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Incidence of haemophilia, genealogical inheritance and transmission of haemophilia into a family line in Macedonia

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----------ABSTRACT----------
Introduction: Haemophilia is a state of bleeding. In the blood there is a lack of coagulation factor that controls blood flow.

GOAL: *to show the number and treatment of cases of haemophilia, their treatment, and display a family tree.*

MATERIALS AND METHODS*: a descriptive and epidemiological method of data capture and are presented in a tabular and graphical way.*

RESULTS AND DISCUSSION: *Familial positive history in 53 individuals or 91.38% has not been done prenatal diagnosis, or only in 3,45% a prenatal diagnosis has been made. Bloody symptoms have 55 or 94.83%, with 40 or 68.9% of them having spontaneous bleeding episodes. Out of 40 people or 68.97% are on permanent treatment. Of these, indicative treatment is 32 persons or 55.17%, prophylaxis is 9 persons or 15.52%, 11 persons change the treatment or 18.97% and 6 people are unfamiliar or 10.34% are treated. Of the examinees, 39 people or 67.24% receive a coagulation factor, and 19 people or 32.76% do not receive a coagulation factor.*

CONCLUSION: *the available therapeutic possibilities are concentrated on an indicator factor and a small percentage of prophylactic treatment, an institutional therapy, but there are also therapeutic agents that are not available for people with coagulopathies.*

KEYWORDS: *haemophilia, coagulopathy, prophylaxis.*

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I. INTRODUCTION

Haemophilia is a state of bleeding. In the blood, there is a lack of coagulation factor that controls bleeding. Haemophilia is coagulopathy that occurs as a consequence of a coagulation factor of factor FVIII (haemophilia A) or factor FIX (haemophilia B). It is inherited recessively, due to the mutation of the gene located on the X chromosome (Benedik, 1998, 155). The cause of the condition is in the deficiency of specific blood protein plasma, called an antihyphilic globulin (AHG), which is necessary for blood clotting. The main symptom of haemophilia is prolonged bleeding that is difficult to stop. Today, many different mutations are known as the cause of haemophilia (NIH, 2013a). The incidence of haemophilia A is 1 in 5,000 to 10,000 male children. In haemophilia, B is less common, and is found in 1 in 25,000 male children. About 1 in 5,000 women is a carrier of haemophilia A, and 1 in 20,000 is carrier of haemophilia B. The incidence of haemophilia is placed in the group of rare conditions (Naumovska et al., 2014, 102). According to the 2015 World Health Report, 304,362 people with blood disorders have been diagnosed. Of these, 187,183 people with hemophilia, and only 20% of these people have adequate treatment, mostly in developed countries. The number of people with hemophilia is increasing, which is explained by the progress of treatment.

Types of hemophilia : In people with hemophilia A there is a deficiency of coagulation factor VIII. Factor VIII circulates in a plasma bound to a larger molecule, vWF (von Willebrand factor), and together build a complex.

The functional characteristic of this complex that is necessary for coagulation is indicated by VIIIc. Haemophilia B is a rare type of haemophilia. In this condition, there is a lack of coagulation factor IX (Chemo Will, 2016).

Inheritance To Haemophilia : Haemophilia may occur without a positive familial history or known as haemophilia. About 30% of people with hemophilia appeared for the first time. Hemophilia is inherited from a parent to a child. The genes for Hemophilia A and B are on the X chromosome.
When the father is a person with hemophilia, and the mother is not the carrier of the hemophilia gene, none of the sons will have hemophilia, but daughters will be carriers of the gene. Women who have the haemophilia gene are conductors. And they sometimes show symptoms of hemophilia and they can transfer it to their children. For each child, there is a 50% chance that the son will have Haemophilia and 50% that the daughter will be a conductor (NIH, 2013b). The most common form of female hemophilia is found in a small number of heterozygous carriers that may occur with deactivation on chromosome X in an unusually early stage of embryogenesis, resulting in an abnormally low level of factor VIII. The second cause of hemophilia in females is: a child of a father with hemophilia and a carrier mother. 50% is the possibility for a female child to have haemophilia. And this condition in female children is compatible with life and it has been confirmed in homozygous form in female faces with haemophilia (Friedman / Rogers, 2013, 1382).

