The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) Study Protocol

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Background and Purpose—Epidemiological studies of intracerebral hemorrhage (ICH) have consistently demonstrated variation in incidence, location, age at presentation, and outcomes among non-Hispanic white, black, and Hispanic populations. We report here the design and methods for this large, prospective, multi-center case-control study of ICH.

Methods—The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a multi-center, prospective case-control study of ICH. Cases are identified by hot-pursuit and enrolled using standard phenotype and risk factor information and include neuroimaging and blood sample collection. Controls are centrally identified by random digit dialing to match cases by age (±5 years), race, ethnicity, sex, and metropolitan region.

Results—As of March 22, 2013, 1655 cases of ICH had been recruited into the study, which is 101.5% of the target for that date, and 851 controls had been recruited, which is 67.2% of the target for that date (1267 controls) for a total of 2506 subjects, which is 86.5% of the target for that date (2897 subjects). Of the 1655 cases enrolled, 1640 cases had the case interview entered into the database, of which 628 (38%) were non-Hispanic black, 458 (28%) were non-Hispanic white, and 554 (34%) were Hispanic. Of the 1197 cases with imaging submitted, 876 (73.2%) had a 24 hour follow-up CT available. In addition to CT imaging, 607 cases have had MRI evaluation.

Conclusions—The ERICH study is a large, case-control study of ICH with particular emphasis on recruitment of minority populations for the identification of genetic and epidemiological risk factors for ICH and outcomes after ICH. (Stroke. 2013;44:000-000.)

Key Words: cerebral hemorrhage genetics genomics hypertension minority groups risk factors stroke

See related article, p 2679

Hemorrhagic stroke occurs in ≈100000 people in the United States each year, of which 40% to 50% die within 30 days. Despite constituting <20% of all strokes, hemorrhagic stroke accounts for 50% of the mortality associated with stroke and 30% of stroke-related costs. Hemorrhagic stroke is a heterogeneous disease with intracerebral hemorrhage (ICH) accounting for two thirds of all the cases. In ICH,
half of the mortality occurs within the first 2 days after stroke, and there are no proven effective treatments. Thus, prevention and prediction are of paramount importance for reducing the healthcare burden related to ICH.

The word ethnicity is used in this article to capture the combined and interacting concepts of race and culture. According to the 2010 US Census, 12.9% of Americans self-report as black and 12.5% as Hispanic.1 Ethnic differences in ICH risk are striking. Among blacks, the risk of ICH is double that of whites.4 The annual incidence rates per 100,000 for ICH has been reported to be 48.9 for blacks compared with 26.6 for whites.3 Hispanics in the United States have twice the risk of ICH of non-Hispanic whites (odds ratio, 2.6; 95% confidence interval, 1.4–6.1).5 Our long-term goal is to identify the genetic variation that affects risk of ICH in a multi-ethnic population. In addition, we will determine differences in the distribution of risk factors and imaging characteristics based on race and ethnicity. To address these goals, we are performing a prospective, multicenter, case–control study of ICH.

Methods and Research Design

The ERICH Study Group

The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study consists of a coordinating center (University of Cincinnati), neuroimaging cores (Massachusetts General Hospital, Georgetown University), a sample biorepository (John P. Hussman Institute for Human Genomics at the University of Miami), a biostatistical core (Wake Forest University), and 19 clinical recruitment centers that encompass 42 recruitment sites (Figure 1). The goals of the study are to recruit 1000 non-Hispanic white, 1000 non-Hispanic black, and 1000 Hispanic ICH cases and 3000 demographically-matched controls from the same population as the cases. Our scientific aims are to achieve the following:

1. Identify differences in risk factor distribution by ethnicity and location of ICH.
2. Determine differences in the presence of microbleeds and other MRI characteristics by ethnicity of ICH.
3. Determine differences in outcomes of ICH by ethnicity.
4. Determine the level of population admixture between centers and ethnicity.

Definition of Phenotype

The primary phenotype is a spontaneous ICH. All cases must meet the following eligibility criteria:

1. Age 18 years or greater.
2. Resident for at least 6 months within 75 miles of the recruiting center (100 miles for population centers with <1 million).
3. Be of non-Hispanic white, non-Hispanic black, or Hispanic race/ethnicity by self-report.
4. Diagnosis of spontaneous ICH (see definition).
5. Ability of the patient or legal representative to provide informed consent.

