RESEARCH LETTER

Evaluation of the prevalence of hepatitis C virus infection in patients with hemophilia treated in a single hemophilia center in Poland

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Introduction Before the introduction of donor virological testing, patients with inherited bleeding disorders used to be at a high risk of viral infections, such as hepatitis C virus (HCV) infection, due to frequent transfusions of blood and blood products.[1-3] It has been determined that by 1985, approximately 63% to 98% of patients with severe hemophilia were infected with HCV.[1,4-7] In 2000, Poland introduced molecular tests to screen blood donors for HCV RNA, and since 2005, the donors have also been screened for HIV RNA and hepatitis B virus DNA. Thanks to these procedures, the possibility of infection with the aforementioned viruses among the recipients with hemophilia treated with plasma-derived products has been practically eliminated. Since the 1990s, recombinant clotting factor concentrates have been used in children, which further increased the safety of hemophilia treatment.[1,2,4,6-9] The highly effective and safe interferon-free options were a breakthrough in the treatment of patients infected with HCV, and improved their prognosis.[10] Given that the understanding of the epidemiology of infection and associated factors is useful in planning more effective programs to control the disease and its complications, the aim of this study was to determine the prevalence of chronic HCV infection in patients with congenital hemophilia treated in Greater Poland.

Patients and methods This retrospective analysis included 102 adult male patients with hemophilia A and hemophilia B treated at the Department of Hematology and Bone Marrow Transplantation of the Poznan University of Medical Sciences in Poland between 2019 and 2021. The hemophilia type was classified according to the World Federation of Hemophilia guidelines.[4]

First, the results of anti-HCV antibody (using the Atellica IM Hepatitis C assay (Siemens Healthcare Diagnostics Inc., Erlangen, Germany) and HCV RNA tests were analyzed all participants. The samples with reactive results were tested with the same test in duplicate, following the manufacturer's instruction. To confirm the infection, molecular testing for the presence of HCV RNA genetic material in plasma was performed using reverse transcription–polymerase chain reaction (Bosphore HCV Quantification Kit, Anatolia Geneworks CE IVD, Montania 4896 analyzer, Life Technologies, Kadikoy / Istanbul, Turkey). The analytical sensitivity (detection limit) of the test is 75 copies/ml (25 IU/ml).

Statistical analysis The data were analyzed using Statistica version 13.3 (Statsoft, Kraków, Poland). The significance level was set at a P value of 0.05. Continuous data were presented as medians and interquartile ranges, whereas categorical data were expressed as numbers and percentages. The Shapiro–Wilk test was performed to assess the normality of data distribution. For the assessment of percentage differences between the study groups, the following tests were used, depending on the fulfilment of the conditions of the expectancy tables: the Pearson χ^2 test, the χ^2 test of highest reliability, and the V^2 test when required for categorical variables, and the Mann–Whitney test for continuous variables. To compare more than 2 variables, the Kruskal–Wallis test was used.

Results Out of 2804 individuals with hemophilia registered in Poland,[1] 122 adult patients are treated in Greater Poland. Of those, 102 patients gave their permission to be included in this study: 82.4% (84/102) had hemophilia A and

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17.6% (18/102) had hemophilia B. The median age of the study patients was 39 years (range, 18–70 years) (TABLE 1). Severe hemophilia was diagnosed in 68.6% of the patients (70/102) and 2.9% of the participants (3/102) developed inhibitors. A total of 54 patients received prophylactic treatment for hemophilia, while 48 individuals were treated in the case of bleeding (on-demand treatment). Reactive anti-HCV antibodies were found in 51.9% of the study participants (53/102), while a positive HCV RNA test result was confirmed in 12.7% of the patients (13/102), who were then referred for hepatitis C treatment. Among the patients with a negative HCV RNA test result, the group with reactive anti-HCV antibodies (44.9% [40/89]) included individuals after previous treatment with interferon (n = 15) or oral HCV replication inhibitors (n = 10), or those after spontaneous elimination of the virus (n = 15).

No HCV DNA was detected among the individuals with mild hemophilia. HCV infection was significantly more frequent in the patients with moderate hemophilia than in those with severe disease. Among the patients without an inhibitor, the prevalence of HCV infection was 52.5% (52/99), while HCV DNA was detected in a single patient among those with hemophilia A with an inhibitor. A correlation was established between the presence of anti-HCV antibodies and HCV RNA and the age of the patients. Reactive anti-HCV antibodies were present significantly more frequently among the individuals above the median age (75% [39/52]) than among the younger patients (28% [14/50]) (P <0.001). The prevalence of HCV infection, as determined by HCV RNA testing, was significantly higher among the patients above the median age, at 24% (12/50), while it was only 1.9% (1/52) among the patients below the median age (P = 0.001). No differences were found in the prevalence of reactive anti-HCV antibodies and HCV RNA when comparing the prophylactic group with the group treated on demand (62.9% [34/54] vs 37.5% [18/48] and 9.3% [5/54] vs 16.6% [8/48], respectively). The patients with HCV DNA had significantly higher aminotransferase activity. Among the HCV-infected patients, 3 individuals died during the follow-up, including 1 death from complications of liver cirrhosis and 2 deaths from hepatocellular carcinoma. Detailed characteristics of the study group are presented in TABLE 1.

