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Impact of Family History of Haemophilia on Diagnosis, Management and Outcomes in Severe Haemophilia

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ABSTRACT

Introduction: Patients with severe haemophilia A (HA) with no family history of haemophilia will be diagnosed upon their first bleeding event.

Methods: Herein, we studied the effects of lack of family history in HA and the subsequent delay of diagnosis on bleeding pattern and early treatment, as well as on the risk of inhibitor development. For this purpose, data on 1237 severe HA patients with known family history ("positive" or "negative"), born between 2000 and 2022, were collected in 29 participating centres.

Results: At diagnosis, 45.9% (554/1208) of patients had a positive family history of HA and 54.1% (654/1208) had a negative family history. A positive family history significantly shortened the time to diagnosis (8 months) and the treatment initiation (2 months). Prophylaxis was more frequently the first treatment in those with a positive family history compared to the negative family history group (21% vs. 13%). Bleeding was the main reason for first exposure day (ED) in both groups, but less frequently in the family history group than in those without a family history (67% vs. 80%). Positive family history was associated with fewer peak treatments at first five EDs (12% vs. 16%). In non-inhibitor patients, bleeding occurred earlier in those with positive family history (9.2 months vs. 10.6 months). The inhibitor incidence was similar in both groups (33% vs. 30%), and a positive family history was associated with earlier inhibitor development (13 months vs. 15 months).

Conclusion: The majority of patients presented without a family history of HA which led to a delayed diagnosis and treatment initiation.

1 | Introduction

1.1 | Haemophilia Is an X-linked Recessive Disorder. The Diagnosis of Severe Haemophilia

Haemophilia A (HA) is typically based on family history or the presence of bleeding symptoms. Delayed diagnosis may affect early treatment patterns and the subsequent risk of developing neutralizing factor VIII (FVIII) antibodies. Such antibodies (i.e., inhibitors) develop in approximately 20%–35% of patients with severe HA, usually during the first 50 exposure days (EDs) to FVIII [1–3]. Until recently, the presence of inhibitors complicated the management of bleeds, resulting in increased morbidity and mortality, and induced higher therapy costs due to the use of expensive bypassing agents and immune tolerance induction [4, 5]. Several new therapies have been incorporated to the haemophilia treatment, such as emicizumab, with the ability of rebalancing haemostasis with no need for FVIII replacement. In the era of new treatments, the prophylaxis landscape in patients with inhibitors has changed [6–8]; nevertheless, when bleeding occurs in these cases FVIII replacement is still necessary. Therefore, in these cases, the risk of developing inhibitors remains relevant.

Recently, significant progress has been made in our understanding of the mechanisms that lead to inhibitor formation. Genetic as well as environmental factors have been identified to play decisive roles [9, 10]. The genetic factors include the factor eight (*F8*) gene variants, MHC Class II genotypes, certain immune response gene variants (IL-10, TNF-alpha, CTLA-4), family history of inhibitor development and ethnicity [11, 12]. The environmental factors include intensity of early treatment, type of clotting factor concentrate used, and the effects of early prophylactic replacement therapy to prevent bleeding [13–16].

No family history of haemophilia at birth is expected in around 30% of cases [17–19]. *De novo* haemophilia refers to cases in which *F8* variants occur during embryogenesis and is observed in approximately 30% of cases [17–19]. However, in severe forms, no family history of haemophilia has been reported in up to 60% of cases of HA [17, 20, 21]. When family history is lacking, the term sporadic haemophilia applies, including both *de novo* haemophilia and cases with unawareness of maternal carrier status [20].