Intracerebral hemorrhage is defined as (adapted from the Classification of Cerebrovascular Disease III-1989) a spontaneous, nontraumatic, abrupt onset of severe headache, altered level of consciousness, or focal neurological deficit that is associated with a focal collection of blood within the brain parenchyma seen on neuroimaging or at autopsy and is not attributable to hemorrhagic conversion of a cerebral infarction.2 This includes warfarin-associated ICH as well as peripartum ICH. Exclusions include malignancies that lead to coagulopathy, dural venous sinus thrombosis-associated hemorrhage, hemorrhages attributable to vascular malformations, aneurysms, tumors, or hemorrhagic conversion of recent ischemic stroke. To determine a patient’s eligibility as a study case, study neurologists review the patient’s clinical presentation and neuroimaging.

Case Identification and Screening

Our study uses hot-pursuit to enroll subjects to limit survival bias. Each recruitment center reviews admission logs, emergency room logs, and neurology/neurosurgery/neurosurgical ICU admission logs for potential ICH cases. Included in screening is review of “hemorrhagic infarcts,” “traumatic hemorrhages,” “stroke” and “CVA,” “subarachnoid hemorrhage,” “focal weakness,” “unresponsive,” “round down,” and “mental status change” because some cases of true ICH may be misclassified. Site investigators review all potential cases, including those with a questionable diagnosis.

Ongoing training and quality checks are in place. For example, each month, a challenging phenotype is presented at the study conference call for both coordinators and principal investigators. The phenotype challenging cases include examples of hemorrhagic infarction, hemorrhage into tumor, or traumatic ICH. In addition, once a year per center, 5 consecutive cases of ICH that were excluded from the study are reviewed for verification of ineligibility. In addition, neuroimaging core review includes verification of case status and discrepancies are reviewed.

Control Identification

To minimize biases in control recruitment, 2 random-digit dialing centers are used for the study. The Institute for Policy Research (IPR) has been performing random-digit dialing since the 1970s and has previously identified >2000 controls for the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study. The Survey Research Center at the University of Alabama, Birmingham has been the call center for the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.6 The control identification centers use
random-digit dialing methods to identify ICH-free controls to be matched by age (±5 years), sex, race/ethnicity, and metropolitan area. Certain demographics (eg, very elderly minority populations) may require the use of friend controls in which a randomly-selected control is asked whether he or she has a nonbiologically-related friend who meets a specific demographic for recruitment.

**Subject Enrollment and Interview**

By design, the ERICH study is a hot-pursuit study with recruitment of often critically ill ICH cases with special emphasis of minority populations into a genetic epidemiology study without an intervention. The study addressed general recruitment barriers and incorporated strategies that address minority recruitment barriers such as cultural competence, cultural perceptions, education on prior unethical treatment of minority populations, and training by those with particular experience in recruitment of minority populations for research studies (Table).

Each recruiting center must have personnel certified for biological sample handling/shipping. Frequently, remaining clinically drawn blood is available in moribund cases of ICH. If families are unable to decide on participation but have not refused to participate, study personnel request permission to have their clinically drawn blood held/not destroyed to give families additional time to consider enrollment into the study. If at a later date the family agrees to participate and the patient has expired, clinically drawn blood is used and the sample is labeled for quality assurance review.

Institutional Review Board approval at each participating center is required before initiation of study enrollment. Informed consent is obtained from each enrolled subject or legally authorized representative. A Spanish language consent form is available for Spanish-only speaking subjects or those that prefer the Spanish consent. Before interview of a patient, a capacity is screened using a consent comprehension questionnaire. If the patient fails, a proxy/legally authorized representative is contacted for enrollment with priority to guardian/power of attorney, spouse, adult children, parents, and siblings, in that order. Once informed consent has been obtained, screening for dementia is performed using the Telephone Interview Cognitive Screen, which is a validated dementia screen that can be used in subjects with motor impairment. A score of ≥21 is required to provide interview data. Cases or proxies are interviewed using a standardized case report form. In addition, subjects undergo 3 blood pressure readings using an appropriate size cuff. Weight, height, and waist:hip ratio are also recorded.

