Intracranial hemorrhage before start of prophylaxis in children with hemophilia: incidence, timing, and potential for prevention

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Abstract

Children with hemophilia have a significantly higher risk of intracranial hemorrhage (ICH) compared to the normal population. Prophylaxis reduces the risk of ICH and earlier initiation of prophylaxis may now be feasible, especially in hemophilia A (HA). The aim of the study is to explore the potential for preventing ICH by earlier start of prophylaxis by assessing the natural course of ICH before the initiation of prophylaxis and describe timing and incidence (*clinicaltrials gov. Identifier: NCT02979119*). In total, 2,727 children (2,275 with HA; 452 with hemophilia B [HB]) were included from the PedNet Registry, followed from 28 days until 36 months of life. ICH was observed in 61 children (incidence 2.2%; 10 per 1,000 patient years), with 75% of cases occurring before 1 year of age. Cumulative incidence was significantly lower in HB (0.9%) compared to HA (2.5%) and in non-severe HA (0.7%) compared to severe HA (3.5%). ICH occurred early, with a rise at 3 months, and a median age of 7.0 months in severe HA and 5.4 months in severe HB. In 40% of children, ICH occurred before the diagnosis of hemophilia was established, underscoring the importance of early diagnosis. Assuming that prophylaxis would have been started at the time of diagnosis and preventing all ICH in children with severe HA, the number needed to treat with prophylaxis would be 44 patients to prevent one ICH. Hopefully, prophylaxis options allowing initiation early in life, ideally before 3 months of age for children with severe HA, will reduce the incidence of ICH in the future.

Introduction

Children with hemophilia have a significantly increased risk of intracranial hemorrhage (ICH) compared to the normal population.[1] The consequences of ICH in children with hemophilia can be severe, ranging from acute neurological impairment to long-term developmental disabilities or even death.[2-4] Studies of children with hemophilia with ICH have reported mortality rates ranging from 2.5% to 30.4%.[5-8] Instrumental delivery by forceps or vacuum extraction significantly increases the odds of ICH more than 4-fold in neonates with hemophilia.[9-11] When compared with later childhood, neonates have the highest incidence of ICH, where mode of delivery, especially instrumental delivery, and prematurity have to be taken into account, followed by children up to 2 years of age.[4, 12] In a UK national cohort study the median age at presentation of ICH was 5 months for children with hemophilia and 91% of ICH occurred <2 years of age.[10] ICH can occur after trauma or spontaneously, especially in patients with severe hemophilia. In a recent meta-analysis, ICH was classified as spontaneous in 35-58% of patients with hemophilia.[8]

Prophylactic replacement therapy with factor concentrates has not only significantly reduced the occurrence of joint bleeds, but also the incidence of ICH, especially in severe hemophilia A (HA).[13,14] Prophylaxis with factor concentrates has become the standard of care for severe and moderate HA and hemophilia B (HB) patients and has been started earlier over the past decades in many countries with access to these therapies.[15] However, starting earlier than around 1 year of age remains challenging, mostly due to difficulties with regular intravenous access, the risk of development of inhibitors and adherence.[16-18] In recent years, new treatment options with non-replacement therapies have emerged. Emicizumab, a bispecific antibody administered subcutaneously every 1-4 weeks is licensed for all ages and available in many countries. Prophylaxis with emicizumab can be initiated very early in life in children with HA.[19,20]

The PedNet (Pediatric Network on Hemophilia Management) Registry collects prospective data on children with HA or HB born since January 1, 2000, in 32 hemophilia centers in 19 countries. Children are followed prospectively from birth until 18 years of age and data are collected at least annually including data on start of prophylaxis, treatment details and major bleeds such as ICH.[21]

The aim of this study is to assess the incidence of ICH in children with hemophilia after the neonatal period before the initiation of prophylaxis in the PedNet Registry to explore the potential of preventing ICH by earlier start of prophylaxis.

Methods

Study group

Data were retrieved from the 'PedNet Registry', which is owned and administered by the 'PedNet Hemophilia Research Foundation', consisting of 32 international hemophilia treatment centers, and registered at *clinicaltrials gov. Identifier: NCT02979119*. The PedNet Registry includes all consecutive patients diagnosed and treated in each center born after January 1, 2000. Patient data are collected prospectively from birth onwards and detailed information is collected on the first 50 exposure days of treatment with factor concentrate; thereafter at least annually. All major bleeds, including ICH are recorded with detailed information. Approval for data collection was obtained from the Institutional Ethics Boards of each of the participating center, and written informed consent was obtained from the parents or guardians of all participants in accordance with the Declaration of Helsinki. The data quality in the PedNet Registry is monitored regularly and independent audits are carried out in all participating centers. A list of all contributors is found in the *Online Supplementary Appendix*.

