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NT-PRO BNP LEVELS AS A BIOMARKER FOR CARDIOEMBOLIC STROKE

Neurology

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ABSTRACT

Stroke is a leading cause of mortality and morbidity. Stroke may be ischemic or hemorrhagic. Ischemic stroke may be due to cardioembolism, large vessel disease, small vessel disease or multiple pathologies. Of them, cardioembolism is the commonest etiology, accounting for up to 40% of all ischemic strokes, having higher recurrence rates as well as poorer outcomes. Atrial fibrillation is the commonest cause of cardioembolism. The treatment also involves anticoagulants and not antiplatelets. Unfortunately detection of cardioembolism requires complicated long term monitoring through devices to detect paroxysmal atrial fibrillation, which is as deadly as persistent atrial fibrillation. The use of biomarkers would simplify the process of detecting cardioembolism, leading also to earlier detection. NT-pro BNP is one such biomarker, which has been shown to be useful in identifying cardioembolic stroke within 72 hrs of symptom onset. This review addresses the role of NT-pro BNP in the detection of cardioembolic stroke.

KEYWORDS

cardioembolic, biomarker, NT-pro BNP

INTRODUCTION

Stroke is a major public health issue globally. In the Global Burden of Diseases (GBD) study in 1990 stroke was identified as the second leading cause of death worldwide, second only to ischemic heart disease. [1] Subsequently updating of GBD study reported nearly 5.87 million stroke deaths globally in 2010, as compared to 4.66 million in 1990 which indicates a 26 percent increase in global stroke deaths over the past two decades. [2] The Global Health Observatory Data of 2016 reports the number of stroke related deaths to be nearly 6 million. [3] In India, the crude stroke prevalence ranged from 105 to 152/100,000 persons per year during the past two decades [4] The prevalence of stroke is likely to increase in the near future since the proportion of population aged more than 65 years is rapidly increasing as well as due to rising incidence of stroke in younger population. Stroke is the second leading cause of death for people aged more than 60 years and the most important cause of permanent disability. [5]

Stroke is broadly classified as ischemic or hemorrhagic, with ischemic stroke accounting for approximately 85% of all cases. [6] Cardiac embolism is a leading etiology of ischemic strokes, the cause of 25 to 40% of cerebral infarctions worldwide with potentially even higher rates in developing countries like India. [7] The incidence of embolic heart disease in the population is estimated at about 30 cases per 100,000 inhabitants per year, and its prevalence between 5 and 10 cases per 1,000 persons aged 65 years or older [8] Cardioembolic strokes are associated with poorer outcomes and higher recurrence rates than other causes of ischaemic stroke. This population has a recurrence rate of nearly 12% within first 2 weeks of index event [9] as opposed to the overall recurrence rate of only 1-4% in ischaemic stroke. [10] Also cardioembolic stroke has the highest in-hospital mortality amongst all causes of ischaemic stroke. [11]. As per the clinical series of Caplan et al [12], the in-hospital mortality rate of cardioembolic infarction was 27.3% as compared with 0.8% for lacunar infarcts and 21.7% for atherothrombotic stroke. Non valvular atrial fibrillation is the most common etiology of cardioembolic stroke, accounting for nearly 50% of cases. The other sources of embolism include myocardial infarction, intraventricular thrombus, valvular heart disease and a miscellany of causes.[13] Atrial fibrillation may be both persistent and paroxysmal, both carrying equal risk of stroke, which is an annual risk of ischemic stroke of about 5–7%. [14] Therapy also differs for cardioembolic strokes which require anticoagulants as opposed to atherothrombotic strokes which are treated with antiplatelet agents. In fact, a meta-analysis indicates that oral anticoagulation therapy with warfarin reduces stroke risk by 64% on an intention to treat basis. [15] Diagnosis of cardioembolic stroke by conventional methods requires prolonged or continuous rhythm monitoring through various means like Holter monitoring, external loop recorders or implantable devices. However this is difficult since post stroke patients are not ideal candidates for prolonged monitoring due to various co-morbidities. There is thus an increasing need for blood biomarkers capable of identifying patients at high risk of paroxysmal atrial fibrillation. NT Pro BNP is one such biomarker which has been identified as an independent predictor of paroxysmal atrial fibrillation.

