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ORIGINAL ARTICLE

Risk factors for neurologic sequelae in children and adolescents with hemophilia after intracranial hemorrhage

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Abstract

Background: Intracranial hemorrhage (ICH) is reportedly rare but has high morbidity and mortality risk in persons with hemophilia. Although the risk factors that facilitate bleeding are known, the factors affecting the sequelae are not well known.

Objectives: We planned to investigate the risk factors for neurologic sequelae in children and adolescents with hemophilia suffering from ICH.

Methods: An invitation was sent to pediatric hematology centers via email. Clinical and laboratory findings, neurologic sequelae, and recurrence of bleeding in persons with hemophilia who developed ICH were questioned.

Results: Eighty-six patients from 21 centers were evaluated. All patients were less than 18 years of age at the time of ICH. Thirteen patients had ICH in the neonatal period, while 40 patients had a known diagnosis of hemophilia before ICH, and 33 patients were undiagnosed before ICH. Five patients died, 2 of whom died in the neonatal period. The rate of neurologic sequelae was 25 of 81 (30%). The most common neurologic sequela was epilepsy (n = 11/25), followed by hemiparesis (n = 5/25). Cerebral shift (odds ratio, 3.48) and development of ICH in the neonatal period (odds ratio, 4.67) were significant for the development of neurologic sequelae in multivariate analysis. On follow-up, recurrence of ICH occurred in 8 of 81 (10%).

Conclusion: ICH in the neonatal period and cerebral shift were the two main risk factors for the development of neurologic sequelae. Neonatal departments must be alert to the signs of bleeding. It is important for healthcare professionals to overcome the barriers to primary prophylaxis and to take trauma-related precautions.

KEYWORDS
adolescents, children, hemophilia, intracranial hemorrhage, outcome

Essentials

- Neonatal period and cerebral shift were risk factors for neurologic sequelae in hemophilia with intracranial hemorrhage.

1 | INTRODUCTION

Spontaneous or posttraumatic bleeding into the musculoskeletal system is a typical manifestation of hemophilia. Intracranial hemorrhage (ICH) is a rare but life-threatening complication and has high morbidity and mortality risk in these patients [1]. Severe disease phenotype, presence of inhibitor, previous history of ICH, young age (under 2 years and especially in the newborn period), and trauma are known risk factors for ICH [2–4]. The prevalence of ICH and mortality rate are estimated at 1.9% to 12% and 2.5% to 20%, respectively [2,5,6]. As ICH may be asymptomatic, the actual frequency may be higher than the reported rates. Prophylactic factor replacement significantly decreases ICH incidence, but some patients may not receive prophylactic treatment due to economic or patient-related factors [7,8]. In addition, some patients may present with ICH before the diagnosis of hemophilia.

Although the factors predisposing to ICH are well-defined in the literature, the factors that determine long-term neurologic sequelae have not been clearly identified, and there are few studies on this subject [3,6]. The objective of this study was to investigate the risk factors for ICH and the rate of neurologic sequelae in children with hemophilia in Turkey.

2 | METHODS

A national retrospective study of ICH in persons with hemophilia was planned by the Thrombosis, Haemostasis, and Haemophilia Subcommittee of the Turkish Society of Paediatric Haematology. This study was approved by the Uludag University Ethics Committee on February 28, 2022 (decision number 2022-4/12). The study protocol, including the following parameters, was sent to all pediatric hematology departments via email. Data concerning the type of hemophilia, clotting factor (F)VIII and FIX levels, age at diagnosis of hemophilia and age at ICH, labor type for newborns with ICH, history of trauma or factor inhibitor before ICH, clinical symptoms, cranial imaging report, operation status, operation time after ICH, mortality, neurologic sequelae, and ICH recurrence were requested. The first 28 days

of life were considered the neonatal period. Patients with intracranial bleeding due to other causes, radiologically unproven ICH, or spinal hemorrhages were excluded. The cerebral shift was accepted as presence of brain midline shift of greater than 5 mm [9].