Inclusion criteria

Children included in the Registry by January 1, 2023 with HA and HB were enrolled following the inclusion criteria of the PedNet protocol (available at www.pednet.eu).

To describe the natural course of ICH before the start of prophylaxis, data was extracted on each patient from 28 days of life until start of prophylaxis or until occurrence of ICH or until 36 months of age. Children with ICH occurring before 28 days of life were excluded from this analysis to exclude birth related bleeding such as instrumental delivery and prematurity.

Definitions

Hemophilia severity was defined as severe with a factor VIII/IX activity less than 0.01 IU/dL, moderate with a factor VIII/IX activity of 0.01-0.05 IU/dL, and mild with a factor VIII/IX activity of 0.06-0.25 IU/dL. Start of prophylaxis was defined as a minimum of one factor injection per week for standard half-life factor VIII and IX concentrates and for extended half-life FVIII concentrates over a period of 2 months. For HB, prophylaxis with extended half-life FIX concentrates was defined as a minimum of one injection per 2 weeks over a period of at least 2 months. For emicizumab, the first injection was counted as start of prophylaxis. The primary outcome was ICH requiring treatment with factor concentrate as reported and confirmed by the investigator of each center. Events when patients were treated preventively with factor concentrate after a head injury without evidence for ICH were not considered as ICH in this analysis.

Data collection

Data was collected on type of hemophilia, severity, sex, date of hemophilia diagnosis, ICH including information on whether traumatic or spontaneous, whether neurosurgery needed and start of prophylaxis.

Statistical analysis

Patient characteristics are presented as medians and P25-P75 percentiles (interquartile range [IQR]). Statistical comparisons between different groups were made using χ^2 test or Fisher´s exact test at a significance level of 0.05. Kaplan-Meier survival curves were used for analyzing time until ICH with log rank tests for comparison of subgroups. Statistical power was shown by the width and magnitude of the 95% confidence interval (95% CI). All analyses were performed using IBM SPSS Statistics for Windows, Version 29.0.0.0 Armonk, NY: IBM Corp., NY, USA. Numbers needed to treat (NNT) was calculated by the formula NNT=1/absolute risk reduction, assuming that prophylaxis could prevent all ICH.

Results

Cohort demography

In total, 2,727 patients were included in this study: 2,275 with HA (83.4%) and 452 HB (16.6%), the observation covering a total of 5,629 patient years. Regarding severity and details of the cohort demography, see Table 1. The cohort included 23 girls, including four with severe hemophilia and four with moderate hemophilia. Median age at diagnosis of hemophilia was 3.9 months (IQR, 0.0-9.8) for severe HA and 4.2 months (IQR, 0.0-9.8) for severe HB. Diagnosis was delayed in mild HA and HB (Table 1). Patients were analyzed until start of prophylaxis with factor concentrate or emicizumab or occurrence of ICH or reaching 36 months of life; 121, 4.4% of the cohort, did not reach the end of follow-up. The median follow-up time was at 13.0 months (IQR, 9.4-18.9) in HA and 14.4 months (IQR, 9.5-19.3) in HB.

Intracranial hemorrhages

In the total cohort of 2,727 children, 61 ICH occurred, resulting in a cumulative incidence of 2.2% (95% CI: 1.7-2.8), and incidence rate of 10 ICH per 1,000 patient years (95% CI: 8-14), see Table 2. Of the 61 patients with ICH, 51 had severe HA, four had severe HB, three had moderate HA and three mild HA (Table 2). ICH was not observed in moderate or mild HB. The incidence for ICH in severe hemophilia, 23 per 1,000 patient years, was significantly higher compared to non-severe patients, 1.8 per 1,000 patient years (P<0.00001).

HA had a significantly higher incidence rates of ICH than HB: 12 *versus* four per 1,000 patient years (P=0.018). Incidence rates for ICH followed the severity of hemophilia: 24 for severe HA and 11 for severe HB, four for moderate HA and two per 1,000 patient years for mild HA (Table 2). One of the three girls with severe HA had an ICH.

The cause of ICH for severe HA was traumatic in 19 children (37.2%), spontaneous in 17 (33.3%) children and unknown in 15 cases (29.4%). The distribution of causes was about similar between patients with or without established diagnosis of hemophilia. Three ICH occurred in the moderate HA group: one in a patient with a FVIII activity level of 1 IU/dL (traumatic, at age 4 months), one in a patient with a FVIII activity level of 2 IU/dL (traumatic, at age 5 months) and one in a patient with FVIII activity level of 3 IU/dL (spontaneous, at age 30 months), respectively. Three children in the mild HA group had ICH secondary to trauma. Two of these children were diagnosed with HA only at the time of ICH, at age 7 and 11 months and FVIII activity 6 and 15 IU/dL, respectively.