Epidemiology

Stroke is the second leading cause of death worldwide. As reported by the Global Burden of Diseases (GBD) study in 1990, over 85 per cent of the global burden of stroke was borne by low- and middle-income countries. [1] In a longitudinal study on stroke conducted during 2003-2010 in Kolkata involving total 1041 participants, the age-adjusted, annual cumulative stroke incidence was estimated as141/100,000 persons [16] These values were much higher than the global figures of 94/100,000 person-years during the years 2000-2008. The overall stroke mortality was 59 per cent in the first five years and 61 per cent at seven years. A two year survey conducted by Dalal et al in Mumbai in 2005-2006 as a part of the Mumbai stroke registry surveillance also estimated age-standardized cumulative incidence of first ever stroke as 152/100,000 persons per year. The pooled data analysis from all studies estimates that in India, 68-80% of all strokes are ischemic. [4] Ischemic stroke comprise large vessel (41%), lacunar (18%), cardioembolic (10%), other determined (10%), and undetermined (20%) subtypes. However, in a study conducted by Ganesh et al at Chennai in 2003-2004 it was estimated that cardioembolic strokes account for 23% to 36% of all ischaemic strokes in the population aged less than 45 years of age, which is comparable with global data. [17]

Globally there are more than 50 million stroke and transient ischaemic attack survivors. More than 1 in 5 survivors will suffer a subsequent stroke in the following 5 yrs [18] which translates to a huge financial and healthcare burden. 15-20 % of stroke survivors are permanently disabled, while 20% require institutional care within first 3 months of the event. [19] In 2004, the stroke-related DALY (disability-adjusted life year) loss in India was 597.6 per 100,000 person-years. [20]

Etiology of Ischemic Stroke

The Trial of Org 10172 in Acute Stroke Treatment classified ischemic stroke into 5 major subtypes based on clinical features as well as diagnostic modalities such as brain imaging (CT/MRI), cardiac imaging eg echocardiography, duplex imaging of extracranial arteries, arteriography and laboratory assesments for a prothrombotic state. These include:

1. Large artery atherosclerosis (embolus/thrombosis)
2. Cardioembolism (high-risk/medium-risk)
3. Small vessel occlusion (lacunae)
4. Stroke of other determined etiology

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5. Stroke of undetermined etiology
a) Two or more causes identified
b) Negative evaluation
c) Incomplete evaluation [21]

Cardioembolic Stroke

The source of embolus arises in the heart and is divided into high-risk and medium risk groups based on the evidence of relative risk for embolism. [21] High risk sources of embolus include mechanical prosthetic valve, mitral stenosis with atrial fibrillation (valvular heart disease), atrial fibrillation, left atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma and infective endocarditis. Medium risk of cardioembolic stroke is with mitral valve prolapse, mitral annulus calcification, mitral stenosis without atrial fibrillation, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bio prosthetic cardiac valve, non bacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, myocardial infarction (>4 weeks, <6 months), myocardial infarction (>4 weeks, <6 months) and plaque formation > 4mm in aorta. In order to diagnose a possible or probable cardioembolic stroke, at least one cardiac source of embolus must be identified. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke.

Atrial fibrillation is the most common sustained arrhythmia, currently affecting nearly 33 million people worldwide, [22] presenting as disorganized, rapid, and irregular atrial activation leading to irregular ventricular response. There is loss of atrial contractility with inability to completely empty blood from atrial appendage and thus increased risk of clot formation and subsequent thromboembolic events. Irrespective of etiology, atrial fibrillation is the most important cause of cardioembolism worldwide. [23] Nearly a third of patients with ischemic stroke have been found to have either clinical or subclinical AF due to high prevalence of left atrial thrombosis. [24] The presence of AF increases risk of stroke by about 5 fold in all age groups. [25]

Atrial fibrillation could be either paroxysmal (lasting more than 30 seconds and terminating spontaneously or within 7 days of treatment) [26] or persistent. Both types of AF carry equal risk of cardioembolic stroke, which is an annual risk of ischemic stroke of about 5–7%. [27]