**Chart Abstraction and Follow-up**

In addition to the personal interview, chart abstraction is performed for each case to provide additional clinical data including blood pressure treatment, surgical interventions, complications, and laboratory testing, including coagulation parameters. Discharge status and outcome are recorded. Each surviving case also is contacted for 3-, 6-, and 12-month follow-ups, which include evaluation of modified Rankin scale,11 Barthel Index,12 medication use, EuroQol-5D (EQ-5D),13 and Health State Scale.14

**Neuroimaging**

Central to the diagnosis and prognosis in ICH is neuroimaging review. Diagnostic challenges include traumatic hematoma, infarction with hemorrhagic transformation, hemorrhage into a tumor or hemorrhage from a venous sinus thrombosis, and intracranial aneurysms. Volume of ICH as well as the presence of intraventricular hemorrhage is critical to determining outcomes related to ICH. We perform centralized neuroimaging review in a standardized fashion. All centers obtain baseline and follow-up neuroimaging CT/MRI deidentified and in digital format.

Because the ordering of MRI may be physician dependent, an MRI is sought on every fifth case to avoid bias. If an MRI is not ordered for clinical care and is safe to perform, a study MRI is requested. If the fifth consecutive case is unable to have an MRI performed, subsequent cases are selected for MRI until one is completed. Neuroimaging studies are stored on DICOM software, deidentified on site, and uploaded electronically to the neuroimaging repository. All MRIs are performed on 1.5 to 3.0 T scanners with the following required sequences: gradient echo, diffusion weighted imaging with apparent diffusion coefficient map, and fluid attenuated inversion recovery. Analyses include ICH volume, location, number of microbleeds by location, presence and severity of small vessel disease and presence, and volume of intraventricular hemorrhage. White matter hyperintensities are analyzed by a visual rating scale and by segmentation using computer-assisted volumetric methods. Intraparenchymal and intraventricular volumes are measured by planimetric analysis using Alice software (Parallax Corporation, Waltham, MA), which has an excellent inter-rater reliability. At quarterly neuroimaging review meetings, CT and MRI reading progress is reviewed and a committee adjudicates discrepancies.

**Biorepository**

The biorepository for the ERICH study provides a standardized blood collection kit with a unique ERICH study ID number for each subject. This ID number allows the local PI to retain identifying information with the consent form, and it protects the subject’s privacy as the sample is processed. The blood draw consists of two 6-mL EDTA tubes. The biorepository records receipt of the sample into the laboratory information management system (LIMS). Plasma, to a maximum of 1 mL, is sought on every fifth case to avoid bias. If an MRI is not ordered for clinical care and is safe to perform, a study MRI is requested. If the fifth consecutive case is unable to have an MRI performed, subsequent cases are selected for MRI until one is completed. Neuroimaging studies are stored on DICOM software, deidentified on site, and uploaded electronically to the neuroimaging repository. All MRIs are performed on 1.5 to 3.0 T scanners with the following required sequences: gradient echo, diffusion weighted imaging with apparent diffusion coefficient map, and fluid attenuated inversion recovery. Analyses include ICH volume, location, number of microbleeds by location, presence and severity of small vessel disease and presence, and volume of intraventricular hemorrhage. White matter hyperintensities are analyzed by a visual rating scale and by segmentation using computer-assisted volumetric methods. Intraparenchymal and intraventricular volumes are measured by planimetric analysis using Alice software (Parallax Corporation, Waltham, MA), which has an excellent inter-rater reliability. At quarterly neuroimaging review meetings, CT and MRI reading progress is reviewed and a committee adjudicates discrepancies.

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<tr>
<th>Barrier</th>
<th>Strategies</th>
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<td>Early mortality</td>
<td>• Hot pursuit – Active screening of emergency rooms, neurosurgical, neurology, intensive care unit census and early identification of cases</td>
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<td>• Clinical blood – Request clinical laboratories not to destroy clinically obtained blood samples to give families time to consider participation. If decide to participate, clinical blood can be used if unable to obtain a sample from the patient</td>
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<td>• Training – Specific education and strategies regarding recruitment of cases who are severely ill/moribund state</td>
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<td>• Follow-up – Identification of centers with high rates of exclusion for “early mortality” and addressing approach</td>
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<td>Minority recruitment</td>
<td>• Involvement of centers with high minority populations</td>
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<td></td>
<td>• Education on cultural sensitivity</td>
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<td>• Education on prior unethical treatment of minority populations, particularly in context of research studies</td>
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<td>• Training and development of best approaches techniques for recruitment of minority populations</td>
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<td></td>
<td>• Follow-up – Identification of centers with high rates of subject or proxy refusal based on minority status and addressing approach</td>
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<td>Genetic research</td>
<td>• Certificate of Confidentiality – Obtained through the Department of Health and Human Services</td>
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<td>• Education on deidentification, storage within repositories and common misconceptions regarding genetic research</td>
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<td>Severity of condition</td>
<td>• Education on end of life stages and applicability to life-changing events</td>
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<td>• Training and development of best approaches for education of families</td>
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is isolated from each tube (beginning in 2013). DNA is extracted and analyzed for quantity and quality, and then stored for genetic studies. In the rare case that the quantity or quality of the DNA sample is unacceptable, the second EDTA blood tube will be extracted. Otherwise, this second tube is stored at –80°C.

