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Hemophilia in pediatric age

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ABSTRACT

Hemophilia represents the most common inherited bleeding disorder linked to the X chromosome, which, if not properly treated, can lead to lifelong disabilities. This article presents the cases of 18 patients with hemophilia admitted between 2006-2022 to the Pediatric Oncohematology Department, Clinic II Pediatrics, Emergency County Hospital Craiova. Clinical and evolutionary aspects of the hospitalized patients are presented, including age at the time of diagnosis, heredocolateral history, symptoms at onset, clinical manifestations during the course of hospitalization, complications and prophylactic treatment.

Keywords: hemophilia A, hemophilia B, child, prophylaxis

INTRODUCTION

Hemophilia is the most common among severe bleeding disorders and benefits the most effective and safe treatment among all monogenic diseases [1]. If not appropriately administered from early childhood, it can lead to chronic illnesses and disabilities throughout life [2].

There are two types of hemophilia: hemophilia A (deficiency of coagulation factor VIII) and hemophilia B (deficiency of coagulation factor IX). The severity of hemophilia depends on the plasma levels of factor VIII and IX: severe (<1%), moderate (1-5%), mild (5-40%) [3].

Hemophilia A and B are recessive X-linked inherited diseases. In approximately one-third of cases, so-called sporadic cases, where there are no family histories of hemophilia, a new mutation on the X chromosome of the factor VIII or IX gene will be found. Hemophilia occurs due to mutations in the F8 gene (Xq28), which encodes coagulation factor VIII, or in the F9 gene (Xq27), which encodes factor IX, both located on the X chromosome and transmitted from mother to fetus [4].

The prevalence of hemophilia A is 1:5000-10000 births, and hemophilia B is 1:30000 births in males. Within a family, affected individuals always manifest the same type and severity of hemophilia. Carrier females of the genetic anomaly may exhibit mild bleeding manifestations [5,6].

Hemophilia affects males of all social groups, races, and ethnicities, from all geographical regions. Hemophilia has often been called the "Disease of Kings" because it has affected some of the royal personalities of Europe through the daughters of Queen Victoria of England. Hemophilia is one of the oldest known genetic diseases, described in the Talmud in the 2nd century AD. The first modern description of the disease and its mode of transmission is credited to the American physician John Conrad Otto in 1803. Research continued until the years 1982-1984 when the production of recombinant factors VIII and IX through genetic engineering was pioneered [7].

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MATERIAL AND METHOD

The study was conducted on children with hemophilia under the care of the Pediatric Oncohematology Department, Clinic II Pediatrics, during the period 2006-2022. Data were collected from the observation sheets of patients diagnosed with hemophilia type A and B.

RESULTS

The study included 18 male children with hemophilia. Regarding the clinical form of the disease, 11 children (61%) had hemophilia A, and 7 children (39%) had hemophilia B. Regarding the year of diagnosis: one child in 2006, 2 children each in 2007, 2008, and 2009, one child each in 2010, 2011, 2012, and 2013, 2 children in 2015, one child each in 2018, 2019, 2020, 2021 and 2022.

The origin was rural for 16 children (89%), including 10 with hemophilia A and 6 with hemophilia B, and urban for 2 children (11%), one with hemophilia A and one with hemophilia B. The county of origin for hemophilia patients: 17 children in Dolj (94.4%) and one child in Olt (5.6%).

The diagnosis of hemophilia was established for 12 children (66.7%) at the Pediatric Oncohematology Department in Craiova, for 5 children (27.8%) at the Pediatric Clinic at the Fundeni Institute in Bucharest, and for one child (5.5%) at "Louis Turcanu" Hospital in Timisoara. For all children in the study, the diagnosis was established by measuring the level of factor VIII and factor IX (Table 1).

TABLE 1. Hospital where kids were diagnosed with hemophilia

Hospital	Number of patients	Percentage
Pediatric Oncohematology Department, Clinic II Pediatrics, Emergency County Hospital Craiova	12	66.7%
Pediatric Clinic – Clinical Institute Fundeni Bucharest	5	27.8%
Louis Turcanu Hospital Timisoara	1	5.5%

Distribution by age groups at the time of diagnosis: 0-1 years – 5 children, 1-3 years – 8 children, 3-6 years – 3 children, 6-12 years – 2 children (Figure1).

The average age at the time of diagnosis was 2 years and 6 months ± 2 years and 4 months (1 year and 3 months - 8 years).

