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Morbidities and mortality in patients with hereditary thrombotic thrombocytopenic purpura

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Key Points

- More women (117) than men (85) were diagnosed with hTTP. The difference was caused by 34 women who were diagnosed during pregnancy.
- Half of patients with hTTP who were older than age 40 years had had stroke, kidney injury requiring dialysis, and/or severe cardiac injury.

Hereditary thrombotic thrombocytopenic purpura (hTTP) is a rare disorder caused by severe ADAMTS13 deficiency. Major morbidities and death at a young age are common. Although replacement of ADAMTS13 can prevent morbidities and death, current regimens of plasma prophylaxis are insufficient. We identified 226 patients with hTTP in 96 reports published from 2001 through 2020. Age at diagnosis was reported for 202 patients; 117 were female and 85 were male. The difference was caused by diagnosis of 34 women during pregnancy, suggesting that many men and nulliparous women are not diagnosed. Eighty-three patients had severe jaundice at birth; hTTP was suspected and effectively treated in only 3 infants. Of the 217 patients who survived infancy, 73 (34%) had major morbidities defined as stroke, kidney injury, or cardiac injury that occurred at a median age of 21 years. Sixty-two patients had stroke; 13 strokes occurred in children age 10 years or younger. Of the 54 patients who survived their initial major morbidity and were subsequently observed, 37 (69%) had sustained or subsequent major morbidities. Of the 39 patients who were observed after age 40 years, 20 (51%) had experienced a major morbidity. Compared with an age- and sex-matched US population, probability of survival was lower at all ages beginning at birth. Prophylaxis was initiated in 45 patients with a major morbidity; in 11 (28%), a major morbidity recurred after prophylaxis had begun. Increased recognition of hTTP and more effective prophylaxis started at a younger age are required to improve health outcomes.

Introduction

Hereditary thrombotic thrombocytopenic purpura (hTTP) has a long history, but accurate diagnosis has only recently become available.[1] In the first report of hTTP in 1975, 3 of the 4 affected children in 1 family died.[2] The exacerbation of hTTP with pregnancy was recognized in 1976. Two sisters had their initial symptoms in the third trimester of their first pregnancy; both died.[3] In 1977, plasma infusion was recognized as an effective treatment.[4] In 1998, a severe deficiency of plasma von Willebrand–cleaving protease was identified as the etiology of hTTP.[5,6] In 2001, biallelic *ADAMTS13* mutations were identified in 7 patients from 4 families.[7] Documentation of biallelic *ADAMTS13* mutations confirms the diagnosis of hTTP. The first large case series of patients with documented hTTP was published in 2011, describing that those at greatest risk are newborn infants and pregnant women.[8,9] These observations have been confirmed by reports from the United Kingdom[10] and International[11] Hereditary TTP Registries.

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The full-text version of this article contains a data supplement.

The goal of our study was to determine the health outcomes and survival of patients with hTTP. We reviewed the clinical course of 226 patients described in 96 reports, documented the age at initial symptoms and the age at diagnosis, identified major morbidities and deaths and the ages when they occurred, evaluated the effectiveness of plasma prophylaxis for prevention of major morbidities, and calculated survival compared with the age- and sex-matched US population. Understanding the clinical course of patients with hTTP is essential for providing effective preventive management.

Methods

To identify published reports of individual patients with hTTP, we searched MEDLINE and PubMed from 2001 (when the etiology of hTTP was first defined[7]) through December 2020 using our previously published search strategy.[12] We included all patients whose genetic and clinical data were described. We defined stroke, kidney injury, and cardiac injury as major morbidities because of their high risk for persistent or recurrent organ injury and impairment of health. We combined transient ischemic attack with stroke, which we report as stroke, because most reports did not describe magnetic resonance imaging, which is essential for confirming or excluding cerebral infarction.[13] We defined kidney injury as a requirement for renal replacement therapy, which commonly indicates persistent or progressive impairment of kidney function.[14] We selected renal replacement therapy, often described as hemodialysis, as our definition of kidney injury because it was a consistent and uniform term that was apparent in the descriptions of the patients' clinical course. We recognize that requiring renal replacement therapy may underestimate the potential for long-term kidney injury. Cardiac injury was defined as myocardial infarction, congestive heart failure, or cardiomyopathy.

We compared the probability of survival of patients with hTTP to the expected values based on the life expectancy of the 2017 US reference population obtained from the Centers for Disease Control and Prevention lifetables. We acknowledge that the US population may be an imprecise comparison for the deaths of these patients because only 15 (7%) of the 226 patients were from the United States where life expectancy is age 79 years.[15] This limitation may not affect our observation that the probability of survival of patients with hTTP was decreased, because the life expectancy may be greater in other countries with more reported patients (eg, Japan, 48 patients [21%]; life expectancy, 84 years[15]). We used sex and the age at death to determine the expected probability of survival. If the authors did not report death, we used age at the time of publication as a surrogate for the time of last follow-up and censoring. We used Kaplan-Meier methods with point-wise limits and right censoring to estimate the probability of survival and the corresponding 95% confidence interval (CI) and to compare between males and females. We used a log rank test to determine whether the probability of survival differed between males and females.