2.1 | Statistical analysis

The data were examined by Shapiro–Wilk test to determine whether or not it was normally distributed. The results are presented as SD, median, or frequency and percentage. Mann–Whitney U-test was used to compare nonnormally distributed data. Categorical variables were compared using Pearson's chi-square and Fisher's exact tests between groups. The Bonferroni test was used as a multiple comparison test. Binary logistic regression was performed, and odds ratios, along with accompanying 95% CIs, are reported. Variables with a P value of <.20 in the univariate model were included in the multivariate model. A $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed with IBM SPSS, version 23.0 (IBM Corporation).

3 | RESULTS

Twenty-two out of 35 centers reported cases. Two patients reported by 1 center were not included in the study because they had isolated spinal hemorrhage, so in total, 86 patients from 21 centers followed up between 1992 and 2021 were evaluated. All patients were less than 18 years of age at the time of ICH. The ratio of hemophilia A to B was 65:21. Severe, moderate, and mild hemophilia numbers were 65 (75.6%), 15 (17.4%), and 6 (7.0%), respectively. Seizure was the most common complaint and was present in 34 (39.5%) patients, followed by loss of consciousness (n = 21; 24.4%) and nausea/vomiting (n = 10; 11.6%). Other complaints were focal neurologic findings (n = 4; 4.65%), headache (n = 3; 3.5%), cardio-respiratory arrest (n = 2; 2.3%), irritability (n = 2; 2.3%), and hypotonia (n = 1; 1.2%). Nine patients (10.5%) had no complaints. These 9 patients were all diagnosed with hemophilia before ICH, and all had posttraumatic ICH. The intracranial bleeding sites were parenchymal (n = 29; 33.7%), combined (n = 21; 24.4%), subdural (n = 18; 20.9%), epidural (n = 9; 10.5%), subarachnoid (n = 5; 5.8%), and intraventricular (n = 4; 4.65%).

Thirteen patients (15.1%) had ICH in the neonatal period. In this group, the hemophilia A–to–hemophilia B ratio was 11:2, and the numbers of patients with severe, moderate, and mild hemophilia were 6, 3, and 4, respectively. The ratio of normal vaginal delivery to cesarean section was 12:1. Only 1 of these patients had a net vacuum applied (severe hemophilia), and there was no special note in the file for the others. Cerebral shift was detected in 54% (7/13), and surgery was performed in 8 patients (62%). Two of the 13 patients died, and 7 of 11 (64%) suffered from neurologic sequelae. None of them developed inhibitors. Two patients whose factor levels were measured as 8% and 10% were admitted in 1998; a single measurement was made, and the patients received fresh frozen plasma before blood sampling. There were no control samples as patients had died.

TABLE 1 Characteristics of patients with intracranial hemorrhage excluding those occurring in the newborn period.

Patient characteristics	Unknown hemophilia diagnosis (n = 33)	Known hemophilia diagnosis (n = 40)	P value
Age (mo) at the time of ICH, median (range)	7 (1-122)	31 (1-232)	<.001
Hemophilia A	25 (76%)	29 (72.5%)	>.05
Hemophilia B	8 (24%)	11 (27.5%)	
Mild	2 (6%)	0	>.05
Moderate	6 (18%)	6 (15%)	
Severe	25 (76%)	34 (85%)	
Trauma			>.05
Yes	21 (64%)	26 (65%)	
No	12 (36%)	14 (35%)	
Shift			>.05
Yes	8 (24%)	12 (30%)	
No	25 (76%)	28 (70%)	
Surgery			>.05
Yes	16 (48%)	20 (50%)	
No	17 (52%)	20 (50%)	
Inhibitor development after ICH			>.05
Yes	4 (12.5%)	5 (13%)	
No	28 (87.5%)	33 (87%)	
Sequelae			>.05
Yes	10 (31%)	8 (21%)	
No	22 (69%)	30 (79%)	
Exitus	1 (3%)	2 (5%)	-

ICH, intracranial hemorrhage.