Based on the severity of the disease, three forms were identified. 11 children (61%) presented the severe form, of which 8 had hemophilia A and 3 had hemophilia B; 5 children (28%) presented the moderate form, of which 3 had hemophilia A and 2 had hemophilia B; and 2 children (11%) had the mild form, both with hemophilia A (Figure 2).

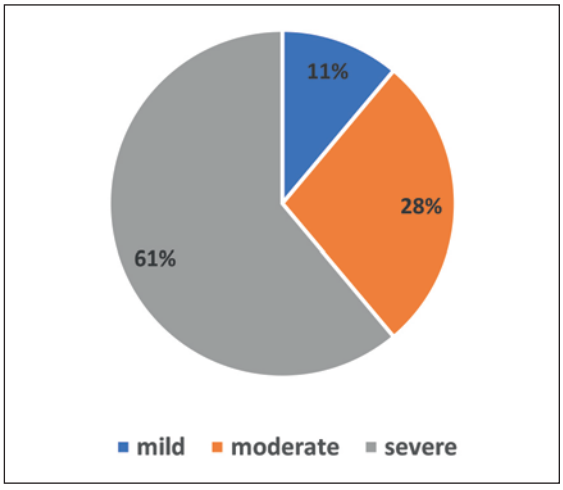

FIGURE 2. Distribution by severity of the disease

The heredocollateral history in children with hemophilia is as follows: 2 brothers with hemophilia B, mild form – one diagnosed at 6 years and 3 months, the other at 8 years; another 2 brothers with severe hemophilia A – one diagnosed at 1 year and the other at 1 year and 11 months; 2 twin brothers with severe hemophilia A – diagnosed at the age of 1 year and 2 months. A child with hemophilia B, moderate form - in his family, the maternal grandfather died of hemophilia, and a maternal nephew is known to have hemophilia B, moderate form.

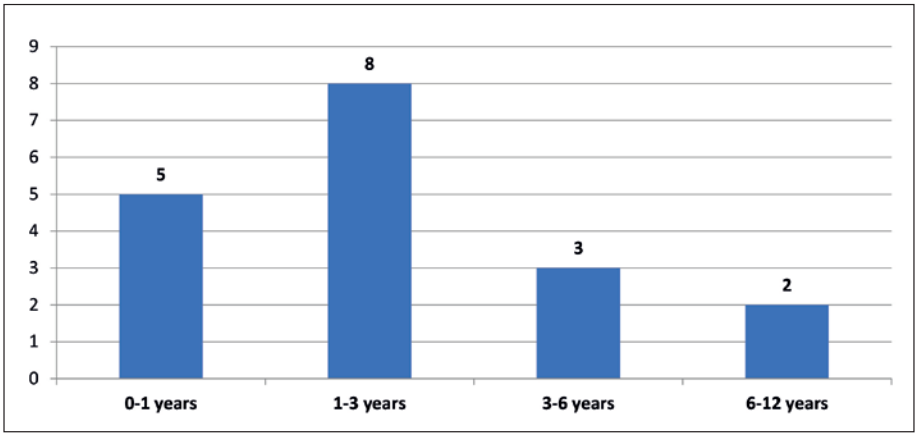

FIGURE 1. Distribution by age groups at the time of diagnosis

Clinical manifestations at the time of diagnosis were: muscular hematomas, ecchymosis, recurrent epistaxis (Table 2).

TABLE 2. Clinical manifestations at the time of diagnosis

Hemophilia type	Clinical manifestations at the moment of diagnosis	Number
Hemophilia A	Muscle hematomas	6
	Ecchymosis	5
	Recurrent epistaxis	4
	Subcutaneous hematoma	4
	Hematoma on the upper lip	1
	Prolonged bleeding on the upper lip	1
Hemophilia B	Muscle Hematomas	3
	Ecchymosis	2
	Recurrent epistaxis	3
	Prolonged bleeding at the venous access site	3
	Rectal bleeding	1

The distribution by age groups in the year 2022 for children with hemophilia is as follows: ages 1-3 years – 3 children, ages 6-12 years – 7 children and ages 12-16-8 children (Figure 3).