In severe HB, the diagnosis of hemophilia was made at the time of presentation with ICH in three of four ICH. Two of four ICH were due to trauma (Table 2). No spontaneous ICH were reported in children with HB or in children with mild HA.

Neurosurgical intervention was required in 23 of 61 patients (37.7%) with ICH, 22 with severe hemophilia (22/51; 43.1%)

Table 1. Demographics of the study cohort.

Hemophilia	Severity	Number of patients (female)	Age at diagnosis in months, median (IQR)	Follow-up time in months, median (IQR)	Patient years
A	all severe moderate mild	2,275 (15) 1,466 (3) 292 (2) 517 (10)	4.5 (0.0-12.0) 3.9 (0.0-9.8) 3.4 (0.0-17.7) 7.0 (0.1-32.7)	13.0 (9.4-18.9) 12.8 (9.4–18.5) 16.1 (10.9-21.6) 31.3 (14.7-32.9)	4,613 2,382 756 1,475
B	all severe moderate mild	452 (8) 214 (1) 116 (2) 122 (5)	4.3 (0.0-13.9) 4.2 (0.0-9.8) 0.6 (0.0 – 15.4) 10.5 (0.1-39.2)	14.4 (9.5-19.3) 14.4 (9.6-18.8) 14.2 (9.4-24.7) -*	1,016 357 302 357
Total	-	2,727 (23)	4.4 (0.0-12.2)	13.2 (9.4-19.0)	5,629

Follow-up time is shown as median and interquartile range (IQR) in months for patients in the study (from 28 days of age until start of prophylaxis), patient years in years. *Indicates that numbers are too low for analysis; only 2 mild HB patients on prophylaxis

and only one with moderate hemophilia (1/3; 33.3%). No data on neurological sequelae was collected for this study.

Timing of intracranial hemorrhage in relation to age

Only one ICH was observed before the age of 3 months, at the age of 1.2 months (observation time starting from 28 days of life). By 6 months of age, 37% (21/57) of ICH had occurred in HA and 50% (2/4) of HB and by 12 months 79% (45/57) of ICH had occurred in HA and 75% (3/4) of ICH in HB (including both patients diagnosed with hemophilia and undiagnosed patients), see Table 3. The median age at the time of ICH was 7.0 months (IQR, 4.4-11.1) for severe HA and 5.4 months (IQR, 4.0-12.8) for severe HB. Figures 1 and 2A, B show the timing of ICH for all patients - severe and non-severe for all hemophilia (Figure 1) and separately for HA (Figure 2A) and HB (Figure 2B). Similar timing of ICH was observed in all three categories of ICH cause - traumatic, spontaneous, and unknown without any significant difference in timing (*data not shown*).

Timing of intracranial hemorrhage in relation to diagnosis of hemophilia

In 25 of 61 ICH (40.9%), ICH occurred before the diagnosis of hemophilia was made, in most cases ICH was the reason for diagnosis. Inversely, 36 of 61 ICH (59.1%) occurred in children whose diagnosis of hemophilia was already established, 33 in children with severe HA. Children without a diagnosis of hemophilia had ICH at an earlier age compared to children with an established diagnosis (*P* value 0.021 in log rank, see also *Online Supplementary Figure S1* in the *Online Supplementary Appendix* for illustration). Table 3 shows, for children with and without an established hemophilia diagnosis at time of ICH, the cumulative proportion of ICH per 3 months age periods.

Table 2. Frequencies of intracranial hemorrhage before initiation of prophylaxis by hemophilia type and severity.

Hemophilia	Severity, N	ICH, N	Cause: traumatic/ spontaneous/ unknown, N	Cumulative incidence % (95% CI)	Incidence rate per 1,000 patient years (95% CI)
A	all, 2,275 severe, 1,466 moderate, 292 mild, 517	57 51 3 3	24/18/15 19/17/15 2/1/0 3/0/0	2.5 (1.9-3.1) 3.5 (2.5-4.4) 1.0 (0-2.2) 0.6 (0-1.2)	12 (9-16) 24 (16-27) 4 (0-8) 2 (0-4)
B	all, 452 severe, 214 moderate, 116 mild, 122	4 4 0 0	2/0/2 2/0/2 - -	0.9 (0-1.7) 1.9 (0.1-3.7) 0 0	4 (0-8) 11 (0-22) - -
Total	2,727	61	26/18/17	2.2 (1.7-2.8)	10 (8-14)

CI: confidence interval; ICH: intracranial hemorrhage.

