DOWNTOWN CAMPUS

UNIVERSITY CHILDREN'S HOSPITAL MUNICH / GERMANY
DR. VON HAUNERSCHES KINDERSPITAL
Director: Prof. Dr. Dr. Christoph Klein

Hämophiliezentrum München
Pädiatrie

The medical and economic burden of mild hemophilia in comparison to the severe type: long term data from a german single center

[3]Christoph Bidlingmaier, [1]Susanne Knorr, [2]Veit Grote, [1]Martin Olivieri, [1]Karin Kurnik
[1]Pediatric Hemophilia Centre, [2]Pediatric Epidemiology, University Children's Hospital Munich, Germany

Background: Mild hemophilia A (HA) is generally rated a milder bleeding disorder. However, delayed diagnosis and under treatment may lead to severe morbidity. Compared to severe hemophilia our knowledge on the actual medical and economic burden of mild hemophilia is still limited. Only recently, an increasing number of studies are published (e.g. den Uijl IE 2011; Tagliaferi 2012; Nilson 2012).

Methods: Data of 35 mild and 7 moderate patients with hemophilia diagnosed and continuously treated at our centre between 1985 and 2008 were retrospectively compared to 46 birth year matched severe patients (age: 1-24 years, median 13). Since no patients with mild HA suffered from an inhibitor, inhibitor patients were generally excluded.

Results: Mild HA was diagnosed later (mean 46.3 months, with known positive family history 14.1 mo) than moderate (16.9/8.7) or severe HA (11.7/3.7, p<0.001). *See Figure 1*

Reason for diagnosis was bleeding in 43% (mild), 57% (moderate) and 54% (severe) versus family history in 31%, 43% and 39% respectively. Despite a family history, 18% of mild PWH were only diagnosed after bleeding (moderate 14%, severe 9%). This indicates a lack of knowledge in both patient's families and pediatricians. *See Figure 2*

The first bleed occurred in mild HA at a median age of 46.3 mo (1-181 mo), moderate 16.9 (3-29) and severe 11.7 (1-54, p<0.001). Treatment of bleeds was delayed in patients with mild hemophilia (2.6 days) compared to severe type patients (1.4 d). 40 % (mild) vs. 71% (moderate) vs. 91% (severe) experienced joint bleeds, 6% vs. 43% vs. 50% suffered from arthropathy. *See Figures 3 and 4*

Factor usage per kg bodyweight (BW) and year increased with school age. In median, mild PWH used 296.8 U/kg BW/year (30-892.9, all treated on demand), moderate 1659.8 (77.3-4009.2) and severe 4053.6 (121.7-9219.2, 93% on prophylaxis). *See Figure 5*

Genetic mutations were found in 33% (mild), 86% (moderate) and 96% (severe) of patients. *See Table 1*

Discussion: Mild HA was diagnosed late, even though some patients had a positive family history. This, together with a delay in treatment, might be responsible for the encountered bleeds. Although mild hemophilia is generally rated as a "mild bleeding disorder", some of our patients encountered arthropathy even during early adolescence. The factor usage of some patients on demand is comparable to the usage of patients with severe hemophilia. For these individual patients, intensified treatment – i.e. prophylaxis – might be effective from both a medical and an economic view.

Conclusion: Better teaching of affected families and pediatricians could help to identify patients earlier. This would prevent more patients from being only diagnosed after the first bleeding. Further studies are needed to evaluate whether the treatment of mild HA should be intensified, since complications such as chronic arthropathy are possible.

FVIII Mutation	Mild Hemophilia (n=35)	Moderate Hemophilia (n=7)	Severe Hemophilia (n=46)
Missense	25	6	8
Stop			3
Splice	2		3
Insertion			3
Big deletion			4
Small deletion			2
Intron 22 Inversion			2
Unknown / nd	2 / 6	1	1 / 4

Table 1: Overview of the genetic findings

Further reading:
Clinical severity of haemophilia A: does the classification of the 1950s still stand?
Den Uijl IE, et al. *Haemophilia*. 2011 Nov;17(6):849-53.
The natural history of mild haemophilia: a 30-year single centre experience.
Tagliaferri A, et al. *Haemophilia*. 2012 Mar;18(2):166-74.
A qualitative study identifying the knowledge, attitudes and behaviours of young men with mild haemophilia.
Nilson J, et al. *Haemophilia*. 2012 May;18(3):e120-5.

