Thrombosis in paroxysmal nocturnal hemoglobinuria: sites, risks, outcome. An overview

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Historical data, despite their limitations, may serve as a pool of accumulated knowledge and a basis for prediction. Thrombosis in paroxysmal nocturnal hemoglobinuria (PNH) remains a leading cause of death [1–4], but individual risks have not been estimated so far.

Data extraction and statistical processing

MEDLINE Database (1953 to 2006) has been extensively reviewed using the terms 'PNH, Thrombosis' and 'Paroxysmal Nocturnal Hemoglobinuria, Thrombosis' as search criteria; 294 citations were retrieved. Eligible articles were reviews, cohort studies, and case reports providing individual patient data on the site of thrombosis and outcome (death or survival) related to the thrombotic event. Ninety-three articles (nine cohort studies and 84 case reports and reviews of published cases) provided data on 363 PNH cases with thrombosis and outcome in 339 cases. When the same case was reported twice, in a review article and as a case report, only one of the citing articles was included as a data source. When either the site of thrombosis or the outcome was not evident, this case was excluded. Our study population finally consisted of 339 cases of PNH with thrombosis. Treatment options were available in 162 cases and were classified as conventional ($n = 118$) (for those receiving unfractionated heparin, low molecular weight heparin, or warfarin) and interventional modalities ($n = 44$), either to restore blood flow (thrombolysis, anatomic shunts, angioplasty) or reverse coagulation defect (bone marrow transplantation).

Odds ratios with their corresponding 95% confidence intervals (CIs) were measured to quantify relative risk of death (RR) in univariate and multivariate logistic regression models. A score chart was developed to facilitate the practical application of the multivariate regression model. The regression coefficients of the significant covariates were rounded off to the proximal 0.5. The value of each predictor (site of thrombosis) has a corresponding score in the chart. The scores are added, resulting in a sum score, which corresponds to a probability according to a logistic transformation.

For the significant sites of thrombosis associated with mortality, the population attributable mortality (PAM) was also calculated and depicted. PAM is defined as the proportion of deaths occurring in the total study population (PNH patients with thrombosis) that can be explained by the risk factor (site of thrombosis). Assigned score corresponds to an *individual's probability to die* when a thrombosis at this specific site occurs. Instead, PAM refers to *the proportion of deaths in the whole study population that is attributed to the particular exposure* (specific site of thrombosis). Significance was set to 0.05. The STATA V8 (Stata Corporation, College Station, TX, USA) package was used for statistical analysis.

Data analysis

A summary of data is depicted in Table 1. Twenty-five percentage of thrombotic events have proven fatal; 20.5% involved more than one site (range: 2–5). Venous thromboses accounted for the majority, occurring mostly at unusual sites. Age at thrombosis was an independent predictor of death overall (RR, 1.04; 95% CI: 1.01–1.07, per 1-year increase). Eleven thrombotic episodes during pregnancy and the postpartum period were also identified, involving hepatic veins, CNS arteries and veins, cerebral sinus, pulmonary vasculature, portal vein, inferior vena cava, and deep veins. Three fatalities occurred.

Data analysis showed that for 15 patients treated with thrombolysis since 1985 for hepatic vein and/or inferior vena cava thrombosis, no deaths were reported. The risk of dying from hepatic vein thrombosis was eliminated after stratifying for thrombolysis treatment [RR 0 for thrombolysed vs. 2.76 (CI: 1.08–7.29), $P < 0.001$ test for homogeneity], which represents a significant reduction in overall risk [adjusted RR, 2.19 (CI: 0.96–4.96), $P = 0.05$ Mantel-Haenszel test].

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Table 1 Descriptive analysis of the sample (demographics, distribution of thrombosis and associated risks)

Outcome ($N = 339$)	*n*, %			
Death	86 (25.4)			
Survival	253 (74.6)			
	Mean ± SD	Range	RR (CI)	*P*-value
Age ($N = 163$)	34.5 ± 13.7	11–76	1.04 (1.01–1.07)	0.01
	n, %	Deaths		
Sex ($N = 161$)				
Male*	77 (47.8)	17	–	–
Female	84 (52.2)	14	0.69 (0.31–1.52)	ns
Year reported				
Before 1985*	51 (14.4)	18	–	–
1986–1995	107 (30.2)	28	0.64 (0.31–1.34)	ns
1996–2006	196 (55.7)	38	0.42 (0.21–0.83)	0.01
Site of event ($N = 363$)				
Venous events*			–	–
Hepatic veins	147 (40.7)	47		
Deep veins	54 (14.9)	1		
CNS veins	51 (14.0)	17		
Portal vein	37 (10.2)	7		
Pulmonary embolism	26 (7.2)	10		
Inferior vena cava	26 (7.2)	7		
Mesenteric veins	26 (7.2)	10		
CNS sinuses	25 (6.9)	9		
Splenic vein	21 (5.8)	3		
Renal vein	12 (3.3)	5		
Skin	2 (0.6)	–		
Arterial events			0.60 (0.29–1.22)	ns
CNS arteries	18 (4.9)	4		
Coronary arteries	12 (3.31)	7		
Hepatic artery	5 (1.4)	1		
Aorta	1 (0.3)	0		
Mesenteric arteries	2 (0.6)	0		

N, the sample size; *n*, the number of observations; %, proportion *n*/*N*; RR, relative risk; CI, confidence interval; ns, not significant.
*Indicates reference category to calculate RR.