Results

Patient selection

Ninety-five articles reported clinical data on 208 patients with hTTP documented by biallelic *ADAMTS13* mutations. We included 17 additional patients reported in these articles who were siblings (or the father) of patients with hTTP and who had clinical features of TTP and/or autopsy evidence for thrombotic microangiopathy but died without *ADAMTS13* sequence analysis. One additional patient was diagnosed with TTP by ADAMTS13 activity $<10\%$ before her death during her first pregnancy. After her death, hTTP was diagnosed when single-allele *ADAMTS13* mutations were identified in both of her parents and her brother.[16] We describe these 18 patients with their citations in supplemental Table 1. Supplemental Table 2 provides demographic, genetic and clinical data, country of origin, citation, and purpose for publication for each of the 226 patients. The patients were from 26 countries; 194 (86%) were from Europe, Japan, Israel and the United States, countries which have similar health care and life expectancy (79-84 years[15]).

Diagnosis

Ten (5%) of the 208 patients who had biallelic *ADAMTS13* mutations were asymptomatic (supplemental Table 3). Eight of these 10 patients (7 families) were siblings of previously diagnosed patients; 1 patient was the father. These 9 patients were identified by *ADAMTS13* sequence analysis of family members. The other patient was a 17-year-old woman who was evaluated after discovery of asymptomatic thrombocytopenia on a routine laboratory test. Her evaluation revealed ADAMTS13 activity $<2\%$. Subsequent *ADAMTS13* sequence analysis confirmed the diagnosis of hTTP.[17]

Among all 226 patients, 216 were symptomatic. The age of initial symptoms was reported for 204 patients; the median age was 2 years (Table 1). Eighty-three (42%) of these 204 patients had severe jaundice at birth, and anemia and thrombocytopenia were often described. Nine of 83 newborn infants died soon after birth (supplemental Table 1). hTTP was suspected in 1 of these 9 infants before death, but she died when her parents refused plasma exchange. *ADAMTS13* sequence analysis confirmed the diagnosis of hTTP after her death.[18] *ADAMTS13* sequence analysis confirmed the diagnosis in 2 other infants in whom hTTP was first suspected after death.[19,20] The other 6 infants who died had clinical and/or autopsy features consistent with TTP. They were older siblings of patients who were subsequently diagnosed with hTTP. In 3 of the 74 surviving infants, hTTP was promptly suspected, effectively treated, and subsequently confirmed.[21,22] Among the remaining 71 infants, 37 were treated with empirical whole blood exchange transfusion. hTTP was diagnosed in these 71 patients at age 1 month to 21 years (median age, 5 years).

Among the 216 symptomatic patients, the age of diagnosis was reported for 202 patients. The median age was 16 years; 117 patients were female, and 85 were male (Table 1). Figure 1 illustrates the age at diagnosis. For patients age 0 to 19 years, the frequency of diagnosis of boys (58) and girls (56) was similar; 2 girls were diagnosed during pregnancy. For patients age 40 years or older, the frequency of diagnosis of men (12) and women (11) was also similar; 1 woman was diagnosed during pregnancy. For patients age 20 to 39 years, the frequency of diagnosis of men (15) was much less than the diagnosis of women (50). The difference was caused by diagnosis of women during pregnancy (31). Omitting the 34 diagnoses of hTTP during pregnancy, the frequency of diagnosis in women (83) and men (85) was similar across all ages. For men, the frequency of diagnosis steadily decreased after age 10 years.

Table 1. Health outcomes of 226 patients with hTTP

	No. (%)	Median (range)
All patients	226	
Females	129 (57)	
Patients with symptoms of TTP*	216	
Females	121 (56)	
Patients with age at first symptoms reported	204	
Females	114 (56)	
Patients with age at diagnosis reported	202	
Females	117 (58)	
Age, y†		
At first symptoms		2 (0-63)
At diagnosis		16 (0-77)
At death‡	32 (14)	
Neonatal	9	0-17 d
Pregnancy	4	23 (20-26)
Children	9	5 (2-13)
Adults	10	40 (21-79)
Last follow-up§		23 (0-79)
Major morbidities		
Patients‖	73 (34)	
Age at initial morbidity		21 y (1 d-77 y)
Females	38 (52)	
Types of major morbidities¶		
Stroke	62 (27)	
Kidney injury	23 (10)	
Cardiac injury	8 (4)	

*Ten patients who had no symptoms of TTP were diagnosed with hTTP by documentation of biallelic ADAMTS13 mutations (described in supplemental Table 3).

†Units for age are years, unless otherwise indicated.

‡Nine patients died during their first days of life. When these neonatal deaths were excluded, the frequency of death was 11%, the youngest age was 2 years, and the median age was 22 years.

§Age at last follow-up was not reported for 5 of the 194 surviving patients.

‖Percent of 217 patients, omitting the 9 infants who died at birth.