It has been assessed that the diagnosis of severe HA is delayed in patients with a sporadic form. In these cases, bleeds are usually the reason for diagnosis [19]. We hypothesized that the age and the conditions of the first bleeding and first treatment, as well as the *F8* variant profile, may differ between patients with sporadic and familial HA. Thus, the environmental factors for inhibitor development may be influenced by whether the diagnosis of haemophilia is already known at the time of birth or is obtained at the time of the first bleeding in early childhood. In addition, the start of early prophylactic treatment, which seems to be effective to prevent inhibitor development [2, 14, 22], may not be feasible in patients with a negative family history. Nor is it likely that these patients will be enrolled in studies evaluating new concentrates in previously untreated patients (PUPs). The PedNet-RODIN (research on determinants for inhibitors) cohort comprises a large international birth cohort of patients with severe HA with information on up to 75 first EDs to FVIII containing products [23]. Twenty-nine haemophilia treatment centres participate to complete this prospective cohort, enabling further investigation based on these data.

Based on the PedNet-RODIN cohort of patients with severe HA, this study aimed to confirm the delayed haemophilia diagnosis in the absence of family history. The objective was to investigate whether a delayed diagnosis may impact on the onset and management of first bleeds, the start of prophylaxis, the variant distribution and subsequent risk of inhibitors.

2 | Methods

2.1 | Patients Included

Patients with severe HA (FVIII activity <0.01 IU/mL) born between January 2000 and January 2022 were included. The included patients were PUPs and minimally treated patients (MTPs), who were diagnosed in one of the 29 haemophilia treatment centres in Europe, Israel and Canada, participating in the PedNet registry. Patients who were referred to the participating centres because of the presence of an inhibitor were excluded to avoid selection bias. Patients with missing data on the family history of haemophilia at diagnosis (present or absent) were excluded.

2.2 | Data Collection

Anonymised data were collected by the participating centres by means of specially designed log books for the patients. They were submitted to the databases through web-based case report forms. Patients' demographics, bleeding history and treatment exposures were recorded. An ED was defined as a calendar day during which one or more infusions of clotting factor were given. Detailed data, which were continuously updated, were collected for all factor administrations for at least 50 first EDs or until inhibitor development, including dates of infusion, doses and types of product, reasons for treatment, types of bleeds and surgery. Details on all performed inhibitor tests and recovery measurements (in case of borderline positive inhibitor tests) were collected for a correct assessment of inhibitor development in patients who ever had a positive inhibitor measurement.

All data collected were repeatedly checked for completeness and inconsistencies using prespecified protocols (www.pednet.eu). Data-monitor visits, including ascertainment of all included and excluded patients, as well as 10% of source data, were performed regularly according to protocol. For the current analysis, data collected until January 2022 were used.

Authorisation for the study was obtained from Institutional Review Boards. Written informed consent was obtained from the parents or guardians of all the participants.

2.3 | Study Design

We prospectively followed the included patients until the study endpoint, which was either the development of a clinically

relevant inhibitor or a cumulative number of 50 EDs to factor concentrates. The threshold of 50 EDs, rather than 75 EDs, was established in line with other studies based on previous data showing a significant decrease in inhibitor development beyond the first 50 EDs [1–3]. For each patient, the family history of haemophilia at the time of diagnosis was defined as: "positive" or "negative".

The primary outcome of the study was the onset of bleeding and treatment intensity expressed by various parameters, including the timing of first bleed and the time and reason for the first FVIII treatment. Secondary outcomes were the mutation distribution and inhibitor development within the first 50 EDs.

The age at diagnosis was recorded for the analysis. A bleeding was reported when treatment with factor concentrate was considered necessary. Treatment decisions were at the discretion of the physician and no prespecified protocol was used. We studied the age of the first bleed and at first joint bleed, as well as the presence and number of bleeds during the first 50 EDs.

Treatment parameters included age and data of first treatment at first EDs. All replacement treatments were included irrespective of the product used; including treatment with FVIII concentrates or bypassing agents. None of the patients included in this cohort received non-replacement therapies as primary prophylaxis due to the timing of the study. Peak treatments were defined as episodes of treatment with clotting factor for a bleed or surgery on at least three consecutive days, and the data about them were collected. In addition, the prophylactic treatment was analysed by recording the age at start of prophylaxis, whether it was started before any bleeds and the number of EDs prior to the start. The start of prophylaxis was defined as the moment on which preventive FVIII infusions had been given at a fixed interval for at least three consecutive EDs within a period of 15 days.

