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Genealogical and Dermatoglyphic Investigations of Families with Hemophilia[1]

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Five large families with hemophilia were investigated. For each propositus a circumstantial family anamnesis was taken and a detailed genealogical tree of each family was drawn and analyzed. In all the genealogical trees the typical characteristics of the illness as a X-linked recessive defect were established. On the other hand, our analysis demonstrated that, despite the genetics of hemophilia and the manner of its hereditary transmission have been elucidated long ago, the genealogical analysis in hemophilic families is far of having exhausted its possibilities. In our sample, it allowed to make both social and genetic conclusions. The social applications concern the Muslim hemophilic families and their behavior concerning the *circumcision*. The genetic findings allow to hypothesize that the gene of hemophilia could show its effect with different expressivity. Among dermatoglyphic findings, the increased asymmetry in hemophilic patients should be noted and this concerns both finger and palm dermatoglyphics.

Key words: hemophilia, genetics, pedigree analysis, dermatoglyphics, social applications.

Introduction

The only study of dermatoglyphics of hemophilic patients which we found in foreign and Bulgarian literature [8] reported dermatoglyphic peculiarities in certain patients, but it reminded somewhat isolated, probably because of the lack of statistical significance of most of the findings. On the other hand, numerous studies reported the importance of the X-chromosome for dermatoglyphic traits. As early as forty years ago P a r s o n s [5] assumed that the higher dermatoglyphic variability in women is due to different proportions between mother's and father's X-chromosomes remaining active after inactivation of one of them accordingly to Lyon's hypothesis. Although dermatoglyphic traits are mainly autosomically determined [6], the possibility for a considerable impact of the sex-chromosomes was also widely accepted [3, 4]. What is more, it was concluded that additional X-chromosomes strongly reduce the finger ridge counts [1, 2, 7].

[1] This article is dedicated to the memory of Professor Dr. Rumiana Mishkova.

The current study was devoted to dermatoglyphic and genealogical analysis of families with hemophilia A and B.

Since the genes of hemophilia are X-linked, it could be expected that dermatoglyphic examination of hemophilic patients would reveal relationships , if any, between the two packages of genetic information: this determining the lack of blood coagulation factor VIII or IX and that governing dermatoglyphic patterns and ridge counts as well as their asymmetry.

Material and Methods

Five large families with hemophilia were investigated, four of them with hemophilia A (factor's VIII deficiency) and one with hemophilia B (factor's IX deficiency), the latter belonging to the Turkish ethnical community in Bulgaria. The propositi varied in age between 13 and 30 complete years. They themselves, as well as some of their hemophilic relatives have been hospitalized and treated many times in the Clinics of Hematology at the Department of Internal Diseases, Medical University (at the time — High Medical Institute) — Varna. Among the clinical findings, hemorrhages and posttraumatic intra-articulation bleedings of retarded type prevailed. A circumstantial family anamnesis was taken of each patient and a detailed genealogical tree was drawn. Complete dermatoglyphic analysis was carried out in seven patients (all of them Bulgarians with hemophilia A) whose clinical and laboratory investigation had undoubtedly confirmed the diagnosis. All the dermatoglyphic findings were compared to criteria elaborated by the first of us [9] on a large sample of Bulgarians from the same region.

Results

All the pedigrees under analysis showed the typical peculiarities of the hemophilia as a X-linked recessive defect of the blood coagulation. In most of the cases all the patients belonging to a given family have received the pathologic gene from a common progenitor — female heterozygous career.

Fig. 1 presents the pedigree of a Turkish family with 7 hemophilic patients; in three of them the diagnosis has been clinically approved and the death of the remaining four at age between 7 and 12 years because of blooding after *circumcision* makes the diagnosis more than probable. The transmission of the pathologic gene could be traced between all the hemophilic persons in the family and their common progenitor, I — 1, Seniha. The family member III -3, Ravie, is an object of particular interest here. She has suffered a heavy haemorrhage syndrome, with clinics practically identical to those in the hemophilic men in the same family. Despite Ravie has been hospitalized and treated a lot of times, the clinics of the illness has become more and more heavier and she committed suicide at age of 23 years.

Concerning the second pedigree, presented in Fig. 2, the hemophilia of the propositus Todor (III — 3) and in his nephew Krasimir (IV -1) could be easily explained with the presence of hemophilic gene in the heterozygous career Nedialka (II — 1). However, there are another six hemophilic men in the same family : the propositus' father and five other father's line relatives. Evidently, all these cases have to do with the very rare accidental coincidence of two heterozygous careers in the same family; in our case those are Neda (I — 1) and her daughter-in-law (II — 1), Nedialka.