Table 3. Cumulative proportion of total intracranial hemorrhage occurrence by age, separate for patients with and without established hemophilia diagnosis and by hemophilia type.

Age in months	HA: ICH without established hemophilia diagnosis % (N/N)	HA: ICH with established hemophilia diagnosis % (N/N)	HA total % (N/N)	HB: ICH without established hemophilia diagnosis, % (N/N)	HB: ICH with established hemophilia diagnosis,% (N/N)	HB total % (N/N)
3	0 (0/22)	2.9 (1/35)	1.8 (1/57)	0 (0/3)	0 (0/1)	0 (0/4)
6	45.5 (10/22)	31.4 (11/35)	36.8 (21/57)	66.6 (2/3)	0 (0/1)	50 (2/4)
9	81.8 (18/22)	57.1 (20/35)	66.7 (38/57)	66.6 (2/3)	100 (1/1)	75 (3/4)
12	95.4 (21/22)	68.6 (24/35)	78.9 (45/57)	66.6 (2/3)	100 (1/1)	75 (3/4)
15	100 (22/22)	74.3 (26/35)	84.2 (48/57)	66.6 (2/3)	100 (1/1)	75 (3/4)
18	100 (22/22)	82.9 (29/35)	89.5 (51/57)	100 (3/3)	100 (1/1)	100 (4/4)
36	100 (22/22)	100 (35/35)	100 (57/57)	100 (3/3)	100 (1/1)	100 (4/4)

HA: hemophilia A; HB: hemophilia B; ICH: intracranial hemorrhage.

In children with an established diagnosis of hemophilia before occurrence of ICH, 31% of ICH had occurred by 6 months of age, thus the remaining 69% could potentially have been prevented by starting all children on prophylaxis by 6 months. By 12 months of age, 69% of ICH had occurred, etc. For further illustration, see also *Online Supplementary Figure S1*.

Discussion

This prospective multicenter study, which included 2,727 children observed for 5,629 patient years with HA and HB from 32 hemophilia centers without prophylaxis, shows that ICH in hemophilia after the neonatal period occurs early from the age of 1 month with an increase at 3 months of age. The cumulative incidence for ICH was 2.2 % for the whole cohort and, as expected, was higher for severe hemophilia patients than for non-severe hemophilia patients. Also, the incidence of ICH was higher for HA (2.5%) than HB (0.9%). One of 23 girls was diagnosed with an ICH. In the children with an established diagnosis of hemophilia before ICH (N=36; 59.1%) and in whom ICH could potentially be prevented, 31% of ICH had already occurred by 6 months of age and 69% by 12 months of age. No ICH was reported in moderate and mild HB.

The cumulative incidence of 2.2 % for ICH and incidence rate of 10 ICH per 1,000 patient years for the whole cohort, 2.5%, 12 per 1,000 patient years for HA and 0.9%, 4 per 1,000 patient years for HB is in line with other studies: a review noted that ICH affects between 3% to 10% of all hemophilia patients.[1] In a UK national study, in a cohort from birth until 16 years of age and including patients on prophylaxis, an incidence of 6.4 per 1,000 patient years (95% CI: 4.8-8.6) for HA and 4.2 per 1,000 patient years (95% CI: 1.9-9.5) for HB was found.[10] Our cohort displays the natural course of ICH in young children below 36 months of age. This is in line with several studies, showing a relatively high occurrence of ICH in young children with hemophilia: a US study showed that children in the youngest age group (2-9 years) exhibited the highest odds ratio of 1.92 for the occurrence of ICH[14] and in addition, an Italian study observed the highest risk of ICH during the first 2 years of life, but also later during adulthood.[7] The incidence of ICH was significantly higher for HA than HB. This is in accordance with other studies reporting a tendency for a difference in ICH incidence between HA and HB.[10] It has been discussed whether patients with severe HB probably have a generally less severe clinical phenotype than severe HA patients with e.g., less joint replacement by arthroplasty.[22,23] Future studies with a focus on the differences between HA and HB need to be done to further explore this topic.

