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Whipple's disease review, prevalence, mortality, and characteristics in the United States

A cross-sectional national inpatient study

Akram I. Ahmad, MD[a], Colin Wikholm, MD[b], Ioannis Pothoulakis, MD[a], Claire Caplan, MD[b], Arielle Lee, BS[b], Faith Buchanan, MD[a], Won Kyoo Cho, MD[a,c]

Abstract

Whipple's disease is a rare multiorgan systemic disease caused by *Tropheryma whipplei* infection that may present with a wide range of signs and symptoms. This study aim to comprehensively review and determine the inpatient prevalence, mortality, risk factors, and reasons for hospitalization of patients with Whipple's disease. ICD-10 codes were used to identify admissions with Whipple's disease during the years 2016 to 2018. Characteristics of admissions with and without Whipple's disease were compared. The most common reasons for hospitalization were identified in admissions with Whipple's disease. The prevalence of Whipple's disease was 4.6 per 1 million hospitalizations during the study period. Whipple's disease admissions were significantly older than other hospitalizations, with a mean age of 60.2 ± 1.6 years compared to 50.0 ± 0.1. Males were more likely to have Whipple's disease and represented approximately two-thirds of hospitalizations. A disproportionate number of admissions occurred in the Midwest. Patients with Whipple's disease were most commonly admitted for gastrointestinal disease, followed by systemic infection, cardiovascular/circulatory disease, musculoskeletal disease, respiratory disease, and neurological disease. High mortality was seen in admissions for central nervous system (CNS) disease. Whipple's disease has heterogeneous presentations for inpatient admissions, and disproportionately affects older males. High hospitalization rates in the Midwest support environmental and occupational disease transmission likely from the soil. Hospitalists should be aware of the various acute, subacute, and chronic presentations of this disease, and that acute presentations may be more common in the inpatient setting.

Abbreviations: aRR = adjusted relative risk, CNS = central nervous system, GI = gastrointestinal, NIS = National Inpatient Sample, TW = *Tropheryma whipplei*, WD = Whipple disease.

Keywords: Whipple's disease - Tropheryma whipplei - Gastrointestinal infection - gastrointestinal epidemiology

1. Introduction

Whipple disease (WD) is a rare systemic disease caused by *Tropheryma whipplei* (TW) infection. Classic WD presents as weight loss, diarrhea, and arthralgia, although involvement of the heart, central nervous system (CNS), or any other organ systems may occur. Cases are disproportionately reported in middle-aged Caucasian males.[1–5]

T whipplei is a gram-positive bacteria from the phylum "*Actinobacteria*."[4,6] Hypothesized methods of transmission include human-to-human fecal-oral transmission and/or environmental exposure to bacteria in the soil.[4,7] TW is ubiquitous in nature and present in stool samples of 1% to 11% of healthy individuals.[7] However, it is estimated that less than 0.01% of people infected with TW will develop WD,[8] and that susceptibility depends on host genetic factors and immune response.[4,5,9,10] TW cultures can only be achieved in specialized laboratories, which makes diagnosis difficult.[11] Most often, diagnosis is made with duodenal biopsy showing Periodic acid-Schiff-positive staining macrophages in the lamina propria; however, PCR testing has emerged as an easier alternative, with high sensitivity and specificity.[9,12]

Our understanding of WD is limited by its rarity and dependence on case-based methods. Here, we present a large cross-sectional inpatient study of WD using the National Inpatient Sample (NIS) database, with detailed review of WD.

2. Methods

2.1. Data source

The NIS is the largest publicly available all-payer inpatient database in the United States. It contains data from approximately

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The datasets generated during and/or analyzed during the current study are publicly available.

[a] Department of Internal Medicine, MedStar Washington Hospital Center Rather than Georgetown, Washington, D.C., USA, [b] Georgetown University School of Medicine, Washington, D.C., USA, [c] Department of Gastroenterology, MedStar Georgetown University Hospital, Washington, D.C., USA.