After removal of the patients who had ICH in the neonatal period, the remainder were grouped into previously diagnosed or undiagnosed hemophilia at the time of ICH. When ICH occurred, hemophilia diagnoses were known in 40 (54.8%) and unknown in 33 (45.2%). Only 8 of 40 patients who were diagnosed before ICH were receiving regular factor prophylaxis and all of them had severe hemophilia. The characteristics of these patients are given in Table 1. The median age at ICH was significantly younger in the undiagnosed group compared with the diagnosed group ($P < .001$). There was no difference between these 2 groups in terms of hemophilia type, severity, surgery rate, presence of shift, sequelae rates, and history of trauma. Parenchymal bleeding was common in the diagnosed group (17 vs 7), and combined bleeding was common in the undiagnosed group (14 vs 4). Another

TABLE 2 Characteristics of patients with intracranial hemorrhage according to age stratification excluding newborn period.

Patient characteristics	1 mo to 5 y (*n* = 61)	6-12 y (*n* = 8)	13-18 y (*n* = 4)
Unknown	32	1	-
Known	29	7	4
Hemophilia A	47	6	1
Hemophilia B	14	2	3
Mild	1	5	-
Moderate	8	2	2
Severe	52	1	2
Trauma			
Yes	69	6	2
No	22	2	2
Shift			
Yes	19	-	1
No	42	8	3
Surgery			
Yes	30	5	1
No	31	3	3
Inhibitor			
Yes	8	1	-
No	53	7	-
Sequelae			
Yes	16	-	1
No	45	6	2
Exitus	-	2	1

difference between the 2 groups was that the diagnosed group was operated on more frequently in the first 24 hours (18/40 vs 6/33). However, the surgery time of 5 patients whose diagnosis was previously unknown could not be reached.

Because the age ranges were very wide, patients outside the neonatal period were divided according to 3 different age groups (1 month to 5 years, 6-12 years, and 13-18 years) and reevaluated. However, statistics could not be performed because the distribution between the groups was not homogeneous (Table 2).

In the study group, including the neonates, 5 patients (5/86) died during the first episode of ICH. The characteristics of these patients are given in Table 3. The rate of mortality in the neonatal period was higher compared with the other periods (15% [2/13] vs 4% [3/73]; $P > .05$), but this was not significant. One of 3 patients who died outside the neonatal period had an inhibitor before ICH, and 1 other patient developed an inhibitor during ICH treatment. The patient who was diagnosed and died after a traffic accident also had multiple organ traumas outside the central nervous system.

On follow-up of children with ICH, the rate of neurologic sequelae was 25 of 81 (30%). The sequelae distribution according to the period in which ICH occurred is shown in Table 4. Neurologic sequelae were more common in the neonatal period (7/11 vs 18/70; $P < .05$).

Only 20% (8/40) of patients with a known diagnosis of hemophilia were receiving regular prophylaxis before ICH. Of these patients, 3 had hemophilia B, and 5 had hemophilia A. Three of the 8 patients receiving prophylaxis were receiving prophylaxis once a week, and the remaining were receiving prophylaxis 2 days a week. Three patients receiving prophylaxis once a week had hemophilia A and experienced bleeding at 20, 34, and 36 months. Traumas of these patients included falling out of bed (2), falling from the stairs (1 patient, 2 weeks ago), falling from a horse (1), falling while running (1), and hitting his head on the door (1). The patient who had no history of trauma had a history of concurrent drug use due to viral upper respiratory tract infection. The last prophylaxis of the patients was between 36 and 72 hours. Patients who received prophylaxis compared with the no-prophylaxis group were more likely to have a history of trauma (7/8 vs 19/32; $P > .05$) and a lower rate of sequelae (1/8 vs 7/32; $P > .05$) but these differences were not found to be significant.

There were 9 patients who developed inhibitors during the follow-up period after the first ICH. Eight of them had hemophilia A, and immune tolerance therapy was given, but the inhibitor became negative in only 3. The patient who could not be given immune tolerance therapy had hemophilia B. Sequelae were reported in 2 of these 8 patients. The effect of new inhibitor development on sequelae could not be demonstrated.

