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THE ROLE OF BAR BODY, BIOCHEMICAL ANALYSIS IN TYPE A HEMOPHILY, AND GENEALOGY

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Abstract

This paper includes 8000 individuals of the population of Presevo and 5 villages of this municipality. During family interviews we encountered many genetic diseases where we will discuss type A hemophilia. During the direct observation, we found that only males were infected with this disease while females were not affected by this type of hemophilia. Based on the statements of the scientist Bar that one X chromosome in the early embryonic stages becomes inactive, then women must also be affected by this disease. This case introduced us to another study about the type of inheritance, and to ascertain whether the body of Bari is genetically inactive or not? Based on the fact that in genetic trees we did not have cases of women with hemophilia, we asked ourselves why this happens when we are equal with the dose of the X chromosome. However, from many genealogical, biochemical analyzes we came to the conclusion that this body of Bari is genetically active, but morphologically changes its original form. Based on the discussions, biochemical analysis proved that the X chromosome from the father is inactivated and takes the form of a black spot. From biochemical analysis and knowing that the egg cell is approximately 10000 times larger than the sermatozoid made us analyze the biochemical structure of the egg cell. In the egg cell it was observed that inside the cytoplasm is rich in numerous enzymes which at the time of fertilization will promote the division of the zygote into two new cells. In this case we found that the cause of X chromosome DNA condensation in the sperm is the egg cell environment factor.

This means that enzymes, mitochondrial DNA have many redox enzymes that can affect the condensation of the X chromosome coming from the father. Assuming that the sex X chromosome is inactive we did not have the opportunity for women to be hemophilic as well. By doing the genealogical analysis of these families we will present the thoughts about the role of Bar's body when it comes to type A hemophilia. For these cases of hemophiliacs laboratory, biochemical and genetic analyzes have been done to observe the level of penetration and expressiveness of factor VIII. We will present through the genetic tree the origin or genealogy of the gene for this disease. Based on biochemical and genetic analysis using PCR, we will present the level of factor I, IX, XI, aTTP, vWF- Von Willebrandov factor, locus Xq28, genotype ccddee, fibrinogen, blood group, rhesus factor in hemophiliacs included in this study.

Keywords: Bar body, egg cell cytoplasm, DNA-mitochondrial, hemophilia

Introduction

Barry and Bertram in 1949 observed that the X chromosome made inactivation in the embryonic stage at the time of implantation, at the end of the first week of pregnancy. This X chromosome from the father is condensed in the form of a spot (black dot) and for which the genes in it are thought to be inactive. The research was conducted in the population of Presevo, which lies in the east of Kosovo, in the south-east of Serbia and the border of Northern Macedonia on the E75 road line. Hemophilia A is inherited through the sex X chromosome. Women have a 50% chance of transmitting the factor VIII mutation in any pregnancy. Boys who inherit factor VIII from their mother will be affected by hemophilia. If the sex X chromosome is inactive in females then the dose of the chromosome is equal to the male sex. For this reason the likelihood of getting hemophilia would be equal, does not in reality this stand. So with this paper we will give our thoughts about the body of Bar or gender heterochromatin regarding the dilemma of this case (Fig.1).