Prophylaxis is known to reduce the incidence of ICH[13,14] and should ideally start as early as possible. Some of the barriers for the start of prophylaxis such as the need for intravenous access have now been addressed: for patients with HA, emicizumab can be started early. The pivotal study in neonates and infants (HAVEN 7) is still ongoing, but the recently reported primary analysis show promising results in this patient group, with no ICH reported, however, in a very limited number of 52 patients with a 95% CI: 0-5.6%

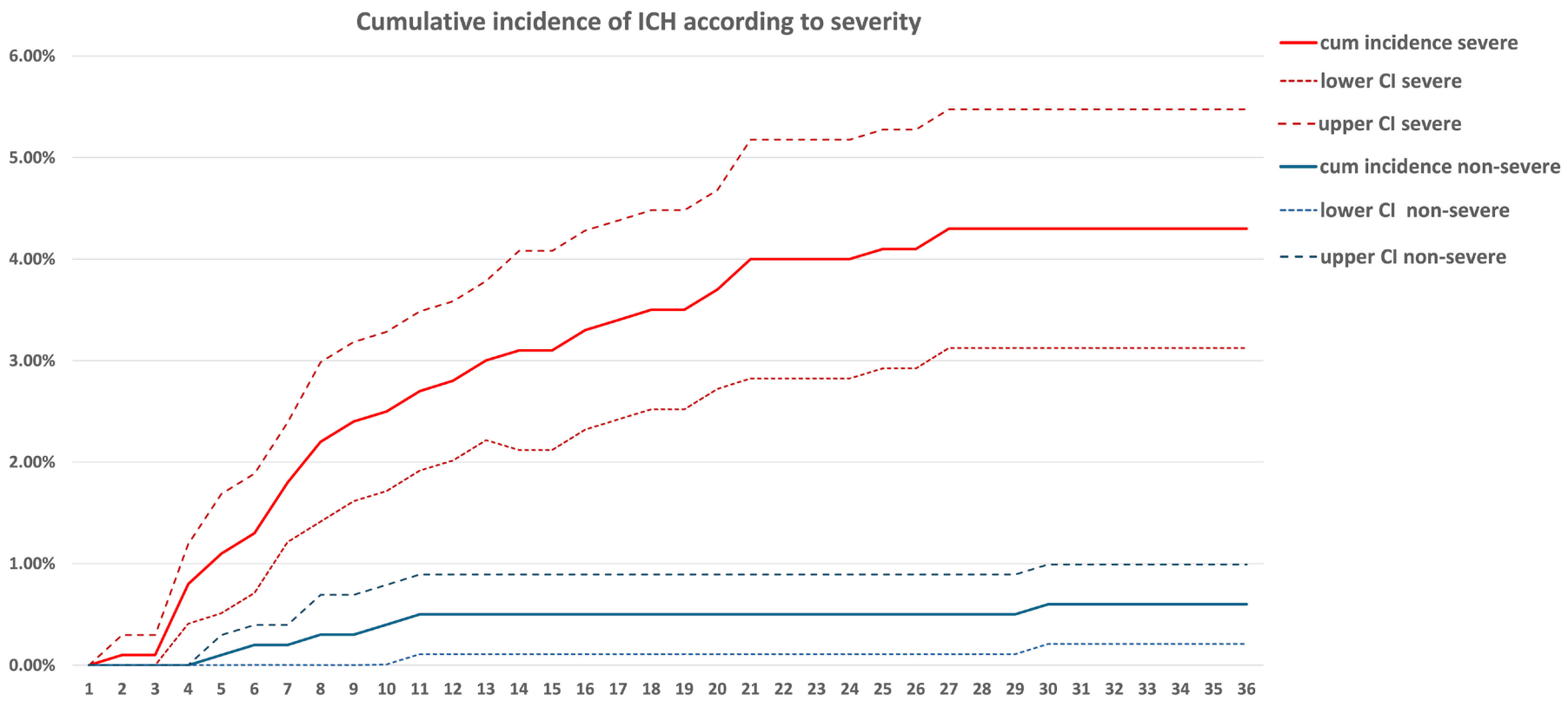
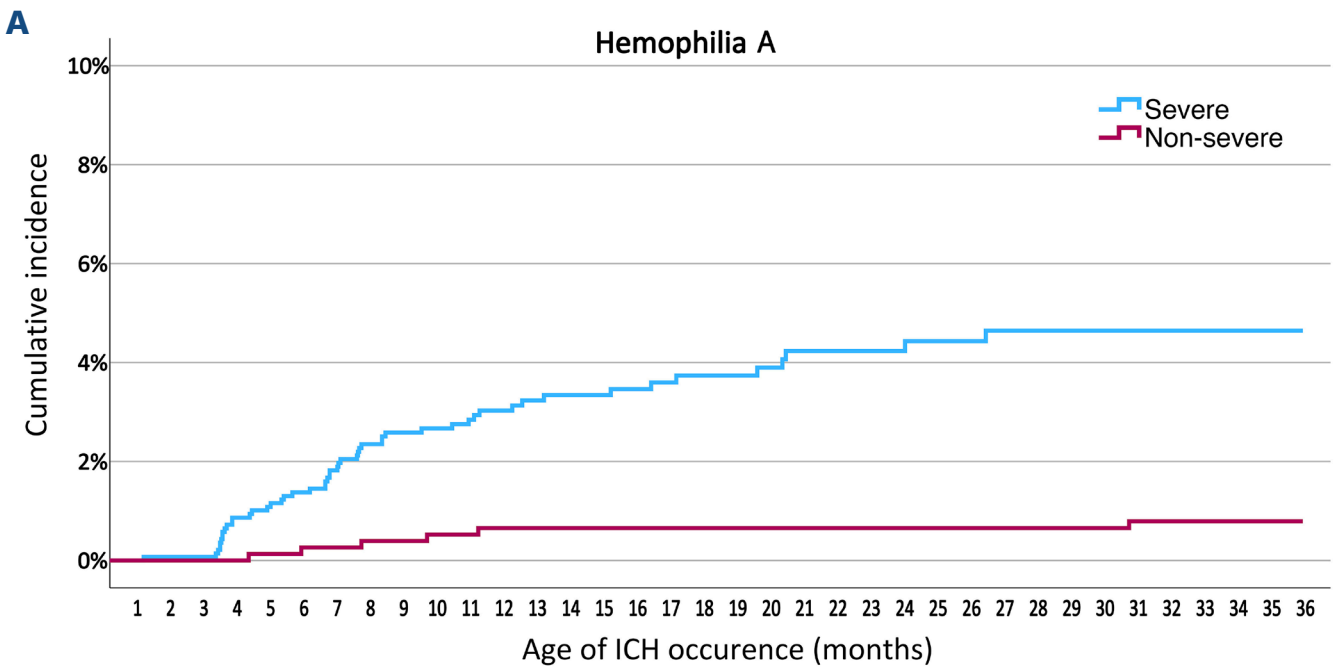