¶Eighteen of the 73 patients initially had 2 of the 3 categories of morbidities; 1 patient initially had all 3 morbidities. Cardiac injuries were myocardial infarction (5 patients), cardiomyopathy (2 patients), and congestive heart failure (1 patient).

Major morbidities

One or more of the 3 major morbidities occurred in 73 (34%) of the 217 patients, excluding the 9 infants who died soon after birth (Table 1). Thirty-eight (52%) of the 73 patients were women. Each of these patients is described in supplemental Table 4 with their type of morbidity, age at the time of their initial morbidity, age at their last follow-up (or death), subsequent morbidities, and prophylaxis. The median ages for initial occurrence of the 3 morbidities were similar (20-23 years). The initial occurrence of major morbidities was almost always associated with thrombocytopenia; however, exacerbations of hTTP are often not as discrete as the acute episodes of acquired immune TTP. Stroke was the most common major morbidity. Sixty-two (29%) of all 217 patients had a stroke. Stroke occurred equally among women (28%) and men (29%). Thirteen (21%) of the 62 patients with stroke were 10 years old or younger. Risk factors for stroke (eg, hypertension) were rarely reported. Six (8%) of the 73 patients died at the time of their initial major morbidity; 13 patients had no subsequent follow-up. Thirty-seven (69%) of the 54 surviving patients, who had continued follow-up for a median of 10 years (range, 1-47 years) had a sustained or recurrent major morbidity. Twenty-one patients had recurrent stroke; 14 developed end-stage kidney disease (ESKD). Two patients had kidney transplantation (Table 2; supplemental Table 4).

Table 3 presents the occurrence and frequency of major morbidities. The frequency of initial major morbidities increased with each decade of life. Table 3 also presents the cumulative frequency of major morbidities, including those in patients who survived a previous major morbidity and continued to be observed. Among all 212 patients for whom follow-up was reported, 39 had follow-up after age 40 years; 20 (51%) had experienced a major morbidity. All 4 patients with continued follow-up to age 70 years or older experienced a major morbidity. Figure 2 illustrates these data for each of the 73 patients, presenting the age of initial occurrence of a major morbidity and duration of follow-up. This figure illustrates that initial major morbidities consistently occurred across all ages, with the highest cumulative frequency at age 20 to 40 years.

Prophylaxis

Prophylactic treatment was reported for 110 (53%) of the 207 symptomatic patients who survived infancy. Prophylaxis began at a median age of 14 years (range, newborn[21]-70[23] years). Prophylaxis was almost always with plasma, commonly described as 1 to 3 units of plasma at 2- to 3-week intervals. In some patients, plasma was given to maintain the platelet count above a certain level (eg, 20 000[24]-100 000[25]/μL). Two patients received plasma-derived factor VIII concentrates that contained ADAMTS13 (Koate, BPL 8Y).[26,27] The benefit of prophylaxis was rarely described.

To describe prophylaxis use and effectiveness more clearly, we analyzed the 54 patients with major morbidities who survived their initial morbidity and continued to be observed (supplemental Table 4). Thirty-nine (72%) of the 54 patients were managed with prophylaxis; the age at start of prophylaxis was reported for 37 patients. Seven patients had begun prophylaxis before their first occurrence of a major morbidity; 9 patients began at the time of their first major morbidity; 21 patients began 1 to 40 years after their first major morbidity, often at the time of a recurrent major morbidity. A major morbidity recurred in 11 patients (28%) after the start of prophylaxis (Table 2). Among the 15 patients for whom prophylaxis was not reported, recurrent stroke and/or progression of kidney injury to ESKD occurred in 7 patients (47%).

Death

Thirty-two (14%) of the 226 patients died (Figure 1). Each of these deaths is described in supplemental Table 1. Among all 32 deaths, 18 (56%) occurred before age 20 years (9 boys and 9 girls). At age 20 years or older, the frequency of deaths and age at death seemed to be different between men and women. Nine men died after age 20 years, 1 or more in each decade. Four women died during pregnancy at age 20 to 26 years; 1 woman died at age 55 years. There were 4 distinct categories of deaths: neonatal deaths, deaths in children, deaths during pregnancy, and deaths in adults (excluding deaths occurring during pregnancy) (Table 1).

Nine infants died soon after birth with extreme hyperbilirubinemia caused by severe hemolysis; 5 were girls, 4 were boys. One boy

