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Review Article

Association of Diagnostic Stroke Biomarkers with Post Stroke Cognitive Impairment

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Abstract

Stroke patients are at a higher risk of developing progressive cognitive impairment, often retarding patient rehabilitation. Studies have been carried out to find out the molecular mechanism associated with the stroke and its consequences on the various brain regions implicated in cognitive function. The current available therapy does not improve long- term outcome and remains a substantially unmet medical need. The review is an approach to emphasize the risk factors and diagnostic biomarkers of stroke that can be associated with post-stroke cognitive deficit, which may help in detecting patients at increased risk of cognitive deterioration and prevent or delay the occurrence of post-stroke cognitive impairments.

ABBREVIATIONS

PBA: Pseudo-Bulbar Affect; AD: Alzheimer's Disease; MMSE: Mini-Mental State Examination; NVU: Neurovascular Unit; BBB: Blood Brain Barrier; fMRI: functional Magnetic Resonance Imaging; PSCI: Post Stroke Cognitive Impairment

INTRODUCTION

Stroke is a leading cause of death and functional disability [1] in which a sudden loss of neurologic function results from focal disturbance in the cerebral blood flow due to ischemia or hemorrhage. Cognitive impairment and memory loss is quite common after the stroke. Approximately 30% of stroke patients develop memory impairment within one year of stroke onset. Stroke affects the cognitive domain, which includes attention, memory, language, and orientation etc. There has been a tremendous effort to understand the molecular mechanisms involved in post stroke neural regions in exploring biomarkers for clinical diagnosis of stroke, its prognosis and treatment response [2]. Range of biomarkers is related for its association with risk assessment, diagnostic purpose and to predict post-stroke therapeutic outcome. Various biomarkers associated with risk and even prevention strategies have been reviewed extensively [2-4]. In addition to this, American stroke association reviewed markers of prospective stroke risk for primary and secondary prevention [5]. Moreover, the effect of stroke as a result of reductions in blood flow to the brain for sufficient duration results in damage to neuronal networks or circuitries leading to various mood disorders such as depression, anxiety and pseudo-bulbar affect (PBA), impairment of sensation, movement or cognition [6,7].

The molecular mechanism underlying cognitive impairment after stroke remains uncertain. Evidences suggest that the cognitive impairment develops within 3 months post stroke [8] and the prevalence of stroke induced cognitive impairment varies from 6 to 27%. Though, a recent study shows its prevalence up to41.8% and it appears an exponential increase with age 65 years and older [9,10]. Furthermore, stroke not only involved in the vascular cognitive impairment, which took over vascular dementia, but also the pathogenesis of Alzheimer's disease (AD) suggesting an overlap between both. The clinical study suggests that the pathogenesis of AD makes contribution to 1/3rdof demented cases post stroke [11]. Clinically patients with the cognitive impairment can be divided into the mild cognitive impairment and dementia based on the degree of cognitive decline [12]. The prevalence of short-term post-stroke dementia, including cognitive impairment, has been reported in many studies, that have used various standardized diagnostic measures such as Diagnostic and Statistical Manuals of Mental Disorders IV, or a Mini-Mental State Examination (MMSE) score of <24 as an outcome [13-15].

The association of various biomarkers in the diagnosis of stroke and in post-stroke cognitive impairment has rarely been studied. In this review, we summarize such biomarkers that offer promise to achieve successful candidates in the regulation of post-stroke cognitive impairment.

Mechanism of post-stroke cognitive impairment

The basic concept for stroke development and degree of post stroke cognitive impairment is paucity of energy or oxygen to the brain resulting in region specific neural damage and/or white matter lesions depending on the severity and duration. The neurovascular unit (NVU) consisting of neuro-glial population and the endothelial cells of blood brain barrier (BBB) etc. is a vital to this process and sustains a 'metabolic coupling' between neuronal processes and blood circulation to uphold the high metabolic need of the vascular system and the microcirculation of the brain to altered conditions [16]. Some studies with functional magnetic resonance imaging (fMRI) have shown that following stroke there is an uncoupling among metabolic needs, particularly for oxygen and vascular supply and this can worsen the outcomes [17].

