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Sex Differences in Status Epilepticus; Biological, Statistical, or Societal?

Sex-Related Differences in Adult Patients With Status Epilepticus: A Seven-Year Two-Center Observation

Baumann SM, De Stefano P, Kliem PSC, Grzonka P, Gebhard CE, Sarbu OE, De Marchis GM, Hunziker S, Rüegg S, Kleinschmidt A, Pugin J, Quintard H, Marsch S, Seeck M, Sutter R. *Crit Care*. 2023;27(1):1-14. doi:10.1186/s13054-023-04592-6

Background: Conflicting findings exist regarding the influence of sex on the development, treatment, course, and outcome of status epilepticus (SE). Our study aimed to investigate sex-related disparities in adult SE patients, focusing on treatment, disease course, and outcome at two Swiss academic medical centers. Methods: In this retrospective study, patients treated for SE at two Swiss academic care centers from Basel and Geneva from 2015 to 2021 were included. Primary outcomes were return to premorbid neurologic function, death during hospital stay and at 30 days. Secondary outcomes included characteristics of treatment and disease course. Associations with primary and secondary outcomes were assessed using multivariable logistic regression. Analysis using propensity score matching was performed to account for the imbalances regarding age between men and women. Results: Among 762 SE patients, 45.9% were women. No sex-related differences were found between men and women, except for older age and lower frequency of intracranial hemorrhages in women. Compared to men, women had a higher median age (70 vs. 66, $p = 0.003$), had focal nonconvulsive SE without coma more (34.9% vs. 25.5%; $p = 0.005$) and SE with motor symptoms less often (52.3% vs. 63.6%, $p = 0.002$). With longer SE duration (1 day vs. 0.5 days, $p = 0.011$) and a similar proportion of refractory SE compared to men (36.9% vs. 36.4%, $p = 0.898$), women were anesthetized and mechanically ventilated less often (30.6% vs. 42%, $p = 0.001$). Age was associated with all primary outcomes in the unmatched multivariable analyses, but not female sex. In contrast, propensity score-matched multivariable analyses revealed decreased odds for return to premorbid neurologic function for women independent of potential confounders. At hospital discharge, women were sent home less (29.7% vs. 43.7%, $p < 0.001$) and to nursing homes more often (17.1% vs. 10.0%, $p = 0.004$). Conclusions: This study identified sex-related disparities in the clinical features, treatment modalities, and outcome of adult patients with SE with women being at a disadvantage, implying that sex-based factors must be considered when formulating strategies for managing SE and forecasting outcomes.

Commentary

The impact of sex and gender on medical treatment and outcomes has been understudied and underappreciated. Biological sex differences may affect the presentation of disease, severity of symptoms and sequelae, drug metabolism, and treatment response.[1] At the same time, sociocultural factors related to sex or gender may also impact how a patient presents, communicates, or selects treatment. Finally, sex or gender-based biases and assumptions on the part of health care providers can also have a significant impact on identification of disease, as well as its management and outcomes.[1] It is difficult to disentangle the effects of sex and gender in available epidemiological and clinical data, which cannot be blinded to these variables. Recently, more attention has been paid to sex-based differences in critical care medicine. In one metanalysis, compared to males, female patients were more likely to have higher illness severity scores at the time of admission to an intensive care unit (ICU) as well as higher risk-adjusted mortality scores at 1 year postdischarge.[2] However, when the analysis excluded studies that were at high risk of statistical bias, these findings were not reproduced. Another metanalysis found that female patients were less likely to be treated with invasive mechanical ventilation or renal replacement therapy.[3] These findings raise concern that females may be treated less aggressively than males with similar illness severity. Few studies have investigated the effect of sex on the incidence and outcomes of status epilepticus (SE). The majority of, but not all, prior studies have demonstrated that SE is more common in males.[4] Sex-specific mortality associated with SE has been shown to be higher in males in 2 studies, no different in 1 study, and higher in females in another.[5] Differences in cultural setting, ascertainment, SE etiology, and other confounding variables

certainly play a role in the heterogeneity of these findings necessitating further research.

