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BNP and its Status as a Biomarker in Acute Ischemic Stroke

Khandelwal B.*, Dey R., Khatri D.*****

Author's Affiliation:
*Profesor and Head
***Assistant Professor,
Department of Medicine
**Assistant Professor,
Department of Physiology,
Sikkim Manipal University,
Sikkim Manipal Institute
Of Medical Sciences,
Gangtok.

Corresponding Author:
B. Khandelwal,
Department of Medicine,
SMIMS, 5th Mile, Tadong,
Sikkim – 737102, Gangtok.
E-mail:
drbidita@gmail.com

Abstract

B-Type natriuretic peptide (BNP) has established itself as an important cardiovascular and cardio renal biomarker. Stroke is an emergency having high mortality, morbidity, social and economic implications. Acute ischemic stroke (AIS) accounts for approximately 70% of all strokes and is caused by embolic or atherosclerotic occlusion in the cerebral vessels. Identification of a biomarker for risk, severity and prognosis of stroke would be of great benefit. The mechanism by which the plasma levels of BNP are increased in patients with AIS independently of heart diseases is not clearly defined but the levels of BNP has shown a strong correlation with cardio-embolic stroke and has established its role as a surrogate marker for the same. Biomarkers like BNP should be used to supplement clinically guided therapy and not to substitute it. Proper interpretation of BNP would surely make the diagnosis, management and risk stratification better for stroke subjects.

Keywords: BNP; Biomarker; Acute Ischemic Stroke.

Introduction

Basic science discoveries and technological progress in the last decade have introduced a variety of circulating molecules in clinical research referred to as biomarkers. B-type natriuretic peptide (BNP) has established itself as an important cardiovascular and cardio renal biomarker. Stroke is defined as sudden onset of focal and global neurological symptoms due to cerebral blood vessels leading to haemorrhage and ischemia in brain [1]. Stroke is an emergency having high mortality, morbidity, social and economic implications. Acute ischemic stroke (AIS) accounts for approximately 70% of all strokes and is caused by embolic or atherosclerotic occlusion in the cerebral vessels. Identification of a biomarker for risk, severity and prognosis of stroke would be of great benefit. BNP produced as a result of cardiovascular changes following ischemic stroke has an important role in the hemodynamic of these patients. The mechanism by which the plasma levels of BNP are increased in patients with AIS independently of heart diseases is not clearly defined but the levels of BNP has shown a strong correlation with cardio-embolic stroke and has established its role as a surrogate marker for the same. Robust, widely-available, rapidly processed, inexpensive biomarkers such as BNP could potentially be used in the future to guide management of complex cerebrovascular patients in order to maximize their potential for recovery.

History of BNP and natriuretic peptides

The history of B-type natriuretic peptide (BNP) dates back to 1988 when it was first isolated from porcine brain tissue. It was subsequently also detected in rat brain where its expression is upregulated by middle cerebral artery occlusion[2,3] BNP belongs to the family of natriuretic peptides which comprises of three structurally related molecules, atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) encoded by a gene NPPC. In addition to the mammalian natriuretic peptides (ANP, BNP and CNP), other natriuretic peptides with similar structure and properties have been isolated elsewhere in the animal kingdom. Trevonen (1998) described a salmon natriuretic peptide known as salmon cardiac peptide [4] and dendroaspis natriuretic peptide (DNP) is found in venom of the green mamba [5].

Physiology, Synthesis & functions of BNP

BNP is a 32-amino acid polypeptide released mainly from the ventricular myocardial cells and to some extent from cardiac fibroblasts in response to stretching secondary to pressure or volume overload. The release is modulated by calcium ions. BNP is synthesized as a 134-amino acid preprohormone (preproBNP), encoded by the human gene NPPB. Removal of the 25-residue N-terminal signal peptide generates the prohormone, proBNP, which is stored intracellularly as an O-linked glycoprotein, proBNP is subsequently cleaved between arginine-102 and serine-103 by a specific convertase, corin into NT-proBNP and the biologically active 32-amino acid polypeptide BNP-32, which are secreted into the blood in equimolar amounts. BNP is cleared from plasma through binding to the natriuretic peptide clearance receptor type C, but it seems relatively resistant to proteolysis by neutral endopeptidase NEP 24.11. The biological effects include diuresis, vasodilatation, and inhibition of renin and aldosterone production thus leading to natriuresis and inhibition of cardiac and vascular myocyte growth. BNP binds to and activates the atrial natriuretic factor receptors (NPRA). The biological half-life of BNP is twice as long as that of ANP.

Factors affecting levels of BNP

BNP is measured by immunoassay. There is no single cut off value to differentiate a normal level from an abnormal level. The value of less than 50pg per ml has a sensitivity of 97% and specificity of 62% in ruling out acute decompensated heart failure. There is a diagnostic 'grey area' between 100pg / ml & 500pg / ml. As with any biomarker several factors should be considered when interpreting BNP levels. BNP increases with age and is higher in women subjects without cardiovascular disease or cardiac dysfunction. An inverse relation exists between BNP and body mass index. Renal dysfunction increases the BNP levels. Cardiovascular drugs such as diuretics, spironolactone, angiotensin converting enzyme inhibitor and angiotensin receptor blockers may decrease BNP levels while with beta blockers the levels may increase for weeks and then decrease after a few months. There also exists intra-individual biologic variation. Several cardiac diseases, ventricular assist devices, sepsis etc., also have effect on the levels.