Outcome of thrombosis has improved in the decades 1986–1995 (RR, 0.64; 95% CI: 0.31–1.34) and 1996–2006 (RR, 0.42; 95% CI: 0.21–0.83) compared with preceding years (before 1986), as a reflection of accumulated evidence in PNH pathogenesis, early recognition, better imaging techniques and proper management of thrombosis.

In site-adjusted multivariate analysis (Table 2), hepatic vein thrombosis (RR, 5.64; 95% CI: 2.26–14.02), pulmonary embolism (RR, 5.70; 95% CI: 1.70–19.11), mesenteric vein thrombosis (RR, 8.27; 95% CI: 2.50–27.41), and venous stroke (RR, 4.87; 95% CI: 1.79–13.30) were significant predictors of thrombosis-related mortality. Despite the relatively low incidence of arterial events, acute myocardial infarction (RR, 20.53; 95% CI: 4.42–95.28), and arterial CNS stroke (RR, 4.00; 95% CI: 1.07–14.93) were also high-risk events. Each patient can be stratified as low risk, intermediate risk and high risk by simply summing scores assigned to the sites of thrombosis (Table 3). Sum of scores corresponds to the calculated probability of death (Fig. 1). Therefore, high-risk patients are those suffering either a life-threatening thrombosis at a single site or thrombosis at multiple sites.

PAM in descending order was 23% for hepatic veins, 7% for CNS veins, 5% for mesenteric veins, 5% for myocardial infarction, 4% for pulmonary emboli, and $<1\%$ for CNS arteries.

Table 2 Multivariate logistic regression analysis [sites of thrombosis are the independent covariates and adjusted relative risks for death (RRs) are reported]

	β	RR	95% CI	*P*-value
Venous thrombosis				
Hepatic veins	1.73	5.64	2.26–14.02	<0.001
Deep veins	−1.64	0.19	0.03–1.61	ns
CNS veins	1.58	4.87	1.79–13.30	0.002
Portal vein	−0.12	0.88	0.29–2.67	ns
Pulmonary embolism	1.75	5.70	1.70–19.11	0.01
Inferior vena cava	−0.17	0.84	0.28–2.54	ns
Mesenteric veins	2.11	8.27	2.50–27.41	0.001
CNS sinus	0.82	2.28	0.77–6.75	ns
Splenic vein	−1.13	0.32	0.05–1.86	ns
Renal vein	0.58	1.79	0.32–10.14	ns
Arterial thrombosis				
Coronary arteries	3.02	20.53	4.42–95.28	<0.001
CNS arteries	1.38	4.00	1.07–14.93	0.04
Hepatic artery	1.24	3.46	0.33–36.89	ns

β, β coefficient of the independent variable; RR, relative risk; CI, confidence interval; ns, non-significant.
RR equals exp (β) in the logistic model.

Table 3 Score system to individualize probability of death, based on the sites of occlusion

Site	Score
Abdominal vessels	
Hepatic veins	2
Mesenteric veins	2
CNS vessels	
CNS arteries	1.5
CNS veins	1.5
Coronary arteries	3
Pulmonary embolism	2
Other sites	0

Sum 0 for low risk ($<10\%$), ≤ 2 for intermediate risk ($<30\%$), 3 for high-risk (50%), >3 for very high risk ($>50\%$).

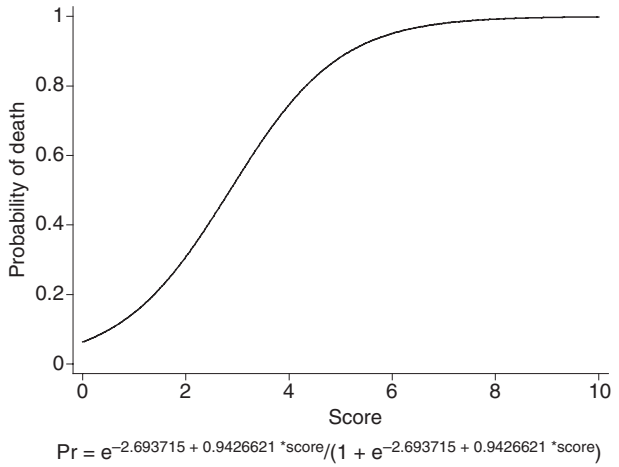

Fig. 1. Score model and predicted probabilities of death.

