจจะเป็นไปไม่ได้ใน ผู้ป่วยที่มีอาการรุนแรง เพราะอาจมีข้อห้ามในการทำหรือภาพถ่ายคลื่นแม่เหล็กไฟฟ้าอาจไม่สามารถทำได้ ทันที มีการศึกษาตัวบ่งชี้ของโรคหลอดเลือดสมองขาดเลือดหลายตัวซึ่งอาจช่วยในการวินิจฉัยโรคหลอดเลือดสมองตีบ ตัวบ่งชี้หลายตัวเกี่ยวข้องกับพยาธิสรีรวิทยาพื้นฐานของโรคหลอดเลือดสมองตีบ รวมทั้งภาวะขาดเลือดของเนื้อเยื่อระบบประสาทส่วนกลาง ภาวะเลือดแข็งตัวและการตอบสนองต่อการอักเสบ แม้ว่ามีตัวบ่งชี้จำนวนมากที่ได้รับการศึกษา แต่ตัวบ่งชี้เหล่านี้ก็ยังไม่ถูกนำมาใช้ในเวชปฏิบัติในปัจจุบัน

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