History of Contemporary Medicine in Iran

The History of Hemophilia in Iran

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Early History of Hemophilia

The mutations giving rise to hemophilia are probably of great antiquity, because they occur in at least three orders of placental mammals: the Ungulata; the Carnivora, and the Primates. Hemophilia has been described in the horse[1] and in nine breeds of dog,[2] as well as in all races of man. The orders to which these groups belong may have been distinct from the end of the Cretaceous – say, 65 million years ago, and the mutations have probably recurred independently many times in all three, since it must be lethal in the wild state.[3] The mutation rate has been estimated at about $1 – 4 \times 10^{-5}$.[4]

The earliest references to what may have been human hemophilia are attributed to Jewish records of the second Century A.D. A ruling of Rabbi Judah the Patriarch, exempts a woman's third son from circumcision, if two older brothers had died of bleeding following the operation.[5]

In the tenth Century, males of a certain village bled to death from trivial wounds, described by Khalaf ibn Abbas, known in Europe as Albucassis.

The first description in more modern times, which probably refers to hemophilia, is from the 19th Century. For instance, Otto, in 1803,[6] describes families in which the males suffer abnormal post-traumatic bleeding. He noted that although only males were symptomatic, the disorder was transmitted by unaffected females to some of their sons. He traced a pedigree back to a woman from Plymouth, New Hampshire, in 1720.

Gradually, the clinical syndrome took shape as a considerable literature developed. The curious current name hemophilia or 'love of blood' first occurred in the title of Hopff's treatise of 1828.[7] Involvement of joints, the hallmark of hemophilia today, which had been often thought to be due to tuberculosis or rheumatism, was first ascribed to bleeding by Konig in 1890.[8]

It is now well-known that Queen Victoria herself (1819 – 1901) was a carrier of hemophilia B, affecting coagulation factor IX (rather than FVIII, as in hemophilia A). No evidence of the disorder exists among her antecedents, so we must assume that the mutation occurred at spermatogenesis in her father, Edward, the Duke of Kent.[9] The disorder only manifested itself for the first time with the birth of her eighth child in 1853, when Leopold Duke of Albany was born with hemophilia, which proved fatal when he died of a cerebral hemorrhage at the age of 31.

Leopold's sisters, Beatrice and Alice, were both carriers. Alice married the Grand Duke of Hesse, and two of her daughters, Irene and Alix, had hemophilic sons. Alix, better known as Alexandra (Queen Victoria's granddaughter), married Tsar Nicholas II of Russia, and their son, probably the most famous hemophilic in the world, was Alexei, who was born in 1904. Alexei was also the most tragic case, who created so much anguish in the Romanov family. It was through his successful treatment of Alexei's extreme pain with hypnosis when he was eight years old (probably due to a psoas hemorrhage), that Rasputin, the charismatic monk, gained such a sinister influence upon the entire household of the Tsar.

The last known carrier of Queen Victoria's mutation was Princess Alice, wife of the Earl of Athlone, who represented the British Crown at the celebration in Tehran, of Crown Prince Mohammad Reza Pahlavi's marriage to Princess Fowziyeh, the sister of Malek Farouq of Egypt in 1941.

Inherited deficiency of the eleven or more other blood coagulation factors is relatively rare and often less clinically severe. The one exception is a group of autosomally inherited, mostly dominant (except for vWD types 2N and type 3) bleeding disorders affecting both males and females, called von Willebrand's Disease (vWD), which is now known to be the commonest congenital bleeding disease, comprising vWD type 1; type 2A, 2B, 2M and 2N, as well as the most severe form-type 3 vWD-which can resemble severe hemophilia in its intensity, and is more common in Iran due to the strong tradition of consanguineous marriage. The correct diagnosis of vWD is particularly important among young women, because of menorrhagia, which can cause severe iron-deficiency anemia and debility during their most vulnerable reproductive years.

The Establishment of Hemophilia Diagnosis and Care in Iran

Up to 1964, no one took any interest in the inherited bleeding disorders, such as the hemophilias in Iran. These were truly clinical orphans, and those unfortunate children suffering from the severe form of hemophilia A (coagulation factor VIII deficiency less than 1%), or hemophilia B (factor IX deficiency) who had survived into adulthood, were already hopeless cripples. In addition, they had little recourse to treatment, as the sole available form of therapy was fresh whole blood carrying infinitesimal quantities of the relevant coagulant factor.

