

Epidemiology and clinical management of adult patients with severe hemophilia A without a history of FVIII inhibitors in Spain: results from a Delphi study

Epidemiología y manejo clínico de pacientes adultos con hemofilia A grave sin antecedentes de inhibidores del FVIII en España: resultados de un estudio Delphi

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Abstract

Introduction: Hemophilia A (HA) is a rare X-linked bleeding disorder causing defective coagulation. Severe HA (sHA) results in spontaneous bleeds and degenerative joint disease. **Objective:** The objective of the study is to understand the epidemiology, disease burden, management, and unmet needs of adult patients with sHA without a history of factor VIII (FVIII) inhibitors. **Methods:** Ten leading hematologists participated in the Delphi study. A literature review was conducted to develop the first Delphi questionnaire. Responses were analyzed descriptively. Prevalence and incidence of sHA were estimated based on expert reported numbers and hospital population covered, extrapolated to Spain's overall population. **Results:** Prevalence of adults with HA was estimated at 3081. Out of these, 1263 (41%, interquartile range [IQR] [28-46%]) were diagnosed with sHA and 998 (79%, IQR [71-88%]) would not have a history of FVIII inhibitors. Incidence of sHA was estimated in 43 patients per year. Most patients with sHA are treated with continuous prophylaxis (88%, IQR [75-97%]). About 20% IQR [7-41%] of patients with sHA treated with FVIII replacement therapy still experience spontaneous bleeds in many cases despite continuous prophylaxis. **Conclusion:** Prevalence of sHA in adult population in Spain was estimated at 0.265/10,000 inhabitants, which means 1263 adult patients with sHA in Spain, of which 998 (79%) would not have a history of FVIII inhibitors.

Keywords: Severe hemophilia A. Epidemiology severe hemophilia A. Factor VIII inhibitors. Continuous prophylaxis. Severe hemophilia A clinical management. Severe hemophilia A disease burden.

Resumen

Introducción: La hemofilia A (HA) es un trastorno poco frecuente que resulta en un proceso de coagulación defectuoso, causando hemorragias espontáneas y enfermedad articular degenerativa en pacientes con HA graves (sHA). **Objetivo:** Comprender

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mejor la epidemiología, carga de la enfermedad, manejo y necesidades no cubiertas de pacientes adultos con sHA sin antecedentes de inhibidores frente al factor VIII (FVIII). **Métodos:** Diez hematólogos participaron en un estudio Delphi. Se realizó una revisión bibliográfica para desarrollar el primer cuestionario. Se analizaron las respuestas con estadísticas descriptivas. La prevalencia e incidencia se estimaron considerando pacientes reportados y la población cubierta por el hospital, extrapolándose a la población total española. **Resultados:** Se estimó una prevalencia de adultos con HA de 3.081. De estos, 1.263 (41%, RIC [28-46%]) presentan sHA y 998 (79%, RIC [71-88%]) no tendrían antecedentes de inhibidores de FVIII. La incidencia de sHA se estimó en 43 pacientes/año. La mayoría de los pacientes con sHA reciben profilaxis continua (88%, RIC [75-97%]). Alrededor del 20%, RIC [7-41%], de estos pacientes aún experimentan hemorragias espontáneas a pesar de la profilaxis continua. **Conclusión:** La prevalencia de sHA en la población adulta se estimó en 0,265 por cada 10.000 habitantes, que corresponderían a 1.263 pacientes adultos con sHA en España. De estos, 998 (79%) no tendrían antecedentes de inhibidores de FVIII.

Palabras clave: Hemofilia A grave. Epidemiología. Inhibidores del Factor VIII. Profilaxis continua. Manejo clínico Hemofilia A grave. Carga enfermedad Hemofilia A grave.