**Statistical Methods**

Numerous hypotheses may be explored through the ERICH study regarding risk, treatment, and outcome. The study uses a Data Access Committee to review queries for data analysis for design, appropriateness, scientific merit, and impact on study resources. The goal of matching in epidemiological studies is to ensure that the controls are comparable with the cases with respect to the matching variables. In genetic studies, this strategy can reduce confounding introduced by age-specific penetrance or sex-specific effects and population stratification. In general, the analysis of a 1:n matched case–control design with covariates can be analyzed using proportional hazards modeling or linear mixed models for logistic regression, which reduces to a conditional logistic regression for a 1:1 matched-pair design. Preliminary data suggest that significant differences in risk factors exist by ethnicity. Therefore, we will formally test for these differences in the ICH regression models by including an ethnicity-by-risk factor interaction variable. If multiple interactions are anticipated or observed, data may be more appropriately modeled by stratifying by ethnicity and they may be meta-analytically combined to test for interactions using the test for homogeneity of the effect size.

We will perform a case-only analysis as a complement to the case–control analysis. To test for interactions between 2 variables that are independent, a case-only analysis can be more powerful than a classic case–control design. We will corroborate the results of a case-only analysis with the case–control analysis. We will apply generalized linear models to test for differences in the presence of microbleeds among blacks and Hispanics after adjusting for all relevant covariates such as age, hypertension, and alcohol usage. We will consider logistic regression modeling of presence versus absence of microbleeds, Poisson regression to model the count of microbleeds, and multiple linear regression for other quantitative variables. These analyses may be stratified by ethnicity or jointly analyzed adjusting for the individual admixture proportion estimates.

Finally, we will test for differences among ethnicities in the location of ICH. These logistic models will use the white cases of ICH as the baseline comparison group in their formal tests.

**Estimating Individual Admixture Proportions**

Mating among long-separated European, African, and Amerindian populations during colonization of the New World originated admixed populations in the United States. Blacks and Hispanic Americans are 2 such admixed populations. The genome of an admixed individual is made up of consecutive blocks of markers inherited from each of the ancestral populations. Numerous ancestry informative markers have been identified for estimating ancestry proportions in blacks and Hispanic Americans. For example, Halder et al selected markers which were informative enough to distinguish between the 4 main ancestral groups represented in the United States: Europeans, Africans, Indigenous Americans, and Asians. We will use existing software such as Structure and Admixmap to compute individual admixture proportion. Structure implements a hidden Markov model to infer the underlying ancestry at the chromosomal region. Admixmap uses a combination of Bayesian and frequentist statistical methods to compute similar estimates. The 2 methods are expected to provide comparable results, thereby providing a check of the estimation procedures in these data.

To determine the number of ancestral populations in the admixed population of interest, we will be using the likelihood ratio test implemented. The admixture estimates will serve two purposes: (1) because they are more homogeneous genetically than self-reported ethnicity, they can be used instead of self-reported ethnicity in all analyses where the objective is to determine racial/ethnic differences in ICH and related outcomes; (2) they will be used in the candidate gene analysis. We note here that principal component analysis can also be applied to these ancestry informative markers to provide similar control variables.

**Modifications to the Study Protocol**

In year 2 of the study, control enrollment was identified to be lagging behind target. Recruiters with an exceptionally high rate of recruitment were interviewed for suggestions, which along with a review of the process were codified to require that each control have contact information sent to the recruiting center within 24 hours of identification and a minimum number of calls to be made within the first 72 hours and in the following weeks. To facilitate the communication of control information and tracking of reasons for refusal, a Web-based interface was developed. The institution of the Web-based control calling page was initiated in July of 2012 and rolled out to all centers in August of 2012 and has led to a 31.3% increase in the rate of recruitment of controls from May 2012 to April 2013.

It was also identified that Hispanic control enrollment was lagging behind white and black control enrollment. A review found that Hispanic controls were enrolling at the same or higher rate as white or black controls identified but fewer controls were being identified. Random-digit dialing methods were adjusted to focus calling in targeted zip codes.