Forms of haemophilia : The shape of hemophilia determines the severity of the condition. The shape depends on the level of the missing factor. The normal level of the factor is from 50% - 100%. Compared to that level there are:
Mild form of haemophilia: with a factor of 5% to 40%.
An intermediate severe form of haemophilia: with a factor of 1% to 5%.
Severe hemophilia: with a factor of less than 1% (Sukarova et al.2002).

Bloody symptoms : Persons with severe haemophilia are bloated more often in muscles and joints and skin. Bloody in severe haemophilia occurs spontaneously or with minor injuries, burdens or interventions.

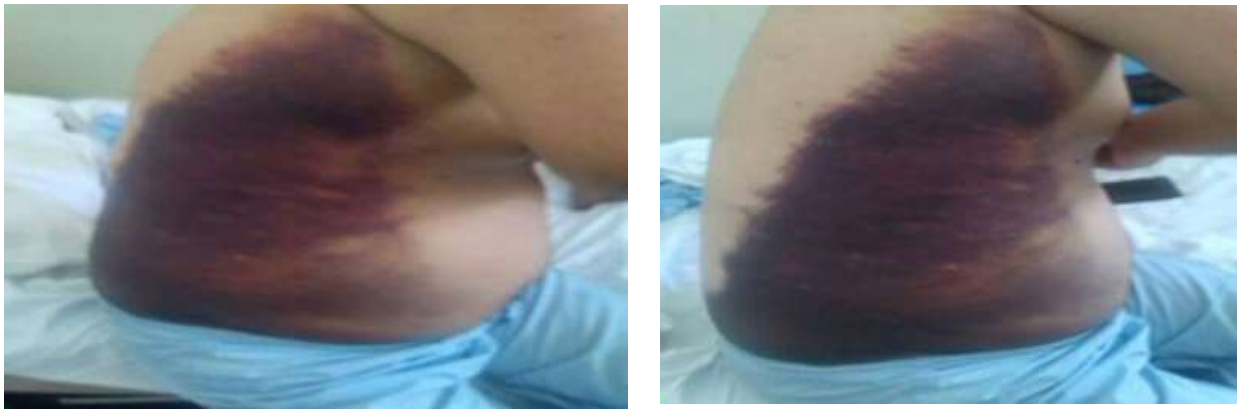


Figure 1. Bleeding into softtissues and muscles of a person with hemophilia A severe.

Bleeding in soft tissues leads to the creation of larger collections of clotted blood, which presses the surrounding healthy tissue and leads to damage to the muscles and nerves. This may result in calcified masses or cystic formations that are suspected of having tumors and are called pseudotumors (false tumors). Persons with severe hemophilia are most often diagnosed at birth due to headache hematoma[2]. People with severe hemophilia bleed into large joints, such as hips, knees, feet, elbows, shoulders and wrists.

The damaged joint usually becomes a place of repetitive bleeding.

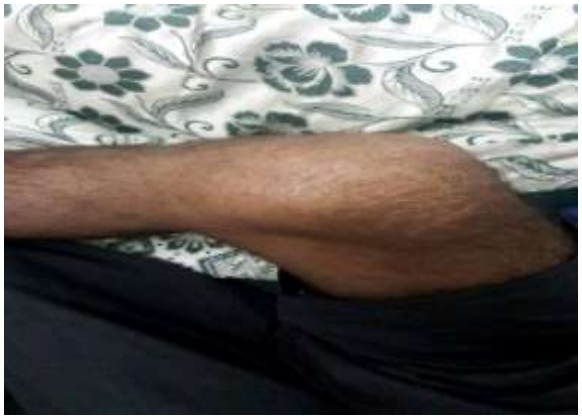


Figure 2. Repetitive joint bleeding in a person with hemophilia B intermediate form.

Haematuria rarely appears. Bleeding in the central nervous system can occur without previous trauma but is in the group of life-threatening conditions as well as bleeding in the tongue and throat, respiratory organs and surgical interventions. They need to be treated urgently (Benedik, 1991; Baebler, 1998). Persons with moderate severe haemophilia are bloody. They bleed for longer after surgery, injury or dental interventions. A person with an intermediate form of haemophilia will rarely receive spontaneous bleeding. In moderately severe haemophilia bleeds begin with the onset of a child's crawling and walking when blows are frequent, while mild haemophilia is diagnosed later in injuries. Sometimes the haemophilia gene carriers bleed and show symptoms of bleeding due to a possible reduced level of factor. It is therefore necessary for them to be registered and controlled in the hemophilia center. Therefore, it is necessary for people to classify the diagnosis according to the severity of their condition.