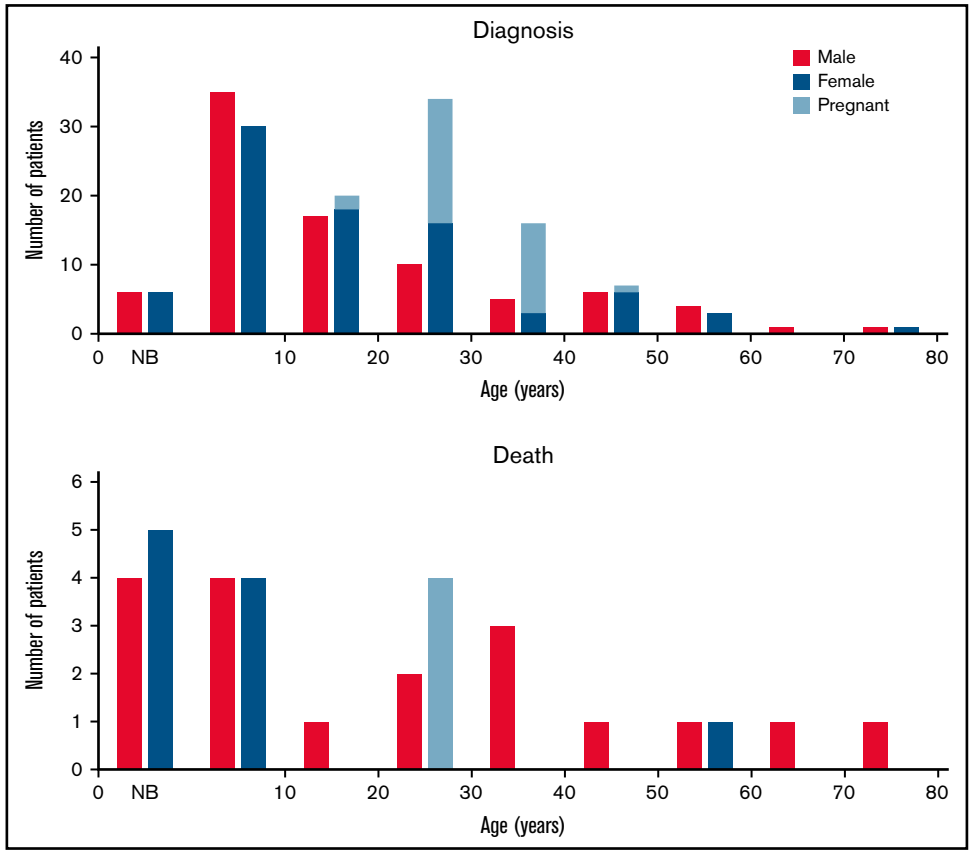

Figure 1. Age at diagnosis and death in patients with hTTP. Age at diagnosis was reported for 202 (89%) of the 226 patients (85 male, 117 female). Deaths were reported for 32 patients (18 male, 14 female). Patients whose age at diagnosis or death occurred at a decade marker are counted in the following decade. Newborn infants (NBs) are distinguished from children age 0 to 9 years because they were recognized by their severe hyperbilirubinemia. Twelve infants were diagnosed at birth; 9 died. The diagnosis of newborn infants occurred within several days of birth. Among the other children age 0 to 9 years, the youngest child diagnosed with hTTP was a 1-month-old girl; the youngest death was in a 2-year-old boy.

had an autopsy that showed systemic microvascular thrombosis. Nine children age 2 to 13 years died; 4 were girls, 5 were boys. Although none of the 9 children had a preceding major morbidity, they had previous acute episodes of severe thrombocytopenia and microangiopathic hemolytic anemia. Only 1 girl (3 years old), had been previously diagnosed with TTP. Five of the children had autopsies that showed systemic microvascular thrombosis.

Deaths of 4 women age 20 to 26 years were associated with pregnancy. Three women died at 20, 23, or 28 weeks of gestation; 1 woman died postpartum. None of the 4 women had a preceding major morbidity; none had been previously diagnosed with TTP. One woman had an autopsy that showed systemic microvascular thrombosis.

Ten adults (9 men and 1 woman) age 21 to 79 died. Eight patients had been previously diagnosed with hTTP. Nine patients had preceding major morbidities; 1 man died at age 23 years with no previous major morbidity. Six patients had ESKD for 1 to 19 years (median, 9 years) preceding their death. One of these 6 patients and 2 additional patients had strokes 14 to 19 years (median, 6 years) preceding their death. One man had a myocardial infarction 17 years preceding his death.

Beginning at birth, survival of patients with hTTP was significantly less than survival of the age- and sex-matched US population (Figure 3A). At age 10 years, the estimated survival of patients with hTTP was 92% (95% CI, 88%-96%) compared with 99% for the US population. At age 40 years, the estimated survival of patients with hTTP was 82% (95% CI, 75%-89%) compared with 96% for the US population. After age 30 years, the survival of women seemed to be greater than that of men (Figure 3B), although the difference was not significant.

Discussion

Our analysis of these 226 case reports increases our understanding of the lives of patients with hTTP. However, long-term health outcomes remain uncertain because confirmation of the diagnosis of hTTP has been possible only within the past 20 years.[7] Of the 226 case report patients, 160 (71%) were reported after 2010 when measurements of ADAMTS13 activity became commonly available.[28]

Major morbidities are common in patients with hTTP. Among the 217 patients who survived their neonatal days, 73 (34%) had stroke, kidney injury requiring renal replacement therapy, and/or