** Correspondence: Akram I. Ahmad, Department of Medicine, MedStar Washington Hospital Center Rather than Georgetown, 110 Irving St, NW 2A50, Washington, D.C. 20010, USA (e-mail: Akram.I.Ahmad@medstar.net).*

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20% of all inpatient discharges in the US and can be used to make national estimates of diseases and associated hospitalizations.[13] The NIS contains deidentified data and thus our study was exempt from review by the Medstar Health Research Institute and Georgetown University Hospital Institutional Review Boards.

2.2. Study variables

International Classification of Disease, Tenth Revision (ICD-10) codes were used to identify patients with a primary or secondary diagnosis of WD (K90. 81) during the years 2016 to 2018. Patients with a co-diagnosis of pancreatic malignancy (C25.x) were removed from the WD group to exclude patients who received a Whipple procedure that was miscoded as Whipple's disease.

Whipple's disease prevalence was calculated as a proportion of total hospitalizations with a diagnosis of WD. Nine baseline admission characteristics were selected for univariate and multivariable analysis, including age in years at admission (<30, 30–59, ≥60 years), sex (male, female), race and ethnicity (white, black, Hispanic, other), median household income for patient's ZIP Code (0–25th, 26–50th, 51–75th, 76–100th percentile) expected primary payer (Medicare, Medicaid, Private insurance, and self-pay, no charge, or other) geographic region (Northeast, Midwest, Southern, West), hospital location and teaching status (rural, urban nonteaching, urban teaching), bed size of hospital (small, medium, large), and season based on the Gregorian calendar (spring, summer, fall, winter).

2.3. Statistical analysis

Statistics were performed using SAS 9.4 (SAS Institute Inc). Adjustments for weighting, clustering, and stratification were performed using SURVEY procedures in accordance with NIS guidelines. Frequencies of baseline characteristics were compared between admissions with and without WD using omnibus Rao-Scott χ^2 tests. Due to the paucity of reliable data on potential Whipple's disease risk factors, all patient and hospital characteristics were included in multivariable analysis. Adjusted relative risks of WD based on baseline admission characteristics were determined using a multivariable survey logistic regression model.

Frequency rank procedures were used to determine the 6 most common reasons for hospitalization based on major diagnostic criteria. The most frequent diagnostic related groups and ICD-10 diagnoses within each major diagnostic criteria were also reported. Other reasons admissions were grouped together as "Other Reasons for Admission" due to low individual frequencies. Frequencies of presentations were compared between males and females using the Rao-Scott χ^2 test.

Length of stay and total hospital charges were compared using a univariate survey logistic regression. In-hospital mortality was compared between WD and non-WD encounters using a Rao-Scott χ^2 test. Categorical variables were reported as weighted frequencies and percentages. Continuous variables were reported as means and standard errors. Significance was considered $P < .05$.

3. Results

540 admissions had an ICD-10 diagnosis of WD among 107,001,355 total inpatient encounters. Of the hospitalizations with WD, 50 had a co-diagnosis of pancreatic malignancy and were removed from the WD group. The remaining 490 patients were designated as having WD, an inpatient prevalence of 4.6 per 1 million hospitalizations during the years 2016 to 2018.

Patients with WD were significantly older than other hospitalized patients ($P < .001$) with a mean age of 60.2 ± 1.6 years compared to 50.0 ± 0.1 years, respectively. Most patients with WD were white (67.3%) and admitted to large hospitals (50.0%) and urban teaching hospitals (70.4%). Univariate analysis demonstrated different admission frequencies by age groups, sex, and expected primary payer between WD and non-WD groups ($P < .05$) (Table 1). Frequencies of race/ethnicity, median household income, geographic region of hospital, location/teaching status of hospital, bed size of hospital, and season were not significantly different ($P > .05$).