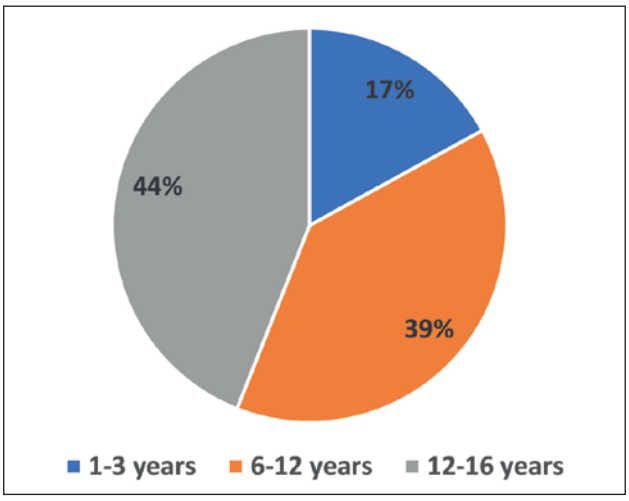

FIGURE 3. Distribution by age groups in 2022

Average age in 2022: 9 years and 6 months ± 4 years and 8 months (1 year – 16 years).

Clinical manifestations in children with hemophilia A during the course of the disease were as follows (Table 3):

- Hemarthrosis (bleeding into joins): knee – 6 children, ankle – 5 children, elbow – 6 children, shoulder: 3 children
- Muscular hematomas: leg – 9 children, thigh – 2 children, arm – 1 child, buttocks and abdomen – 1 each
- Subcutaneous hematomas: 5 children
- External bleedings: gum bleeding – 6 children, recurrent epistaxis – 4 children, conjunctival bleedings – 3 children, dental bleedings – 2 children
- Bruising: 5 children

Clinical manifestations in children with hemophilia B during the course of the disease were as follows (Table 3):

- Hemarthrosis: ankle – 2 children, elbow – 3 children, shoulder - 1 child;
- Muscular hematomas: leg – 2 children, arm – 1 child
- Subcutaneous hematomas: 2 children
- External bleedings: gum bleeding – 4 children, dental bleeding – 1 child, rectal bleeding – 1 child
- Bruising – 4 children

TABLE 3. Clinical manifestations of children with hemophilia during the course of the disease

Hemophilia A	Number of cases	Hemophilia B	Number of cases
Hemarthrosis		**Hemarthrosis**	
a. Knee	6	a. Ankle	2
b. Ankle	5	b. Elbow	2
c. Elbow	5	c. Shoulder	1
d. Shoulder	3		
Hematomas		**Hematomas**	
• Muscular		• Muscular	
a. Legs	9	a. Legs	2
b. Arms	1	b. Arms	1
c. Thigh	2		
d. Hips	1		
e. Abdomen	1		
• Subcutanate	5	• Subcutaneous	2
External bleeding		**External bleeding**	
• Gum bleeding	6	• Gum bleeding	4
• Epistaxis recidivated	4	• Epistaxis recidivated	2
• Dental bleeding	2	• Dental bleeding	1
• Conjunctival bleeding	3	• Rectal bleeding	1
Ecchymosis	5	**Ecchymosis**	4

We present 2 cases:

First case: A boy diagnosed at the age of 3 months with blindness in both eyes, affecting the optic nerve, and with severe congenital hemophilia A. At the age of 3, he attends a special school for the blind in Bucharest; he received prophylactic treatment less frequently. At the age of 14, while at home, he presented with a left fronto-temporo-parietal subdural hematoma, which was surgically treated at the Emergency Children's Hospital "Grigorie Alexandrescu" in Bucharest, with subsequent favorable evolution and no sequelae. We considered that it would have been possible for him to have had a cerebral hemorrhage with optic nerve involvement at birth, leading to blindness.

Second case: A boy diagnosed with severe congenital hemophilia B at the age of 1. The mother refused the diagnosis and did not return to the hospital with the child. At the age of 4, he presented with abundant rectal bleeding, for which he was hospitalized. He was diagnosed with a polyp in the large intestine, which was surgically treated. At the age of 7, he had gangrenous appendicitis, requiring another surgical intervention. The mother did not consistently come to the hospital according to appointments, and the child repeatedly presented with bleeding manifestations (gum bleeding, nosebleeds).

Complications of the disease in children with hemophilia A: secondary iron-deficiency anemia due to repeated bleeding in 10 children, chronic synovitis in the knee in 4 children, and in the elbow in 2 children. In those with hemophilia B: secondary iron-deficiency anemia due to repeated bleeding in 4 children, chronic synovitis in the knee in 1 child, and in the elbow in one child (Table 4).