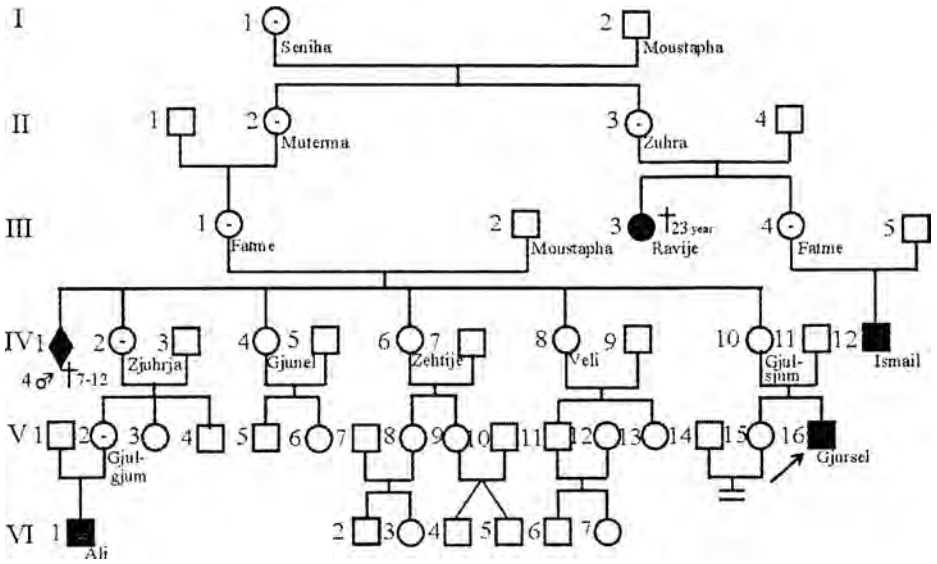

Fig. 1. Pedigree of a Turkish family comprising seven hemophilic patients, four of them deceased after *circumcision* and three of them clinically confirmed. All have received the pathologic gene from a common progenitor, I — 1, Seniha

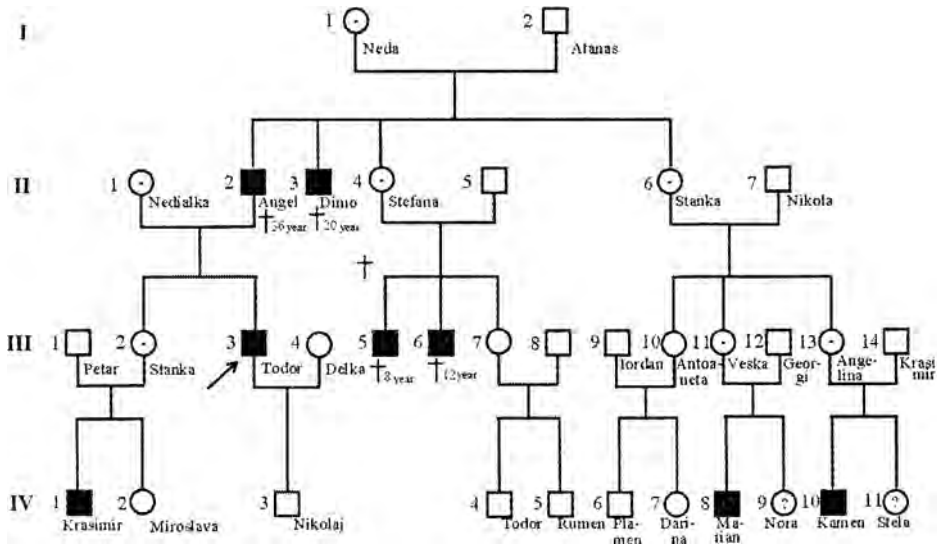

Fig. 2. Pedigree with eight hemophilic men. The transmission of the hemophilic gene could be traced to two distinct progenitors : I — 1, Neda and II — 1, Nedialka

Dermatoglyphic analysis showed that three out of four values of the finger ridge count of hemophilic patients demonstrated statistically significant differences as compared to the corresponding values in healthy men. The difference is especially expressed in the total finger ridge count (TFRC) : mean values of 169.29 versus 145.64. Of course, the question arises as to the different contributions of the separate fingers to this difference. The comparisons realized finger-by-finger showed that, except the fifth fingers of both hands, all the remaining fingers participle in the total difference with almost equal contributions. As far as the TFRC is an indicator of the model size, it is evident that bigger finger patterns prevail in hemophilic patients.

The absolute finger ridge count (AFRC) is also higher in the hemophilic patients; the difference between the latter and the healthy men being especially expressed concerning its internal structure, i.e. concerning the relationship between its two components, the radial (RFRC) and the ulnar (UFRC) ridge counts. We found a significantly lower UFRC and significantly higher RFRC in the hemophilic patients in comparison with the healthy controls.

Undoubtedly, the question arises as to whether these differences are caused by an unusual proportion between the radially and ulnarly directed finger patterns. Assessment of the radio-ulnar index [9] evidenced that such is the case. Except the first three fingers of the right hand, a decrease of this index was observed on all the rest fingers. As a result, its mean value was 0.21 in the hemophilic patients versus 0.25 in the healthy men. Consequently, the changed proportion between the ulnar and the radial finger ridge counts is due to an "ulnarization" of the finger patterns — much more expressed preponderance of the ulnar patterns over the radial ones in the hemophilic patients as compared to the healthy men.