In the multivariable model, the baseline characteristics of age, sex, and geographic region conferred a significantly different risk of WD. Compared to admissions aged < 30 years, admissions aged 30 to 59 years and ≥ 60 years had an adjusted relative risk (aRR) of 7.42 (95% CI 2.56–21.53; $P = .0002$) and 5.94 (95% CI 1.92–18.39; $P = .0020$), respectively (Table 1). Males were more likely to have WD (aRR = 2.77, 95% CI 1.77–4.33; $P < .0001$) and accounted for 67.3% of hospitalizations. An increased adjusted relative risk of WD was seen among admissions in the Midwestern United States (aRR = 2.34, 95% CI 1.06–5.15; $P = .0345$). Race/ethnicity, household income, expected primary payer, hospital location and/or teaching status, bed size of hospital, and season did not confer a significant risk of WD.

The most common reasons for admission were gastrointestinal diseases (25.5%), most often a primary diagnosis of WD (11.2%), and less commonly esophagitis/gastroenteritis (4.1%) or abdominal pain (3.1%) (Table 2). Systemic infections were the second most common cause for admission (13.3%), most frequently septicemia or sepsis (11.2%). Circulatory/cardiovascular and musculoskeletal diseases each comprised 11.2% of primary diagnoses. Cardiovascular admissions occurred for cardiac procedures such as valve replacement (4.1%), and less commonly myocardial infarction (2.0%). Respiratory diseases comprised 8.2% of primary diagnoses, most commonly pneumonia or pleurisy (4.1%). Nervous system diseases represented 6.1% of primary diagnoses, most commonly encephalopathy (2.0%) or meningoencephalitis (2.0%). Ten inpatient deaths occurred in patients admitted for either systemic infection (5 deaths, 7.7% mortality) or CNS disease (5 deaths, 16.7% mortality). The remaining 5 deaths occurred during hospitalizations for other reasons (Table 2). There was no significant difference in reasons for hospitalization between males and females ($P > .05$).

The mortality rate of WD was 3.1%, which was not significantly higher than the 1.9% mortality rate of other hospitalizations (Table 3). Inpatient mortality was primarily associated with admissions for systemic infections or nervous system diseases (Table 2). The mean length of stay for WD hospitalizations was 7.4 ± 0.7 days, significantly higher compared to 4.6 ± 0.0 days for non-WD hospitalization (p-values < 0.001). Moreover, the total hospital charges for WD hospitalizations were $88,254 ± $12,926, which was significantly higher than $49,927 ± $356 for non-WD hospitalizations (P values < .001).

4. Discussion

We analyzed the NIS database to better understand the risk factors for WD and associated reasons for hospitalization. This study aids in recognition of varying disease presentations in the US inpatient setting, and to better identify patients who are at higher risk of symptomatic disease.

We estimated the inpatient prevalence of WD to be 4.6 per 1 million hospitalizations, which is the first national estimate of WD prevalence in the inpatient setting. Historically, case-dependent estimates have placed the prevalence of WD in the general population at around 1 in 1 million.[14] However, a recent population-based study estimated the US prevalence to be as high as 9.8 in 1 million,[15] compared to the prevalence in Italy which is 3 in 1 million.[16]

We found an increased prevalence of WD among males (67.3% of cases), who had more than a twofold adjusted relative risk of disease. This male predominance is in accordance

Table 1

Characteristics of admissions with Whipple's disease (WD) compared to admissions without Whipple's disease.