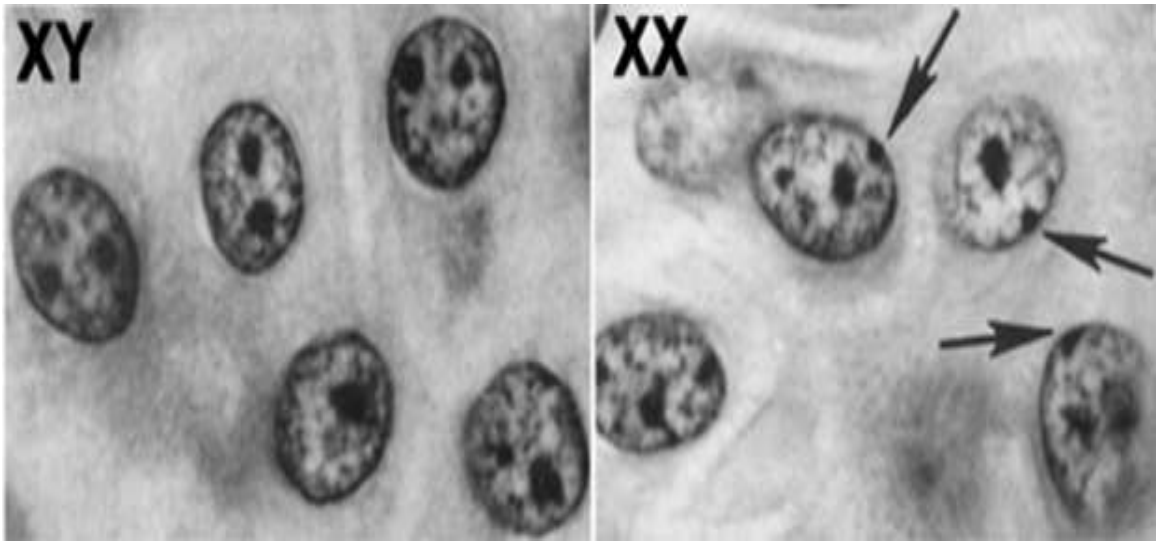

Fig.1. The Bar body

Material and methods

The material for this paper was collected in the form of a questionnaire in families both in Presevo and in the villages. During this questionnaire we encountered cases of hemophilia type A where out of 8000 inhabitants we identified 4 cases of hemophilia A male but one of them died. From the detailed analysis we learned that these are the first three cousins from the maternal line who are genetically close in the 4th degree of kinship. For this study we did the genealogical research of the family that were affected by factor VIII of hemophilia.

In order to know the level of action of hemophilic factors and to know their genotype for this disease, laboratory, biochemical and genetic analyzes were performed at the Nis Institute. For molecular analysis we have the results from PCR by which the genotype for ccddee hemophilia was determined, the location of the hemophilic gene locus on the sex chromosome X in the Xq28 region. Analyzes of aTTP coagulation factors, factor VIII level, vWF factor-Von Willebrandov factor and other analyzes presented in Table 1 were performed.

Analysis and discussion of results

a) Genealogical analysis of haemophilus A

Through the genealogical analysis with hemophilia A in three families it is seen that the source of this disease is from female generation III-8. We ascertain this from the analysis of previous generations where we have no cases with this disease. Doing the analysis it is clear that we have a death from hemophilia which is in generation IV- and serial number 10 (IV-10). Of the three cases with hemophilia we also have the son with hemophilia disease in the 5th generation and with serial number 9 (V-9) and two brothers with hemophilia in the 5th generation with serial number 11 (V-11) who is dead and the brother of the same generation V with serial number 12 (V-12) alive but hemophilic.

From the genealogical analysis (Fig.2) it is clear that the carrier of factor VIII for hemophilia type A is the individual in generation III with serial number 8 (III-8) which is inherited from her mother stock II with serial number 3 (II-3). The generation IV-10 individual presented as the proposition with the arrows is a dead male.

According to genealogical cases, this dead brother IV-10, has two sisters who are carriers of type A hemophilia who are underlined with arrows in generation IV with serial numbers 14 and 15. Both married sisters (14 and 15) in different families have three hemophilic sons one dead in generation V with serial number 11 (V-11). While the other two hemophiliacs are alive of the V-9 and

V-12 generation. These are in the 4th degree of kinship 1/16. If they get married in this family with fourth degree relatives, every 16th born will be with hemophilia.