2.4 | F8 Variant Profile

F8 gene variants were determined at each site and collected. Variant effects were classified as either "high risk variants"–including large deletions, inversions and nonsense variants, or "low risk variants"–including small deletions, missense variants, frameshift and splice site variants. The patients with unknown disease-causing variant or in whom they were not tested were included as a separate category: "unknown risk".

2.5 | Inhibitor Testing

Clinically relevant inhibitor development was defined as the occurrence of at least two positive inhibitor titres combined with a decreased in vivo FVIII recovery up to the first 50 EDs. The secondary outcome was high responder inhibitor development, defined as the occurrence of a clinically relevant inhibitor with a peak titre of at least five Bethesda Units per mL (BU/mL). A positive inhibitor titre was defined according to the local cutoff level of the used inhibitor assay at each centre. The FVIII recovery was considered to be decreased when it was less than 66% of the expected FVIII activity level 15 min after infusion of FVIII.

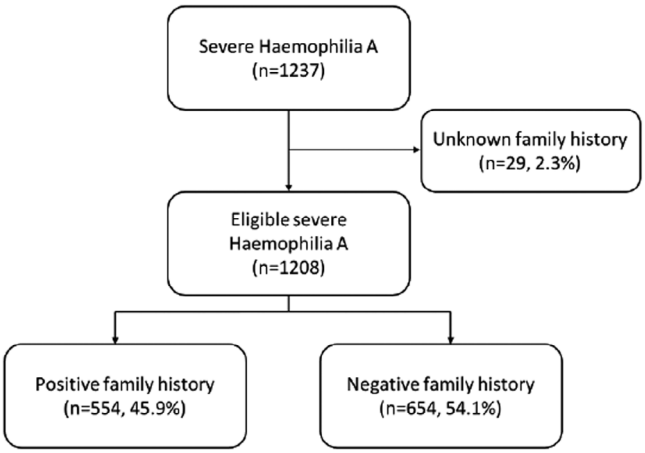

FIGURE 1 | Overview of the inclusion and exclusion processes.

Inhibitor testing was routinely done after every one to five EDs during the first 20 EDs and at least every 3 months thereafter. All centres closely monitored for clinical signs of inhibitor development and performed inhibitor and recovery testing at any clinical suspicion of it.

2.6 | Statistical Analysis

Descriptive statistics were used to summarize the results. The categorical data were described as frequencies and percentages, and the continuous variables as means, medians and interquartile ranges (P25–P75). Subsequently, treatment, bleeding pattern, variant distributions and inhibitor development were compared according to the presence or absence of a family history of haemophilia at diagnosis. For the categorical outcomes, the Chi-square test was applied. The Mann–Whitney test was employed for the comparison of continuous outcomes. A p value less than 0.05 was considered significant. All analyses were performed using IBM SPSS Statistics version 26.

3 | Results

3.1 | Family History of Haemophilia

As shown in Figure 1, of 1237 registered patients with severe HA, 1208 were included in the present study; 554 (45.9%) with a positive family history and 654 (54.1%) with a negative family history of HA at diagnosis.

3.2 | Diagnosis, Onset of Treatment and Prophylaxis

Data on the diagnosis, onset of treatment and prophylaxis are shown in Table 1. A positive family history shortened the time to diagnosis by about 8 months (p value < 0.0001). Similarly, patients with a positive family history started treatment earlier (p value < 0.0001), but mostly more than 1 month after diagnosis. All patients received their first treatment within 1 year.

TABLE 1 | Diagnosis, onset of treatment, prophylaxis according to family history.