Admission characteristics	Non-WD hospitalizations (n = 107,000,865)	WD hospitalizations (n = 490)	Strength and significance of association	
	Weighted frequency (%)	*Weighted frequency (%)*	*Adjusted relative risk (95% CI)*	*P value*
Age (yrs)				**<.0001**†
<30	27309261 (25.5%)	20 (4.1%)	Ref	—
30–59	27309261 (30.3%)	200 (40.8%)	7.42 (2.56–21.53)	.0002‡
≥60	27309261 (44.1%)	270 (55.1%)	5.94 (1.92–18.39)	.0020‡
Sex				**<.0001**†
Female	60339122 (56.4%)	160 (32.7%)	Ref	—
Male	46631133 (43.6%)	330 (67.3%)	2.77 (1.77–4.33)	<.0001‡
Race or ethnicity				**.4160**†
White	66545002 (65.0%)	330 (67.3%)	Ref	—
Black	15604500 (15.2%)	50 (10.2%)	0.70 (0.33–1.47)	.3500‡
Hispanic	12836557 (12.5%)	60 (12.2%)	1.46 (0.77–2.77)	.2500‡
Other	27309261 (7.3%)	50 (10.2%)	1.90 (0.96–3.73)	.0641‡
Household income (percentile)*				**.4510**†
0–25th	31740126 (30.2%)	140 (29.5%)	Ref	—
25–50th	27626653 (26.3%)	105 (22.1%)	0.85 (0.47–1.52)	.5775‡
51–75th	24995814 (23.8%)	105 (22.1%)	0.94 (0.51–1.76)	.8513‡
76–100th	20857500 (19.8%)	125 (26.3%)	1.36 (0.71–2.60)	.3520‡
Expected primary payer				**.0129**†
Medicare	43165365 (40.4%)	260 (53.1%)	Ref	—
Medicaid	24577116 (23.0%)	50 (10.2%)	0.53 (0.23–1.23)	.1409‡
Private insurance	31475932 (29.5%)	150 (30.6%)	1.05 (0.58–1.89)	.8745‡
Self-pay, no charge, or other	7621112 (7.1%)	30 (6.1%)	0.69 (0.28–1.66)	.4038‡
Geographic region of hospital				**.3798**†
Northeast	19637505 (18.4%)	60 (12.2%)	Ref	—
Midwest	23824774 (22.3%)	130 (26.5%)	2.34 (1.06–5.15)	.0345‡
South	42111174 (39.4%)	210 (42.9%)	2.05 (0.98–4.30)	.0575‡
West	21427412 (20.0%)	90 (18.4%)	1.66 (0.76–3.63)	.2070‡
Location/teaching status of hospital				**.9162**†
Rural	9552185 (8.9%)	40 (8.2%)	Ref	—
Urban nonteaching	24170302 (22.6%)	105 (21.4%)	0.84 (0.36–1.97)	.6892‡
Urban teaching	73278377 (68.5%)	345 (70.4%)	1.04 (0.47–2.28)	.9291‡
Bed size of hospital				**.8503**†
Small	21264560 (19.9%)	90 (18.4%)	Ref	—
Medium	31220947 (29.2%)	155 (31.6%)	1.34 (0.73–2.45)	.3511‡
Large	54515358 (50.9%)	245 (50.0%)	1.18 (0.66–2.10)	.5799‡
Season				**.2968**†
Winter	26811821 (25.1%)	145 (29.9%)	Ref	—
Spring	26988461 (25.2%)	125 (25.8%)	0.86 (0.50–1.48)	.5847‡
Summer	26692142 (25.0%)	135 (27.8%)	0.91 (0.54–1.55)	.7322‡
Fall	26400577 (24.7%)	80 (16.5%)	0.53 (0.28–1.02)	.0566‡

† Rao-Scott χ^2 test comparing characteristics of admissions with WD versus admissions without WD.

‡ Multivariable survey logistic regression comparing characteristics of admissions with WD versus admissions without WD.

* Median household income for patient's ZIP code.

with previous literature, which typically reported a male-to-female ratio of 2-3:1.[17] However, 2012 to 2017 US population study showed a narrow, nonsignificant male predominance, with a prevalence of 10.6 cases per million in males and 9.6 cases per million in females.[15] Increased awareness of WD in female patients has been cited as a possible explanation for the decreasing difference in prevalence between sexes, a trend observed in Germany during 1965 to 1985.[15,18] In our study, race and ethnicity were not significant predictors of WD. This is in contrast to the 2012 to 2017 US study which found that African Americans had a significantly decreased risk of WD compared to Caucasians.