The other cells of the NVU, astrocytes play a key role in supporting neurons and maintaining synaptic functions [18]. Since end feet structures of astrocytes are in close contact with cerebral endothelial cells and deliver a physical link to the microvasculature. Hence, astrocytes are therefore uniquely placed to exercise control over local alterations in cerebral blood flow as well as modifiable tight junction integrity. Astrocytes, and other cellular components of the NVU, seem to play a critical role in monitoring changes in synaptic activity and signaling between micro vascular units. The BBB, is a critical interface that maintains the brain's need for constant perfusion and consists of a dynamic and functional NVUs that are formed from astrocytes, microglia, capillary endothelium, neurons, pericytes and extracellular matrix all acting in a corresponding manner. In CNS disease, however, the well-organized structure of the NVU breaks down resulting in breaches in the BBB leading to neuronal damage and cognitive impairment.

Several CNS conditions include molecular mechanisms leading to disruption in the NVU that share common pathways such as neuro-inflammation (interleukin IL-6, tumor necrosis factor-alpha [TNF-α]), oxidative stress (reactive oxygen species), apoptosis (caspase-3), neurotrophic alterations (brain-derived neurotrophic factor [BDNF]), astrocytic loss (GFAP, S100β) other factors resulting in the neurovascular damage and degeneration. The combined effects of this are the synaptic loss and, ultimately, a progressive cognitive impairment [19] (Figure 1).

Stroke leads to impairment in memory function by alteration of diverse molecular mechanisms that ultimately cause drop in neuronal and glial cell population. (-) sign indicates deleterious mechanism followed by stroke.

Apart from these factors several other biomarkers contribute to the diagnosis of stroke and are involved in post-stroke cognitive impairment such as neuron-specific enolase (NSE), Homocysteine, hFABP (Heart fatty acid-binding protein), CRP (C-reactive protein), MMP2 (matrix metalloproteinase-2, PARK7 (Parkinson disease protein 7), NDKA (Nucleoside diphosphate kinase A), ASIC-1 (Acid-sensing icon channel-1). In brief, NSE is an enzyme in the glycolysis pathway and similar to S100β, NSE concentration rises in the CSF following ischemic stroke and becomes detectable between 4 and 8 h after the onset of stroke. One study has reported that NSE levels along with S100β predict cognitive dysfunction [20]. The concentrations of total homocysteine (tHcy) represent a potentially modifiable risk factor for stroke [21] and its elevated levels have been a risk factor in stroke patients [22]. One mechanism could be that the reduced level of SOD1 leads to hyper-homocysteinemia thus promoting ischemic stroke [23]. Another marker, hFABP, elevated early in acute ischemic stroke indicates that especially hFABP might have the potential to be a rapid marker of brain damage and clinical severity [24]. Furthermore, an increase in CSF and serum levels of hFAB has been reported in the patients with neurodegenerative diseases [25]. Another biomarker in same family namely B- Fatty Acid Binding Protein (B-FABP)

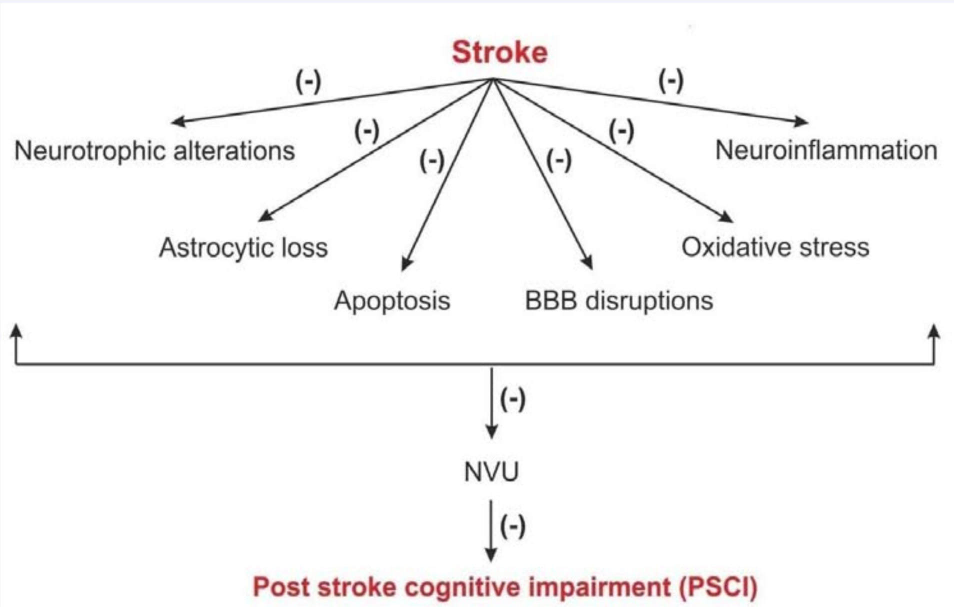

Figure 1 Different molecular mechanism associated with post stroke cognitive impairment.

