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Hemophilia or "Royal Disease"

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Abstract: Introduction: Hemophilia is an inherited sex-linked and life-threatening disorder of hemostasis, preventing proper blood coagulation due to the absence of a specific coagulation factor. Purpose: The purpose of this study is to review all data related to hemophilia disease. Material and Methods: The study material consisted of recent articles on the topic found mainly in valid databases such as PubMed and the Hellenic Academic Libraries Association (HEAL-Link). Results: For patients with hemophilia there is no damage to the original hemostasis function (where platelets are mainly involved), but the fault lies in coagulation. As such, flow time testing and *in vivo* monitoring of platelet function are completely normal. Consequently, a simple slip that happens to everyone does not lead to hemarthrosis—since initial hemostasis is normal—the same happens to hemophilic patients. Conclusions: Proper collaboration of the therapeutic team with the patient in conjunction with an individualized treatment program adapted to the needs of each patient and especially the child leads to effective improvement of the hemophilic patient.

Key words: Hemophilia, royal disease.

1. Introduction

Hemophilia is a sex-linked recessive and lifelong rare inherited haemostatic disorder that prevents proper blood coagulation in the absence of a specific coagulation factor. There are two types of hemophilia: hemophilia A, which is caused by a lack of factor VIII, and hemophilia B, which is caused by a lack of factor IX [1].

Hemophilia affects males and is passed on to daughters by the father. A hemophilic daughter will be the carrier of the disease. Her sons will have a 50% chance of being hemophilic and her daughters will have a 50% chance of being carriers. A girl can be hemophilic only in the case where her mother is a carrier and her father suffers, which is very rare. Sometimes hemophilia is not inherited, but sporadic, where a hemophilic boy is born by a mother who is not a carrier. In this case, the damage is to the same person's gene, called gene mutation [2].

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Hemophilia A accounts for 85% of cases, while B is about five times less common than hemophilia A (incidence of hemophilia A, 1/10,000 inhabitants, and hemophilia B, 1.4/100,000 inhabitants). Today in Greece about 900 people suffer from Hemophilia, while in Europe it is estimated that about 33,000 and about 250,000 worldwide [3].

The separation between hemophilia A and B was made only in 1952 and can only be performed by blood test. Hemophilia B is also called Christmas, taking the name of the first young patient diagnosed with it [1].

2. Purpose

The purpose of this study is to review all data related to hemophilia disease. Specifically, it refers to the disease's diagnosis, its clinical manifestation, symptoms, treatment as well as its complications.

3. Material and Methods

The study material consisted of recent articles on the topic found mainly in valid databases such as PubMed and the Hellenic Academic Libraries

Association (HEAL-Link), using the following keywords: hemophilia, royal disease. The exclusion criterion for articles was a language other than Greek and English.

4. Historical Background

The earliest historical reference is found in a Jewish text of the 2nd century BC (Rabbinical Rulings), which states that boys who had previously lost two former brothers from bleeding during the circumcision were excluded from this procedure. The Jewish physician Moses Maimonides (1135-1204) made this decision for the sons of a woman who had been married twice, clearly considering the hereditary nature of the disease [4, 5]. The Arab physician Albucasis (1013-1106) also describes the case of a family where men died after minor injuries [4, 5].

The first contemporary description of hemophilia is attributed to Dr. John Conrad Otto, a physician in Philadelphia, who published a treatise in 1803 entitled "An Account of a Hemorrhagic Disposition Existing in Certain Families", where he clearly demonstrated the tendency of males to bleed. However, the first use of the term "haemophilia" was made in 1823 by Hopff in his study on the disease [6, 7].

4.1 The Spread of the Disease within the Kings

Hemophilia is often described as a "royal disease", mainly due to the disease of many members of royal families of Europe. Queen Victoria had no ancestors with the disease, but after the birth of her 8th child, Leopold, in 1853, it became obvious that he was suffering from hemophilia. Leopold died at only 31st years old by cerebral hemorrhage after falling [8].

Two of Queen Victoria's daughters, Alice and Beatrice, were carriers of the disease and, through them, the disease was transmitted to several royal families in Europe, including Spain and Russia. The most famous hemophilic is Tsar's son, Nicholas II of Russia, Alex (Alexei), born in 1904. His disease was considered the cause of Rasputin's access to the royal family's interior leading to the downfall of the royal dynasty [9].