Our study found that patients with WD had a mean age of 60.2 years, and that 55.1% of patients were ≥ 60 years of age. Some studies have shown a mean age as low as around 50 years.[19,20] However, a 30 year study in Germany found that mean age increased over time, increasing from 50 to 60 years by the 1995 study endpoint.[18] It is unknown why the age of diagnosis has increased, although it has been hypothesized that greater rates of antibiotic usage may assuage symptoms and thus delay diagnosis.[15,18]

Prevalence of WD has been found to vary depending on location,[7] but no study has investigated the geographic distribution of WD within the United States. Our data indicates that the Midwestern United States is associated with higher risk of WD. It has been theorized that WD is acquired via environmental exposure to soil. A 1987 study found that, of more than 600 WD cases spanning the 20th century, a disproportionate number occurred in farmers with a recent history of exposure to soil or livestock.[21] Geographic analysis supports this mode of transmission.[22] The Midwest makes up approximately 20% of the US population, yet produces 87% of agricultural exports.[23] Therefore it is conceivable that high rates of occupational and environmental exposure are responsible for higher rates of WD in the Midwest. Interestingly, we did not see a significantly higher rate of WD in rural hospitals. Greater rural exposure to *TW* may be offset by the fact that WD is a rare and complex disease, and thus disproportionately more WD cases may be referred to, diagnosed, or treated at urban and academic hospitals. This would explain why the majority of WD cases occurred in urban teaching hospitals in the Midwest.

Table 2

Major reasons for admission, sex-dependent presentation, and mortality in patients with Whipple's disease.

Reason for admission	Whipple's disease (n = 490)	Male (n = 330)	Female (n = 160)	Deaths (n = 15)
Gastrointestinal disease	125 (25.5%)	90 (27.3%)	35 (21.9%)	0 (0.0%)
Whipple's disease	55 (11.2%)			
Esophagitis, gastroenteritis, or miscellaneous	20 (4.1%)			
Abdominal pain	15 (3.1%)			
GI obstruction	15 (3.1%)			
GI hemorrhage	15 (3.1%)			
Peritoneal adhesionolysis	5 (1.0%)			
Systemic infection	65 (13.3%)	35 (10.6%)	30 (18.8%)	5 (33.3%)
Septicemia or sepsis.	55 (11.2%)			
Infections with O.R. procedure	10 (2.0%)			
Circulatory disease	55 (11.2%)	30 (9.1%)	25 (15.6%)	0 (0.0%)
Endovascular procedures, including valve replacement	20 (4.1%)			
Myocardial infarction	10 (2.0%)			
Musculoskeletal disease	50 (11.2%)	35 (10.6%)	15 (9.4%)	0 (0.0%)
Total joint replacement or revision.	20 (4.1%)			
Hip and femur procedures (non-major-joint)	10 (2.0%)			
Respiratory disease	40 (8.2%)	35 (10.6%)	5 (3.1%)	0 (0.0%)
Simple pneumonia and pleurisy	20 (4.1%)			
Pulmonary edema, respiratory failure, and/or mechanical ventilation.	10 (2.0%)			
COPD.	10 (2.0%)			
Nervous system disease	30 (6.1%)	20 (6.1%)	10 (6.3%)	5 (33.3%)
Cerebral infarction (including embolic)	10 (2.0%)			
Metabolic encephalopathy/infectious meningoencephalitis	10 (2.0%)			
Other reasons for admission	125 (25.5%)	85 (25.8%)	40 (25.0%)	5 (33.3%)

GI = gastrointestinal.

Table 3

Inpatient outcomes of Whipple's disease compared to other hospitalizations.

	Other hospitalizations (n = 107,000,865)	Whipple disease (n = 490)	*P* value
In-hospital deaths (% mortality)	2077839 (1.9%)	15 (3.1%)	.423
Length of stay (mean days [SE])	4.6 (0.0)	7.4 (0.7)	<.001
Total hospital charges (mean US dollars [SE])	49927 (356)	88254 (12926)	<.001

TW infection has 4 distinct presentations: classical WD, focal disease, acute infection, and asymptomatic carriage. Classic WD presents as a triad of arthralgias, diarrhea, and weight loss. Chronic, focal disease usually presents as a subacute, culture-negative endocarditis. Acute disease often presents as a combination of bacteremia and sepsis, acute gastroenteritis, or pulmonary disease. The fourth type of infection, asymptomatic carriage, is by far the most common.[21] In our study, each of these organ systems were affected in patients with WD, while only a minority resulted in death.