Table 2. Number of patients with major morbidities

Initial major morbidity	No. (%) 73	Median (range)
Death	6 (8)	
No follow-up	13 (18)	
Surviving patients (with follow-up)	54	
Duration of follow-up, y		10 (1-47)
No subsequent morbidities	17 (31)	
Subsequent morbidities*	37 (69)	
TIA/stroke	21	
Other neurologic abnormalities (hemiparesis, cognitive impairment)	6	
Acute kidney injury (without ESKD)	2	
ESKD (2 patients, kidney transplants)	14	
Cardiac injury (cardiomyopathy, congestive heart failure)	2	
Deaths attributed to subsequent morbidities (stroke, 5; ESKD, 3)	8	
Prophylaxis	54	
Patients	39 (72)	
Prophylaxis began:		
Before initial major morbidity	7	
At the time of initial major morbidity	9	
After initial major morbidity	21	
Not reported	2	
Recurrence of major morbidity after prophylaxis	11 (28)	

*10 patients had multiple subsequent major morbidities.

cardiac injuries (infarction, cardiomyopathy, or congestive heart failure). The frequencies of all major morbidities were similar in women and men. Major morbidities consistently occurred across all ages beginning at birth. Half the patients age 40 years or older had experienced 1 or more of these 3 major morbidities. Among the major morbidities, the occurrence of stroke (62 patients; 27%) was much more common than myocardial infarction (5 patients; 2%). This disparity was also apparent in the reports from the United Kingdom (stroke, 25%; myocardial infarction, 0%)[10] and International (stroke, 31%; myocardial infarction, 4%)[11] Hereditary TTP Registries (Table 4).

The young age of occurrence of stroke in patients with hTTP is similar to the reported age of stroke in patients with sickle cell anemia.[12,29] As in hTTP, in patients with sickle cell anemia, myocardial infarction is much less common than stroke.[29] In patients with sickle cell anemia, strokes occur in the cerebral vessels with the lowest blood flow.[30] Brain imaging studies were not reported in these patients with hTTP, as they were in the published studies of patients with sickle cell disease. The much greater frequency of stroke compared with myocardial infarction in both hTTP and sickle cell disease may be caused by their similar embolic obstruction of normal vessels in contrast to the vascular disease that causes stroke and myocardial infarction in most people.

Among all 32 deaths, 9 occurred in the first days of life. Failure to recognize hereditary TTP in newborn infants with extreme hyperbilirubinemia caused by severe hemolysis is common.[8] Among all 226 case report patients, 83 newborn infants (37%) had severe hyperbilirubinemia. Only 3 infants were suspected of having hTTP and were appropriately treated and survived.[21,22] The diagnosis of hTTP should be considered in all newborn infants who have severe hyperbilirubinemia. Although documenting ADAMTS13 deficiency may require several days, empirical plasma infusion is a simple, life-saving treatment.

Exacerbation of hTTP in newborn infants is caused by the occurrence of high-velocity, turbulent blood flow through the patent ductus arteriosus[31] because pulmonary vascular resistance decreases after birth.[32] Turbulent blood flow increases thrombotic risk by causing the ultra-large multimers of von Willebrand factor (VWF) in patients with hTTP to unfold, which exposes their platelet binding sites[33] and allows them to assemble into bundles.[34] The thrombotic risk caused by platelet binding to VWF is supported by the prompt

Table 3. First occurrence of major morbidities and duration of subsequent follow-up

	Patients with major morbidities (n = 73)		Patients for whom follow-up was reported (n = 212)	
Age group (y)	First occurrence of a major morbidity* No. (%)	First occurrence + survivors of a previous major morbidity†	Patients with continued follow-up	Frequency (%) of patients who had a major morbidity‡
0-9	12 (6)	12	212	6
10-19	21 (12)	25	170	15
20-29	17 (13)	30	129	23
30-39	11 (14)	28	79	35
40-49	7 (18)	20	39	51
50-59	4 (18)	14	22	64
60-69	0	8	11	73
70-79	1 (25)	4	4	100

These data describe only the first occurrences of a major morbidity and document the steadily increasing frequency of patients who have had the first occurrence of a major morbidity. Recurrent major morbidities are not addressed. These data are also presented in Figure 2 to illustrate the initial occurrence of major morbidities across all ages and the duration of subsequent follow-up after the initial major morbidity. These data do not include the 9 patients who died in their first days after birth and the 5 patients for whom no follow-up was reported. The initial occurrence of a major morbidity and the subsequent clinical course of each the 73 patients are reported in supplemental Table 4.

*Age of patients at the time of their first occurrence of a major morbidity. The percent is the fraction of all patients with continued follow-up at each age.

†Age of patients at the time of the first occurrence of a major morbidity plus patients who had a previous major morbidity and continued to survive and be observed.

‡The frequency of major morbidities among all patients who continued to be observed at each decade of age, calculated from columns 3 and 4.