considered as a biomarker for small sub-cortical and lacunar infarcts but might be non-specific since it's also associated with mild Traumatic Brain Injury (TBI) and electroconvulsive therapy. Growing evidence suggests that CRP is not only an inflammatory marker but also has influential pro-atherogenicaction which directly involved in the process of atherogenesis, causing stroke, leukoaraiosis and vascular dementia [26]. Experimental studies also showed its potential role in neurotoxicity [27]. Among matrix metalloproteinase (MMPs), gelatinases (MMP-2 and MMP-9) are the most investigated enzymes and are widely reviewed [28], that possess ability to active numerous pro-inflammatory agents. Furthermore, clinical studies had shown that lipid-lowering drugs possess the ability to inhibit the activity of MMP-9 during acute ischemic stroke also synthetic inhibitors decreases the infarct volume in animal models of ischemic stroke and also prevents the cognitive impairment [28-30]. PARK7 protein and nucleoside diphosphate kinase A in the spinal fluid were identified as candidates for ischemic stroke biomarkers [31,32]. The ASIC1a channels are highly populated in the neurons and has shown its association with cerebral ischemia [33]. While melondialdehyde was found to be associated with post-stroke depression condition [34].

Among the haemostatic factors, studies showed that increased fibrinogen levels increases the risk of cognitive impairment [35]. Others biomarkers do not show any direct relevance associated with the post stroke cognitive decline, however their role in the in the diagnosis of stroke could not be overlooked. On the contrary few biomarkers like Apolipoprotein C1 and C3, plasma DNA, baseline levels of thrombin activablefibrinolysis inhibitor, MMP3 and tissue inhibitor for metalloproteinase 2(TIMP-2) helps in hemorrhagic stroke detection [3,36]. Different biomarkers in the diagnosis of different types of stroke and its association with post stroke cognitive impairment was elaborated in Table 1.

CONCLUSION

A number of potential biomarkers of ischemic stroke have been identified, which will improve patient quality life. Many of these markers relate to the pathophysiology of ischemic

Table 1: Different biomarkers in the diagnosis of Ischemic stroke and its association with post stroke cognitive impairment.

	Types of stroke	Biomarkers	Description of Biomarker	Association of marker with post stroke cognitive impairment	Reference
CNS related markers	Ischemic	BNDF (Serum	Neurotrophin, essential for neuronal plasticity and long term potentiation	++	[37]
	Ischemic Hemorrhagic and Traumatic Brain injury	S100β (Serum	Calcium binding protein secreted by astrocytes. In general promote neuroplasticity but in disease condition like stroke exacerbates gliosis.	++	[38]
	Ischemic and Hemorrhagic	GFAP (Plasma	GFAP is principle intermediate filament protein secreted by astrocytes	++	[38]
	Ischemic and Hemorrhagic	NSE (Plasma, CSF	Prognostic indicator followed by cardiac arrest	++	[38]
	Ischemic and Transient Ischemic Attack (TIA	NMDA-R Ab (Autoantibodies to the NR2A / NR2B subunits of the NMDA receptor	By decreasing SK2 Channel activity by repolarization /depolarization of Ca2+ influx, Specific to ischemic condition	++	[39, 40]
	Ischemic and Small vessel stroke	MBP (Myelin basic protein (Blood, CSF	Rarefaction of white matter due to loss of nerve fiber degeneration, gliosis and demyelination. Also it predominantly expressed in acute sever ischemic condition	++	[41]
	Ischemic	NAA (Serum	Acts as a molecular water pump which helps in flow of metabolic water	++	[3]
	Ischemic and Hemorrhagic	VLP1 (Plasma , CSF	Neuronal Ca2+ sensor protein abundantly fund in neurons	++	[42, 43]
	Ischemic	UFDP-1	Degradation of ubiquitin		[44]
	Ischemic and Hemorrhagic	hFABP(serum	Involved in transport of long chain fatty acid which influences the functions like cellular growth and differentiation	++	[24, 45]
	Ischemic	GST-π	Detoxifying ROS	-	[46]
	Ischemic	IMA (Blood	IMA produced in ischemic – hypoxic condition, binding affinity for metal ions reduces under ischemic condition	-	[47]
	Ischemic	Plasma glutamate	Excitotoxic,progression of ischemic stroke but no direct correlation with ischemic output	-	[48]
	Ischemic	ASIC-1a	Calcium regulation	+	[33]