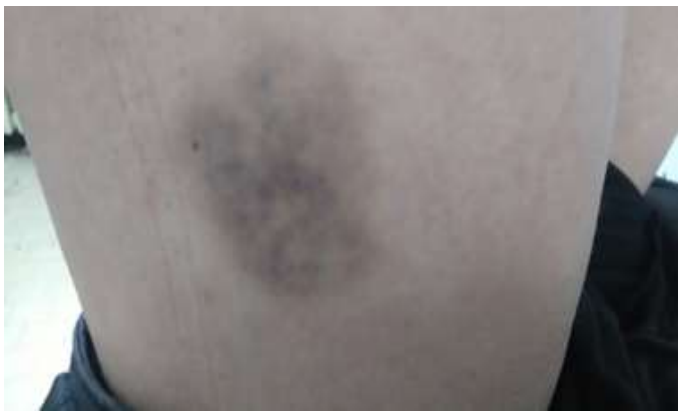


Figure 3. Bruise the carrier of haemophilia

Treatment of people with coagulopathies in the Republic of Macedonia is carried out in a center for hemophilia and regional units by a multidisciplinary team. The team consists of dispersed work profiles of specialists, highly qualified for the treatment and care of persons with haemophilia and other coagulopathies. Comprehensive care includes care and care of physical and psychosocial health and quality of life for reducing morbidity and mortality (WHF, 2012,11). Priorities in promoting health and quality of life include: Prevention of bleeding and joint damage; Bleeding and management of complications, Bleeds should be treated quickly, rapid treatment of bleeds leads to the reduction of pain, joint damage, muscle and other organs. If bleeding is treated quickly then a less coagulation factor is needed to stop the bleeding (Gurcinovska, 2015, 148). With an adequate amount of treatment products and proper care, people with coagulopathies can live a wholesome healthy life.

The dose and duration of substitution therapy depends on the severity of the factor deficiency, the location and extent of bleeding, as well as the patient's clinical condition.

GOAL: to show the number and treatment of patients with hemophilia, their treatment, display of a family genetic lineage of a patient with Hemophilia.

Materials and methods: descriptive and epidemiological method of taking statistical data and they are presented in tabular and graphical

II. RESULTS AND DISCUSSION

In the Republic of Macedonia, 320 persons with hemophilia were registered, of which 213 patients with haemophilia A, and 107 patients with haemophilia B. With von Willebrand disease, 170 people with deficiency of factor VII 2 persons, factor XI 1, deficiency of factor XII 12 and deficit of factor XIII 4 persons were registered with von Willebrand disease. They are treated at the University Hematology Clinic, the University Clinic of Pediatric Diseases, the Institute of Transfusion Medicine and the Hemophilia Center, as well as in the regional units (Dejanova, 2014).

Consumption of factor VIII per year for the treatment of haemophilia in Macedonia for haemophilia A is 2.887IE, and for haemophilia B is 0.481 IE (WHF, 2015, 15). Consumption per capita in the region according to the World Federation for hemophilia and global reports in the period from 2011 to 2015.

Table 1. Use of a coagulation factor per capita in the region.

Држави/ States	**Хемофилија А / Hemophilia A**	**Хемофилија Б/ Hemophilia B**
Македонија/ Macedonia	2,887	0,481
Грција/ Greece	3,747	0,480
Словенија/ Slovenia	7,739	0,463
Црна Гора/ Montenegro	2,085	0,161
Србија/ Serbia	2,400	0,344
Албанија(2014)/ Albania	0,464	0,232
Бугарија(2011)/ Bulgaria	2,140	0,134

