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Neurological complications after tuberculous meningitis in a multi-state cohort in the United States

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ABSTRACT

Background and purpose: To assess the rate of neurological complications and mortality after tuberculous meningitis in the United States.
Methods: The authors performed a retrospective cohort study of all patients 18 years or older hospitalized for tuberculous meningitis in California between 2005 and 2010, New York between 2006 and 2012, and Florida between 2005 and 2012. Outcomes of interest were mortality and the following neurological complications: stroke, seizure, hydrocephalus requiring a ventriculoperitoneal shunt, vision impairment, and hearing impairment. Kaplan–Meier survival statistics were used to assess the cumulative rate of neurological complications and death. Cox proportional hazards regression was used to compare rates of complications in patients with and without human immunodeficiency virus (HIV) after adjustment for comorbidities.
Results: 806 patients with tuberculous meningitis were identified, among whom the cumulative rate of any complication or death was 55.4% (95% CI, 51.5–59.3%). More than two-thirds of complications occurred during the initial hospitalization for tuberculous meningitis. Individual neurological complications were not uncommon: the cumulative rate of stroke was 16.8% (95% CI, 14.0–20.0%), the rate of seizure was 18.8% (95% CI, 15.4–22.8%), and the rate of ventriculoperitoneal shunting was 8.4% (95% CI, 6.4–10.9%). Vision impairment occurred in 21.6% (95% CI, 18.5–25.1%) of patients and hearing impairment occurred in 6.8% (95% CI, 4.9–9.4%). The mortality rate was 21.5% (95% CI, 18.4–24.9%). Patients with HIV infection were not at increased risk of complications compared to patients without HIV (hazard ratio, 1.2; 95% CI, 0.9–1.6).
Conclusions: Tuberculous meningitis is associated with significant risk of neurological complications and death in the United States.

1. Introduction

Tuberculosis (TB) is a global disease epidemic, with an estimated 9.6 million new cases occurring in 2014 [1]. Tuberculous meningitis (TBM) occurs in 1–5% of patients with TB and is characterized by a progressive granulomatous inflammation of the basal meninges. TBM is associated with a mortality of 19–28% in HIV-uninfected patients and 40–58% in HIV-infected patients [2–5]. TBM also frequently leads to neurological complications including hydrocephalus [6–11], stroke [9,10,12–24], seizure [5,6,9,24], vision loss [5,25,26], and hearing loss [27–29]. However, the majority of studies on TBM have been performed in resource-limited settings where there may be suboptimal prevention, diagnosis, and treatment of the disease [2–5]. Furthermore, the average length of follow-up in previous studies was relatively short and therefore may not have accurately captured delayed neurological complications [2–5]. Our aim was to evaluate the mortality and long-term risk of neurological complications after TBM in a high-resource setting such as the United States using a large heterogeneous cohort of patients.

2. Methods

2.1. Design

The authors performed a retrospective cohort study using administrative claims data from all emergency department (ED) visits and hospitalizations at nonfederal acute care hospitals in California from 2005 to 2011, New York from 2006 to 2013, and Florida from 2005 to 2013. Trained analysts used standardized methods to collect data regarding discharges and reported these to state health agencies for regulatory purposes. After quality checking, these data were provided in a de-

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identified format to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project [30]. Each patient was assigned an anonymous, unique linkage number that allowed for longitudinal tracking of ED encounters and hospitalizations [30,31]. The Weill Cornell Medicine institutional review board approved our analysis of these data.

2.2. Patient population

Our cohort consisted of all patients 18 years or older discharged at the time of their first recorded hospitalization for TBM, as defined by the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* code 013.x in any discharge diagnosis position. Non-residents of New York, Florida, and California were excluded to maximize follow-up. In order to ensure at least 1 year of follow-up, patients whose index visit for TBM occurred in 2013 in New York or Florida or 2011 in California were excluded.

2.3. Measurements

Our outcomes of interest were death and the following neurological complications: stroke, seizure, hydrocephalus requiring ventriculoperitoneal shunt (VPS), vision impairment, and hearing impairment. Stroke was a composite of both ischemic and hemorrhagic stroke; ischemic stroke was defined using *ICD-9-CM* codes 433.x1, 434.x1, or 436 in any diagnosis code position in the absence of a primary discharge code for rehabilitation (V57) or any codes for subarachnoid hemorrhage (430), intracerebral hemorrhage (431) or trauma (800–804 and 850–854). Hemorrhagic stroke was defined by the presence of a discharge code for intracerebral hemorrhage (431) or subarachnoid hemorrhage (430) in the absence of a primary discharge code for rehabilitation (V57) or trauma (800–804 and 850–854). This algorithm has been validated to have a sensitivity of ≥82% and a specificity of ≥93% for both ischemic and hemorrhagic stroke subtypes [32]. Seizure was defined using *ICD-9-CM* codes 345.x in any discharge diagnosis position; this schema has a positive predictive value ranging from 84 to 98% in adult patients [33,34]. Hydrocephalus was considered as only those cases that required a permanent VPS, defined by the presence of an *ICD-9-CM* procedure code 0.23 and 0.24 in any discharge diagnosis position; these codes have a 95% sensitivity and 100% specificity based on medical record review [35]. Using the methods of prior studies [36], vision impairment was defined as *ICD-9-CM* codes 360–379 in any discharge diagnosis position and hearing impairment as *ICD-9-CM* codes 380–390 in any discharge diagnosis position. Finally, subgroup analyses were performed stratified by the presence or absence of HIV, and compared the risks of complications associated with HIV after adjustment for the following covariates: age, sex, race, insurance status, HIV status, and the Elixhauser comorbidity index [37].