Figure 1. Natural course of intracranial hemorrhage: children with severe and non-severe hemophilia A and B before initiation of prophylaxis. Cumulative incidence (cum incidence) of intracranial hemorrhage (ICH) in children with hemophilia before initiation of prophylaxis by severity with 95% confidence interval (CI) month by month.



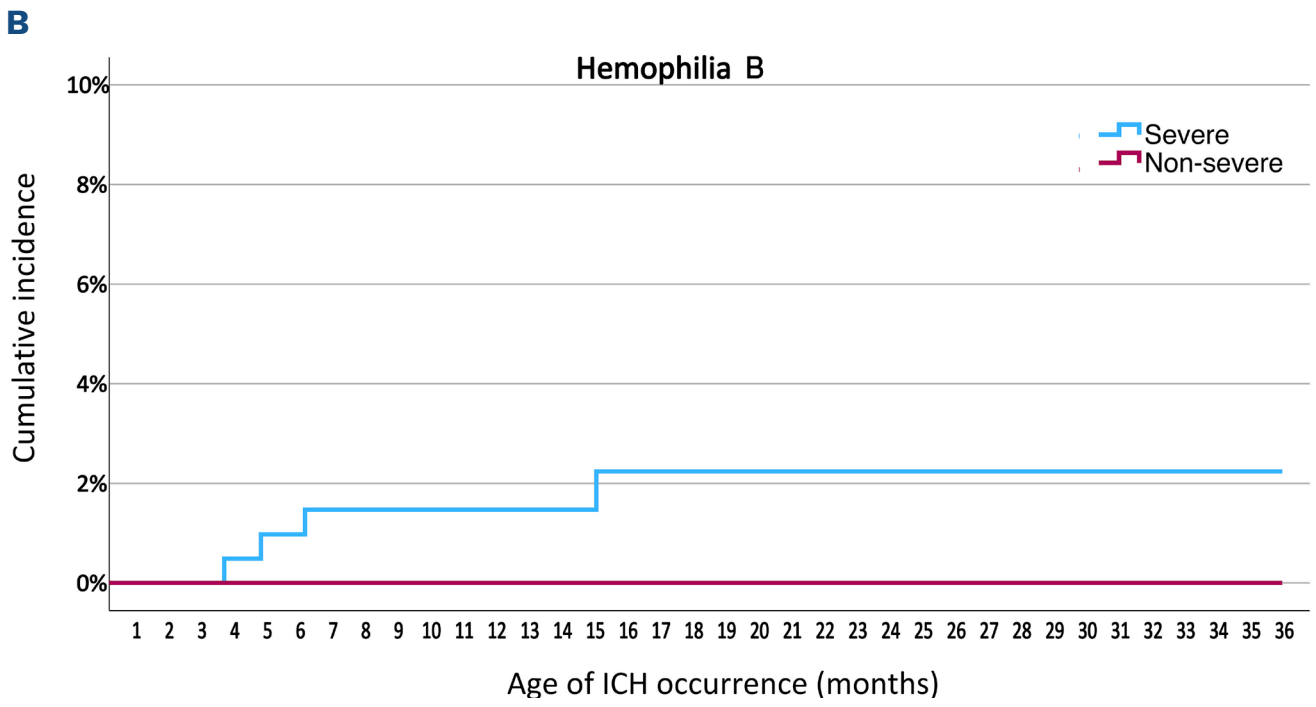


Figure 2. Natural course of intracranial hemorrhage in hemophilia A and B. (A) Cumulative incidence of intracranial hemorrhage (ICH) in children with hemophilia A before initiation of prophylaxis by severity month by month; including all patients, with and without established diagnosis of hemophilia at the time of ICH. (B) Cumulative incidence of ICH in children with hemophilia B before initiation of prophylaxis by severity month by month; including all patients, with and without established diagnosis of hemophilia at the time of ICH.

for ICH incidence.[20] Given the relatively low incidence of ICH, further evaluation is required in a larger number of patients to assess the effect of emicizumab prophylaxis on ICH incidence. In addition, other non-replacement therapies such as fitusiran[24,5] or concizumab[26,27] could also be started early and could also be used in HB, which lack alternatives to CFC in young children, but these products are still under investigation in clinical trials. More research is needed to determine if these products are suitable in neonates and infants. Earlier prophylaxis for patients with HA could also be possible with a new extended half-life FVIII concentrate, EHL rFVIII-Fc-VWD-EXTEN, which has reached the market due to its longer half-life and 1-week injection intervals,[28,29] avoiding the need for central venous devices.

However, only patients diagnosed with hemophilia can be started on prophylaxis, emphasizing the importance of early diagnosis for both, boys and girls. As recommended in the WFH hemophilia guidelines, the training and educating of both medical staff and families with hemophilia is of high importance.[30] In families with a known family history of hemophilia, carriers should get diagnosed and when pregnant, prenatal or early postnatal diagnosis can be made. In our study, approximately 40% of patients did not have an established diagnosis of hemophilia at the time of ICH and in this group, ICH occurred earlier and was frequently the reason for the diagnosis of hemophilia. In these cases, unexpected bleeding and/or a prolonged activated partial thromboplastin time (aPTT) are the most typical indicators of suspected hemophilia and their immediate diagnosis is crucial to offer the best treatment in children with ICH.[31] To improve diagnosis even more in this group and due to advances in genomic sequencing, some countries have projects to implement screening for hemophilia into newborn screening, e.g., “The Generation Study” in the UK (https://www.genomicsengland.co.uk/initiatives/newborns).[32] This possibility for an early diagnosis of hemophilia would most likely have an impact on the timing of prophylaxis initiation and with that on the prevention of early bleeding in the hemophilia population.[33] However, in our study, the majority of 60% of ICH occurred when the diagnosis of hemophilia was already established