Background

Hemophilia A (HA) is a rare, congenital (X-chromosome) recessive bleeding disorder that affects approximately 1 in 5000 males^{1,2}. It is caused by mutations in the *F8* gene that encodes for factor VIII (FVIII) protein, an essential cofactor in the coagulation cascade. These mutations can ultimately lead to a defective coagulation process, resulting in bleeding episodes. Based on the level of endogenous FVIII activity, patients with HA are classified as having mild (5-40 IU/dL), moderate (1-5 IU/dL), or severe (< 1 IU/dL) disease³.

Severe HA (sHA) patients are particularly symptomatic and present with spontaneous bleeds from early childhood, primarily in the musculoskeletal system (muscles and large joints) and, less frequently, mucosal, or cerebral hemorrhages⁴. Approximately 80% of bleed events are intra-articular (hemarthrosis) in nature, two-thirds of which are reported in the knees, elbows, and ankles. Intra-articular bleeding causes synovial hypertrophy and cartilage damage, with gradual joint destruction (hemophilic arthropathy)^{3,5}. The debilitating process of hemophilic arthropathy restricts patients' activity and productivity and has a negative impact on their quality of life (QoL) and in the development of another systemic and chronic pathologies (diabetes, obesity, vascular pathology) due to the limitation of mobility⁶.

The recommended standard of care for patients with sHA in Spain is continuous prophylactic treatment, either with several times a week of FVIII replacement concentrates, or 1, 2 or 4 times a month with non-replacement therapies such as emicizumab^{7,8}. Although management of sHA has improved in the last years, unmet needs remain. The development of inhibitors against exogenous FVIII is relatively frequent and occurs in 20-30% of patients with sHA treated with FVIII replacement concentrates^{9,10}. In addition, existing

treatments require frequent infusions, which are associated with complications and may have a negative impact on health-related QoL and in familiar, educational or work performance¹¹. The advent of new advanced therapies for the treatment of hemophilia, especially aimed at the adult population, requires greater understanding of Spanish sHA clinical management, epidemiology, and patient unmet needs. Thus, the aim of this study is to better understand the epidemiology, disease burden, clinical treatment and management, and unmet needs of adult patients with sHA without a history of FVIII inhibitors.

Methods

Study design and procedure

A Delphi methodology was used in this study, with two rounds of consultation^{12,13}. This methodology consists of a structured process that uses interactions between a panel of leading experts through self-completed questionnaires¹². Two questionnaires were developed and used in two rounds. The first questionnaire was sent to the experts through the Microsoft Forms platform (© Microsoft 2023). These experts were asked to complete the questionnaire between December 22nd of 2022 and January 10th of 2023. After the analysis of the responses to the first questionnaire, a second questionnaire was developed focused to validate the data and to obtain consensus on the questions where there was a greater dispersion of responses during the 1st round. The second questionnaire was sent on February 14th and completed by the experts before February 23rd of 2023.

Panel selection

The experts invited to participate in the study were hematologists actively working in the management and

treatment of HA patients in Spanish leading hospitals. The following inclusion criteria were applied for the selection of the participating clinical experts: (1) Experience in hematology and/or congenital coagulopathies, thrombosis, and hemostasis; (2) experience with HA management in Spain; (3) working in HA treating hospitals from different Spanish regions; (4) relevant scientific publications in HA as peer-reviewed articles, guidelines, proceedings of conferences or grey literature after 2015; and (5) willing to participate in the study.

Questionnaire development

A systematic literature review was conducted to understand the current environment of adults with sHA in Spain to develop the first Delphi questionnaire. International biomedical databases (PubMed, Google Scholar, and Cochrane), national biomedical databases (Spanish MEDES database), and grey literature sources (Spanish Ministry of Health website, Spanish Federation of Patients with Hemophilia, clinical guidelines, clinical expert consensus documents, national, regional and hospital product evaluations, and general web search engines) were consulted.