Gastrointestinal (GI) disease is widely reported as the most common presentation of symptomatic WD. Previous studies indicate that weight and diarrhea occur in 90% and 80% of symptomatic WD cases, respectively, while symptoms such as abdominal pain are less frequent.[5,24–26] While we could not examine prevalence of symptomatology, GI disease was the reason for admission in only 25.5% of cases. Interestingly, a substantial proportion of admissions resulted from acute pathologies, including gastroenteritis/esophagitis (4.1%), bowel obstruction (3.1%), and GI hemorrhage (3.1%). These results may be explained by the fact that classic WD presents with chronic GI symptoms that may not be severe enough to warrant hospitalization. In contrast, acute GI disease may be more concerning to patients and healthcare providers, and thus may result in higher rates of hospitalizations.

Acute presentations of *TW* are well documented, and include syndromes such as gastroenteritis, GI bleed, and bowel obstruction. In Marseille, France, a study of children ages 2 to 4 years found *TW* in the stool of 36 of 241 (15%) gastroenteritis patients compared to 0 of 47 (0%) of controls. In rural Senegal, *TW* was detected in the stool of 49% of children with diarrhea and in 31.1% of asymptomatic individuals. In both studies, the children returned to normal health after resolution of the gastroenteritis.[27,28] Blood loss has also been described in WD, and usually occurs as a gross or occult GI bleed. Bleeding usually arises in the small intestine—often with nutritional or vitamin deficiency—but colonic bleeding may also occur.[29–31] Various laboratory derangements are often reported, the most common of which is microcytic or normocytic anemia.[5,32]

Other acute, life-threatening presentations of WD such as intestinal obstruction have also been reported.[33] Multiple mechanisms may lead to intestinal obstruction in WD, including mesenteric lymphadenopathy, retroperitoneal lymphadenopathy, or intestinal wall thickening.[33,34] Usually, these changes lead to chronic constipation in late stage disease before evolving into obstruction and/or intestinal perforation.[33,35] Obstruction typically involves the small bowel, but colonic obstruction may also occur.[36] Rarely, WD may involve the peritoneum and cause primary sclerosing peritonitis with formation of intraabdominal adhesions.[37] Notably, a small proportion of our patients were admitted for peritoneal adhesionolysis (1% of WD admissions). Together, our findings demonstrate the heterogenous GI presentations of WD in the inpatient setting, which should be considered as a rare but potential differential diagnosis in cases of atypical diarrhea, idiopathic intestinal obstruction, lymphadenopathy, or sclerosing peritonitis.

Cardiovascular disease is a common symptomatic presentation of systemic *TW* infection, second only to classic WD.[24] In our study, cardiovascular disease was the cause of admission in more than 11% of WD hospitalizations. Previous studies indicate that WD may be among the most common causes of culture negative endocarditis, often leading to complications such as systemic embolization.[24,25] A study in France found that WD endocarditis only affected males.[24] However, our study found that 15.6% of females and 9.1% of males with WD were

admitted for cardiovascular disease. Cardiac involvement may eventually lead to heart failure in cases of constrictive pericarditis, valvular destruction, or myocarditis.[38]

More than 11% of WD patients were admitted for musculoskeletal disease, often for the purposes of joint surgery. Previous studies have shown that joint pain is the first reported symptom of WD and often precedes weight loss and diarrhea by several years.[19] Usually WD arthritis manifests as oligo- or polyarthritis involving the knees, ankles, or wrists.[39] A 2010 single-center study in France found that, of 113 patients with confirmed classic WD, 50% were initially misdiagnosed as inflammatory rheumatoid disease and 43% experienced rapid worsening of disease after attempted therapy with corticosteroids or TNF inhibitors.[24] Less commonly, *TW* infection presents as a persistent or recurrent monoarticular arthritis. In some cases, patients with WD arthritis may undergo orthopedic surgery before WD is diagnosed.[11,40,41] Consequently, PCR testing of synovial fluid is recommended in cases of culture-negative joint infection.[11]