Depending on the site of thrombosis, interventional strategies may reduce associated mortality (Table 4). Overall, these approaches resulted in an *absolute* decrease of the risk of dying by 25% (risk difference, −0.25; CI: −0.37% to −0.13%).

Discussion

Hepatic vein thrombosis leading to Budd-Chiari syndrome (BCS) appears as the most frequent (40.7%) thrombotic complication of PNH, accounting for the majority of deaths (PAM 0.23). The aim of the therapeutic procedure includes prevention of the propagation of the clot, decompression of the congested liver and prevention of consequences of fluid retention and portal hypertension [5]. Anticoagulation alone is unlikely to restore the previous hepatic flow, thus invasive interventions have been proposed such as angioplasty of inferior vena cava and hepatic veins (occasionally accompanied by stent, which cannot be removed), transjugular intrahepatic portosystemic shunts (TIPS) (not feasible in many cases, high risk of occlusion) and surgical approaches including portocaval, splenorenal and mesocaval shunts (considered risky and cost extensive). Early intervention with thrombolytic therapy is warranted because hepatic venous outflow obstruction can be relieved with total recovery of the hepatic function. The initial success is $>80\%$ with long-term patency of 65%. While thrombolytic therapy is most helpful when initiated within 48–72 h, attempting this treatment may be worthwhile even in patients who have had symptoms for 2–3 weeks [6–9]. In contrast, the results of liver transplantation in PNH were not very good [10–12].

Cerebral vein and sinus thrombosis was the second most common type of thrombosis in this cohort, with superior sagittal sinus being the most frequently involved site. However, only cerebral vein thrombosis was associated with a significant risk of death.

Table 4 Summary of interventional therapies in PNH thrombosis

Therapies ($N = 162$)	*n* (%)	Clinical syndrome	Deaths	
Thrombolysis	17 (10.5)	Budd-Chiari (13) Abdominal pain (2) Ischemic bowel (1) Myocardial infarction (1)	1	
Anatomic shunts	17 (10.5)	Budd-Chiari (12) Abdominal pain (2) Ischemic bowel (1) Portal hypertension (1) Not reported (1)	1	
Angioplasty	10 (6.2)	Budd-Chiari (5) Myocardial infarction (2) Ischemic bowel (1) Stroke (1) Portal hypertension (1)	0	
Bone marrow transplantation	5 (3.1)	Budd-Chiari ± abdominal thrombosis (4) Deep vein (1)	0	
				Risk difference (CI)
Interventional therapies	44 (27.2)		2	−0.25 (−0.37 to −0.13)
Conventional therapies	118 (72.8)		27	

Thrombosis of the mesenteric venous tree appears as a high-risk site. It can initially affect the small peripheral mesenteric veins, inducing transient intestinal ischemia or limited intestinal infarction, and might account for the recurrent episodes of abdominal pain, fever, obstruction, and rectal bleeding.

Pulmonary embolism was not associated with deep venous thrombosis, and in a significant number of affected individuals it was incidentally detected at autopsy. *In situ* generation of thrombi in the pulmonary vasculature, rather than thrombi migration from other sites, is a hypothesis yet to be confirmed [13].

Arterial events occurred mostly in young patients (median age 35 years, range 22–47 for myocardial infarction, median 41.0 years, range 11–76 for stroke), supporting the hypothesis that thrombosis in PNH may occur *de novo* in arteries without significant predisposing atherosclerotic disease [14].

Pregnancy in patients suffering from PNH should not be recommended. There are both maternal and fetal risks when PNH complicates pregnancy. Supportive therapy is usually needed and venous thromboembolism during both pregnancy and postpartum periods is not a rarity, sometimes leading to a fatal outcome [15]. The maternal mortality may rise up to 20% and the perinatal mortality up to 10% [16]. In another series of pregnancies in patients with aplastic anemia [17], an uncomplicated course was possible in up to 50% but risks appear to be greater in those with low platelet counts and PNH.

Currently, anticoagulation therapy is the foundation for treating the thromboembolic complications of PNH. There is no proven benefit for primary prophylactic anticoagulation, with the exception of pregnancy, where an uncomplicated course is not the rule. Primary prophylaxis should also be considered in selected patients with large clones ($>50\%$), stable platelet counts $>100\,000\ \mu L^{-1}$ and no known contraindication for anticoagulation, as this approach minimizes the risk of thrombosis [2].

Despite improvement in understanding and managing thrombosis in PNH, one-quarter of patients succumb to this complication, and mortality largely depends on the site of occlusion. Bone marrow transplantation appears as the only potentially curative option for both PNH and associated thrombophilia, but the benefits are overwhelmed by the lack of suitable donors and high rates of treatment-related mortality [18]. Gene therapy remains a tantalizing possibility, although a greater understanding of the pathophysiology of PNH is required, as well as advances in gene therapy techniques, before such an approach can be seriously considered.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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