Sex-Related Differences in the Risk of Hospital-Acquired Sepsis and Pneumonia Post Acute Ischemic Stroke

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Background and Objective: Infectious complications after ischemic stroke are frequent and lead to neurological deterioration, poor functional outcomes, and higher mortality. Local and systemic inflammatory responses to brain ischemia differ between males and females, but little is known about differences in poststroke susceptibility to infection by sex. The purpose of this study was to compare sex-related differences in the risk of hospital-acquired sepsis and pneumonia after acute ischemic stroke (AIS). *Materials and Methods:* This is a retrospective, secondary analysis of the 2010-2011 California State Inpatient Database. Previously validated International Classification of Disease, Ninth Revision (ICD-9) codes were used to identify adult hospitalizations for AIS. The primary outcome was hospital-acquired sepsis or pneumonia, also identified using ICD-9 codes. Associations between sex and hospital-acquired sepsis or pneumonia were adjusted for baseline characteristics and comorbidities using multivariable logistic regression. *Results:* There were 91,643 hospitalizations for AIS included in this analysis, of which 1027 had hospital-acquired sepsis and 1225 had hospital-acquired pneumonia. The in-hospital mortality without infection was 4.6%; the presence of hospital-acquired infections was associated with higher mortality for sepsis (32.7%) and pneumonia (21.9%). Female (versus male) sex was associated with lower adjusted odds of hospital-acquired sepsis (odds ratio [OR] .74, 95% confidence interval [CI] .65-.84) and pneumonia (OR .69, 95% CI .62-.78). This difference was similar across age strata. Among hospitalizations with either hospital-acquired sepsis or pneumonia, sex did not influence mortality. *Conclusions:* Female sex was associated with a lower risk of hospital-acquired sepsis and pneumonia after AIS. Further investigation is needed to determine the mechanisms underlying this clinical observation. **Key Words:** Ischemic stroke—sepsis—pneumonia—sex—epidemiology.

Introduction

Acute ischemic stroke (AIS) is a leading cause of death and adult neurological disability worldwide. Sepsis and pneumonia are common, and highly morbid, infectious complications in stroke patients.[1] The development of poststroke infection leads to multiple poor outcomes including neurological deterioration,[2] prolonged hospital length of stay,[3] poor functional outcome, and death.[4] The high clinical impact and limited effective strategies for prevention or treatment of poststroke infection indicate the need for further investigation into underlying mechanisms and potential therapeutic options.

From the University of Colorado School of Medicine, Aurora, CO.
Received December 3, 2015; accepted June 3, 2016.
Grant support: Dr. Colbert was supported by National Institutes of Health grant 5T32AG000279. Dr. Ginde was supported by NIH grant 1K23AG040708.
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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.06.008

The etiology for increased susceptibility to infection during the poststroke period is multifactorial; however, compelling evidence indicates that brain ischemia leads to clinically important changes in immune function.[5] In addition to local brain inflammatory responses contributing to the evolution of injury, emerging evidence indicates that depression of immune function is a natural defense mechanism to minimize excessive inflammation in the injured brain.[5] While likely limiting inflammation-related brain injury after stroke, this immunosuppression also leads to increased susceptibility to infection. This pathway is mediated by dysregulated autonomic signaling and changes in peripheral immune cell numbers and function.[6]

Sex-related differences in ischemic stroke outcomes have been the topic of prior epidemiological research,[7] but little has been focused on poststroke infectious complications. One prior retrospective study reviewed 568 admissions for AIS to develop a scoring system to predict the likelihood of poststroke infection. Friedant et al[8] identified age, diabetes, and stroke severity as predictors of infection, whereas sex was not found to be predictive of this outcome. Rodent studies have shown sexual dimorphisms in functional outcomes and inflammatory response after experimental brain ischemia, suggesting that poststroke infectious complications may also be sex dependent.[9] The objective of the present study was to compare sex-related differences in the risk of hospital-acquired sepsis and pneumonia after AIS.

Materials and Methods

Study Design

This was a secondary analysis of the 2010-2011 California State Inpatient Database, which includes data from all hospitalizations in California. We chose California because it has a large and diverse population, and equivalent national data do not contain a "present on admission" indicator variable, considered key to our analysis. Detailed methodology for the State Inpatient Database is provided by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (www.hcup-us.ahrq.gov). The analysis of these deidentified data was approved by the Colorado Multiple Institutional Review Board as "not human subjects" research.

Cohort Definition

We included adult (age ≥18 years) hospitalizations with explicit International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes for AIS present on admission (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91. 434.0, and 436.0) in any of the 25 diagnosis fields using a previously validated approach, which is a modified version of the AHA/ASA classification system.[10] We excluded outside hospital transfers to focus the analysis on acute hospital presentations.

Primary Predictor

The primary predictor variable in the present study was sex.

Outcome Variables

The primary outcome variable of interest was hospital-acquired sepsis or pneumonia defined by ICD-9 diagnosis. We used Clinical Classification Software grouping of ICD-9 diagnoses in any of the 25 listed fields to define sepsis (code 2) and pneumonia (code 122). The infections were considered hospital acquired when coded as "not present on admission." Urinary tract infections were not included in this analysis due to the well-known association between female sex and frequency of urinary tract infections. Secondary outcomes included sepsis or pneumonia that was present on admission as well as clinical outcomes (in-hospital mortality, hospital length of stay, and hospital discharge to a post–acute care facility).

Covariates

We included other demographic characteristics (age and race/ethnicity) and relevant comorbidities (end-stage renal disease, diabetes mellitus, congestive heart failure, and cancer diagnosis).

Statistical Analysis

We summarized characteristics of our cohort using descriptive statistics, stratified by a diagnosis of sepsis or pneumonia. We used multivariable logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sex and outcomes of interest, adjusting for demographic and clinical characteristics. The analysis was also stratified by age (<50 years, 50-69 years, and ≥70 years) to evaluate for potential age–sex interaction. All analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX), and a 2-tailed *P* value less than .05 was considered statistically significant.

Results

We identified 91,643 California hospitalizations for AIS in 2010-2011, of which 1027 met our case definition for hospital-acquired sepsis and 1225 for hospital-acquired pneumonia. Table 1 shows the baseline characteristics and comorbidities of hospitalizations with diagnoses of sepsis or pneumonia stratified by whether the diagnosis code was hospital acquired or present on admission. As previously described, the presence of hospital-acquired infection markedly increased in-hospital mortality, median