The incidence of haemophilia A is 1 in 5,000 to 10,000 male children. In haemophilia, B is less common, and is found in 1 in 25,000 male children. About 1 in 5,000 women is a carrier of haemophilia A, and 1 in 20,000 is carrier of haemophilia B. The incidence of haemophilia is placed in the group of rare conditions (Naumovska et al., 2014, 102). According to the 2015 World Health Report, 304,362 people with blood disorders have been diagnosed. Of these, 187,183 people with haemophilia, and only 20% of these people have adequate treatment, mostly in developed countries. The number of people with hemophilia is increasing, which is explained by the progress of treatment. The majority of people with coagulopathies have been diagnosed for up to a year, which is directly related to the severity of the condition, while newly diagnosed diagnoses have been diagnosed in the last ten years as far as they are able to be detected. How much the form is easier, it is revealed later in life or in conditions of evident bleeding. The majority of people are diagnosed after apparent bleeding or 40 or 68.97%, others are diagnosed as a result of familial screening or preoperative screening in which surgery has been established in recent years. Despite familiarity with familial positive history in 53 individuals or 91.38%, prenatal diagnosis has not been performed, or only in prenatal diagnosis of only 3.45%. Most people face bleeding episodes and it is tied to the shape of the coagulopathy. Bloody symptoms have 55 persons, or 94.83%, and in 40, or 68.97%, there are spontaneous bleeding episodes. The most common causes of bloody episodes are burdens, and in the second place the combined causes are credited with bloody diathesis. In general, joint bleeding episodes are the biggest problem for people with coagulopathy, and immediately behind them are bruises, gums, muscles, gynecological bleeds, urinary, abdominal, gastrointestinal and in few but not excluded and brain bleeds..

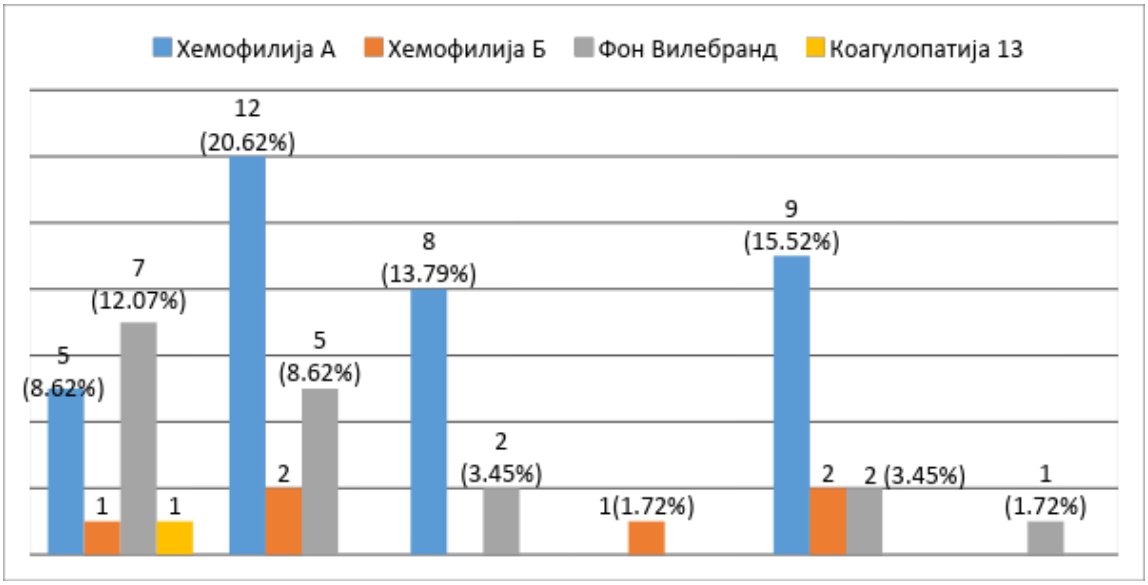


Chart 1.: The most common bleeding according to the manner of occurrence

The control examinations of the examinees are performed in non-standard forms from the rare visits to the center to more than three times a year.

The same is due to the different need, but also the people give a positive opinion on the control checks that will be performed as needed. Of the respondents, 40 people or 68.97% are on permanent treatment. Of these, indicative treatment is 32 persons or 55.17%, prophylaxis is 9 persons or 15.52%, the substitution therapy is 11 persons or 18.97% and for unknown treatment 6 persons or 10.34%. Of the examinees, 39 people or 67.24% receive a coagulation factor, and 19 people or 32.76% do not receive a coagulation factor. Percentually using factor in the Republic of Macedonia in an upward trend began in 2002 with 17.24%, while 26 persons or 44.83% of the respondents can not provide data. Currently available therapeutic options are with concentrate factor indicative and a small percentage of prophylactic treatment, substitution therapy, but there are also therapeutic drugs that are unavailable for people with coagulopathies. The coagulation factor used by the persons is of human origin in 38 persons or 65.52%, of recombinant origin in 3 persons or 5.17% and there are no data in 17 persons or 29.31%. The human factors in use are Koate, Octanate, Immunate, Aimafix, Wilate, Fibrogammin. Constantly at home, patients receive a factor, other patients with a minor form of coagulation factor receive in a medical facility because there is no factor for home or lack of factor due to the indicative type of treatment. Of the total number of respondents, 41 persons or 70.69% were hospitalized in a medical facility for the treatment of blood derivatives, which in certain conditions and in recent years is a practice. The percentage of 55% of people with haemophilia who have hepatitis B / C forms is evident.