Pulmonary WD most commonly presents as a pleural effusion, but has various acute and chronic presentations.[42–45] A multicenter intensive care unit study in Marseille, France, found *TW* in bronchoalveolar lavage of 6 patients out of 210 confirmed cases of pneumonia.[42] In addition to monomicrobial infection, *TW* has been found to cause severe pneumonia due to co-infection with opportunistic species.[46] Chronic pulmonary disease has distinctive clinical manifestations. In these cases, lung involvement appears as an interstitial or granulomatous lung disease that may mimic pulmonary sarcoidosis or fungal infections.[43] In our study, 10.6% of males were admitted for pulmonary disease compared to only 3.1% of females.

CNS disease is a feared complication of WD and may appear alongside longstanding classical disease or as an isolated manifestation of *TW* infection.[47] When CNS involvement occurs, prognosis is poor and death may occur in as little as a month.[48] Our study showed high mortality rates in patients admitted for neurological disease. In total, admissions for CNS disease had a mortality of 16.7%, and included hospitalizations for cerebral infarction, encephalopathy, and meningoencephalitis (Table 2). Other CNS manifestations have been reported in the literature, most commonly memory loss and cognitive changes with or without central symptoms such as ophthalmoplegia (especially supranuclear gaze palsies) or altered mental status.[48,49] Movement disorders may also occur, and oculomasticatory myorhythmia and oculofacial skeletal myorhythmia are considered the only pathognomonic features of CNS WD.[49] CNS WD is difficult to diagnose, as brain imaging and conventional CSF analysis is variable and usually nonspecific. Often, CSF PCR is needed to diagnose CNS involvement.[47]

In comparison to non-WD hospitalizations, WD hospitalizations had a significantly higher length of hospital stay and higher hospitalization cost. Although it was not statistically significant, the reported mortality rate was also higher. These factors can be explained by the complex multi-systemic involvement of the WD, which leads to difficulty and delay in diagnosis and treatment. Moreover, our findings indicate that WD is still most likely to present with GI disease in the inpatient setting, a significant proportion of inpatient admissions are also driven by acute disease or involvement of other organ systems.

4.1. Limitations

Our study is limited by its retrospective nature and characteristics of the NIS. Although the NIS provides substantial sample sizes for rare diseases like WD, the database is limited due to the de-identified admissions data, lack of longitudinal outcomes, and diagnostic uncertainty inherent to ICD codes that have yet to be thoroughly validated. The NIS database includes data only from the inpatient setting, which add to the limitation of the study. Nonetheless, we believe that the consistency and concordance of our data with the preexisting body of literature (prevalence, demographics, disease presentations) confirms our successful identification of WD cases and thus support the validity of our findings.

5. Conclusion

Our study shows that patients with WD are likely to be hospitalized for GI disease, but are also frequently admitted for cardiopulmonary disease, musculoskeletal disease, or CNS disorders. Notably, admissions for CNS disease were associated with high rates of inpatient mortality. Our demographic findings reaffirm that WD disproportionately affects middle-aged and elderly males, and showed no significant association by race or ethnicity. Our study is the first to examine geographic distribution of WD in the United States, and showed a greater risk of WD in the Midwest United States. We believe that this study provides useful information to help identify and diagnose WD in the inpatient setting, as well as better appreciate the complex multisystem involvement of this disease.

Author contributions

Conceptualization: Akram I. Ahmad.
Data curation: Colin Wikholm, Ioannis Pothoulakis, Claire Caplan, Arielle Lee.
Formal analysis: Akram I. Ahmad.
Investigation: Akram I. Ahmad, Won Kyoo Cho.
Methodology: Akram I. Ahmad.
Writing – original draft: Akram I. Ahmad, Won Kyoo Cho.
Writing – review & editing: Akram I. Ahmad, Colin Wikholm, Ioannis Pothoulakis, Claire Caplan, Arielle Lee, Faith Buchanan, Won Kyoo Cho.

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