Discussion The high prevalence of HCV infection is a significant problem worldwide—it is estimated that 80 to 160 million people are infected with the virus. In Poland, the percentage of individuals with HCV RNA is about 0.5%, which corresponds to 165 000 people, while 1.9% have anti-HCV antibodies.[3,11] It has been determined that in northern Europe and Canada, reactive anti-HCV antibodies are present in 0.1% to 0.3% of the population, in the United States and Japan in 1%–2%, and in Egypt in up to 19.2% of the population.[12]

The present retrospective analysis involving the patients with hemophilia treated in Greater Poland showed that 51.9% of them (53/102) were infected with HCV. Only 12.7% (13/102) were positive for HCV RNA at the time of the analysis, and they were referred for treatment with direct-acting antivirals. Twenty-five patients had a history of effective antiviral treatment, while in 15 cases the virus had been eliminated spontaneously. In comparison, an analysis carried out in Poland in 2008 showed that reactive anti-HCV antibodies were present in 76.9% of the respondents (164/213), with a positive molecular test result confirmed in 134 cases (62.9%).[13] In 2015, a positive HCV RNA result was detected in 70.4% of the tested individuals (50/71).[5] However, in the European Union, the prevalence of HCV currently ranges from 0% to 27.6%, and in first-time blood donors it is only 0.1%.[14] At the same time, no transmission of HCV through blood products has been reported in Europe since 1994.[15]

Patients with severe hemophilia with a bleeding phenotype (both severe and moderate factor deficiency), due to the increased intensity of treatment with replacement products, have historically been the group at the highest risk of infection with blood-borne viruses. HCV infection was observed far more frequently in this group, with 64.3% of cases showing reactive anti-HCV antibodies and 17% having positive HCV RNA. The preparations used nowadays in Poland to treat adult and pediatric patients with hemophilia are obtained by genetic engineering and show high safety in terms of the risk of viral transmission (including HCV). Their introduction, together with implementation of the procedures described earlier to prevent viral transmission from blood donors, has contributed to a marked decrease in the incidence of HCV among patients with hemophilia since the 1990s. This is confirmed by our results showing that in the patients older than 39 years the prevalence of anti-HCV antibodies was 75% and the rate HCV RNA positivity was as high as 24%. In comparison, among the younger patients, anti-HCV antibodies were detected in 28% of cases, while positive HCV RNA was found in only 2% of patients.

Conclusions The prevalence of HCV infections among the patients with hemophilia treated in Greater Poland is relatively high, reaching almost 52%. Analysis of the patients treated at the Hemophilia Treatment Center in Greater Poland, which implements the current guidelines of the National Program for Treatment of Patients with Hemophilia and offers, among other services, comprehensive care for patients with congenital bleeding disorders, has allowed us to assess the virological status of the individuals included in the program. Consequently, they could be treated with modern therapies leading to the elimination of viremia and regression of lesions.

TABLE 1 Detailed characteristics of the study group

Parameter		HCV RNA				Age		
		Overall (n = 102)	Negative (n = 89)	Positive (n = 13)	*P* value	<39 years (n = 50)	≥39 years (n = 52)	*P* value
Treatment	Prophylaxis	54 (52.9)	49 (55.1)	5 (38.5)	0.26[b]	29 (58)	25 (48.1)	0.32[a]
	On-demand therapy	48 (47.1)	40 (44.9)	8 (61.5)		21 (42)	27 (51.9)	
Type of hemophilia	B	18 (17.6)	15 (16.9)	3 (23.1)	0.29[c]	7 (14)	11 (21.2)	0.34[b]
	A	84 (82.4)	74 (83.1)	10 (76.9)		43 (86)	41 (78.8)	
Age, y		39 (27.9–53.7)	36 (27.7–50.7)	59 (46–64)	<0.001[d]	28 (22.1–34.3)	54 (44.5–62.7)	<0.001[d]
Severity of hemophilia	Mild	20 (19.6)	20 (22.5)	–	0.031[b]	10 (20)	10 (19.2)	0.86[b]
	Moderate	12 (11.8)	9 (10.1)	3 (23.1)		5 (10)	7 (13.5)	
	Severe	70 (68.6)	60 (67.4)	10 (76.9)		35 (70)	35 (67.3)	
Platelet count, × 10^9/l		234 (201–282)	229 (203–284)	239 (175–272)	0.72[d]	245 (212–297)	215 (178–272)	<0.001[d]
ALT, U/l		27.5 (20–40)	26 (19–37)	41 (32–68)	<0.001[d]	26.5 (19–37)	29.5 (20.5–50)	0.23[d]
AST, U/l		23.5 (19–31)	23 (19–26)	42 (40–52)	<0.001[d]	22 (19–25)	24.5 (20.5–39.5)	0.033[d]
Anti-HCV antibodies	Reactive	53 (52)	40 (44.9)	13 (100)	<0.001[b]	14 (28)	39 (75)	<0.001[a]
	Negative	49 (48)	49 (55.1)	–		36 (72)	13 (25)	
Outcome	Alive	96 (94.1)	86 (96.6)	10 (77)	0.001[c]	50 (100)	46 (88.5)	0.001[c]
	Dead	6 (5.8)	3 (3.4)	3 (23)		–	6 (11.5)	

Data are presented as number (percentage) or median (interquartile range).

SI conversion factors: to convert ALT and AST to µkat/l, multiply by 0.0167.

a Pearson χ^2 test; **b** χ^2 test of highest reliability; **c** V^2 test; **d** Mann–Whitney test

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; HCV, hepatitis C virus

ARTICLE INFORMATION

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