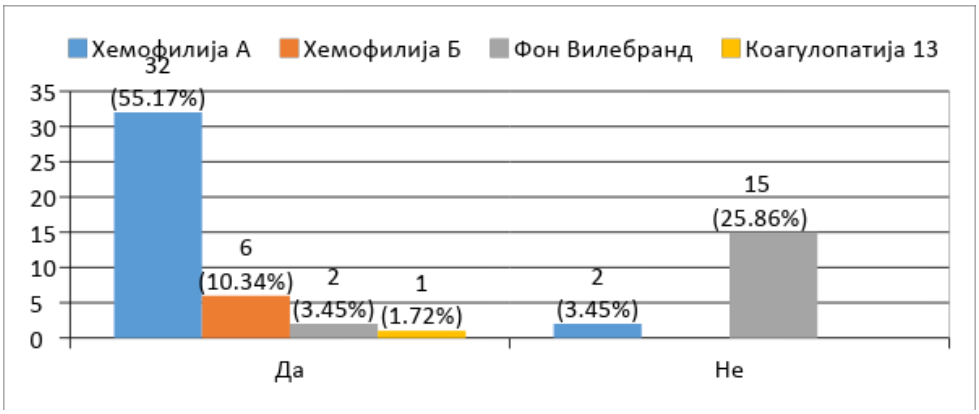


Chart 2.:Treated patients with blood derivatives in hospital conditions

When asked if the number of bleeds decreased with the use of a coagulation factor, 30 respondents answered yes or 51.72% due to timely application and rapid response to aura and the need for treatment, and the amount of factor is reduced by timely application of the drug for treatment.This also entails reducing the number of hospital days and staying in a hospital facility of as many as 35 people or 60.34%.

The surgical intervention rate is high with 65.52%, due to interventions that are necessary to perform which are urgent, which are planned and have a certain time range of waiting. But the percentage of orthopedic interventions is 25.86% of the examined group and is not an objective variable due to the lack of a reference value for the percentage of necessary planning interventions to be performed. Dental interventions are a standard procedure

and they are performed in 37 of the examinees or 63.79% with at least one dental intervention. As undesirable effects of medicinal nature occur to some extent and in the target group with side effects of blood derivatives are registered in 29 persons or 72.50%, the largest percentage is hepatitis and allergic reactions, adverse consequences of a coagulation factor are registered at 7 persons or 17.50% of the type of allergies, inhibitors in one of the subjects and sensations at the time of receiving a factor that was repaired by changing the type of factor. Undesirable consequences of antifibrinolytic therapy have not been observed in any of the examined group and the adverse effects of hormonal therapy in 4 persons or 10.00% as anxiety, elevated body weight, secondary sterility, and irregular menstrual cycles.

Table 2. Drugs that are prohibited for use.

/ Drugs that can cause bleeding	Herbal drugs that can cause bleeding
Acetylsalicylic acid (Aspirin)	Ginkgo biloba
Diclofenac	Garlic in large amounts
Ibuprofen	Ginger (not dried ginger)
Ketoprofen	Ginseng (Asian)
Piroxicam	Feverfew
Ticlopidine	Saw Palmetto (Serenoa repens)
Warfarin	Willow bark

Physical treatment

Physical therapy is attended by 26 persons, or 44.83%, due to the positive effect of the treatment itself, lack of spatial conditions for adequate physical therapy and, of course, the financial burden for the physical treatment itself, which is not borne by the fund for certain categories of patients with coagulopathies. The frequency of visiting physical treatment is variable, and the most common cause for which people with coagulopathies attend physical therapy is preventative. In 20 individuals or 34.48%, physical activity improved after visiting physical treatment, and in 10 people or 17.24% the number of bleeds decreased after physical treatment. On a direct disability issue, although the answer is subjective, 28 people or 48.28% answered yes, with limited movements 37 persons or 63.79%. Target regions and joints have 31 persons or 53.45%, which is a high percentage despite practicing and respecting the recommendations for physical activities and sports in 27 persons or 46.55%.