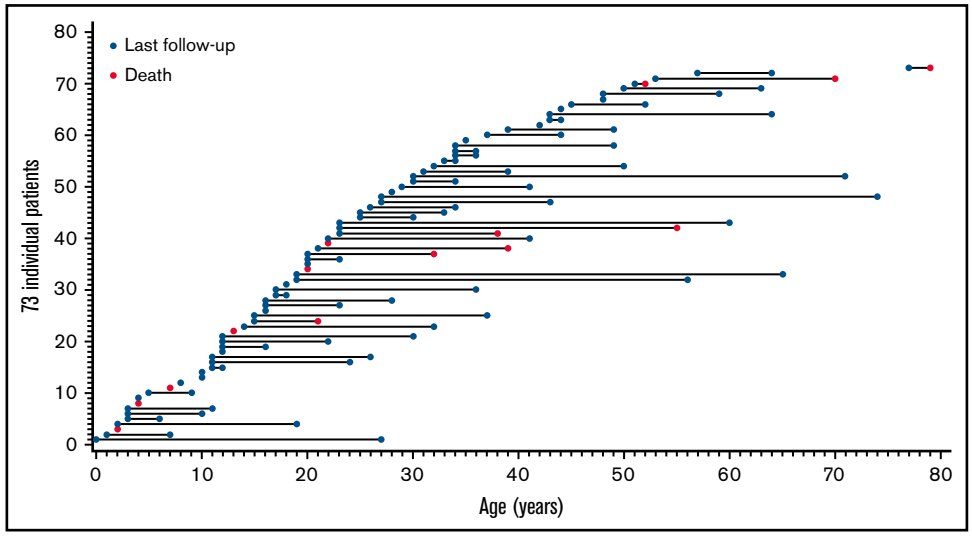

Figure 2. Age at occurrence and follow-up of major morbidities in patients with hTTP. Each of the 73 patients is shown at the age of their initial major morbidity by a blue circle (living) or red circle (died). If patients survived their initial major morbidity and were subsequently observed, the duration of survival or follow-up is indicated by the horizontal line. These data are also presented in Table 3.

effectiveness of caplacizumab, which blocks platelet binding to VWF in patients with acquired immune TTP.[35]

Nine deaths occurred in children, age 2 to 13 years old. None of the children had a preceding major morbidity and only 1 had been previously diagnosed with hTTP. Combining the deaths in children with the neonatal deaths, 9 occurred in boys and 9 occurred in girls.

Four deaths occurred in women age 20 to 26 years that were associated with pregnancy. Severe complications during pregnancy almost always occur in women with hTTP. In our previous analysis of pregnancies in 35 women with undiagnosed hTTP, 34 (97%) had severe complications.[36] Exacerbation of hTTP with pregnancy may be caused by turbulent blood flow, similar to the exacerbation of hTTP in newborn infants. The high-velocity turbulent blood flow of maternal spiral arterioles that supply the developing placenta[37] may expose platelet binding sites on VWF[33] and create bundles of VWF.[34] hTTP causes placental arteriolar thrombosis and infarction[38] described as maternal vascular malperfusion.[37] The placental pathology of severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is also described as maternal vascular malperfusion.[37] The similar placental pathology is consistent with the similar clinical features (thrombocytopenia, microangiopathic hemolytic anemia) of hTTP, severe preeclampsia, and HELLP syndrome.[39] An additional risk for exacerbation of hTTP during pregnancy is the increase of VWF. In healthy pregnancies, the plasma concentration of VWF antigen increases throughout pregnancy to reach threefold prepregnancy levels at 38 weeks of gestation.[40] Excluding the 4 women whose deaths were associated with pregnancy, 10 deaths occurred in adults: 9 men and 1 woman, ages 21 to 79 years. Nine had preceding major morbidities; 8 had been previously diagnosed with hTTP.

The frequencies of diagnosis and death emphasize the sex disparities among adults with hTTP. More women (117) than men (85) were diagnosed with hTTP. The difference occurred at age 20 to 39 years and was caused by the frequent diagnosis of hTTP during pregnancy.[8,10] Excluding the 34 women who were diagnosed during pregnancy, the number of women (83) and men (85) diagnosed with hTTP and the ages at which they were diagnosed were similar (Figure 1). This observation suggests that many men and nulliparous women with hTTP are not diagnosed.

Among reported deaths in patients age 30 years or older, there are more men (7) than women (1). Our survival analysis also suggested that there are fewer deaths among older women (Figure 3B). This survival disparity may also be related to pregnancy. Women may have died during pregnancy with unrecognized hTTP. Death during pregnancy may be attributed to other causes that are much more common such as severe preeclampsia and HELLP syndrome. Misdiagnosis may occur because both the clinical and pathologic features of severe preeclampsia and HELLP syndrome are similar to hTTP.[37-39] Although the clinical features are similar, hTTP may occur earlier during gestation than severe preeclampsia and HELLP syndrome. The gestational age at death of 3 women who died during pregnancy was 20, 23, and 28 weeks when preeclampsia and HELLP syndrome rarely occur.[41] Another possible reason for fewer deaths in women older than age 30 years may be that subsequent management of women who are diagnosed and effectively treated during pregnancy could prevent subsequent deaths.

The possibilities of unrecognized hTTP suggest that the current prevalence estimate of hTTP (0.5-2.0 cases per million population[1]) is an underestimate. One report described a search for hTTP in Central Norway using multiple case-finding strategies.[42] These data reported an estimated prevalence of hTTP of 16.7 cases per million population. This estimate was supported by identifying the common pathologic *ADAMTS13* mutations c.4143insA and p.R1060W in 0.33% to 1.0% of blood donors.[42] As measurements of ADAMTS13 activity become more common, more patients with hTTP will be identified.