Brain Ischemia & BNP

There is limited data on the physiological and pathological role of BNP in human brain. Hypoxia increases cardiac BNP gene expression in pigs and circulating BNP levels in humans, and occlusion of the middle cerebral artery stimulates BNP mRNA expression in rat brain tissues [6]. Moreover, the human BNP gene promoter region contains a hypoxia-inducible factor (HIF)-1 binding site and BNP gene expression is activated by HIF-1 In this context, considerable attention should be paid to the positive correlation between brain infarct volume and the plasma BNP level in AIS and the possibility that the infarct or ischemic area in the brain could be a potential source of circulating BNP. Studies have shown that elevated plasma NTproBNP levels are involved in the pathogenesis of brain edema in ischemic and hemorrhagic stroke [7]. These findings suggest that the ischemic brain itself may also release NT-proBNP into the circulation. It has been reported that S-100protein, a calcium-binding protein abundant in glial and Schwann cells, is increased in blood and cerebrospinal fluid (CSF) after ischemic stroke and its plasma concentration correlates positively with the size of infarct volume [8]. Thus, it may be important to investigate whether the concentration of BNP in CSF would be increased after brain infarction or ischemia and BNP released from the ischemic brain tissues would exert a neuro-protective effect around the ischemic area. Handke et al reported that left atrial appendage (LAA) flow was closely related to elevated thromboembolic risks in the cerebral ischemia patients irrespective of the basic rhythm. To detect LAA flow transesophageal echocardiography (TEE) has to be done during the acute stroke. TEE being invasive, requiring expertise and having risk of pneumonia, a non-invasive marker to predict cardio-embolic stroke would be beneficial.

BNP and Stroke

Increase in the life expectancy of humans has led to increased number of stroke patients. Early diagnosis is required for applying efficient treatment like thrombolysis in ischemic stroke. Subsequent to differentiation of ischemic and haemorrhagic stroke, it is important to differentiate cardioembolic stroke from non-cardio-embolic stroke, since cardio-embolic stroke generally results in more severe disability and acute treatment and secondary prevention differ in cardio-embolic stroke from non-cardio-embolic stroke. However, it is difficult to diagnose the subtypes of ischemic stroke accurately at admission. In determining subtypes of ischemic strokes, combination of biomarkers such as BNP, D-dimer, Matrix metalloproteinase 9 (MMP-9) and C-reactive protein may be more predictive rather than using a single biomarker.

BNP & Acute Ischemic Stroke

The levels of BNP are higher in patients with Acute Ischemic stroke (AIS) as compared to haemorrhagic stroke and are higher in cardio-embolic stroke as compared to non-cardio embolic ischemic stroke. [9] BNP is increased in AIS presumably due to myocardium damage or elevated blood pressure. Tomita et al however clearly demonstrated after exclusion of heart disease, the plasma BNP level at admission was significantly higher in large artery occlusion (LAA) than in small artery occlusion (SAO) and control. (70.6±53.9 vs 38.2±28.4 and 28.5±19.9 pg/ml respectively, both $p < 0.05$). In LAA group there was no difference between supratentorial and subtentorial lesions [10]. Yukiri et al observed significantly higher BNP levels at admission in cardio-embolic infarctions as compared to atherothrombotic infarctions. ($P<0.001$) and concluded that BNP can be a surrogate marker for CES with strong predictive power independent from atrial fibrillation. BNP levels positively correlate with infarct volume.

BNP & Stroke Severity

Plasma BNP level can be a clinically useful marker indicative of the severity of acute ischemic stroke. Significant correlations ($P=0.003$) are found between BNP level and the NIH stroke score (NIHSS) in AIS at admission. Since higher plasma BNP levels reflect greater infarct area, the correlation is compatible with the clinical manifestations [10]. Cakir et al found no statistically significant correlation between NIHSS score and BNP levels [11].

BNP & Functional Outcome of Stroke

Plasma levels of BNP in the acute phase of ischemic stroke predict post stroke mortality [12] and patients with high plasma BNP levels have four fold higher mortality. Long term functional outcome after stroke is one of the most important and difficult variables to predict and is subjected to complex interactions with multiple factors. The potential role of BNP in predicting long term functional outcome is controversial.

BNP & Intra-cerebral Haemorrhage

Tomita el al found no difference in BNP levels in ICH (47.3±26.6 pg/ml) and controls.[10] Nakagawa et al found that although patients with intracranial haemorrhage (ICH) had higher MAP levels than patients with ischemic stroke, the serum BNP levels were higher in patients with ICH [13].

Conclusion

Biomarkers like BNP should be used to supplement clinically guided therapy and not to substitute it. Proper interpretation of BNP would surely make the diagnosis, management and risk stratification better for stroke subjects. Using combination of biomarkers increases its predictive value. In stroke patients, elevated serum BNP on admission may not only further confirm a cardio-embolic etiology of stroke event, but also may signal increased risk for poor long-term outcome, including death. BNP testing has a role in risk stratification, identifying those likely to require intensive rehabilitative intervention. In addition, particularly in cases of cryptogenic stroke, the BNP level could help in forming the choice of antithrombotic agent for secondary stroke prevention.

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