Recommendations by the world federation for hemophilia for prophylactic treatment of major forms are supported by 36 people or 62.07% and, if possible, they would use it. In the family interview, which was done on February 10, 2015, 5 people from the Republic of Macedonia, who are members of the family tree and members of the family, took part. The data are provided with a signed consent for the use of personal data and a statement of accuracy of the data. They respond to questions about genealogical inheritance and transmission of hemophilia to their family line. (Display genetic lineage of Hemophilia A major form of DL from Skopje), case report

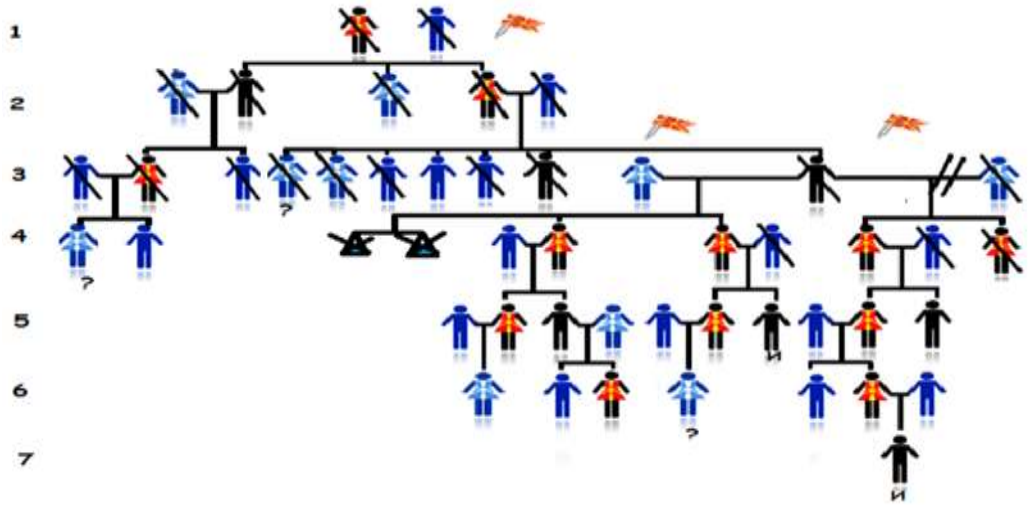


Figure 4. Genetic lysis of Haemophilia A major form of D. L.from Skopje

The gene originally appeared in the first generation of a mother carrier in 1873, which transmits it to a daughter and son with hemophilia. It has been confirmed that from an early age in the same tree there are also previously deceased males. The three children of the second generation were born in 1913, 1893 and 1896. Second generation - the son with hemophilia has two children: a male healthy and a daughter carrier who has no reliable data on