At the newly established Clinical Hematology Department in the former 500-bed Pahlavi (now Imam Khomeini) Hospital, the associated laboratory was only equipped to carry out blood counts and May-Grunwald staining and microscopy of patients' peripheral blood and bone-marrow aspirates, at the time.

However, a personal grant of 18,000 Pounds Sterling from the Sir Henry Wellcome Trust to the author, who had joined the aca-

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Figure 1. The author's first visit to the Hemophilia Center at the Imam Khomeini Hospital in 1999 (the author is seen in the middle of the photo).

Figure 2. The author at the Imam Khomeini Hospital, Tehran, Iran, 1997. (Available from: URL: http://hemophilia.org.ir)

Figure 3. The posters of the World Hemophilia Day April 17/ 28 Farvardin in Iran. (Available from: URL: https://orphandruganaut.wordpress.com/2015/02/15/world-hemophilia-day-2015-april-17/; Available from: URL: http://hemophilia.org.ir/)

demic staff of Tehran University Medical School in 1964, provided sufficient funding for the purchase of all the equipment required to set up a modern clinical hematology laboratory. These included facilities for hemoglobin electrophoresis; radio-isotopic equipment for determining blood volume, Cr^{51} red-cell mass and survival, Vitamin B_{12} absorption, radio-technetium platelet survival; red cell enzyme allotypes such as G6PD and PK; serum folate assay, and so forth.

Whilst awaiting the delivery of all these myriad items of equipment from abroad, the author became interested in the investigation of inherited bleeding disorders. Using the Thromboplastin Generation Test of Biggs and Douglas (1953), together with the classic Prothrombin Time test of Armand Quick, it became possible to distinguish hemophilia A from hemophilia B, then known as Christmas disease in the UK, and to carry out bio-assays of these factors, using a broken 37°C water-bath and hand-pulled Pasteur pipettes. Although it was exciting to have been able to actually demonstrate the hemostatic defect in the laboratory for the first time in Iran, this academic exercise was of little benefit to the wretched children affected by these bleeding disorders.

As a result of repeated acute hemarthroses, particularly affecting weight-bearing joints, such as knees and ankles, many of them were bed-ridden due to contractures and muscle-wasting. Some had become drug-addicted because of pain and despair. Mothers felt guilty for being carriers of the disease; sisters were in an agony of doubt as to whether or not they were carriers of the genetic disorder, and would pass it on to their sons. The education of affected boys was disrupted, resulting in unemployment and a sense of inadequacy. The cost of these inherited bleeding diatheses to society is enormous, not only because of the premature death of potentially useful members of society, but also because, if left untreated, patients end up hopelessly crippled, and a burden upon their families and the health facilities of their country.

Thanks to a further research grant, the author was able to obtain a large-capacity, refrigerated centrifuge, which immediately provided the possibility of separating whole blood into components: concentrated red cells, platelets and plasma. The fresh plasma could be used for treating acute bleedings of hemophilic children. However, since polyvinyl blood bags were not yet available, bottles washed and re-sterilized at the Pasteur Institute, were still used.

Better still, Dr. Judith Graham Pool's discovery of Cryoprecipitate in 1964,[10] allowed for the preparation of a crude, home-made concentrate of Factor VIII in the Hematology Department laboratories. Bottles of cell-free fresh plasma were snap-frozen in a mixture of dry ice and alcohol, and subsequently thawed slowly at 4°C. A precipitate at the bottom of the bottles, contained most of the Factor VIII, fibrinogen and Factor XIII from the original crude plasma, and was stock-piled in deep freeze cabinets for future use. The cryo-supernatant plasma was also stored for use in hemophilia B, burns or hypovolemia.

Major orthopedic surgery, mainly arthrodesis of knees, was suc-

cessfully carried out in the late 1960s, in cases of severe hemophilia A, by a few intrepid surgeons, such as Dr. Shojaeddin Sheikh ol-Eslamzadeh or Dr. Gorgi, using only cryoprecipitate to prevent bleeding, and circulating factor VIII levels were assayed daily, before and after each infusion, to ensure hemostatic levels were maintained at all times for at least ten days. Soft-tissue surgery, such as pyloroplasty and vagotomy for repeated hematemeses, or pulmonary lobectomy for a hydatid cyst causing life-threatening hemoptyses were also undertaken with success by Dr. Kazemi, with similar replacement therapy.