TABLE 4. Complications of the disease in children with hemophilia

Type of hemophilia	Complications	Number of cases
Hemophilia A	Iron-deficiency anemia secondary to bleeding	10
	Chronic synovitis in the knee	4
	Chronic synovitis in the elbow	2
	Osteitis of the maxilla	1
Hemophilia B	Iron-deficiency anemia secondary to bleeding	4
	Chronic synovitis of the knee	1
	Chronic synovitis of the elbow	1

DISCUSSIONS

Until 2022, in the Pediatric Oncohematology Department, Clinic II Pediatrics, Emergency County Hospital of Craiova, 58 children with hemophilia were recorded, of whom 4 died after the age of 18. From 2006 to the present, 18 children are in our records.

Of the 18 children with hemophilia, 11 (61%) had hemophilia A, and 7 (39%) had hemophilia B. In another study, the ratio of hemophilia A to hemophilia B is approximately 4:1 [1,2]. In our small group of children, this ratio is not relevant. Most children were diagnosed in the Pediatric Oncohematology Department. Severe forms of the disease were present in 11 children (61%), 8 with hemophilia A and 3 with hemophilia B. The average age at diagnosis was 2 years and 6 months ± 2 years and 4 months, ranging from 1 month to 8 years and 3 weeks. In a study by Uijil et al., severe hemophilia is diagnosed earlier, in the infant period, while mild forms are diagnosed around the ages of 5-14 [8]. An infant of 1 month and 3 weeks was diagnosed in Timisoara with severe hemophilia A, while an 8-year-old had mild hemophilia B diagnosed in Craiova. In 2022, the average age was 9 years and 6 months ± 4 years and 8 months, ranging from 1 year to 16 years.

Prenatal diagnosis is done through chorionic villus sampling or amniocentesis, performed between weeks 11-14 of gestation. Non-invasive testing of fetal cells in maternal plasma can be done from week 10 of gestation [9].

As described in the literature, clinical manifestations at the time of diagnosis were hematomas, bruises, and prolonged bleeding in children with hemophilia [10]. Clinical manifestations in the course of the disease in children with hemophilia A included joint bleeding, muscular and cutaneous hematomas with various locations, and external bleeding, similar to those with hemophilia B [11,12]. The child with blindness, being at home, presented with headaches, later speech disorders, and after a cranial CT scan, the diagnosis of cranial hematoma was established. Since he was diagnosed with severe hemophilia A, he received less frequent prophylactic treatment, leading to the development of a cerebral hematoma. After surgical intervention, the child showed no postoperative sequelae.

The child with severe hemophilia B had more often bleeding manifestations (nosebleeds, gum bleeding) because the mother did not adhere to hospital appointments. However, children with hemophilia A and B did not present severe complications as seen in children with hemophilia before the introduction of recombinant factor VIII and IX treatment.

All children with hemophilia receive prophylactic treatment with recombinant factor VIII and IX, and none of the children in the study developed inhibitors. Both in children with hemophilia A and those with hemophilia B treated with recombinant factor VIII and IX, the development of inhibitors against replacement therapy is a major complication [13-15].

The goal of treating a child with hemophilia is to manage the disease as independently as possible and lead a normal, healthy life. Safe prophylaxis has been possible since 1992, with the approval of the first recombinant factor for replacement therapy [16]. In a study with many patients, Manco-Johnson et al. demonstrated the effectiveness of prophylaxis with recombinant factor VIII/IX in reducing joint bleeding and other life-threatening hemorrhages and to decrease the risk of joint damage in children with severe factor VIII/IX deficiency [17].

Due to the development of inhibitors with recombinant factor treatment, Emicizumab, a subcutaneously administered monoclonal antibody, was introduced in 2018 for children with hemophilia A without inhibitors [18,19].

In our clinic, we have submitted requests for Emicizumab, but as of now, we have not received

any response. This treatment could improve the quality of life for our patients with hemophilia A.

In 2020, the White Paper of Hemophilia in Romania was released with the aim of analyzing hemophilia management in Romania and improving the quality of life for patients. World Hemophilia Day is on April 17 in honor of the founder of the Federation, Frank Schnabel, a successful businessman born with severe Hemophilia A on this date.

In 2022, the first gene therapy for adults with severe hemophilia A was approved by the European Medicines Agency (EMA). From February 2023, EMA has granted marketing authorization for gene therapy for adults with severe hemophilia B without inhibitors, but this is considered "an orphan medicine" [20,21].

These gene therapies open new horizons for hemophilia treatment, and their introduction in pediatric patients requires in-depth studies.

CONCLUSIONS

1. Hemophilia A, as well as the severe form, were present in over half of the children.
2. The most commonly encountered symptoms were joint bleeding (hemarthrosis) and hematomas with various locations.
3. All patients in the study did not develop inhibitors following treatment with clotting factors.

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