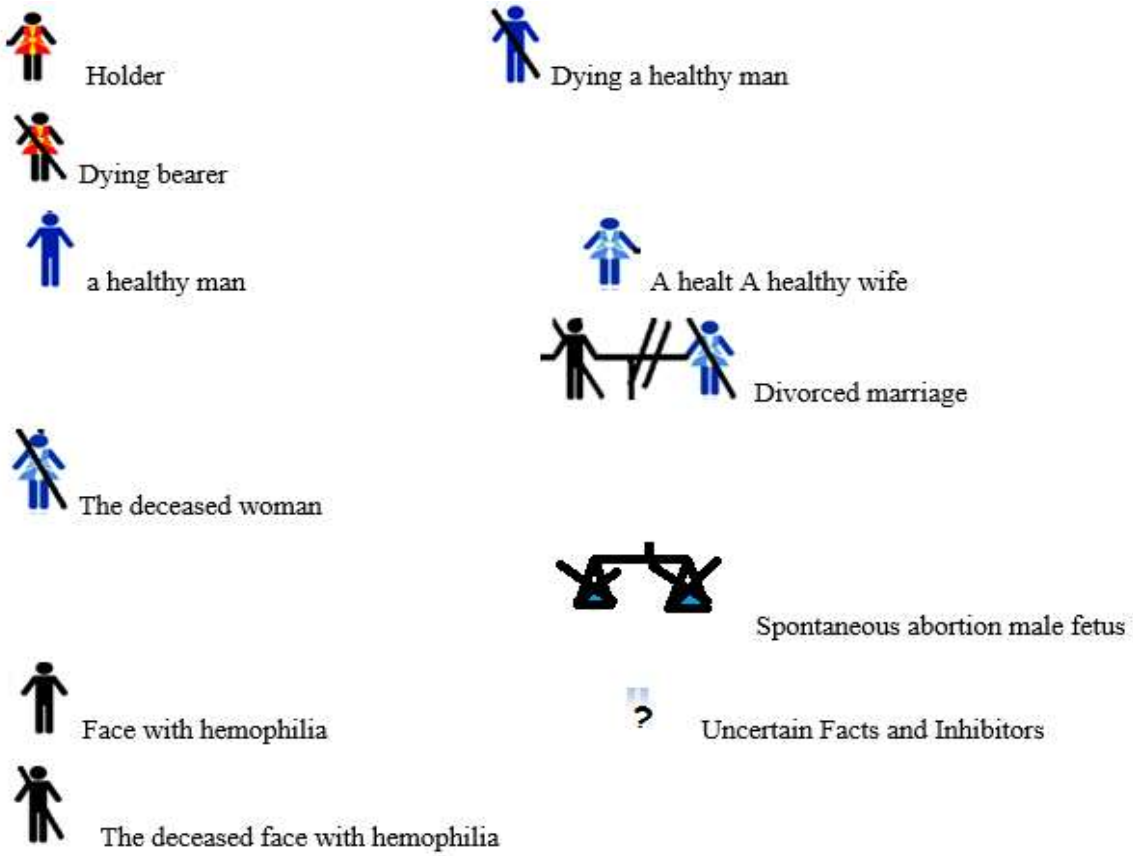
whether the fourth generation has transferred the gene. The second generation - a daughter born in 1893, carries the haemophilia of two of her own sons out of 5 male children. There are two daughters, one of whom is old, and the other is healthy. One of the sons with hemophilia died at the age of seven, and the second one was married and from the first marriage in the fourth generation there are two daughters, one of whom is one year old, and the second daughter is a carrier. The second marriage has two daughters, and one unsuccessful pregnancy that ends with a spontaneous abortion in high pregnancy, and the fetuses are male. In the fifth generation all sisters form marriages and have two male children with hemophilia, and female carriers. Of the three people with hemophilia, one is with inhibitors.

In the sixth generation there is a healthy female individual, two carriers and one unconfirmed. In the seventh generation there is again hemophilia, with inhibitors that were born in 2013. From the genetic mapping of the Bonn University Clinic from the results of the members it has been confirmed that it is a small deletion of the gene that carries a risk of 16 per cent for the onset of inhibitors. The genetic mutation is a small deletion of the exon 19. At the same time, the level of factor is below <1 percent. The actual state of the vine in the seventh generation is 28.57 per cent or 2 out of 7 people are inhibitors.

III. CONCLUSION

Macedonia is striving to achieve equal treatment for all persons with hemophilia, primarily by reducing stigma and raising public awareness of bleeding problems, as well as educating treatment and self-treatment. Consequently, accurate correct diagnostics and proper modern treatment will dramatically reduce disability. Preoperative screening reduces the likelihood of surgery complications and increases the number of diagnosed patients who with proper education will have a quality life. People need to be typed to allow proper treatment and treatment needs, and by determining the severity of weight, the type of treatment will be determined, which in turn directly affects the minimization of bleeding episodes. Indicative treatment leaves great repercussions and is sometimes additionally budgetary ineffective, especially in people with Hemophilia A major form. Worldwide protocols require persons with a major form of haemophilia A to be prophylactically treated as long-term treatment for a long-term period. The benefits of prophylactic treatment are based on short-term and long-term benefits. Due to the use of blood derivatives in 55% of hemophilia patients, hepatitis has been diagnosed.

Physical therapy takes a progression in the lives of people with coagulopathies, as well as evident changes and improvements in the functionality of the people who attended it, although musculoskeletal damage with high percentage is evident. Bleeds should be treated quickly. Rapid treatment of bleeds leads to the reduction of pain, damage to the joints, muscles and other organs. In familial haemophilia research A major form, the genetic lineage is old 7 generations, and the gene with the same expression and invasion with a level of factor with minor variations and changes is constantly transmitted. Treatment naturally prolongs and no longer affects the age limit of persons with hemophilia, progress allows controlling the transmission in the vine, but not eradication of the same. The parallel family lineage for hemophilia gives a realistic picture of the inheritance of the gene with hemophilia. The illness is chronic, and the patient is in constant or periodic contact with the healthcare institution. The goal is to accept the patient's illness and live with it.
Legend of Family Line Picture 4.



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