5. Diagnosis

For patients with hemophilia there is no damage to the original hemostasis function (where platelets are mainly involved), but the fault lies in coagulation. As such, flow time testing and *in vivo* monitoring of platelet function are completely normal. Consequently, a simple slip that happens to everyone does not lead to hemarthrosis—since initial hemostasis is normal—the same happens to hemophilic patients. So the hemophilic continues his activity and he almost forgets that he had stumbled! Later, however, he wakes up frequently during his sleep having intolerable pain due to the swelling of this joint. [10]

After bleeding stops with the decisive involvement of the platelets, and after some time, the permanent clot is normally formed, so there is no bleeding in the joints that creates a problem [11].

In hemophilic patients [1], it takes too long for the permanent clot to form (due to the coagulation disorder).

If formed, it is of poor quality and almost always blood escapes slowly into the joint cavity.

When it is filled with blood, severe discomfort begins, leading the patient to wake up in the night with pain.

6. Disease's Manifestation

Hemophilia is characterized by the onset of bleeding from various organs. Bleeding may be obvious, related to the skin, but it can also affect internal organs, such as the brain. It may occur after an injury or a surgery, but it can also be automatic without a clear cause [12].

The severity of hemophilia manifestations is determined by the amount of coagulation factor present in the blood. Thus, hemophilia may be [13]:

- mild;
- moderate;

- heavy.

In normal subjects, the activity of factor VIII or factor IX ranges from 50-150%. In mild hemophilia there is only 5-30% of the physiological activity of the agent. Patients with mild hemophilia develop prolonged bleeding only after serious injury or surgery; they do not bleed frequently, and may never develop severe bleeding [14].

In moderate hemophilia, 1-5% of the factor's physiological coagulant activity is observed. Patients with moderate hemophilia develop prolonged bleeding after serious injuries, surgery and dental procedures. They bleed about once a month, but rarely do they bleed automatically [15].

Finally, in severe hemophilia, the activity factor is less than 1%. Patients usually have bleeding episodes once or twice a week and these episodes are often automatic. For the most part, patients with hemophilia A suffer from the severe form of the disease (about 7 in 10 patients) [16].

The most common bleeding is as follows [17]:

- contusions (bruises);
- gingival bleeding;
- nasal bleeding;
- hemarthrosis (joint bleeding);
- bleeding in the muscles;
- cerebral hemorrhage;
- bleeding in the nasopharynx;
- hematemesis/melaena (bleeding from the gastrointestinal tract).

As for the clinical manifestations of the disease, these include [17]:

- Joints: in the form of heamarthrosis. In people with severe hemophilia, hemarthrosis appears from the age of 1-3 years. It is continued several times, every 1-2 weeks throughout their lives (70% of episodes);
- Muscles: as superficial or "deep" hematomas;
- Skin: contusions (bruises);
- Mucous membranes: as gastrorrhea;
- Brain: as a meningo-cerebral haemorrhage;
- Surgery, large or small such as tooth extraction: as prolonged bleeding;
- Nasal bleeding (rhinorrhea), gingival bleeding or hematuria.

7. Complications

The most common complications are the following.

7.1 Hemophilic Arthropathy

This arthropathy is the major complication of hemorrhagic disease. It is essentially degenerative arthropathy observed in these patients as a result of hemorrhage into the joints [18]. The cartilage of the articular surfaces undergoes the chronic effect of strong proteolytic coagulant enzymes, and as a result it is altered, denatured and eventually loses its elastic stability. Fibrosis extends even to the surrounding soft tissues of the joint creating an osteoporotic alteration of the adjacent bone elements of the joint that leads to their complete deformation. Hemorrhagic arthropathy is accompanied by muscle atrophy above and below the specific joints (characteristic of the disease) while at the same time developing spinal counterbalancing positions and damaging the major joints, which usually impairs patients' mobility and burdens their already bad psychism [19]. Today, with generalized replacement therapy and regular physiotherapy, impaired mobility (dysfunctional joints) is becoming increasingly rare.

7.2 Hemophilic Dental Disease

It is the second most common major hemorrhagic complication of hemophilic patients. It is characterized by repeated bleeding in the root canal (the dental pulp) with negligible cause—e.g. by chewing foods that are a little harder. These hemorrhages lead to progressive tooth decay, as the patient avoids treatment for fear of bleeding, while the dentist is afraid of dealing with the problem (for the same reason). Eventually damaged teeth lead to poor chewing of food and this can lead to recurrent gastric

ulcers, with minor or major gastric mucosal injuries [20].

7.3 Factor VIII Inhibitors: C

As already stressed, in several patients (approximately 6-10%) inhibitors are grown only after replacement therapy. Hemophilic patients, who have a factor VIII less than 1%, are the most severely affected and those who most easily form factor VIII inhibitors [21].