The first questionnaire was organized into five sections and included a set of 26 questions: (1) Epidemiology of sHA in Spain; (2) burden of disease for patients with sHA; (3) patient journey of patients with sHA; (4) therapeutic management; and (5) unmet needs of patients with sHA in Spain. This questionnaire was reviewed and validated by the study coordinator. A second questionnaire was developed to validate and complement the information gathered after analyzing the first questionnaire.

Data analysis

Microsoft Office Excel v.2309 was used for the statistical analysis of the Delphi data. All questions were reviewed and, when missing or extreme values were found, these were validated with the participants to exclude potential errors. The prevalence of HA was estimated considering the aggregated number of adult patients with HA treated by the experts, and the total population covered by the health-care area of the participating hospitals. To obtain the total number of adult HA patients in Spain, this ratio was extrapolated to the overall Spanish population (as of July 2022¹⁴), and results were presented as number of individuals with HA/10,000 inhabitants. In addition, from the overall

figure of adults with HA, the median percentage of patients with sHA and the median percentage of patients without a history of FVIII inhibitors were calculated based on the data provided by the experts. The same methodology was followed to estimate the incidence of sHA in Spain, using the aggregated number of patients with sHA diagnosed at the participating hospitals annually.

Median and interquartile range (IQR) (Q1-Q3) were calculated for each question. The coefficient of variation (CV) was estimated using the ratio of the standard deviation (σ) of the responses on a specific item to its corresponding mean (μ) ($CV = \sigma/\mu$). For multiple-choice questions, absolute frequencies of responses and percentages were calculated for each option. Consensus was assumed if at least 80% of the experts agreed on the question^{15,16}. The second questionnaire included the questions for which high dispersion was identified ($CV > 1$) in the first questionnaire^{17,18}. Both the individual respondent's rating and the median rating from the entire panel were included. Some questions considered misleading by the experts, were reformulated, and included again in the second questionnaire.

Results

Expert panel

Ten hematologists with experience in the management and treatment of HA patients in Spain completed the first-round questionnaire. Nine out of 10 experts completed the second-round questionnaire.

Epidemiology of sHA in Spain

Patient registries to collect data from patients diagnosed with hemophilia were available in 80% of the participating hospitals. The estimated prevalence of adults with HA in Spain was 0.647/10,000 inhabitants. Considering the Spanish population in 2022, this would represent 3,081 adult patients with HA. Of these, it was estimated that 1263 (41% IQR [28-46%]) would be diagnosed with sHA and, from them, 998 (79% IQR [71-88%]) would lack a history of FVIII inhibitors. Prevalence rates and estimated number of adult patients in Spain with HA, sHA, and sHA without a history of FVIII are shown in [table 1](#).

The estimated incidence of sHA was 0.009/10,000 inhabitants. This would yield into 43 patients with sHA per year. Nevertheless, a higher number of patients ($n = 95$) with sHA was estimated to transitioning each

Table 1. Prevalence rate and number of adult patients with HA, sHA, and sHA without a history of FVIII inhibitors in Spain

Population	Prevalence rate (×10,000 inhabitants)	Number of patients*
Adults with HA in Spain	0.647	3,081
Adults with sHA in Spain	0.265	1,263
Adults with sHA and without a history of FVIII inhibitors in Spain	0.210	998

*Based on the overall Spanish population as of July 2022¹⁴.
sHA: severe hemophilia A; FVIII: factor VIII.

year to adulthood (0.02/10,000 inhabitants). The median number of adult patients with sHA that would develop inhibitors in adulthood was estimated in 1% IQR (0-3%). According to the experts, 97% of adult patients with sHA currently treated in their hospitals were of working age in Spain (18-65 years). The age distribution of patients with sHA without history of FVIII inhibitors is shown in [table 2](#).