Importance of Biomarkers in the Diagnosis of Cardioembolic Stroke

Atrial fibrillation produces almost half of cardioembolic strokes, followed by acute myocardial infarction, ventricular thrombi, structural heart defects, cardiac tumors and valvular heart disease. [28] Thus anti coagulation would evidently be beneficial in a vast majority of cases of cardioembolic stroke as opposed to anti thrombotic therapy that is used in atherothrombotic stroke. A meta-analysis indicates that oral anticoagulation therapy with warfarin reduces stroke risk by 64% on an intention to treat basis. [29] The major issue however remains that atrial fibrillation is notoriously difficult to diagnose. It is estimated that despite extensive stroke workup, no causative factor can be found in upto 20-25% cases, which are labeled as cryptogenic stroke [30] and offered antiplatelet therapy. However, in about 25-30% of these cases, the cause could be underlying paroxysmal atrial fibrillation (PAF). [31] Identifying PAF is extremely difficult in patients presenting with sinus rhythm. The ASSERT study (A Stratified Sickle Event Randomized Trial) revealed that patients with short episodes of atrial fibrillation (>6 minutes within 3 months) have a 2.5 fold increase in the risk of stroke and systemic embolism.[32] The ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) which was done with 6706 patients and compared anticoagulant therapy versus the combination of aspirin and clopidogrel showed that the risk of stroke or systemic embolism was similar in patients with paroxysmal as compared with persistent AF (annual rate of the combined end point of stroke or non-CNS systemic embolism was 2.0 per 100 patient-years in paroxysmal AF compared with 2.2 in sustained AF).[27] The AFFIRM Study (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) randomized 4060 patients with AF to rate- versus rhythm-control strategies. After 5 years of follow up, the stroke risk among the 481 patients with asymptomatic AF was found to be similar to the stroke risk in the patients with symptomatic AF (3.8% versus 4.4%; P=0.52). However the study failed to predict the effect of brief episodes of AF on the risk of stroke, since only 4% of asymptomatic AF episodes were of <6-hour duration [33] The annual risk of ischaemic stroke in AF patients being 5-7%, these patients actually require anticoagulation and not antiplatelet therapy.

Prolonged or continuous rhythm monitoring may enhance the rate of detection of silent PAF. [34] such that longer duration (>=72 hrs) outpatient monitoring is generally recommended.[29]This can be carried out by either implantable cardiac monitors or by external devices like Holter (24-72 hours), mobile cardiac outpatient telemetry devices (upto 4 weeks) and electrocardiographic patch devices (up to 4 weeks). However the median time to detection of AF using implantable cardiac monitors in a large RCT and the largest available observational cohort was as long as 84 days. [35] Unfortunately, post stroke patients are not ideal candidates for prolonged ECG monitoring due to myriad issues like poor compliance, aphasia, limb paresis. Herein lies the importance of biomarkers.

What is a Biomarker?

A working group at the United States National Institutes of Health defined a biomarker as a biological marker that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions. [36].

What is NT-pro BNP?

Natriuretic peptides include ANP, BNP and C type natriuretic peptide which are released from the heart in response to pressure and volume overload. ANP & BNP, by acting as antagonists of the renin-angiotensin-aldosterone system, affect the fluid and electrolyte balance through their natriuretic and diuretic properties.

BNP is a neurohormone, a 32-amino acid polypeptide which is a diuretic factor with vasodilator activity that is synthesized and released primarily from the cardiac ventricles in response to increased wall tension [37], but it is also secreted by the brain. In fact, it was first isolated from porcine brain in 1988. [38] Pro BNP, comprising of 108 amino acids, is secreted by the ventricle and is cleaved into physiologically active BNP (77-108) and the N-terminal fragment NT-pro BNP (1-76) [39] Despite being produced in equimolar amounts, NT-pro BNP has a longer half life (1-2 hours) than BNP (20 minutes) and has less fluctuations of circulating levels.

Mechanism of Rise of NT-pro BNP levels

Although NT-pro BNP levels are increased in acute ischemic stroke, it is not known for certain if BNP is released by the ischemic brain or is a result of concurrent cardiac damage. Also, the fact that BNP levels are higher in cardioembolic stroke independent of infarct volume may indicate that this rise may be attributed to a previous cardiac disorder associated with a potential cardiac source of embolism. In the study by Jensen et al [40] it was shown that increased pro-BNP levels were associated with ECG abnormalities suggestive of myocardial infarction. High levels of pro-BNP have also been found to be associated with atrial abnormalities in patients with ischemic stroke, such as atrial dilatation, low flow velocity, spontaneous echocontrast or intraventricular thrombus and atrial fibrillation. [41] Even in patients with stroke of undetermined etiology, high BNP levels may reflect the presence of paroxysmal atrial fibrillation or any other atrial abnormality as potential cardioembolic source.