Morbidities and deaths in patients with hTTP are preventable by replacing ADAMTS13. In spite of the apparent simplicity of plasma

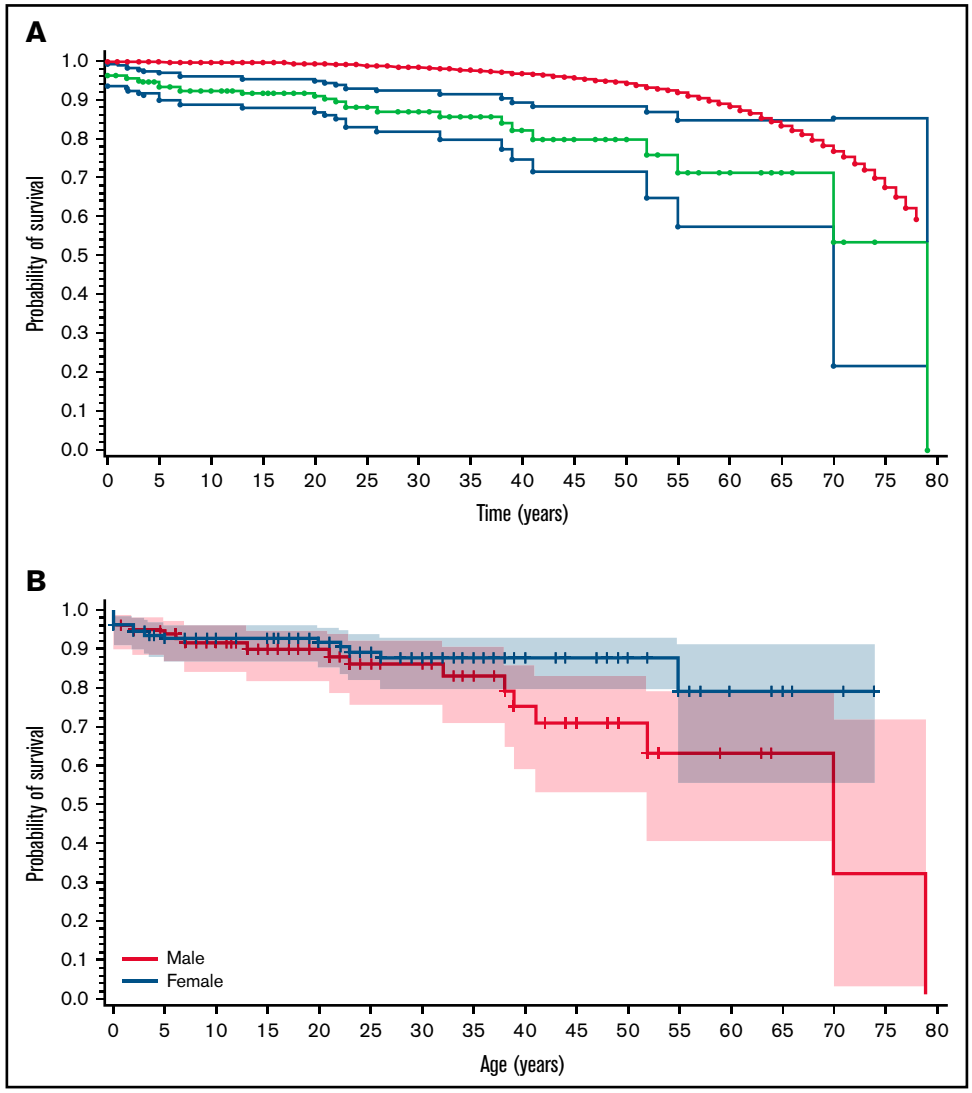

Figure 3. Survival of patients with hTTP. The survival data are from 221 patients, excluding 5 patients for whom the duration of follow-up was not reported. (A) The probability of survival of the patients with hTTP (green line) was compared with the age- and sex-matched US population (red line) values using Kaplan-Meier methods. The difference between the patients with hTTP and the expected deaths in the US population was determined by using 95% CIs for the patients' deaths (blue lines). Beginning at birth, the 95% CIs did not overlap with the survival line for the US population. (B) The probabilities of survival of male and female patients with hTTP were calculated separately by using Kaplan-Meier methods and a log-rank test to determine differences. The 95% CIs are illustrated by blue for female and red for male.

prophylaxis, only 39 (72%) of the 54 patients with major morbidities who survived and continued to be observed were described as receiving prophylaxis. Major morbidities recurred in 28% of patients receiving prophylaxis and in 47% of patients not receiving prophylaxis. Plasma prophylaxis may not be used more often because the usual regimen of 10 to 15 mL/kg once every 2 weeks[1] is a major lifetime inconvenience. In addition, current regimens of plasma prophylaxis may be insufficient. The International Hereditary TTP Registry has documented that the incidence of acute TTP episodes was not different between patients who received prophylaxis (0.36 per person-year; 95% CI, 0.29-0.44 per person-year) and patients without regular plasma prophylaxis (0.41 per person-year; 95% CI, 0.30-0.56 per person-year).[43] More frequent infusions and larger volumes of plasma are more effective[10] and have contributed to the successful management of women with hTTP during pregnancy.[43]