	Positive family history (n = 554, 45.9%)	Negative family history (n = 654, 54.1%)	p value
Age at diagnosis			<0.0001*
Months (median, IQR)	0.0 (0.0–1.6)	8.3 (4.4–11.9)	
Years (median, IQR)	0.0 (0.0–0.1)	0.7 (0.4–1.0)	
Age at first exposure to factor concentrate			<0.0001*
Months (median, IQR)	8.0 (2.9–11.6)	10.3 (6.9–14.1)	
Years (median, IQR)	0.7 (0.2–1.0)	0.9 (0.6–1.2)	
Reason of treatment at 1st ED			
Prophylactic treatment (long/short term)[a] (n, %)	118 (21%)	85 (13%)	<0.0001*
Bleed (n, %)	371 (67%)	523 (80%)	<0.0001*
Surgery (n, %)	23 (4.2%)	23 (3.5%)	0.651
Trauma capitis (n, %)	36 (6%)	21 (3%)	0.651
Other/Unknown (n, %)	6 (1.1%)	2 (0.3%)	N.A.
Peak treatment at 1st ED[b]			
>/ = 3 days (n, %)	105 (19%)	186 (28%)	<0.001*
>/ = 5 days (n, %)	64 (12%)	106 (16%)	0.020*
Prophylaxis started[c] (n,%)	377 (68%)	460 (70%)	0.490
Age at the start of prophylaxis			0.134
Months (median, IQR)	14.7 (10.7–21.4)	15.4 (11.1–23.5)	
Years (median, IQR)	1.2 (0.9–1.8)	1.3 (0.9–2.0)	
ED at the start of prophylaxis (median, IQR)	8 (2.25–16)	9 (3–17)	0.335

Abbreviations: ED, exposure day to FVIII containing product; IQR, interquartile range; NA., not applicable.

[a]Long term prophylaxis: the use of clotting factor product (CFC) in the absence of bleeding with regular intervals for at least two consecutive months. At least once weekly for regular CFC and at least once per 2 weeks for long-acting CFC. No inhibitor at that time.

[b]Peak treatment at 1st ED: for at least 3 or at least 5 consecutive days CFC.

[c]Proportion of patients with prophylaxis started within the first 50 EDs.

*A p value less than 0.05 was considered significant.

The most common reason for treatment at first ED was bleeding in both groups, but the proportion of patients with prophylaxis as first treatment was significantly higher in those with positive family history (p value < 0.0001). Accordingly, reason for first ED in patients without family history was more frequently bleeding than in those with family history (p value < 0.0001). There were significantly fewer peak treatments of three and five consecutive EDs in patients with a positive family history. Patients with a positive family history started of prophylaxis minimally earlier than those without family history, but no significant differences were found in this regard or in the median ED at the start of prophylaxis between groups. The treatment strategy regarding the type of FVIII product and dosing did not differ between groups with positive and negative family history.

3.3 | Bleeding Pattern in Non-Inhibitor Patients

Bleeding pattern of 823 patients without inhibitor is shown in Table 2. Overall, patients with a positive family history had their first bleeding episode and joint bleed diagnosed significantly earlier than those with negative family history (p value < 0.05). The bleeding-free survival is shown in Figure 2. In contrast, there were no significant differences between groups according to the proportion of bleeds and joint bleeds within the first 50 EDs.

3.4 | Inhibitors

In spite of some differences in the age at diagnosis, onset of treatment and age at first bleed; clinically relevant inhibitors were observed in 30% of the patients, similarly in both groups (Table 3). The proportion of high responder inhibitors was also similar: 22% in patients with a positive family history versus 20% in those with negative family history at diagnosis. Conversely, the only differences observed were in the age of inhibitor development, which was significantly earlier in patients with a family history (p value < 0.05).

3.5 | Genetics

The distribution of *F8* variants according to the knowledge of a family history of haemophilia at diagnosis is shown in Table 3. Information on *F8* variants was available in 81% of the included

TABLE 2 | Bleeding pattern in non-inhibitor patients according to family history[a].