and could potentially be prevented by an immediate start of prophylaxis. In this study,[33] ICH occurred in 1,466 children after the diagnosis of severe HA was made, resulting in an incidence of 2.2%. If we assume that prophylaxis started immediately in children with severe HA at the time of diagnosis would lower the incidence of ICH to 0%, the number needed to treat with prophylaxis would be 44 patients to prevent one ICH; traumatic ICH is included in this calculation. Prevention of all traumatic ICH in children on prophylaxis with e.g., emicizumab may not be possible and the number needed to treat could be higher.

Strengths of our study are the large population, multicenter design, and longitudinal follow-up of an unselected cohort. One of the limitations was the challenge in obtaining information on the cause of ICH (spontaneous or traumatic), due to unclear patient histories. Moreover, 4.4% (121 patients) did not reach the end of follow-up, defined as occurrence of ICH, start of prophylaxis, or age of 36 months. Also, data was collected over the past two decades with changes in treatment recommendations during that period. Treatment was started significantly earlier in the PedNet registry during the last decade,[15] which may have resulted in a shorter period at risk for ICH for these patients over time.

Twenty-three girls with hemophilia were included. Girls with hemophilia are likely to be underreported in most studies. However, our study included several girls with severe hemophilia with one girl experiencing an ICH. In accordance with the principles of care, woman and girls who are carriers of hemophilia should be offered factor level analysis and if fulfilling the criteria for hemophilia, should be followed and treated as per hemophilia guidelines by EAHAD and WFH.[30,34]

In this large multicenter study of children with hemophilia, we observed the majority of ICH in severe HA (51/61; incidence 3.5%), while non-severe hemophilia and HB showed significantly lower frequencies of ICH. ICH after the neonatal period occurs early, with a clear increase at 3 months of age and around 75% of cases occurring before the age of 12 months. Approximately 40% of ICH occurred in patients before the diagnosis of hemophilia was made, underscoring the importance of early diagnosis. The majority of 60% of ICH occurred after an established diagnosis of hemophilia and could potentially have been prevented by an immediate start of prophylaxis. Hopefully, prophylaxis options allowing initiation early, ideally before 3 months of age in severe HA, will change the incidence of ICH in children in the future.