7.4 Viral Infections as a Result of Replacement Therapy

While hemophilic replacement therapy has changed their survival, it has also caused a lot of complications. Because of them, some patients have already failed to survive. Thus a significant number of viruses have been transmitted for decades by the transfused material. It is believed that the use of modern technology will prevent the transmission of new viruses in the future. Hepatitis (A, B, C) have been the most recognizable viral infections for many years, while HIV, Parvo-virus B19 and hepatitis D, E and G viruses are the last identified [22].

8. Treatment

The treatment of hemophilia is a replacement therapy. This means that it is based on the administration of the agent that is missing or insufficient in quantity. Thus, depending on the condition, formulations containing factor VIII in hemophilia A and factor IX in hemophilia B are administered [23]. The formulations containing the coagulant are administered intravenously, either precautionarily to prevent the appearance of a bleeding, or involuntarily, i.e. during bleeding episodes to stop the existing bleeding [24]. The treatment of a bleeding episode depends on many factors, such as the severity of the disease as well as the position and the size of the bleeding. In mild hemophilia, the use of agents is rarely necessary, and bleeding episodes are usually treated by simple means, such as applying pressure, using ice or dressing. Moderate hemophilia requires replacement therapy to treat bleeding episodes and no prophylactic treatment is required, with the exception of the patient's participation in specific activities. In severe hemophilia, in addition to replacement therapy, for hemorrhagic episodes, short-term or long-term chronic prophylactic treatment is usually required, i.e. administration of agents 2-3 times a week with no evidence [25].

The main way to treat and prevent bleeding is to administer the missing agent. This is called "factor replacement therapy". It may be given a recombinant agent (prepared in the laboratory by DNA technology) or fresh frozen plasma (it is the liquid component of blood containing large amounts of coagulants). Factor VIII is administered in hemophilia A and factor IX in hemophilia B [26]. The agent is administered to the child through a vein usually in the arm. Children with severe hemophilia receive the missing factor at regular time as prescribed by their physician to avoid bleeding [27].

Other agents used to treat hemophilia are [28]:

- Desmopressin (DDAVP) is a synthetic analogue of the antidiuretic hormone normally produced in the body. It helps stop bleeding in muscles, joints, nose and mouth. Available in both injection and nasal sprays, it can also be used prophylactically prior to surgical interventions.
- Aminocaproic acid is used before dental procedures as well as in the treatment of nose and mouth bleeding. It is given in pill or syrup.

9. Normal Life or Not

The daily life of a hemophilic is normal, but with some restrictions. The young hemophilic goes to the same school as the rest of the kids, goes on vacation and plays sports like everyone else. However, he will not be able to play "wild" games and he should prefer specific sports such as swimming. He may even be

encouraged to deal with other activities such as chess, fishing or music. As he grows and physical activity will be limited, the risk of bleeding episodes will also be reduced. The transition from “difficult” childhood to adulthood, initially with the help of parents and then with personal training and care, will enable him to study and work as other peers [29].

In order for a hemophilic to have a normal life, he has to address the problem with proper psychology. The parents play a key role in dealing with the problem. They first have to be properly trained and in turn to educate the young patient. The start is clearly difficult for everyone. Discussion with the physicians of a Hemophilic Center, with other parents of hemophilic children, as well as with a specialist psychologist or pediatric psychiatrist may help [29]. One should remember that children are always children, regardless of the underlying problems. Therefore, they should be encouraged to play and have fun, even if this requires extra attention [1, 2].

In case of an injury or bleeding, nagging or anger does not benefit. On the contrary, cool and timely handling of events can prevent further complications. This means less pain, minimizing the risk of joint damage, limiting absences from school and normal activities, avoiding frequent visits to the doctor or hospital [16].

It is also necessary to inform the rest of the family and friends about the child’s illness and, above all, to explain the problem to other children in the family. Brothers or sisters of the young patient may feel neglected, especially at the beginning, or experience feelings of guilt if their hemophilic brother develops a hemorrhagic episode during their play [29]. It is therefore important to know as much as possible about their brother’s disease and to be allowed to participate in their own way in dealing with the whole problem.

10. Conclusions

Proper collaboration of the therapeutic team with the patient in conjunction with an individualized treatment program adapted to the needs of each patient and especially the child leads to effective improvement of the hemophilic patient [30]. Moreover, the functionality of these patients, their day-to-day activities, and their socialization will be improved.

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