When recombinant ADAMTS13 is approved, prophylaxis will become simpler and may become more common. In the initial clinical trial, infusion of 40 U/kg of recombinant ADAMTS13 (vial concentration, 300 U/mL) in 9 patients was expected to achieve in vivo ADAMTS13 activity of 100%. ADAMTS13 activity of 94% was achieved, with a half-life of 2.8 days.[44] These preliminary data suggest that prophylaxis with recombinant ADAMTS13 may be effective and can conveniently be self-administered.

With effective and convenient prophylactic treatment with hTTP, management questions will become whom to treat and when to begin. Lifetime prophylaxis beginning at the time of diagnosis may be the optimal management strategy. For asymptomatic and minimally symptomatic patients, careful follow-up without prophylaxis may be sufficient. However, apparently minor symptoms such as

Table 4. Comparison of patients with hTTP described in case reports to patients with hTTP reported by the United Kingdom and International Hereditary TTP Registries

	hTTP					
	United Kingdom Registry[10]		International Registry[11]		Case reports patients	
	No. (%)	Median (range)	No. (%)	Median (range)	No. (%)	Median (range)
Year of publication	2019		2019		2022	
Patients	73		120		226	
Female	51 (70)		62 (52)		129 (57)	
Age, y*						
At diagnosis		24 (newborn-71)		17 (newborn-70)		16 (newborn-77)
At last follow-up		NA		26 (4-60)		23 (0 d-79)
At first symptoms		18 (newborn-67)		5 (newborn-70)		2 (newborn-63)
First symptoms at birth	NA		30 (25)		81 (36)	
Stroke	18 (25)		37 (31)		62 (27)	
Age at stroke	NA		NA			22 (1 d-77)
Myocardial infarction	0		5 (4)		5 (2)	
Age at myocardial infarction	NA		NA		20 (3-53)	
Death	5 (7)		NA		11 (5)†	
Age at death	NA		NA			7 (newborn-79)

Sixty-eight (30%) of the case report patients were included in the International Registry.[11] There were no case report patients included in the United Kingdom Registry.[10]
NA, not available.
*Age is given in years, unless otherwise specified.
†Case report data include 21 patients who died but who would not have been enrolled in the Registries: 18 patients who died without *ADAMTS13* sequence analysis and 3 patients who had *ADAMTS13* sequence confirmation but who died in their first days of life. Including these 21 deaths, the frequency of death would be 14%.

headache, lethargy, and abdominal pain can resolve and platelet counts can increase with plasma prophylaxis.[10] This suggests that microvascular thrombosis with organ ischemia may occur without severe symptoms. It is also essential to focus on the patients' general health. Preventive measures such as not smoking, regular exercise, and a healthy diet are essential for decreasing risk for stroke. Optimal general medical care for risk factors such as hypertension[45] and diabetes is also essential.

An important limitation of our study is the short duration of patient follow-up. Patient follow-up was not an objective of many case reports, and long-term follow-up is rarely reported because confirmation of the diagnosis of hTTP has been possible only for the last 20 years.[7] Another limitation of our study is that case reports may describe exceptional patients. However, the validity of our data is supported by the purpose for publishing these case reports. For 146 patients (65%), the purpose was to describe *ADAMTS13* mutations (supplemental Table 2); the patients' clinical features were provided as supportive data. Validity of our case report data is also supported by the similarity of our data describing sex, age at diagnosis, frequency of stroke and myocardial infarction, and death to the data reported by both the United Kingdom and International Hereditary TTP Registries (Table 4).[10,11] Strengths of our case report data are the description of clinical outcomes of individual patients and the inclusion of patients not eligible for enrollment on the Registry (eg, infants who died). Although inclusion of patients without genetic confirmation may risk including patients without hTTP, it may provide a more accurate estimate of mortality.

These data describe our current knowledge of the health outcomes of patients with hTTP. With more common use of ADAMTS13 measurements, there will be greater recognition of these patients. More common use of ADAMTS13 measurements will identify hTTP as a cause of severe hyperbilirubinemia in newborn infants, stroke in children and young adults, and severe complications during pregnancy. More frequent identification of patients with hTTP and more convenient prophylaxis will prevent major morbidities and deaths.

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Authorship

Contribution: A.B. helped create the concept of the manuscript, performed the literature search and helped review each article, helped organize and interpret the data, and helped write each draft; J.A.R. helped organize the data, performed the statistical analyses, created the figures, and proofread each draft; S.G. contributed to the literature search, reviewed most articles, helped organize and interpret the data; and J.N.G. helped create the concept of the manuscript, reviewed each article, interpreted the data, and wrote the first and successive drafts of the manuscript.

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