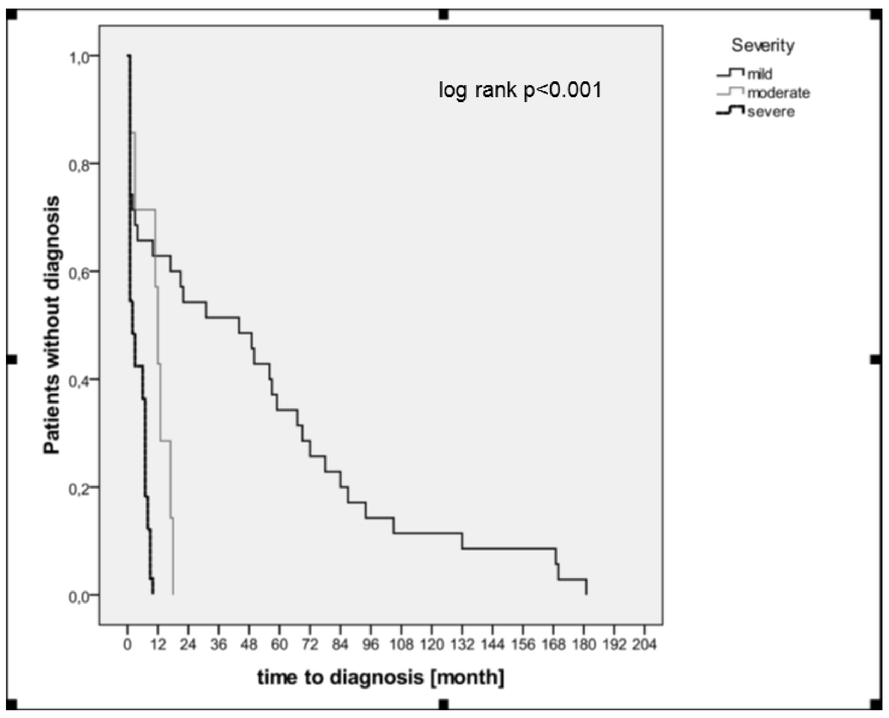

Fig 1: Time to diagnosis (in months of life)

