Plasma Glial Fibrillary Acidic Protein, Copeptin, and Matrix Metalloproteinase-9 Concentrations among West African Stroke Subjects Compared with Stroke-Free Controls

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Background: Measurement of plasma molecular markers among stroke patients has been proposed as an avenue for improving the accuracy of stroke diagnosis. There is paucity of data on the potential role of these markers in resource-limited settings, where the burden of stroke is greatest. *Objective:* To assess the potential diagnostic and prognostic performance of 3 proposed biomarkers for stroke in a resource-constrained setting. *Methods:* Consecutive stroke subjects presenting at a tertiary medical center in Kumasi, Ghana, with radiologically confirmed diagnosis and etiologic subtype information available were recruited along with age- and gender-matched controls in a 2:1 ratio. Plasma concentrations of glial fibrillary acidic protein (GFAP), copeptin, and matrix metalloproteinase-9 (MMP-9) among stroke patients and stroke-free controls were measured in duplicates using enzyme linked immunoassays. Diagnostic and prognostic correlates were assessed using area-under-the-curve (AUC) measures of receiver operator curves and logistic regression analysis, respectively. *Results:* There were 156 stroke subjects with a mean age of 61.3 years of which 47.4% were females and 74 age- and gender-matched stroke-free controls. Median (interquartile range) time from symptom onset to hospital presentation for care was 7 days (5-11). Diagnostic accuracy of a single measurement of the 3 biomarkers for stroke using AUC (95% confidence interval) plots were as follows: .84 (.77-0.91), $P < .0001$, for GFAP; .85 (.79-0.92), $P < .0001$, for copeptin; and .65 (.56-0.73), $P = .0003$, for MMP-9. None of the biomarkers was associated with stroke severity or mortality.

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Conclusion: Plasma concentrations of GFAP and copeptin demonstrated stronger associations with stroke occurrence in this West African cohort compared with controls. **Key Words:** Plasma biomarkers—GFAP—MMP-9—copeptin—Africa—stroke—diagnosis—prognosis.

Introduction

Stroke is defined pathologically as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction or spontaneous intraparenchymal or subarachnoid hemorrhage of central nervous system tissue of vascular origin.[1] The molecular perturbations immediately preceding or occurring after tissue infarction from stroke are accompanied by the elaboration of a diverse array of biomarkers of diagnostic, prognostic, and predictive relevance.[2,3] An elucidation of the biomolecular profile of stroke subjects of African descent is a fundamental prerequisite for understanding its potential roles in settings where stroke patients usually present late for care and diagnostic neuroimaging facilities are seldom available or accessible.

Glial fibrillary acidic protein (GFAP) is an intermediary filament expressed by astrocytes and ependymal cells and found in serum of patients due to necrotic brain cell destruction and blood–brain barrier (BBB) disruption, with a graded increase in circulating concentration from controls, ischemic stroke, and hemorrhagic stroke subjects, respectively.[4-6] Copeptin is the C-terminal part of provasopressin, a neuroendocrine stress marker associated with unfavorable outcomes among ischemic and hemorrhagic stroke subjects.[7-10] Matrix metalloproteinase-9 (MMP-9) is a protease induced by thrombin and blood, which increases capillary permeability, disrupts BBB, acts as a neurotoxic by degrading the endothelial basal lamina and extracellular matrix, and is elevated after intracerebral hemorrhage where correlations between edema and neurological worsening have been identified.[11-14] These biomarkers have been shown to be associated with stroke occurrence and stroke prognosis among predominantly Caucasian subjects, but there is limited information on their potential utility among indigenous African stroke subjects.

Therefore, the objective of this study is to compare plasma concentrations of GFAP, copeptin, and MMP-9 in a cohort of consecutive stroke patients matched with stroke-free control subjects encountered at a Ghanaian tertiary medical center. Our hypothesis is that circulating plasma titers of GFAP, copeptin, and MMP-9 may be significantly higher among stroke patients than among age- and gender-matched stroke-free controls and that these biomarkers could have potential diagnostic and or prognostic relevance for stroke in African populations subject to validation in larger subsequent studies.

Methods

Ethics

This study was approved by the Committee of Human Research Publications and Ethics of the Kwame Nkrumah University of Science and Technology and is part of the Stroke Investigative Research and Educational Networks (SIREN) case-control study with protocol published elsewhere.[15]

Study Subjects

Briefly, SIREN is a multicenter study involving 12 study sites in Ghana and Nigeria and has been running since August 2014. Stroke patients included consecutive consenting adults (aged 18 years or older) with first clinical stroke within 8 days of current symptom onset or "last seen without deficit." Cranial computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 10 days of symptom onset because beyond 10 days, ischemic and hemorrhagic strokes may be difficult to distinguish with great certainty. Stroke classification was based on clinical evaluation and brain neuroimaging (CT or MRI of brain), echocardiography or transthoracic echocardiography, and carotid Doppler ultrasound performed by specially trained clinicians according to standardized protocols. Ischemic stroke was classified clinically using the presumed etiologic subtypes as defined using the Trial of Org 10172 in Acute Stroke Treatment[16] criteria. Intracerebral hemorrhage was classified etiologically into structural, medication related, amyloid angiopathy, systemic or other disease, hypertension, and undetermined causes.[17] Neuroradiological examination based on cranial CT imaging was performed independently by a radiologist who was blinded to all other data and reported on lesion topography, territories of vascular supply, and volume of lesion, which was calculated in all scans showing a clearly demarcated infarct area or hemorrhage. Measurement of intracerebral hemorrhage volume (mL) was performed using the standard ellipsoid method.[18] For ischemic stroke lesion size measurements, the area of abnormal low attenuation was traced on each CT slice, and volume was derived from the area and the slice thickness. Adjudication of stroke subtypes was done by consensus among a neurologist (F.S.S.), a cardiologist (L.A.), and a radiologist (M.A.) after clinical findings, CT scans, and electrocardiography, echocardiography, and carotid Doppler