On follow-up, recurrence of ICH occurred in 8 of 81 (10%) patients between 5 months and 12 years, and 1 of them died during the second ICH. Five of the 8 patients had hemophilia A, and 3 had hemophilia B. Seven of them had severe hemophilia, and 1 had mild hemophilia. The patient who had a recurrence of ICH after 5 months had mild hemophilia and was diagnosed with West syndrome (the triad of epileptic spasms, hypsarrhythmia, and developmental stagnation or regression). The patient who died had severe hemophilia. His first bleeding occurred when he was 6 months old. His second bleeding occurred at the age of 4 years, and an inhibitor developed during his second bleeding; he died 50 days after the bleeding. All patients suffering from ICH were given secondary prophylaxis for at least 6 months. However, in these patients with recurrence, their compliance with prophylaxis had decreased after 1 year, and they did not take their prophylaxis properly during the second bleeding. In 7 of 8 patients, sequelae had developed after the first ICH. Recurrence of ICH was more frequent in patients who developed sequelae ($P < .001$).

In logistic regression analysis, the effect of ICH in the neonatal period, previously known hemophilia diagnosis, type and severity of hemophilia, location of ICH, presence of trauma, presence of cerebral shift, need for surgery, timing of surgery, and the development of inhibitor were analyzed. In univariate analysis, the variables with the greatest effect on the development of neurologic sequelae are given in Table 5. The presence of cerebral shift and development of ICH in the neonatal period were found to remain significant in multivariate analyses.

TABLE 3 Characteristics of patients who died.

No.	Time of ICH	Trauma	Diagnosis	Treatment before ICH	Bleeding area	Shift	Surgery	Exitus time after ICH
1	13 y old	No	Severe hemophilia A (inh+ 74 BU)	Poor compliance with prophylaxis	Intraventricular	No	Yes (after 8 h)	Seventh day
2	7 y old	No	Severe hemophilia A	On-demand	Subarachnoid Subdural	No	Yes (on day 12)	15th day[a]
3	10 y old	Traffic accident	Mild hemophilia A (FVIII, 14.6%)	Newly diagnosed	Subdural	No	No	Third day
4	Newborn	Normal vaginal delivery	Mild hemophilia A[b] (FVIII, 10%)	Newly diagnosed	Parenchymal Ventricular	No	No	Fourth day
5	Newborn	Normal vaginal delivery	Mild hemophilia A[b] (FVIII, 8%)	Newly diagnosed	Parenchymal	Yes	No	Fifth day

BU, Bethesda Units; FVIII, factor VIII; ICH, intracranial hemorrhage; inh+ 74 BU, inhibitor was present and 74 BU.
[a]There was a partial response at the beginning, the inhibitor became positive on the 12th day, and the bleeding reoccurred.
[b]Factor levels were unknown before fresh frozen plasma was given.

4 | DISCUSSION

ICH in persons with hemophilia is a well-known but rare complication. In children, the pooled ICH incidence rate is 7.4 per 1000 person-years; in neonates, the pooled cumulative incidence is 2.1 per 100 live births [10]. Factors predisposing to ICH in these patients have been widely reported, but factors that can lead to neurologic sequelae have been addressed only in a few studies [3,6]. Thus, the main purpose of this study was to evaluate factors affecting the risk of long-term neurologic sequelae in children with hemophilia who had a history of ICH.

In the present study, head trauma was the most important risk factor for ICH and was present in 65% of our patients. This rate has previously been reported to vary between 35% and 69.2% [4,11,12]. Spontaneous ICH occurs more often in adults, while trauma-induced ICH is more prevalent in children [13]. Factor treatment in these patients before any procedure in emergency units is vital [14]. Unfortunately, we could not evaluate the effect of delay in treatment on neurologic sequelae since we could not clearly obtain the time between trauma and the first factor replacement therapy. Surgery was performed in approximately half of the patients. Chalmers et al. [3] and Haque et al. [15] reported surgery rates as 33% and 18%, respectively. The high surgery rate in this study may be due to the presence of an unknown bleeding disorder at the time of initial presentation and the high rate of brain shift. The surgery rate in patients with brain shift was 81.5% (22/27).