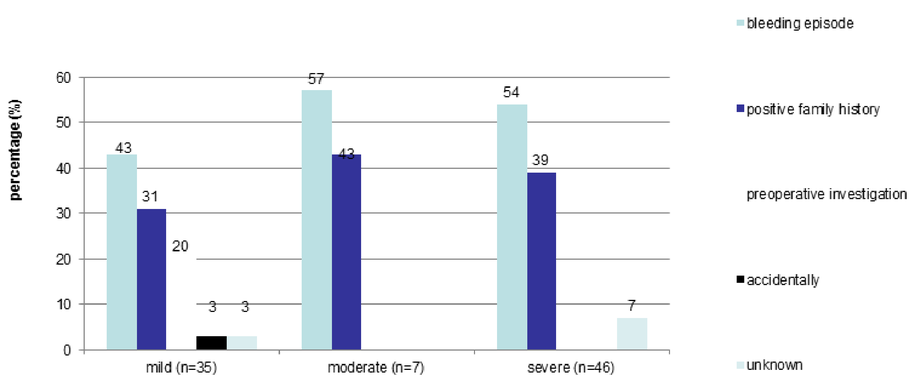

Fig 2: Reason for diagnosis

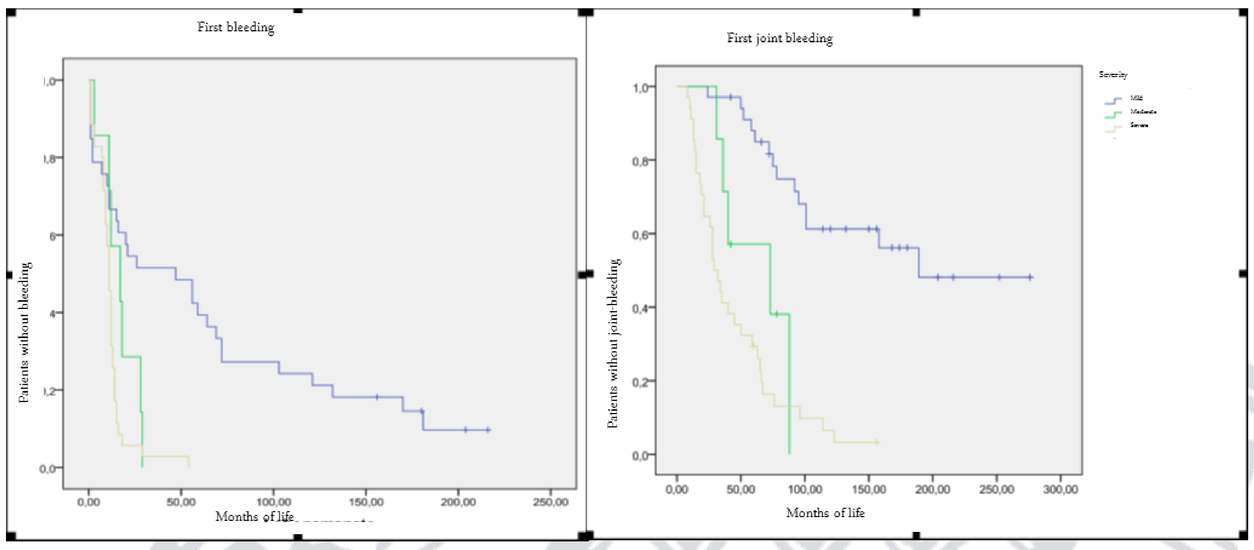

Fig 3 (left) and 4 (right): Time of the first bleed and time of the first joint bleed

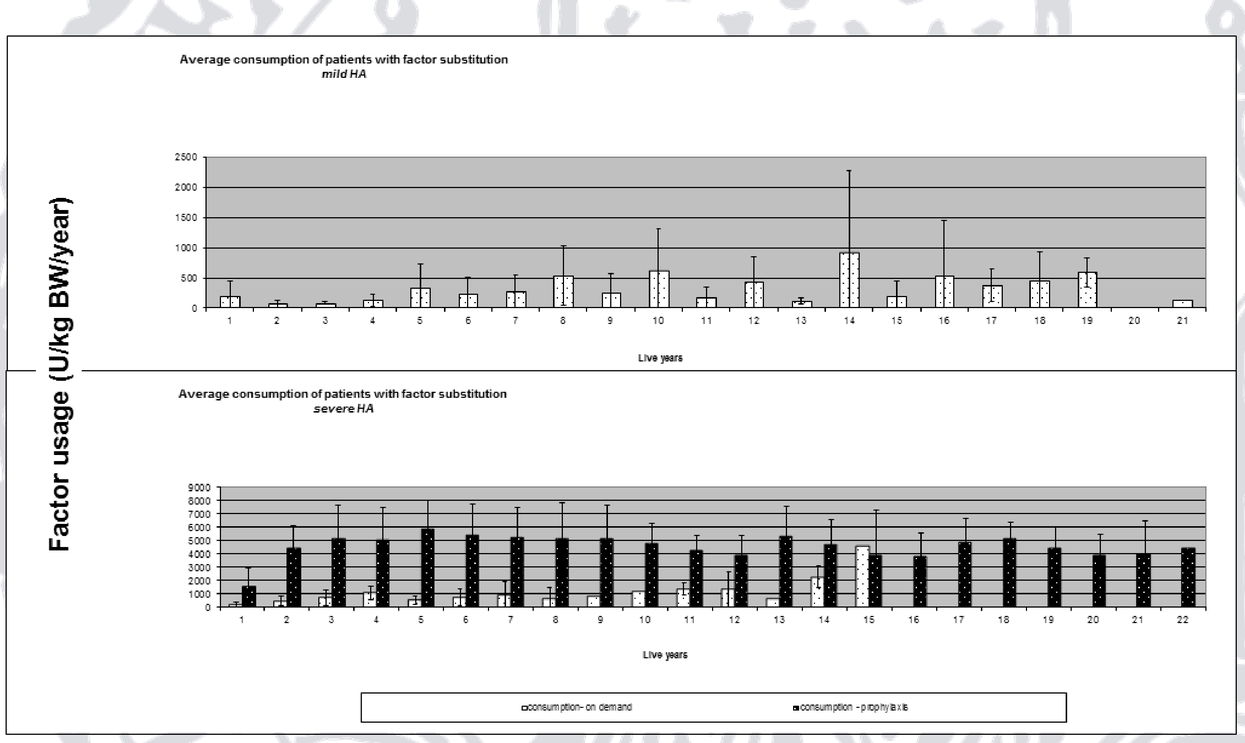

Fig 5: Factor usage per year and kg bodyweight for children and adolescents needing replacement therapy (upper panel: mild HA, lower panel: severe HA).

Email: christoph.bidlingmaier@med.uni-muenchen.de
Acknowledgement: Genetic analysis were carried out at the laboratories of Prof. Dr. Johannes Oldenburg, University of Bonn, Germany.

DOI: 10.3252/pso.eu.WFH2012.2012