It must be emphasized that in the mid-1960s, commercial factor VIII preparations were not easily available anywhere in the world, the sole exception being Fraction 1-O, pioneered by Birger[11] and Margaretha Blomback at the Karolinska Institute in Stockholm, which was later manufactured on an industrial scale by Kabi. The only other alternatives were bovine and porcine factor VIII, produced in the UK, which, although they were very potent, were dangerously antigenic. Indeed, one of the cases treated with bovine factor VIII by the author, developed both thrombocytopenia and a protein-losing nephropathy, probably caused by an immunogenic reaction to this fraction.

A remarkable patient seen in 1970, was the first reported case of acquired hemophilia A,[12] in Iran due to the development of an autoantibody against factor VIII, in an old man with no previous or family history of abnormal bleeding, who turned up at the Hematology Department one day, as an ambulant, confluent ecchymosis! He also suffered from copious hematuria. The story was that he had been given injections of penicillin for pneumonia two weeks before. Soon after, he suffered nosebleeds and extensive bruising. Acquired inhibitors of factor VIII had only been reported in a few cases of pregnancy, rheumatoid arthritis or lymphoma at the time, and were frequently fatal as a result of cerebral hemorrhage. It was fortunate indeed that this patient improved dramatically on corticosteroids alone.[13]

Baruch Blumberg had recently reported what came to be known as 'Australian Antigen' or hepatitis B surface antigen,[14] and since hemophilic patients had been repeatedly exposed to plasma, even though there had been no history of overt jaundice, it was felt that they should all be screened for the antigen by immunodiffusion (the only method available at the time), using the Ouchterlony gel-diffusion technique. This was the first application of a test for hepatitis B in Iran, and it was found that this viral infection was common among blood donors.[15]

Inevitably, seeking treatment for hemophilic patients drew attention to the appalling state of blood transfusion in Iran. Virtually without exception, blood for transfusion, whether in private hospital practice or in government and university hospitals, was procured through disreputable dealers. Professional blood-sellers exploited the poorest sectors of society, who were prey to malnutrition, anemia, and hepatitis, as well as drug-addiction. This was also true of the transfusion services of the Red Lion & Sun Society, the Iranian affiliate of the International Red Cross, currently called the Red Crescent Society. Even the military hospitals relied solely upon soldiers–never officers–who were ordered to volunteer, in return for 72 hours' leave, to allow for their recovery. In addition, modern advances in blood group serology, and proper compatibility testing had made little impact upon the rudimentary, fragmented and grossly commercialized blood services available at the time. Increasing population density and rapid advances in hospital surgery and medicine, together with the growing expectations of both the expanding middle classes and highly trained medical practitioners, revealed the glaring inadequacies and dangers of the blood services, and set the scene for fundamental reforms in this vital sector of public health infrastructure.

The unsatisfactory state of blood transfusion services, led the author to conceive a plan, in 1972, for the establishment of a modern, centralized, national service for blood transfusion, based entirely upon the voluntary, unremunerated donation of blood by healthy members of the public. Implementation of such a program called for a veritable social revolution, and a profound change in public attitudes, together with an extensive public education campaign.

In 1974, the Iranian National Blood Transfusion Service achieved legal status, and within a relatively short time, a technically advanced service, based entirely upon voluntary blood donation replaced the commercialism and inadequacies of the past.[16]

The Later Evolution of Hemophilia Care in Iran

In 1971, the World Federation of Hemophilia (WFH) agreed to hold their VIIth international congress in Tehran–the first time such a meeting had ever been held outside of Europe or Canada.[17] This was a ground-breaking meeting in other ways as well, in that the main thrust of the Congress emphasized the impossibility of providing adequate, comprehensive hemophilia care, without the close support of a safe, modern blood transfusion service, which formed an integral part of the national health services.