Modifications to the case report form were made to remove redundancy as well as to add variables suggested by the investigators. Case report form versions are dated to identify when changes occurred.

**Study Update**

The study began on August 1, 2010, and recruitment officially began for cases on January 1, 2011, with a goal of reaching 3000 cases by February 1, 2015 (Figure 2). Control enrollment officially began on July 1, 2011, with a goal of reaching 3000 controls by August 1, 2015. As of March 22, 2013, 1655 cases of ICH had been recruited into the study, which is 101.5% of the target for that date (1630 cases), and 851 controls had been recruited, which is 67.2% of the target for that date (1267 controls), for a total of 2506 subjects, which is 86.5% of the target for that date (2897 subjects).

Of the 1655 cases enrolled, 1640 cases had the case interview entered into the database, of which 628 (38%) were non-Hispanic black, 458 (28%) were non-Hispanic white, and 554 (34%) were Hispanic. Thus, the study has been able to achieve excellent recruitment of cases with particular emphasis among minority patients.

Of 2217 cases that had undergone DNA extraction, average DNA yield of 143.82 μg was obtained with only 23 (1.0%) of the samples having less than 10 μg of DNA. Genotyping for Apolipoprotein E alleles is complete on 1269 cases.

In addition, 1197 baseline CTs had been received at the neuroimaging repository, of which 959 have undergone analysis for volume and location of ICH. Of the 1197 cases with imaging submitted, 876 (73.2%) had a 24-hour follow-up CT available, of which 612 (70%) have undergone analysis, of which 158 demonstrated expansion of 6 mL or 33% or greater volume from baseline scan. In addition to CT imaging, 607 cases have had MRI submitted with the required sequences (diffusion weighted imaging/apparent diffusion coefficient, fluid attenuated inversion recovery, and gradient echo imaging) and have undergone analysis for volume, location, microbleeds, and diffusion weighted imaging evaluation.

**Discussion**

Blacks and Hispanics are disproportionately affected by ICH in the United States and tend to have a younger age of ICH onset than white populations. However, white populations have a higher proportion of lobar ICH, a higher mortality rate, and a higher volume of ICH compared with blacks and non-Hispanic whites. To explore the underlying biological mechanisms for these differences, we have designed our study
to recruit a large case–control study of ICH with a particular emphasis on minority recruitment. Selection of centers was based, in part, on the distribution of minority populations throughout the United States. This study design permits the recruitment of large numbers of minority ICH populations in a prospective fashion. Specific challenges exist for recruitment within the study, specifically the recruitment of minorities, the high early mortality rate of ICH, participation in a genetic epidemiology study without a treatment agent, and no direct benefit to participants. Heavy emphasis was placed on initial training, and education continues for recruitment personnel regarding these issues.

A prospective cohort study would have advantages in study design, providing knowledge of risk factors prior to the onset of ICH. However, with an annual incidence rate of 20 to 40 per 100,000, a cohort study of roughly 30,000 individuals would need to be followed for 250 years to achieve a sample size of 3000 subjects, assuming stable incidence rates. A population-based study within specific regions would allow for maximum external validity of the findings of the study. However, the largest city in the United States (New York City with 8,244,910 persons per 2011 census) would need to have every hospital/facility in the city prospectively followed for potential cases of ICH for 2 years to identify and enroll 3000 cases of ICH (assuming 50% enrollment rates), of which =750 would be black and 750 would be Hispanic. Both of these study designs would therefore be cost-prohibitive and impractical to perform. Gathering cases of ICH with a genetic sample available from disparate stroke studies throughout the United States would similarly fail to yield significant sample sizes and may have led to biases in case ascertainment, control ascertainment, and phenotype definitions.

Thus, ERICH was designed as a multi-center, prospectively recruited, case–control study. Cases are identified using uniform methodology, case definitions, and phenotype definitions, and controls are identified using a central random digit dialing method. Imaging is centrally analyzed to minimize biases in determination of location of ICH, volume measurements, and presence/absence of intraventricular hemorrhage. Biological samples are centrally housed and processed using uniform methods.

In summary, the ERICH study is the largest, prospective case–control study of ICH with a particular emphasis on minority populations to examine environmental and genetic risk factors for risk of ICH, volume of ICH, and outcomes after ICH. Since initiating the study, recruitment has progressed and we anticipate timely completion of enrollment. At the completion of the study, a large phenotype, neuroimaging, and biological sample database of ICH among white, black, and Hispanic populations along with demographically and geographically matched controls will be available for further study.

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Disclosures

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6 Stroke October 2013

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