Disclosures

NGA has served as a speaker for lectures, educational courses and/or on advisory boards for CSL Behring, Octapharma and Sobi/Sanofi; and received grants/research support to the institution from NovoNordisk and Sanofi. GC has served as a speaker for lectures, presentations, speakers' bureau, or educational events for Bayer, Bioviiix, CSL Behring, Biomarin, Sanofi, Novo Nordisk, Takeda, LFB, Roche and SOBI; and participated on a data safety monitoring board or advisory board for Bayer, CSL Behring, Biomarin, Sanofi, Novo Nordisk, Takeda, LFB and Roche. RdO has received grants or funding outside this study from Shire/Takeda, Biomarin, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche, Sobi/Sanofi, Spark and UniQure; served as a speaker and/or on advisory boards for Shire/Takeda, Biomarin, CSL Behring, LFB, NovoNordisk, Octapharma, Pfizer, Roche, Sobi/Sanofi, Spark and UniQure. GK discloses grant/research support or funding outside this study for BSF, Pfizer, Roche, Tel Aviv University and Sheba research authorities; consulting fees from ASC therapeutics, Bayer, Biomarin, Novo Nordisk, Pfizer, Roche, Sobi, Sanofi- Genzyme, Takeda, UniQure outside this study; and participation on a data safety monitoring board or advisory board for ASC therapeutics, BioMarine, Pfizer, Novonordisk, Uniquore, Roche, Sanofi- Genzyme, Sobi, Spark; is a director for PedNet. CK's institution has received funds for research or clinical trials from Bayer, Biotest, CSL Behring, Intersero, Novo Nordisk, Pfizer, Roche/Chugai, Sobi/Sanofi, Takeda, EU H2020 ITN; and he has served as an advisor or speaker for BFSH, Bayer, Biotest, CSL Behring, MSD, Novo Nordisk, Roche/Chugai, Sobi/Sanofi, Takeda. CM received research support/grants to institution outside the submitted work from Bayer, Biotest, CSL Behring, Novo Nordisk, Swedish Orphan Biovitrum, Takeda; discloses personal honoraria/travel support from Bayer, Biomarin, Biotest, Bioproducts Laboratory, CSL Behring, LFB, Novo Nordisk, Pfizer, Roche, Swedish Orphan Biovitrum and Takeda. BN has received support for pharmaceutical studies of IMP from Roche, Takeda, Sanofi, Sobi and Novo Nordisk; and served at an advisory board for Sobi (fee paid to institution). MO has received grants/research support from Bayer, Biomarin, Biotest, Takeda, CSL Behring Octapharma, Pfizer, Shire, Roche, Stago and Swedish Orphan Biovitrium; discloses consultancy and speaker fees from Bayer, BioMarin, Biotest, Novo Nordisk, Takeda, CSL Behring, Pfizer, Roche and Swedish Orphan Biovitrium. FP has received financial support from Roche for participating in advisory board and for attending meeting. EZ has served as a consultant, honoraria for lectures or advisory boards for NovoNordisk, Roche, Sobi and Takeda; has received a grant from MH CZ - DRO, Motol University Hospital, Prague, Czech Republic 00064203. KF has acted as a consultant and participated in expert groups for Bayer, Biogen, CSL Behring, NovoNordisk, and SOBI; has received research grants from Bayer, NovoNordisk and Pfizer; has given invited educational lectures for Bayer, NovoNordisk, and Pfizer; and has received travel support from Sobi and Bayer. All fees were paid to the institution. All other authors have no conflicts of interest to disclose.

Contributions

NGA, KF and MdK are responsible for the concept and design of the study. All authors participated in the analysis and

interpretation of data; drafting, writing and/or revising of the manuscript. Each author listed on the title page of the manuscript has approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Contributors belonging to the PedNet Study Group are listed as collaborative group "PedNet Group" in the online submission and as Online Supplementary Table S1 in the Online Supplementary Appendix.

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Data-sharing statement
All data used in this study are from the PedNet Registry, which is governed by the non-profit-making organization PedNet Hemophilia Research Foundation. The data that support the findings of this study are available from the Registry of the PedNet Hemophilia Research Foundation. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the PedNet Registry Foundation (www.pednet.eu).

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