Burden of sHA without a history of FVIII inhibitors in Spain

Adult patients treated with FVIII prophylaxis experienced spontaneous bleeds in 20% IQR (7-41%) of the cases, and up to 42% IQR (14-46%) experienced traumatic bleeds. For patients treated with emicizumab, 5% IQR (0-9%) still experienced spontaneous bleeds, and 8% IQR (5-20%) suffer from traumatic bleeds. In those patients who bleed, life-threatening bleeds (1% IQR [0-2%]) were rare. Joint bleeds occurred in 25% IQR [12-34%] of sHA adults, and non-joint bleeds were present in 27% IQR (20-53%). Median number of bleeds per patient per year were 1.3 IQR (1-2), 2.0 IQR (1-2), and 0.0 IQR (0-1) for joint bleeds, non-joint bleeds, and life-threatening bleeds, respectively. Around 3% IQR (1-7%) of adult patients with sHA without a history of inhibitors required hospitalization due to bleeding episodes. It was estimated one annual admission per patient with a median length of stay of 5 days IQR (4-6). According to the data provided, intensive care unit (ICU) admission due to bleeding complications was exceptional.

According to the experts, joint complications and surgery are common among adult patients with sHA. The percentage of adult patients with sHA that required major surgery was estimated at 4% IQR (1-8%), whereas 13% IQR (6-23%) required minor joint surgery annually.

Table 2. Age distribution of patients with sHA without a history of FVIII inhibitors in Spain

Age range	Median (%)	Interquartile range (%)
18-35 years	45	26-59
36-50 years	38	33-44
51-65 years	14	0-25
> 65 years	3	0-9

sHA: severe hemophilia A; FVIII: factor VIII.

The median number of days that patients spend at the hospital due to these surgeries was 7 IQR (7-13) and 2 IQR (1-4), respectively. For both major and minor joint surgeries, the median number of hospitalizations per year was one. The estimated number of follow-up visits per year with a rehabilitation doctor or a physiotherapist were 3 IQR (2-4) visits. Experts reported that other complication added to bleeding events for sHA were hepatic fibrosis or cirrhosis, which was present in up to 10% IQR (2-12%) of these patients. Acute or uncontrolled chronic hepatic infections were very rare.

Clinical management of patients with sHA in Spain

Management and follow-up of patients with sHA were mainly multidisciplinary, involving nurses, orthopedic surgeons, physiotherapists, and pharmacists, in addition to hematologists. For the management of patients with sHA, all experts reported using the guidelines issued by the World Federation of Hemophilia (WFH)³, followed by the Spanish guidelines developed by the Real Fundación Victoria Eugenia for the management of patients with HA⁸ (80% of the experts) and recommendations for the treatment of hemophilia with inhibitors 2019 developed by the Real Fundación Victoria Eugenia¹⁹ (80% of experts). Experts also indicated that 60% of the hospitals have their own specific protocols to manage patients with hemophilia.

Regarding the patient journey, the estimated median time from first symptoms onset to diagnosis of sHA was 7 IQR (5-15) days. Median age at diagnosis for patients with sHA was 6 IQR (5-11) months. The percentage of patients with sHA initiating primary prophylaxis was 30% IQR (23-40%), while 30% IQR (11-45%) were on secondary prophylaxis and 35% IQR (25-50%) on tertiary prophylaxis. In adults with sHA, the number of follow-up visits with the hematologist during the 1st year after initiation of the treatment was six, regardless of

the treatment, and between two and three visits per year when the patient is stable. Based on expert's experience, the median number of days from FVIII exposure until the development of FVIII inhibitors in the treated patients with sHA was 14 IQR (9-20) days.

Most of the adult patients with sHA were treated with continuous prophylaxis (88%, IQR [75-97%]). It was estimated that 9% IQR (0-16%) of adult patients with sHA would receive intermittent prophylaxis and 4% IQR (2-5%) received on-demand treatment mainly due to patients' choice. Other reasons for on-demand treatment were very low bleeding rate, good joint status, and/or inadequate venous access.