Concerning the palm dermatoglyphics, the only our finding which corroborated the corresponding finding of K a l e v a et al. [8] was the increased occurrence of radial loops on the hypothenar. Significant differences were found neither in the localization of the palm triradii, nor in the values of the atd-angle. Neither significant deviations were established concerning two of the main palm lines, A and D, and, since the sum of the fields of their endings gives the main line index, MLI, the values of the latter were practically equal in the hemophilic patients and in the healthy men (14.14 versus 14.04, correspondingly). On the other hand, considerable differences were established in the other two main lines, B and C. The line C ended abortively much more often in hemophilic patients than in the controls. Such an ending was observed in 28.37 % of the hands (right and left) in the patients versus the normal proportions of 6.85 % for the right hand and 14.37 % for the left one. In other words, in hemophilic patients this configuration was observed 4-fold more often on the right hand and two-fold more often on the left hand as compared to the healthy men. The proportions of the field 5 (5′ and 5″) ending of the main line B are higher in hemophilic patients than in the controls (28.57% versus 22.63% on the right hand and in 71.43% versus 42.73% on the left one). Concerning both lines mentioned above, the asymmetry is considerably increased in the patients.

Discussion

The analysis of the pedigrees shown in all of them all the typical characteristics of the hemophilia as a X-linked recessive pathologic trait. On the other hand, our analysis demonstrated that, although the manner of genetic transmission of hemophilia has been established a long time ago, the genealogical analysis is very far from having exhausted its possibilities and perspectives concerning the illness under discussion. In the case of our study, it allowed us to made contributions in two respects — a social and a genetic ones.

The social factors should be carefully examined in every single one of the pedigrees with hemophilia, since they influence considerably the time and the manner of its phenotypic occurrence and, still more importantly, the outcome of the illness. Thus, the pedigree of the Turkish family showed that not so much ago even the death of three boys in a given family because of *circumcision* was not a contra-indication for the parents to perform this procedure on the fourth boy and to lose him in this way. It is known that in the Jewish population, where the same tradition also exists, despite the different religions, the fanatic application of the procedure in question is surmounted long ago and the boys having male mother's line relatives with hemorrhages are discharged from subjection to this manipulation. At the same time, in the younger families from the same pedigrees a considerable effect of the insisting medical advices are observed in this respect. On the other hand, the increased survival and expected longevity of the hemophilic men address new social and medical problems to the society.

Among the findings in finger dermatoglyphics, the most important were the increase of the TFRC in hemophilic patients, as an expression of the augmented finger pattern size, as well as the deviation in the proportion between the UFRC and RFRC, and correspondingly in the proportion between the ulnar and the radial patterns, expressed by the radial-ulnar index. This is a specific and very interesting change in the finger asymmetry. Concerning the palm dermatoglyphics, the findings about the lines B and C in hemophilic patients are oriented in the same direction on the right and the left hand; but, being very different in their extent, the differences increase considerably the palm dermatoglyphic asymmetry in hemophilic patients. Thus, the endings of the line B in the field 5 is augmented by 5.94% on the right hand versus 28.70% on the left and this increases the asymmetry with nearly 23%. The same event is still more prominent about the main line C, whose abortive ending showed a 4-fold increase on the right hand versus a 2-fold increase on the left one.

The finger ridge count is polygenically determined, but it is known that X-linked genes decrease its values. This explains the lower values in females than in males, as well as its decrease in X-chromosome polisomies. The observed higher values in hemophilic patients as compared to the healthy men allow to hypothesize a relationship between the genes coding the blood coagulation factors and those inhibiting the finger ridge counts, in which the pathologic condition of the former suppresses the effects of the latter.

Another finding, still more interesting from a genetic point of view, is Ravie (see III — 3 in Fig. 2), who committed suicide at age of 23 years, exhausted by repeated very heavy hemorrhage accidents. Theoretically, her complaints could be due to causes other than her belonging to a hemophilic family, but such a coincidence seems quite improbable. If so, two other possibilities should be hypothesized, both of them connected with an unusual expressivity of the gene of hemophilia. First, if the gene has been of very low expressivity in Ravie, she could be homozygous by such a gene, and because of its marginally low expressivity, the homozygous combination had not caused the usual letal effect during the embryogenesis. Secondly, if the gene was of very high expressivity, it had not been dominated by the normal one and thus has caused a phenotypic expression quite similar to that observed in hemizygous hemophilic men belonging to the same family.

Conclusion

Our results show that the genealogical analysis is far from having exhausted its possibilities concerning the hemophilia. Its application in the present study allowed to hypothesize two quite probable genetic mechanisms and to make important medico-social recommendations. The findings concerning the increased dermatoglyphic asymmetry in hemophilic patients with hemophilia A are more than promising in both theoretical and diagnostic respects.

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