TABLE 4 The distribution of neurologic sequelae according to the timing of the first episode of intracranial hemorrhage.

Neurological sequelae	Newborn period (*n* = 7)	After the newborn period (*n* = 18)
Epilepsy	3[a] (2)	8[b] (6)
Hydrocephalus	1 (1)	2 (1)
Hemiparesia	2 (1)	3 (2)
Speech abnormality	-	3 (1)
Mild developmental retardation	1 (1)	1
Sixth nerve palsy	-	1

Cerebral shift-related sequelae are given in parentheses.
[a]One of them had developmental retardation.
[b]Two of them had developmental retardation.

In our series, 33 of 73 (45%) who had bleeding outside the neonatal period had no family history or previous hemophilia diagnosis. While the age at which ICH occurred in these patients was around 7 months, it was significantly later at 31 months in previously diagnosed patients. In 2 recent studies involving patients who were previously diagnosed with hemophilia, the median age of ICH was reported as 2 years [5,12]. After the neonatal period, the highest rates of ICH occur in the first years of life and frequently at ages before prophylactic therapy is initiated [8]. Although parents are reluctant about giving regular factor replacement and the rate of primary prophylaxis is low, an "overprotective" attitude within the family can actually protect the sick baby for a limited time, and the median ICH age is in a later period [16,17].

ICH-related mortality has previously been reported to vary from 2.5% to 25% [18,19]. In our series, the mortality rate was at the lower end of this range at 5.8%. Two of these patients died in the neonatal period with no family history. Their factor levels had been high because they were examined after receiving fresh frozen plasma. Another was diagnosed with hemophilia after a traffic accident and had multiple other system traumas. In the rest, 2 patients with previously diagnosed hemophilia had high titer inhibitor levels and died despite aggressive treatment. In the literature, the factors associated with mortality have been reported to be the neonatal period, being previously undiagnosed, and the presence of high inhibitor levels [2–4,15,20]. Öner et al. [21] found that 14 of the 20 patients who

TABLE 5 Univariate and multivariate analysis of risk factors for neurologic sequelae.

Effective risk factors for neurologic sequelae or only effective risk factors	Univariate LR					Multivariate LR				
				95% CI					95% CI	
	Wald	*P*	OR	Lower	Upper	Wald	*P*	OR	Lower	Upper
ICH in newborns	5.615	.02	5.06	1.32	19.31	4.134	.04	4.67	1.06	20.63
Hemophilia type	1.874	.17	2.06	0.73	5.82	2.129	.15	2.38	0.74	7.62
Cerebral shift	8.841	.003	4.67	1.69	12.88	4.301	.04	3.48	1.07	11.28
Surgery	3.666	.06	2.64	0.98	7.10	0.309	.58	1.40	0.43	4.54

ICH, intracranial hemorrhage; LR, logistic regression; OR, odds ratio.

were diagnosed with hereditary bleeding disorders were undiagnosed until ICH. Bladen et al. [6] reported that 4 of the 6 patients who died after ICH were in the neonatal period, and 3 of them were undiagnosed. In the study of Haque et al. [15], 2 of the 5 persons with hemophilia who died were in the neonatal period, and 4 patients were previously undiagnosed. In the series reported by Witmer [5], 3 of the 6 patients who died were reported to have inhibitors. The nonspecific symptoms of ICH in the neonatal period and confusion with sepsis may cause delay in diagnosis and treatment [19]. This has been associated with both increased mortality and morbidity.

