Development and Reliability of a User-Friendly Multicenter Phenotyping Application for Hemorrhagic and Ischemic Stroke

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Background: Annotation and Image Markup on ClearCanvas Enriched Stroke–phenotyping Software (ACCESS) is a novel stand-alone computer software application that allows the creation of simple standardized annotations for reporting brain images of all stroke types. We developed the ACCESS application and determined its inter-rater and intra-rater reliability in the Stroke Investigative Research and Educational Network (SIREN) study to assess its suitability for multicenter

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Received April 12, 2017; revision received June 12, 2017; accepted June 25, 2017.

Grant support: The development of the ACCESS software application and this work was supported by U54HG007479—Investigative Research and Education Network and R25NS080949—Medical Education Partnership In Nigeria—linked Neurologic Outcome Measurement in Research for Intervention and Care grants from the National Institutes of Health, USA.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.06.042

studies. *Methods:* One hundred randomly selected stroke imaging reports from 5 SIREN sites were re-evaluated by 4 trained independent raters to determine the inter-rater reliability of the ACCESS (version 12.0) software for stroke phenotyping. To determine intra-rater reliability, 6 raters reviewed the same cases previously reported by them after a month of interval. Ischemic stroke was classified using the Oxfordshire Community Stroke Project (OCSP), Trial of Org 10172 in Acute Stroke Treatment (TOAST), and Atherosclerosis, Small-vessel disease, Cardiac source, Other cause (ASCO) protocols, while hemorrhagic stroke was classified using the Structural lesion, Medication, Amyloid angiopathy, Systemic disease, Hypertensive angiopathy and Undetermined (SMASH-U) protocol in ACCESS. Agreement among raters was measured with Cohen's kappa statistics. *Results:* For primary stroke type, inter-rater agreement was .98 (95% confidence interval [CI], .94-1.00), while intra-rater agreement was 1.00 (95% CI, 1.00). For OCSP subtypes, inter-rater agreement was .97 (95% CI, .92-1.00) for the partial anterior circulation infarcts, .92 (95% CI, .76-1.00) for the total anterior circulation infarcts, and excellent for both lacunar infarcts and posterior circulation infarcts. Intra-rater agreement was .97 (.90-1.00), while inter-rater agreement was .93 (95% CI, .84-1.00) for TOAST subtypes. Inter-rater agreement ranged between .78 (cardioembolic) and .91 (large artery atherosclerotic) for ASCO subtypes and was .80 (95% CI, .56-1.00) for SMASH-U subtypes. *Conclusion:* The ACCESS application facilitates a concordant and reproducible classification of stroke subtypes by multiple investigators, making it suitable for clinical use and multicenter research. **Key Words:** Stroke—Africa—phenotyping—DICOM application—reporting software intracerebral hemorrhage—ischemic stroke—developing country.

Introduction

Stroke is a leading cause of death and disability globally, especially in low- and middle-income countries (LMICs), which bear the brunt of its worldwide burden.[1-5] Neuroimaging forms the basis for its correct definition, accurate diagnosis, classification, appropriate treatment, and prognostication.[4,5]

Combined large accurate data sets from diverse settings are required to fully understand the genomic and environmental underpinnings of stroke and its discrete subtypes as well as the relationship between stroke neuroimaging phenotype and its clinical manifestations, prognosis, and outcome.[6,7] Such multicenter research involving multiple investigators and large data sets require secure archiving, as well as accurate and reproducible standard classification formats. Thus, there is a need for the development of a comprehensive application for archiving and phenotyping all types of stroke in a standard and secure format that can be shared among researchers and clinicians for training, clinical use, and research purposes, and connected with other clinical, laboratory, and genomic databases.

Therefore, we created a user-friendly software application for this purpose. The Annotation and Image Markup (AIM) on Clear Canvas Enriched Stroke phenotyping Software application (ACCESS, NIH-Sponsored SIREN team, Ibadan, Nigeria) captures both ischemic and hemorrhagic stroke, unlike previous methods,[8-13] which focus solely on ischemic stroke. This is of global relevance because hemorrhagic stroke remains quite common in Africa and other LMIC, where it represents about 30%-40% of all stroke cases.[2,5,8,9] ACCESS combines resources from neuroimaging, information technology, programming language, and the Internet to provide a platform for uniformly reporting on stroke type, subtype, vascular territory, anatomical distribution of lesion, lesion age (hyperacute/acute/subacute/chronic), lesion size, concomitant vascular brain injury (presence and severity of cerebral atrophy and white matter changes), and intracranial atherosclerosis.

We herein describe the development and reliability of the ACCESS software application for accurate concordant stroke phenotyping in multicenter studies.

Methods

Development of the ACCESS Tool

Our goal was to develop simple annotations that are reproducible and consistent for the same type of imaging study (Figs 1, 2; Supplementary Fig S1; Table 1.). The AIM Template Builder (Supplementary Fig S2)[10-14] allowed us to generate a set of well-structured questions and answer choices to facilitate collection of information for the neuroimaging aspect of the Stroke Investigative Research and Educational Network (SIREN) study (Supplementary materials).[11-14] These questions and answers were captured as coded elements, and codes were obtained for the questions and answers from standard lexicon (RadLex, MESH) and the Cancer Data Standards Registry and Repository.[11-14] Where codes could not be found for a particular question-and-answer choice, a user-defined term or private code was created. These sets of questions and