The most common prophylactic treatment used by experts was extended half-life FVIII prophylaxis (60% IQR [40%-77%]), followed by emicizumab (18% IQR [15-22%]). Standard half-life FVIII prophylaxis and plasma derived FVIII prophylaxis were used in 5% (3-20%) and 5% IQR (0-15%) of patients with sHA, respectively. According to the experts' clinical practice, the percentage of patients with sHA without a history of FVIII inhibitors that were adherent to prophylactic treatment ranged between 80% IQR (69-89%) for FVIII prophylaxis and 100% IQR (92-100%) for emicizumab. The median of the average annual bleeding rate reported by the experts in patients with sHA without a history of inhibitors was 2 IQR (1-3) for FVIII prophylaxis regimens and 1 IQR (1-2) for patients treated with emicizumab.

Unmet needs of sHA patients in Spain

All participants considered that there are unmet needs for patients with sHA in Spain. Up to 80% of the experts considered, it is necessary to have treatments that improve adherence and increase the effectiveness in reducing bleeding episodes. Moreover, the need for a safer treatment with lower immunogenic response and minimal thrombotic risk would be even more relevant than improving efficacy. In addition, 60% of participants reported additional unmet needs for patients with sHA, including easier access to new treatments with reduced bureaucracy (17%) and with a cost that can be affordable by the health-care system (67%). Psychological support to patients was also mentioned as an unmet need (17%) for adults with sHA.

Discussion

A group of 10 clinical experts from leading Spanish HA hospitals participated in a Delphi study to better understand the situation of adults with sHA without a history of FVIII inhibitors.

The estimated number of adult patients with HA in Spain would be around 3081, similar to the number of patients with HA in Spain according to the Report for the Situation of Rare Diseases in Spain (ReeR 2022)²⁰, which reports a prevalence of 3178 patients (all ages) with HA in Spain. The ReeR report includes information from rare disease registry available in 13 out of the 17 regions in Spain. On the other hand, these figures are slightly higher than the Spanish HA prevalence reported by Aznar et al.²¹ in their cross-sectional epidemiological study from 2009, which estimated 2081 patients with HA in Spain. It is important to mention that this study included only patients from 85% of hemophilia treatment centers in Spain²¹. In line, the WFH survey results from 2021, which collects and analyzes the data provided by national member organizations, health-care providers, and policymakers, also captured a lower prevalence with approximately 1822 patients with HA²² in Spain. Interestingly, it also reports 2082 patients with unknown hemophilia type²². Hence, the differences in the figures may be explained by the methodology used in each of the studies. Notwithstanding, the results of this study estimated that 41% of HA adult patients in Spain would have sHA. This percentage is in line with the proportion of patients with sHA found in the literature, ranging from 33% to 50%²¹⁻²⁴. In fact, the study by Iorio et al.¹ estimated a global prevalence for sHA of 6.0 cases/100,000 males. This would correspond to 1400 patients with sHA in Spain, in line with the 1263 adult patients with sHA estimated in this study. Some experts also highlighted the potential differences in the prevalence of adult patients with sHA among the regions, due to the high incidence of human immunodeficiency virus (HIV) in the 1980-90s. In the present study, the percentage of adult patients with sHA with FVIII inhibitors was 21%, in line with the existing literature^{9,10}.

The incidence of sHA was estimated at 43 patients per year, which is higher than the incidence of sHA reported by the WFH (9.5 in every 100,000 live male births)²² which would yield around 19 annual cases in Spain¹⁴. In addition, the patients estimated by the experts that would transition to adulthood annually were estimated in 95. Experts highlighted that the number of patients transitioning to adulthood per year are not constant and might change due to population fluctuation. For instance, birth rate decrease, prenatal genetic screening protocols⁸, or immigration could impact these figures. Therefore, the experts considered that a range between 43 and 95 would be more representative.

It was also observed that most patients with sHA are of working age in Spain, and few patients (only 3%) were reported above the age of 65. That would reflect the high mortality of this generation in the past, due to treatment complications, HIV infection, Hepatitis C, transfusion complications and cirrhosis, and hepatocellular carcinoma.