	Positive family history ($n = 367$, 44.6%)	Negative family history ($n = 456$, 55.4%)	p value
Age at first bleed			<0.0001*
Months (median, IQR)	9.2 (5.0–12.8)	10.6 (6.9–14.6)	
Years (median, IQR)	0.8 (0.4–1.1)	0.9 (0.6–1.2)	
Age at first joint bleed[b]			0.048*
Months (median, IQR)	14.0 (9.7–20.2)	14.9 (10.6–24.0)	
Years (median, IQR)	1.2 (0.8–1.7)	1.2 (0.9–2.0)	
Patients with bleeds during 1st 50 ED (n, %)	21 (6%)	25 (5%)	0.999
Patients with joint bleeds during 1st 50 ED[b] (n, %)	143 (39%)	166 (36%)	0.469

Abbreviations: ED, exposure day to FVIII containing product; IQR, interquartile range.

[a]Four patients (two in each group) had an unknown inhibitor status so they were excluded from this analysis.

[b]Joint bleed: Bleed at WFH/ISTH large joints (ankle, elbow, shoulder, knee and hip). [24].

A p value less than 0.05 was considered significant.

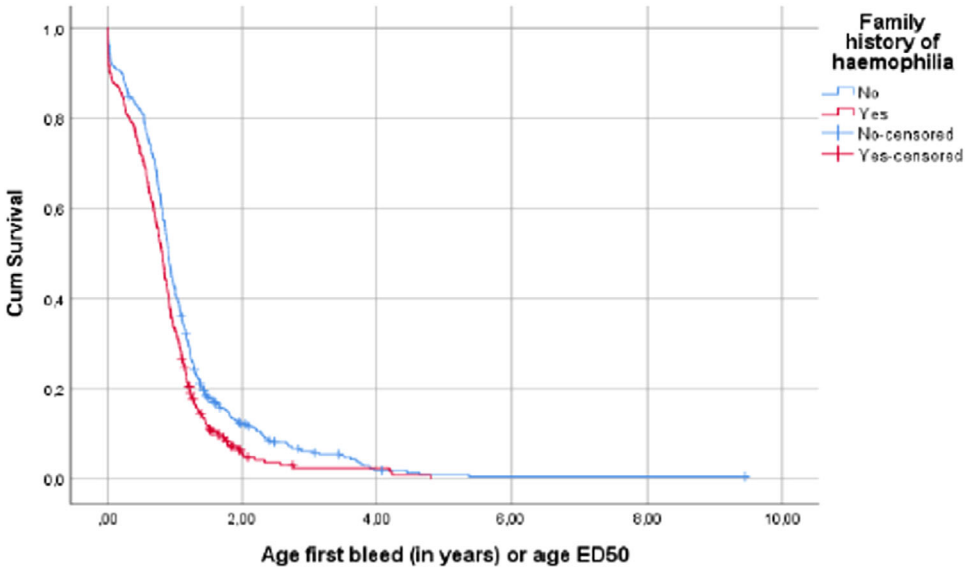

FIGURE 2 | Bleeding-free survival according to family history. Cum survival, cumulative survival; ED, exposure day; 95% CI, 95% confidence interval. Bleeding-free survival in 823 patients without inhibitor according to family history. The median bleeding-free survival was significantly longer in patients with negative family history (median 0.90 years, 95% CI 0.86–0.95), compared to those with positive family history (median 0.79 years, 95% CI 0.75–0.85). Log-rank test = 13.4 (p value < 0.05).

patients. The variant profile was similar between groups for the low-risk variants for inhibitor development: small deletions, missense, frameshift and splice site; as well as the unknown risk variants. In the negative family history group, a slightly higher proportion of high-risk variants for inhibitor development was observed, including large deletions, nonsense variants and inversions; however, this difference was not statistically significant (p value 0.098).