Oxidative Stress	Ischemic	SOD(Plasma	ROS	++	[23, 49]
	Ischemic (serum	Malondialdehyde	Lipid oxidation, post stroke depression		[50]
Inflammatory Biomarkers	Ischemic + TIA	CRP	Acute phase protein associated with inflammation and responsible for BBB disruption	++	[51]
	Ischemic and Hemorrhagic	IL-6	Anti-inflammatory mediators associated with infract volume	++	[52]
		IL-8		+	[53]
		IL-12		++	[53]
	Ischemic	TNF-α	Secreted by endothelial cells, microglia and astrocytes, ROS activation,Associated with infract volume	++	[52]
	Ischemic	VCAM 1 (Blood	Part of immunoglobulin superfamily which plays role in inflammation and immune response as well as migration of leucocytes	-	[54]
	Ischemic	ICAM-1(Blood, CSF	Leucocyte infiltration from blood to brain	-	[55]
	Ischemic and Hemorrhagic	MMP2-2& 9	Proteolytic enzymes secreted by astrocytes and microglia which are responsible for damaging BBB and capillaries and promotes the inflammatory mechanism	++	[30]
	Ischemic	Lp-PLA2	Pro-inflammatory	-	[51, 56]
	Hemorrhagic	ApoC-I, III (Plasma		-	[57, 58]
	Ischemic	Caspase-3(plasma	DNA fragmentation	+	[59]
Haemostatic markers	Ischemic	Fibrinogen		+	[51, 60]
	Ischemic +TIA	D-Dimer	Strongest prognostic indicator	-	[61]
	Ischemic	vWF	Exacerbate stroke outcome by increasing death rate	-	[54, 62]
	Ischemic	Thrombomodulin (Serum	No direct co-relation with stroke condition but elevated levels may responsible for higher death rate	-	[4]
	Ischemic + TIA	Fibrinopeptide A	Increase death rate	-	[63]
	Ischemic +TIA	β-thromboglobulin	Exacerbate stroke outcome by increasing death rate	-	[64]
Miscellaneous	Ischemic and Hemorrhagic (Plasma	Plasma DNA	Nonspecific stroke biomarker since expressed in other disease condition	-	[65]
	Ischemic (CSF, Plasma	PARK7 (Parkinson disease protein 7	Redox sensitive molecular chaperone activated after oxidative stress	+	[31, 66]
	Ischemic (CSF, Plasma	NDKA	Kinase which catalyzes transfer of terminal phosphate from ATP to nucleotide.	-	[32, 46]
	Ischemic (Plasma	Homocysteine	Elevated level causes oxidative stress, endothelial dysfunction , atherothrombosis	+	[23]

Direct Relevance: ++; Indirect relevance: +; No direct relevance: -

Abbreviations: BNDF: Brain Derived Neurotrophic Factor; GFAP: Glial Fibrillary Acidic Protein; NSE: Neuron Specific Enolase; MBP: Myelin Basic Protein; NAA: N-Acetyl-L-Aspartate; VLP1: Visinin Like Protein 1; NDKA: Nucleoside Diphosphate Kinase A; UFDP-1: Ubiquitin Fusion Degradation Protein 1; hFAB: Heart Fatty Acid-Binding Protein; GST-π: Glutathione S Transferase π; IMA: Ischemia Modified Albumin; ASIC-1a: Acid Sensing Ion Channels-1a; SOD: Superoxide Dismutase; ROS: Reactive Oxygen Species; CRP: C-Reactive Protein; IL: Interleukin; TNF-α: Tumor Necrosis Factor; VCAM 1: Vascular Cell Adhesion Protein *1*; ICAM 1: Intercellular Adhesion Molecule 1; MMP: Matrix Metalloproteinase; Lp-PLA2: Lipoprotein-Associated Phospholipase A2; ApoC-I, III: Apolipoprotein C-I, III; vWF: *Von Willebrand Factor*; PARK7: Parkinson Disease Protein 7; NDKA: Nucleoside Diphosphate Kinase A

stroke, including ischemia of CNS tissue, acute thrombosis and inflammatory response. Animal-based research and the outcome of human trials have led to better understanding of the complexity in stroke and comorbid cognitive condition. Identification of early diagnostic markers in stroke associated cognitive impairment could be the successful approach for detection of increased risk of post-stroke cognitive deterioration which can lead to the identification of therapeutic targets and monitor response to treatment, for promising potential therapeutic applications.

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