ICH-related morbidity was reported as 23% to 60% [6,11,19,22]. There are few studies evaluating the factors affecting the development of neurologic sequelae. While Bladen et al. [6] reported that hemorrhages in the neonatal period increased the risk of neurologic sequelae, Chalmes et al. [3] found that intracerebral hemorrhages increased the risk of sequelae compared with those occurring in the subdural area. In the present study, the bleeding site was not a risk factor for neurologic sequelae, but the odds ratio for neurologic sequelae was 4.7 for bleeding in the neonatal period and 3.5 for cerebral shift. Delays in diagnosis due to nonspecific findings in neonates may increase morbidity. Cerebral shift, on the other hand, may be associated with the development of neurologic sequelae because of wide hemorrhage and cerebral damage. After the neonatal period, any persons with hemophilia with a history of trauma and unexplained headaches should undergo a careful physical examination and computed tomography or magnetic resonance imaging scans [23].

Recurrent bleeding was reported in 8 patients in the present series; 7 had developed sequelae after the first ICH. Witmer [5] reported that previous ICH increased bleeding recurrence 3.62 times. In another study, inhibitor positivity was a risk factor for recurrent bleeding [4]. For long-term neurologic well-being, close follow-up of all patients who have had ICH, especially those with sequelae, is important [24].

Prophylaxis has been shown to reduce joint damage and dangerous bleeding, such as ICH [7,8,17]. It has been reported that the risk of developing ICH in patients not receiving prophylaxis is 50 times greater than in those receiving full prophylaxis and 3.35 times greater compared with those receiving partial prophylaxis. In that study, posttraumatic ICH was reported in 2 patients who received complete prophylaxis, and no spontaneous bleeding was observed [7]. Even partial- and low-dose prophylaxis has been shown to reduce the risk of ICH, especially in countries with limited economic resources. In the present study, only 8 out of 40 patients with a previous diagnosis of hemophilia were receiving prophylaxis, and 7 of these patients had a very clear history of trauma, and sequelae were observed in only 1.

Although the World Federation of Hemophilia recommended primary prophylaxis in 1994, its reimbursement by the social security institution in our country and its widespread use began after 2007 [25]. All patients who were diagnosed and received prophylaxis were patients who started prophylaxis and had bleeding after this date. Patients who did not receive prophylaxis were 10 patients born before 2007, 6 patients under the age of 1 year, 3 patients between the ages 12 and 18 years, 5 patients from discordant families, and 1 patient who was an immigrant. Risk of inhibitor development, vascular access problems, and physicians' hesitations contribute to starting prophylaxis later and postponed prophylaxis may lead to intracranial bleeding in this period. Treatment noncompliance continues to be a serious problem for all ages, and efforts are being made to eliminate this problem through education of patients and relatives via health professionals and associations.

There are limitations in our retrospective study. Since the characteristics of patients who did not have ICH were not known, we could not determine the frequency of and risk factors for ICH, although this is widely reported in the literature. Data from centers participating in this retrospective study were included over a wide period (1992-2021), and there were developments in therapy over this period and differences in experience between centers.

5 | CONCLUSION

ICH in the neonatal period and cerebral shift were the 2 risk factors for the development of neurologic sequelae that we identified, and trauma was an important cause of ICH in patients. Therefore, it is important for healthcare professionals to overcome the barriers to primary prophylaxis and to take trauma-related precautions. Long-term neurologic development and cognitive functions of patients who have had ICH should be closely monitored, and the risk of recurrence should be kept in mind during follow-up. Alerts in neonatal departments about the signs of bleeding and awareness among neurosurgeons about bleeding

diseases may contribute to the reduction of neurologic sequelae by recognizing newly diagnosed patients earlier.

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AUTHOR CONTRIBUTIONS

M.S.E., A.Ü., S.K., and H.Ö. designed the project. M.S.E. collected data and analyzed results. M.S.E. produced the first draft of the manuscript, which was subsequently finalized by A.Ü., S.K., and H.Ö. Other authors completed and sent their patients' detailed information. Other authors agreed to share their patients' information and completed the detailed patient form. All authors reviewed and approved the final version of the manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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