Bleeding episodes are still frequent despite regular prophylactic therapy. The most relevant data regarding patients with sHA were spontaneous bleeds, as traumatic bleeds might not be specific to patients with sHA. The numbers presented here are an estimate, but there is a clear perception of the difference between treatments. Only 5% of patients with sHA treated with emicizumab experienced spontaneous bleeds compared to 20% of the patients treated with FVIII prophylaxis. The median number of annual bleeds per patient is in line with the results of a European retrospective study, where the number of bleedings in all sites was 2.7²⁵. As most of the patients with sHA are on continuous prophylaxis, the estimated number of hospitalizations and ICU admissions per year due to bleeding complications was rare among patients with sHA. Experts noted that hospitalizations and visits to the emergency room would probably be more prevalent among moderate or mild patients, which are not treated with continuous prophylaxis.

Regarding the initiation of prophylactic treatment, the percentage of patients with primary and secondary prophylaxis might vary slightly from hospital to hospital, which is reflected in the wide IQR. Furthermore, while most of the youngest patients would have initiated in primary prophylaxis, tertiary prophylaxis was more common in older individuals. Patient's profile would also be a factor in their management. Experts stated that older patients are more reluctant to receive continuous prophylaxis. Despite this fact, up to 88% of adults with sHA were treated with continuous prophylaxis. Only a small percentage of adult patients would receive intermittent prophylaxis and on demand treatment. Aznar et al., reported that 75% of patients with sHA were treated with continuous prophylaxis²⁴. This could be interpreted as an improvement in the control of these patients. The most common prophylaxis treatment used by experts was extended half-life FVIII prophylaxis, followed by emicizumab. However, sHA management could vary across different regions, as access to some treatments might be restricted. In fact, Bernthorp et al.²⁵ argued that the extent to which prophylaxis is available and effectively implemented in European countries is largely unknown. In addition,

experts considered it necessary to have access to treatments that improve adherence and therefore efficacy or that are potentially curative, with the aim of achieving the aspirational target of zero bleeding rate.

One limitation of this study is derived from the methodology used to obtain the information, as experts' opinions must be considered as estimates. Although the number of experts participating in the study would be considered small, the experts participating are from leading hospitals for the management of HA in Spain. Furthermore, a size between 10 and 30 experts has been suggested to be adequate for a Delphi Study^{12,26,27}. In addition, the therapeutic and clinical management of patients with sHA under the care of the experts participating in this study might differ from region to region, and according to hospitals size. Another limitation of the study would be the definition of sHA, which is based only on FVIII activity levels being below 1%, which has been shown to identify 87% of clinically sHA²⁸, and does not consider bleeding phenotype.

Conclusion

This study presents updated epidemiological data and complements existing information on the burden of disease and the management of patients with sHA in Spain. The estimated prevalence of adults with sHA in Spain was 1263 (0.265/10,000 inhabitants) with an incidence of 43 new patients per year (0.009/10,000 inhabitants). 998 (79%) of patients with sHA would not have a history of FVIII inhibitors. The present study also shows that despite 88% of the patients are on continuous prophylaxis treatment, 20% of patients with sHA continue to experience spontaneous bleeds despite increased monitoring and a broader range of therapeutic options. Life-threatening bleeds are rare but joint bleeds still represent a substantial burden for patients with sHA. Although the management of patients with sHA in Spain has improved in the past years, experts are demanding treatments with enhanced safety profiles and increased adherence to ensure their effectiveness.

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Conflicts of interest

VJY, NAE, OBH, ABG, SBB, MFLF, FJLJ, JMA, RNV, and MRL received fees from BioMarin to participate in

the study. AGP is an employee of Omakase Consulting. Omakase Consulting received funding from BioMarin to develop the study. ELV is an employee of BioMarin.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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