The study by Baumann and colleagues reviewed here examines sex differences in a retrospective cohort of 762 cases of SE from 2 Swiss tertiary care centers.[6] In this cohort, female SE patients were older and less likely to have intracerebral hemorrhage (ICH) as an etiology. The authors suggest that the older age at presentation in females may be due to a higher risk of seizures after menopause. However, the 4-year average difference in this cohort could reflect the fact that female patients tend to live longer than males (by 4 years in Switzerland).[7] The difference in ICH is consistent with the known increased risk for ICH in men.[8,9] In the present cohort, female patients were also more likely to have focal nonconvulsive SE without coma, whereas males were more likely to have SE with motor symptoms. This is harder to explain without knowing the precise etiology of the cases, as clinical signs of SE are closely tied to etiology and localization. One curious thing about the clinical seizure categorizations in this study is that within the motor symptoms group 1/3 of the patients (and 18% of the total cohort) were categorized as having myoclonic SE. Anoxic brain injury was excluded from the cohort so it is hard to understand what caused the relatively high number of cases of myoclonic SE, which is otherwise rare. Nevertheless, convulsive SE on its own was also more common in males (45.6% vs 34.6%, $P = .002$).

In addition to describing the differences between SE type and etiology in this cohort, the authors investigated the factors associated with outcome. In both univariate and multivariate analyses, age, but not sex, was associated with the primary outcomes including in-hospital mortality, 30 day postdischarge mortality and return to neurologic baseline. In univariate secondary analyses, females were less likely to be discharged home (29% vs 47%) and more likely to be discharged to nursing home or hospice (17.1% vs 10%). These percentages presented were based on the total cohort, without removing in-hospital deaths, but there are still differences when those who died in hospital are excluded. Of note, these results were not subjected to multivariate analyses or adjusted for the age of the patients. However, the authors note that only 70% of females discharged to a facility were over the age of 65 (data not presented for males).

The study also may suggest sex-specific differences in SE treatment. In multivariate analyses of the whole cohort, females were less likely to receive anesthetics (OR 0.64; 95% CI 0.45-0.91, $P = .013$). Females were also less likely to receive aggressive treatment in univariate analyses of a smaller cohort (n = 279) of patients with refractory status epilepticus (RSE; 49.6% vs 97.2%, $P = .001$ for intubation, 51.2% vs 72%, $P \leq .001$ for anesthetics). Again, this was an unadjusted analysis, so other differences between groups including age and SE type and severity cannot be completely accounted for. The authors do demonstrate that within this smaller RSE cohort, there was no significant difference in the mean age and comorbidity index of males and females who did not receive anesthetics. Finally, they also present a subgroup analysis by SE type which demonstrated that the sex-differences in intubation/mechanical ventilation were present even among patients with motor symptoms (convulsive and myoclonic SE).

To further evaluate the effect of sex in the absence of age differences, the authors performed age-based propensity score matching. Cases without an appropriate match were excluded so this resulted in a smaller cohort of 417 patients. In the multivariate analysis of this smaller cohort, female sex was still not associated with inhospital or 30 days postdischarge mortality. It was, however, now statistically associated with a lower likelihood of return to premorbid neurological status (OR 0.48; 95% CI 0.33-0.68, $P < .001$).

In summary, this retrospective study of SE found no clear association between patient sex and mortality. However, it may be picking up some treatment differences with female patients being less likely to receive anesthetics, including in the setting of RSE. This is a potentially concerning finding, especially considering that similar patterns of decreased intubation rates have been seen in other ICU populations.[3] It is certainly possible that unconscious bias leads to delayed or less aggressive treatment in female SE patients. The differences in return to neurological baseline status and differences in disposition are secondary analyses with some limitations, yet they are worth further evaluation. It is important to note that return to baseline was based on physician notes, which raises the question of whether assessment of neurological status is also affected by unconscious bias. Future research should provide standardized assessments and consider if those assessments need to be normalized by sex. Finally, one limitation of this study, as well as several other similar investigations, is that the parameters with which sex and gender were defined are not clear.[2] Patients were presumably divided based on biological sex in the medical chart, but female sex and "women" are used interchangeably. Future research on the influence of biological sex and gender roles should define each separately.

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Declaration of Conflicting Interests

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