Again, BNP has been shown to be an antagonist of the renin-angiotensin-aldosterone system and has additional sympathoinhibitory effect. [42] Thus it is possible that higher level of NT-pro BNP in stroke patients is associated with increased sympathetic activation after stroke. [43]

NT-pro BNP and Cardioembolic Stroke

NT-pro BNP levels are maximum elevated in acute stroke and decline significantly thereafter. NT-pro BNP levels were maximum on the first day after ischemic stroke and declined significantly from day 3 onwards. [44] NT-pro BNP levels measured any time within 72 hours of ischemic stroke (including cardioembolic stroke) were equally useful. [45] This extended time window increases the utility of NT-pro BNP levels as a diagnostic tool since many patients do not present to medical care within first 24 hours. It also gives NT-pro BNP an edge as a biomarker of cardioembolic stroke over D-Dimer levels, which are useful in the diagnosis of cardioembolic stroke only within first 12 hours.

In a pooled data meta-analysis involving 2834 patients carried out by Llombert et al [46], it was shown that higher levels of BNP/NT-pro

BNP are seen in cardioembolic stroke than in patients with large artery atherosclerosis or small vessel disease with the values remaining significant till 72 hours for BNP and till 1 week for NT-pro BNP. However because of BNP/NT-proBNP values standardization in the study, no cutoff point could be predicted to differentiate cardioembolic strokes from non cardioembolic strokes expressed in units of concentration (ie, pg/mL).

There exists no consensus as yet regarding cut off values of NT Pro BNP for predicting cardioembolic stroke. Cut off points have varied among different studies.

Rodriguez-Yanez et al [47] studied 262 patients of acute ischaemic stroke presenting within 12 hours of onset from February 2008 to July 2011 and showed that Pro-BNP values > 360 pg/mL within 24 hours of hospitalization was independently associated with cardioembolic stroke. This cut off value could correctly diagnose 94.1% of likely cardioembolic strokes amongst those previously diagnosed as stroke of unknown etiology.

Hajsadeghi et al [39] studied 125 patients of acute ischaemic stroke between September 2010 and September 2011 and demonstrated that NT Pro-BNP levels > 342 pg/ml (measured within 24 hours of hospital admission) had a sensitivity of 93% and specificity of 75% in diagnosing cardioembolic stroke.

Renjen et al [48] evaluated 108 patients of acute ischaemic stroke presenting within 72 hours of onset to a tertiary care center in New Delhi and reported that NT Pro-BNP levels > 255 pg/ml had a sensitivity of 92.9% and specificity of 93.8% in diagnosing cardioembolic stroke.

Ray Chaudhuri et al [49] recruited 270 patients of acute ischemic stroke who presented within 48 hours of symptom onset between April 2011 and March 2013 to a tertiary care hospital in Hyderabad and compared them with 110 age- and sex matched controls. They demonstrated that elevated levels of plasma BNP > 100 pg/ml were present in nearly 72% of patients of cardioembolic stroke as opposed to about 46% of patients with small artery disease and around 41% of patients with large artery atherosclerosis. They identified elevated BNP level as an independent risk factor for cardioembolic stroke with 3.5-fold increased risk. It was also shown that among patients with BNP levels more than 500 pg/mL, 50% had cardioembolic stroke.

It is also predicted that high NT-pro BNP levels measured during the acute phase of stroke in cryptogenic stroke patients are associated with a 5 fold increase in the risk of developing atrial fibrillation in the next 2 years.[50]

CONCLUSION

NT pro BNP levels are thus elevated in acute phase of cardioembolic stroke (maximum within first 72 hours). Its use as a biomarker in the etiological diagnosis of acute ischemic stroke would enable the avoidance of unnecessary delays in diagnosis as well as missed diagnoses. The use of an efficient biomarker would also be more convenient for patients and health care professionals both, rather than use of long term recording devices for detection of paroxysmal atrial fibrillation. By reducing the proportion of cases mistakenly labeled as “cryptogenic stroke” when they were in fact, of cardioembolic etiology, would enable us to start appropriate therapy in the form of anticoagulation which can serve to prevent further strokes in future, thereby reducing the disease burden.

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