4 | Discussion

In this extensive cohort of 1208 unselected patients with severe HA, 54.1% of patients did not have a family history of haemophilia and were diagnosed due to the presence of bleeding symptoms. The previous led to a delayed diagnosis in those cases with negative family history, consequently deferring the initiation of treatment and resulting in higher peak treatments at first ED. In contrast, patients with positive family history started treatment 2 months earlier. These observations highlight the importance of an early diagnosis in haemophilia, which relies on a comprehensive family background and bleeding symptoms anamnesis. Nowadays, genetic testing with next-generation sequencing (NGS) have expanded the identification of gene defects in numerous families, thereby improving identification of carriers and prenatal diagnosis [25].

Primary prophylaxis is the standard of care in HA treatment to prevent bleeding events and preserve joint health [26–29]. For this reason, the World Federation of Haemophilia (WFH) 2020 guidelines recommend early initiation of long-term prophylaxis with standard or extended half-life FVIII (or other haemostatic

TABLE 3 | Genetics and inhibitor development according to family history.

	Positive family history (n = 554, 45.9%)	Negative family history (n = 654, 54.1%)	p value
Inhibitor development (n, %)	185 (33%)	196 (30%)	0.214
Age at inhibitor			0.006*
Months (median, IQR)	13 (9.2–17.0)	15 (11.4–19.8)	
Years (median, IQR)	1.1 (0.8–1.5)	1.2 (0.9–1.6)	
ED at inhibitor (median, IQR)	13 (8–20)	14 (9.25–21.75)	0.244
High responder[a] (n, %)	124 (22%)	130 (20%)	0.914
F8 variant			
High risk (n, %)[b]	321 (58%)	410 (63%)	0.098
Low risk (n, %)[c]	175 (32%)	188 (29%)	0.285
Unknown risk/not tested (n, %)	58 (10%)	56 (9%)	0.278

Abbreviations: ED, exposure day to FVIII containing product; IQR, interquartile range.

[a]Inhibitor development according to ISTH guidelines: low responder if ≤5.0 BU/mL; high responder if >5.0 BU/mL.

[b]High risk variants for inhibitor development: large deletions, nonsense and inversions.

[c]Low risk variants for inhibitor development: small deletions, missense, frameshift and splice site.

A p value less than 0.05 was considered significant.

agents) before the onset of joint disease, and ideally at an age younger than 3 years [29, 30]. Our results showed that the main reason for starting treatment in both positive and negative family history patients was bleeding, with a higher proportion of peak treatments at first ED in those cases with negative family history. The positive family history group started prophylaxis as the first treatment more frequently than patients with a negative family history, but no differences were found between groups regarding the timing of prophylaxis initiation. Therefore, it remains essential to remark the relevance of starting prophylaxis early to minimize peak treatment as first ED in children with haemophilia, subsequently mitigating the increased risk of inhibitor development. In our cohort, the median age for initiating prophylaxis was 14.7 months in patients with family history and 15.4 months in patients with negative family history. The need for intravenous administration of FVIII concentrates, especially in newborn and paediatric patients, could be the main reason for the delay in prophylaxis initiation. Since the data shown come from a historical cohort, the results will probably differ with the introduction of non-replacement therapies. Emicizumab, a non-replacement therapy, has shown efficacy in preventing bleeds in paediatric patients with severe HA, with or without inhibitors, and may evolve as a standard prophylaxis option [31]. Recent HAVEN 7 trial data support its safety and efficacy in patients under 12 months without inhibitors, allowing earlier prophylaxis initiation—around 3 months in cases with a family history or at diagnosis otherwise [32]. This early subcutaneous administration could improve joint health and reduce severe complications such as intracranial haemorrhage.

Notably, the age at first bleeding was significantly lower in patients with a positive family history of haemophilia compared to those with a negative family history. The earlier recognition of bleeding in those whose families were aware of the bleeding tendency may justify this difference, rather than an increased haemorrhagic risk in patients with a positive family history. Minor bleeding in the patients without family history possibly went unnoticed, leading to delayed recognition of bleeding in this group. This could contribute to major bleeding episodes, thereby requiring more frequent peak treatments and potentially increasing the risk of inhibitor development.