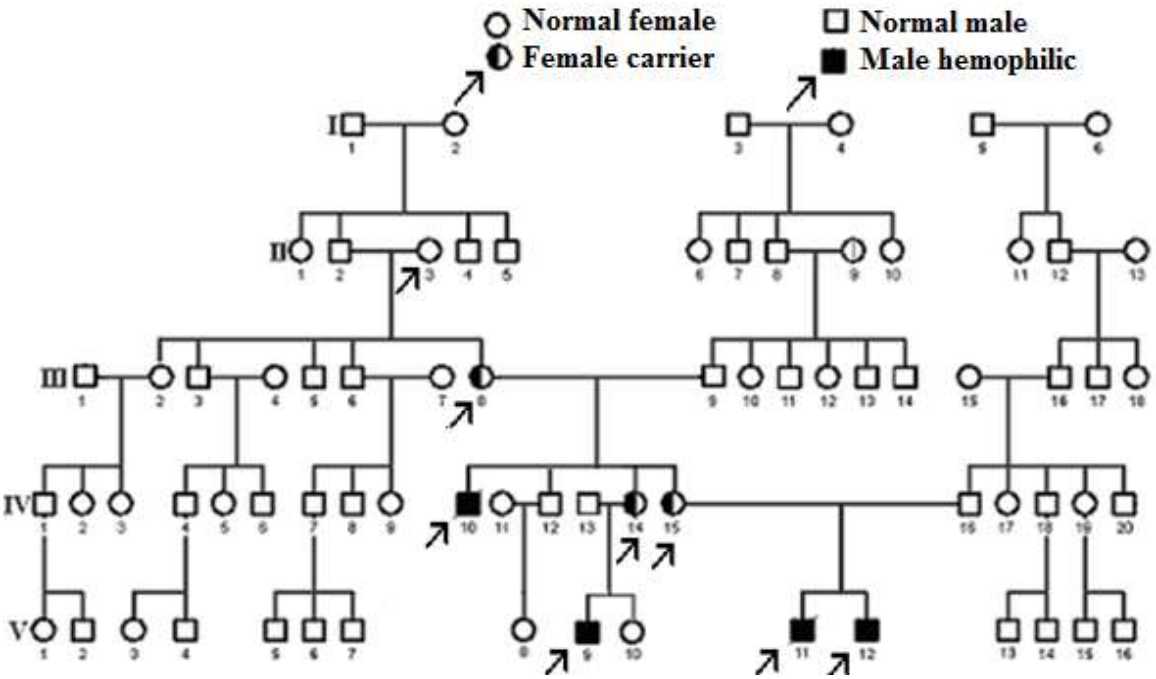

Fig.2. Hemophilia disease in cousins type A-VIII

b) Biochemical and genetic analysis of hemophiliacs

From the analyzes made by PCR it is concluded that it is about factor VIII of hemophilia A. From the results obtained in the case of hemophilia A-VIII it results that it is about the average type of hemophilia with these values 1.5%, 1.7% and 2%.

The hemoglobin level in type A-VIII hemophilia is 10.4, 10.6, and 10.7.

Thromboplastin activation time (aPTT) is clearly seen to be much later 71.7s, 68s and 75s.

The prothrombin test specifically assesses the presence of factors VII, V, and X, prothrombin and fibrinogen. A prothrombin time within the interval of 11-15 seconds (depending on the source of thromboplastin used) indicates that the patient has normal amounts of upper coagulation factors.

With aPTT ratios of 1.5 to 2.5, in the therapeutic range used by many laboratories, variable levels of the anti-Xa heparin factor have been achieved. According to this process it turns out that the defect is related to the negative reversible bond which will lead to a decrease in heparin and an increase in thromboplastin.

These three cases with hemophilia have blood group A, Rh negative and according to the analysis hemophilia has a correlation with rhesus negative factor with genotype dd. We base this on the similarity of the rhesus negative dd genotype with the dd genotype in hemophiliacs. We therefore think that these diseases are caused by a correlation between genes on sex chromosome X and the gene on autosomal chromosome number 1.

Table 1. Laboratory, biochemical and genetic results of haemophilists

Three cases with haemophilia	First person (first brother)	The second individual (second brother)	The third person, the cousin of the two brothers
Type of hemophilia	Hemophilia type A	Hemophilia type A	Hemophilia type A
Blood group	A, Rh negative	A, Rh negative	A, Rh negative
Factor VIII level	1.7% (preferably 50-150%)	1.5% (preferably 50-150%)	2%(preferably 50-150%)
Factor I level	338,5%	338%	339%
Factor IX level	91,5% (66)	91%	91%
Factor XI level	82.8% (117)	83%	83%
Fibrinogen	4.01% (130-300 mg/dL)	4% (130-300 mg/dL)	4% (130-300 mg/dL)
Genotype	ccddee	ccddee	ccddee
Intron 22	Region Xq28	Region Xq28	Region Xq28
aPTT(Partial Thromboplastin Time)	71.7s (preferably 25-35s)	68s (preferably 25-35s)	75s (preferably 25-35s)
Leukocytes	16.5	17	17.1
Erythrocytes	4.20	4.18	4.10
Hemoglobin	10.4 (12-15-g/dL)	10.6	10.7
vWF- Factors Von Willebrandov	46%	46%	45%

Analyzing the average values in Table 2 it is clear that factor VIII has a low level compared to the reference value. Therefore we say that the type of hemophilia in these 3 investigated cases is the average type because the average for these is; 1.37% reference is = 1-5% (F VIIIC> 5 iu dL).