2.4. Statistical analyses

Kaplan–Meier survival statistics were used to calculate cumulative rates of individual complications as well as the composite of any complication or death. Patients were censored at the time of death or at the end of the follow-up period. Cox proportional hazards regression was used to compare the likelihood of complications in patients with and without HIV after adjustment for demographics and the Elixhauser comorbidity index [38]. All analyses were performed using Stata/MP, version 13 (StataCorp, College Station, TX). The threshold of statistical significance allowed for an alpha error of 0.05.

3. Results

806 patients with TBM were identified. Their mean age was 50.7 (±17.1) years, 62.9% were male, and 14.5% had HIV. During a mean follow-up of 2.9 (±2.4) years, the cumulative rate of any complication or death was 55.4% (95% CI, 51.5–59.3%) (Fig. 1). Patients with complications were slightly older and had a higher prevalence of medical comorbidities compared to TBM patients without complications (Table 1).

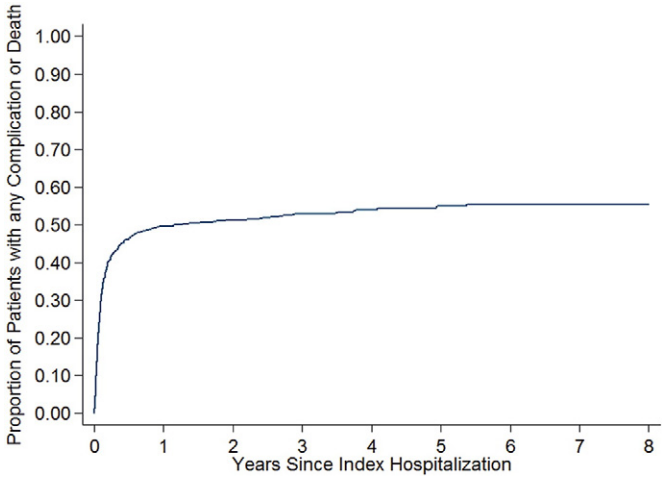

Fig. 1. The cumulative rate of complications or death after tuberculous meningitis: Kaplan–Meier curve showing the cumulative rate of neurological complications or death after tuberculous meningitis.

By 8 years, 21.5% (95% CI, 18.4–24.9%) of patients had died. Individual neurological complications were not uncommon. The cumulative rate of stroke was 16.8% (95% CI, 14.0–20.0%), of which the majority were ischemic (12.8% (95% CI, 10.3–15.7%)). The cumulative rate of seizure was 18.8% (95% CI, 15.4–22.8%) and that of VPS surgery was 8.4% (95% CI, 6.4–10.9%). Vision impairment occurred in 21.6% (95% CI, 18.5–25.1%) of patients and hearing impairment occurred in 6.8% (95% CI, 4.9–9.4%) of patients. The majority of complications occurred during the index hospitalization for TBM (Table 2), although when individually assessed, the cumulative rate of seizures, hydrocephalus requiring ventriculoperitoneal shunt, hearing impairment and death more than doubled throughout the follow-up period. Finally, the results of our study were similar when each state was analyzed separately.

Table 1
Characteristics of patients, stratified by presence of any complication, including death.

Characteristic[a]	Any complication (N = 414)	No complication (N = 392)
Age, mean (SD), y	56.2 (15.3)	46.6 (20.1)
Female	155 (37.4)	144 (36.7)
Race[b]		
White	88 (21.9)	75 (20.0)
Black	97 (24.1)	82 (21.8)
Hispanic	111 (27.6)	96 (25.5)
Asian	75 (18.7)	81 (21.5)
Other	31 (7.7)	42 (11.2)
Payment source		
Medicare	115 (27.8)	92 (23.5)
Medicaid	145 (35.0)	139 (35.5)
Private	112 (27.1)	98 (25.0)
Self-pay	19 (4.6)	32 (8.2)
Other	23 (5.6)	31 (7.9)
State		
California	209 (52.5)	189 (48.5)
New York	107 (48.4)	114 (51.6)
Florida	98 (52.4)	89 (47.6)
HIV	63 (15.2)	54 (13.8)
Elixhauser comorbidities[c], mean (SD)	2.9 (1.9)	2.2 (1.7)

Abbreviations: SD, standard deviation.
[a] Data are presented as number (%) unless otherwise specified.
[b] Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing race/ethnicity data in 3.5% of patients.
[c] The Elixhauser comorbidities represent a comprehensive set of 28 comorbidity measures for use with large administrative datasets.