Follow-up Evaluation of Patients with Congenital Thrombotic Thrombocytopenic Purpura from the International Hereditary TTP Registry: is Frequency and Severity of Acute Disease Episodes influenced by Gender?

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Scientific research question:
Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare disorder characterized by recurring acute episodes of thrombotic microangiopathy. cTTP is autosomal recessively inherited and results from severely reduced or absent ADAMTS13 activity. Clinically, cTTP presents heterogeneously, and currently little is known about frequency and severity of acute disease episodes in cTTP patients.

Methodology
We analyzed data of 136 confirmed cTTP patients in the International Hereditary TTP Registry.Survival, frequency and severity of acute episodes, and treatment were studied prospectively from enrollment until September 2019.

Findings
Follow-up data (since enrollment median 1.6 years, range 0.1-8.2) were available for 85 of 136 patients. The 44 male and 41 female cTTP patients had a median age at clinical diagnosis and at overt disease onset of 19 years (range 0-70) and 6.9 years (range 0-70) in male, and 17 years (range 0-50) and 4.1 years (range 0-32) in female patients, respectively. 25 (57%) male and 18 (44%) female patients received prophylactic plasma treatment. During follow-up five patients died (causes of death: stroke n=2, asystole and sepsis, heart failure, and sudden death of unknown cause, one each), all were male (age range 39-78 years). In addition, 112 acute episodes were observed in 41 of 85 cTTP patients, 36 episodes occurred in male, 76 episodes in female patients. This resulted in gender-specific annual incidence rates of 0.20 (0.14-0.27) in male, and 0.43 (0.34-0.54) in female cTTP patients.
Infections were the most prevalent trigger and present in 68% (n=13, in male) and 75% (n=40, in female) of acute episodes. Alcohol was the trigger of 5 episodes (male n=3), and 4 episodes occurred during pregnancy. Of 112 episodes, 77 were documented under regular plasma prophylaxis in 59 patients during 247 patient-years. The calculated incidence rates under plasma prophylaxis were 0.18 (0.11-0.27) in male, and 0.47 (0.35-0.62) in female patients. Patients not under regular plasma prophylaxis experienced 35 episodes in 105 patient-years, amounting to an incidence rate of 0.29 (0.15-0.50) in male, and 0.36 (0.23-0.54) in female cTTP patients.

Conclusion
We provide the first estimate on annual incidence of acute episodes in cTTP based on prospective data and observed 0.3 episodes per patient-year. Current plasma prophylaxis regimens seem to be insufficient to prevent acute episodes. Female patients had a slightly higher incidence rate, which was not attributable to pregnancy alone. In contrast, mortality was higher in male (n=5) than in female (n=0) patients. Robustness of estimates will improve with the addition of further prospective follow-up and patient years.