Table 2. Laboratory status based on the median values investigated

Test	Average	Reference range	Units
Factor VIII level	1.37%	50-150%	%
Heavy	<1%(F VIIIC(1 iu dL)	50-150%	iu- international unit
Average	1-5%(F VIIIC> 5 iu dL)	50-150%	iu- international unit
Easy	> 5% (F VIIIC>iu dL)	50.150%	iu- international unit
Genotype	ccddee	CCDDEE	Dominant
aPTT(Partial Thromboplastin Time)	71.56-s	25-36-s	Seconds -s
Hemoglobin	10.6	12-15 (120-150g/L)	g/dL or g/L
vWF- Factors Von Willebrandov	46%	50-160%	%

We can therefore conclude that the inheritance of these factors has been done with a high stability because gene expression has given the same results in these cases. Therefore we think that the intervention of factor VIII which results from the mutation in intron 22 in the Xq28 region of the X chromosome had the same penetration.

According to genetic analysis-PCR it is clear that the genotype of three cases with hemophilia A is ccddee. The locus of the gene on the chromosome has the region on the Xq-28 arm.

Conclusion

In abstract we pointed out that women although based on scientific opinions have a sex X chromosome while the other is inactive non-functional, they are not hemophilic like men and this brings us into a doubt about the activity of Bar's body.

However, analyzing the cases, we did not have any female patients even though they are with the same dose of X chromosome as men.

This implies that the "inactive" Barr body chromosome differs morphologically only from the other sex chromosome that has the shape X (X), but is functional and with its genetic radiation contributes to enzymatic processes and thus prevents enzymopathies in females. This is confirmed by the fact that if a hemophiliac gene occurs in both females on both sex X chromosomes, the female will be ill. Therefore there is no dilemma that heterochromatin or Barr body is partially active if only in shape it changes and takes on the appearance of a stain on the nucleus.

Activation of thromboplastin for clotting is approximately the same values as it appears: aPTT- 71.7s (25-35s), 68s (25-35s) and 75s (25-35s). According to the contact protein analysis E-cadherin has a filamentous deformation which slows down the activity of thromboplastin. Also the level of factor VIII in three cases has a very low penetration therefore the expressiveness is lower and thus does not stop the flow of blood. Vitamin K has a very low level in the cases mentioned. The values of factor VIII are as follows: Case 1.Brother 1.7% however (Preferred 50-150%); Case 2. brother 1.5% (Preferred 50-150%) and case 3. Cousin 2% (Preferred 50-150%). Based on these results doctors can determine the doses around these cases of hemophilia. In this case it is suggested that the dose of heparin should be in correlation with the activity of aPTT to avoid thrombin.

Resume

a) In the early stage, at the end of the first week of pregnancy, before the implantation of the embryo in the uterus occurs morphological change, inactivation of the X chromosome originating from the sperm and this confirms that their father was not hemophilic and the Grass Body is not a carrier of hemophilia in these three cases, but the mother was a carrier but not sick. It is clear that the Grass Tree is not inactive because we have no hemophiliac females in the genealogical trunk of the family.
b) With this study we concluded that the cause of condensation of X chromosome DNA in the sperm is the factor of the egg cell environment.
c) From other studies it has been observed that the sensitivity of an aPTT reagent to heparin depends both on its phospholipid content and on the nature of the activator present. Therefore we say that in this case we have an average between these two factors that because the penetration and expressiveness of genes is such.
d) We can say that rhesus negative factor with dd genotype on autosomal chromosome 1 has an epigenetic influence on sex X chromosome (ccddee). This means that hemophilia is an inherited disease of the correlative but also epistatic type because the phenotype is not the result only of the sex X chromosome gene.
e) According to genetic-biochemical analysis it is found that factor VIII results from mutation in intron 22 in the Xq28 region of the X chromosome and their genotype is: ccddee. Through the genealogical analysis of cases with hemophilia A in three families it is seen that the source of this disease is from females of generation III-8.
f) Based on the analysis of laboratory results, it is concluded that it is about Hemophilia type A. From the obtained laboratory and genetic results it is seen that the genetic penetration is very the same of both factor VIII and aPTT factor. They belong to the medium hemophilia because they have a value with an average <1.37.
g) As a solution to this problem, evolution has decided that women should always modify an X chromosome, due to space in the nucleus but not completely inactive. And this is accomplished precisely by methylizing DNA into histones on an X chromosome of the father which undergoes the epigenetic factor of the egg cell because it finds no adaptation to another cell that has a completely different medium from where it came from. And because of the action of the cytoplasm and egg cell enzymes the X chromosome from the father undergoes a condensation in the body of Bar.

Therefore appeal to international associations of hemophiliacs to have a genetic care and counseling of populations endangered by these hemophiliac factors.

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