Even in the 1970s, it was clear that support for the hemophilic population could not remain confined to doctors and scientists alone. There had to be at least a minimal participation by parents of affected children and the patients themselves. Early efforts to establish a viable Hemophilia Society remained unfulfilled for many years. It is a source of satisfaction that today, a strong Iranian Hemophilia Society (IHS) has been created which is devoted to the interests of patients and their families, which defends their rights as citizens, and acts as their advocate at both national and international levels. The IHS has not merely confined its efforts to the conventional range of activities typical of similar societies elsewhere in the world: social services; dormitory services for patients from the provinces; support for employment and education; counselling affected families; providing information booklets, etc. It has gone much further by creating the first comprehensive, interdisciplinary hemophilia care center in Iran as well.

The Iranian Comprehensive Hemophilia Care Center (ICHCC) in Tehran, officially affiliated to the World Federation of Hemophilia, was inaugurated in April 2001, and comprises some 2,000 square meters on four floors. The laboratory services include:

1. A phenotypic laboratory, which carries out the full spectrum of coagulation tests, including specialized High Molecular Weight Multimer analysis and all the various binding assays for confirmation and classification of vWD. This laboratory is a participant in the NEQAS scheme for proficiency testing administered by Sheffield University. This laboratory effectively acts as a reference center for coagulation laboratories throughout the country.

Screening for inherited 'thrombophilia' has also been added to the range of investigations undertaken at the ICHCC.

2. A molecular genetics laboratory, which determines the precise genetic mutations affecting families, by direct DNA sequencing on two ABI capillary sequencing machines. Families in Iran can be exceptionally large, sometimes amounting to as many as a hundred individuals! Once the family mutation has been identified,

the carrier status of all the girls in these huge pedigrees can be confidently established. This provides the opportunity for counselling young women from affected families regarding marriage, future pregnancies, and their reproductive choices.

Once known carriers of a defective gene do become pregnant, pre-natal diagnosis can be carried out to determine whether or not the fetus is affected. The status of well in excess of 700 young women has been determined in this way.

This laboratory also successfully participates in the regular genetic NEQAS exercises sent from Sheffield University.

3. A general laboratory carries out biochemical and hematological investigation, and a molecular virology laboratory investigates patients with HBV, HCV or HIV infection, providing viral load determination and genotyping.

4. Specialist Consultation Clinics:

Dental Clinic–This is a particularly valuable service, since most specialists elsewhere ostracize hemophilic patients for fear that their premises and instruments will become sullied by HCV, or other viral infections which are quite prevalent among these patients.

Physiotherapy Department–An important adjunct to replacement therapy or surgery, in order to provide rehabilitation and build up wasted muscle tissue.

Consultation for Liver Disease–Many patients suffer from viral hepatitis with varying degrees of chronicity, receiving long-term therapy, and require careful follow-up.

Gynecology and Psychiatric Clinics–The former deals mostly with women suffering from forms of von Willebrand's disease, while the latter addresses the significant number of cases with depression or drug addiction.

Orthopedic Clinic–This problem-solving clinic deals with cases of chronic synovitis, assessing the need for reconstructive surgery on hips and knees.

Pharmacy–A specialized pharmacy dispenses coagulation factor concentrates prescribed by the physicians of the ICHCC.

Finally, the ICHCC also fosters academic endeavor, providing a setting for university students' to carry out research for their MSc or PhD theses, as well as undertaking to publish reports mostly pertaining to the genetic analysis and classification of the various hemostatic disorders, such as hemophilias A and B, type 2 von Willebrand's disease, Platelet dysfunctions, as well as the thrombotic disorders.

A network of Hemophilia Centers now exists throughout Iran, often affiliated to regional medical schools. The most prominent clinics currently are: the Hemophilia Clinic at the Mofid Children's Hospital in Tehran; the Hemophilia Center at the Imam Khomeini Hospital, Tehran; The Shiraz University Hematology Department and Hemophilia Center; and further centers in Esfahan, Mashhad, Ahvaz, Gorgan, and Tabriz cities.

Registered Patients suffering from inherited bleeding disorders are covered by a national insurance scheme under the aegis of the Ministry of Health, such that all their laboratory investigation expenses, as well as replacement therapy with plasma-derived or recombinant coagulation fractions are administered free-of-charge.

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