Overall, the absence of knowledge about family history of haemophilia at birth would be expected in approximately 30% of cases [17, 33, 34]. However, in severe haemophilia, the unknown family history status is observed in up to 50%–60% of cases, attributable to *de novo* variants and unaware maternal carriership [20, 21, 35]. It is well established that in families without a history of haemophilia, around 95% of *F8* variants have maternal or grand-parental origin [36, 37]. The results of the present study are in accordance with these previous findings, as 54.1% of the included patients presented without a family history.

The general *F8* variant profiles in our cohort were consistent with earlier reports on severe HA [11, 37]. High-risk variants for inhibitor development (large deletions, nonsense and inversions) represent the most prevalent variants effects in both groups, with a positive or negative family history. Variants considered as low-risk for inhibitor development (small deletions, missense, frameshift and splice site variants) affected between 29% and 32% of patients in both groups. There were no significant differences in the *F8* variant profile based on family history. The slightly higher prevalence of high-risk variants found in the sporadic haemophilia group may be influenced by patient selection related to genetic counselling in patients with severe HA and family history. Previous studies have shown that only 30% of sporadic haemophilia are due to de novo variants, with a considerable prevalence of high-risk variants inherited from previously unrecognized maternal carriers [38].

In the present study, an inhibitor incidence of 30% was observed, similar to the previously reported rates in the literature [1–3]. As expected, sporadic haemophilia patients exhibited delayed

diagnosis, later treatment initiation and more peak treatment episodes. Earlier studies have shown that these factors may influence the risk of inhibitor development, with a higher expected inhibitor rate in cases without a family history. Conversely, despite identifying these effects in the pattern of treatment, differences in inhibitor incidence based on family history were not observed.

The landscape of haemophilia treatment has evolved in recent years, with non-replacement therapies such as emicizumab being incorporated into the setting of primary prophylaxis, enabling the early initiation of treatment, which is not feasible without an early diagnosis. Family history remains crucial for this purpose, and additional efforts should be made to ensure the accurate identification of haemophilia carriers. However, further data on the use of non-replacement therapies in PUPs and MTPs are still needed and are currently under investigation [32, 39, 40]. The impact of these new therapies on inhibitor development was beyond the scope of this study. Nonetheless, future research should explore whether these therapies influence the risk of inhibitors in PUPs and MTPs and whether family history plays a role in this context.

5 | Conclusion

In this large cohort of patients with severe HA, the majority (54.1%) presented without family history of haemophilia and were diagnosed based on bleeding symptoms. In addition, diagnosis in these cases was delayed by 8 months compared to the patients with positive family history. This led to delayed treatment by 2 months and more peak treatments at the first ED. Surprisingly, the previous did not correlate with a higher incidence of inhibitors in the negative family history group of patients. These findings support the benefits of early diagnosis in severe haemophilia and emphasize the need to further investigate family history of haemophilia to enable an adequate management of haemophilia carriers. Due to the unexpected results regarding inhibitor development, further research is needed to explore additional factors that may influence inhibitor occurrence. Whether non-replacement therapies could impact this remains to be elucidated.

Author Contributions

All the authors designed the study protocol, collected the data from the included patients, carried out the statistical analysis and interpreted the data; A.M., I.R. and M.T.A.-R. wrote the manuscript; M.O., S.R., V.L., N.G.A, M.K and M.T.A.-R. critically reviewed the manuscript; and all the authors approved the final version of the manuscript.

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Ethics Statement

Authorisation for the study was obtained from Institutional Review Boards. Written informed consent was obtained from the parents or guardians of all the participants.

Conflicts of Interest

The authors stated that they had no interests which might be perceived as posing a conflict or bias regarding this work.

Data Availability Statement

The data that support the findings of this study are available from the registry of the PedNet Haemophilia 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 Haemophilia Research Foundation (www.pednet.eu).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.