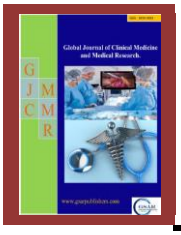

Global Journal of Clinical Medicine and Medical Research [GJCMMR]
ISSN: 2583-987X (Online)
Abbreviated key title: Glob.J.Clinic.Medici.Medica.Res.
Frequency: Monthly
Published By GSAR Publishers
Journal Homepage Link- https://gsarpublishers.com/journal-gjcmmr-home/

Clinical and Genetic Characteristic of Hemophilia Patients in Pakistan: A Retrospective Study

By

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Article History

Received: 15/02/2025
Accepted: 26/02/2025
Published: 28/02/2025

Vol – 3 Issue – 2

PP: -19-26

DOI:10.5281/zenodo.14956690

Abstract

Background*: A clotting factor (VIII/IX) deficiency causes hemophilia, an X-linked recessive congenital bleeding condition. About 80% of instances of hemophilia are caused by hemophilia-A, while 20% are caused by hemophilia-B.*

Methodology*: The study comprised patients who were attending the Hemophilia Patient's Welfare Society (HPWS). The Armed Forces Institute of Pathology (AFIP) and HPWS provided the hemophilic patients' demographic information, laboratory results, assessment of the disease's severity, and course of therapy.*

Results: *The findings showed that, of the 117 patients, 88.88% had hemophilia A and 11.11% had hemophilia B. The ratio of rural to urban areas was 1.2: 1. In 56.41% of cases, a family history of hemophilia was discovered. According to clinical categorization, 55.55%, 18.18%, and 25.64% of patients had severe, moderate, or mild hemophilia, respectively. Factor concentrates were used to treat about 62% of bleeding events. A single injection was effective in 72% of episodes.*

Conclusions: *The study's findings, which outline the dangers of consanguinity and offer baseline data on the inheritance of uncommon bleeding disorders, might be useful in developing a public awareness campaign and informing the medical community in particular. Additionally, creating comprehensive clinics for hemophilia care, raising knowledge of the disease's transmission, providing prenatal and postpartum counseling, and treating it.*

Key words: *Haemophilia; X-linked diseases; congenital bleeding disorder; Consanguinity; Factors deficiency*

INTRODUCTION

Hemophilia-A, also known as classic hemophilia, and hemophilia-B, often known as Christmas illness, are among the most prevalent hereditary bleeding diseases in the world [1]. X-linked disorders include hemophilia-A and hemophilia-B. The X chromosome's long arm contains the genes for hemophilia-A and hemophilia-B, which are referred to as Xq28 and Xq27, respectively [2, 3]. Hemophilia A [HA] and hemophilia B [HB] are the two most prevalent forms of hemophilia. About 80% of all instances of hemophilia are caused by HA, while 20% are caused by HB [4-6]. Factor deficiencies (factor VIII and factor IX) are the most common coagulation disorders. Both hemophilia A and hemophilia B are X-linked and recessive [2].

The bleeding problems are regarded to treating physicians considering that 16th century [7]. Medical literature within the West is complete of expertise concerning one-of-a-kind components of those disorders. Congenital bleeding issues are found in all racial groups and have global distribution but very restrained statistics is available in growing countries like Pakistan about their incidence and so on. Figure 1 and Figure 2 shows how this disease is transmitted to their offspring.

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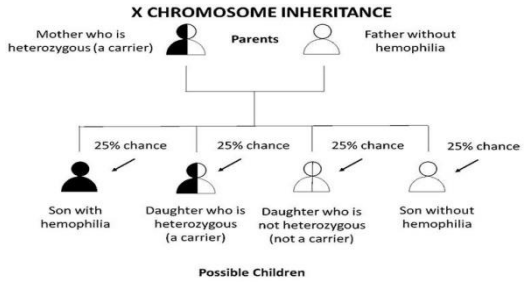

Figure 1: X-Chromosome Inheritance from Carrier Mother

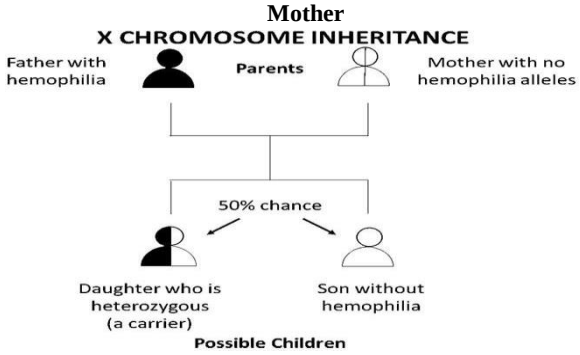

Figure 2: X-Chromosome Inheritance from Affected Father

Patients who have congenital coagulation factor deficiencies experience bleeding issues. The most prevalent of these are hemophilia A (HA), hemophilia B (HB), and von Willebrand disease (vWD), which are distinguished by low levels of either von Willebrand component (vWF) or factor VIII(FVIII)/IX (FIX) [7]. Because the degree of bleeding is directly correlated with the degree of factor deficit, X-linked recessive illnesses, such as HA and HB diseases, are classified as moderate, mild, and severe based on the amount of factor present in the plasma [8, 9]. The majority of uncommon bleeding issues are autosomal recessive and arise from either poor platelet functioning or deficits in clotting factors other than factors VIII, IX, and vWD.

India and the Middle East have been shown to have greater rates of platelet-use diseases [10]. Incidences of HA (FVIII deficit) and HB (FIX deficiency) are 1 in 5000 and 1 in 30,000 male births, respectively [11]. Conversely, the most prevalent bleeding illness in women is caused by a vWF deficit or abnormality, which can also have an incidence of 1 in a thousand or higher [12]. Hemophilia is caused by a novel mutation in the FVIII gene in 30% of individuals [8].

Patients with hemophilia are characterized by clinically frequent, spontaneous, and posttraumatic hemorrhages involving deep muscular tissues, which can result in hematoma development, hemarthrosis, and easy bruising. Additionally, babies may experience severe bleeding after circumcision. Repeated bleeding of the muscles and joints eventually results in muscular loss and abnormalities that are incapacitating. There is currently no cure for these disorders. The clotting factor The mainstay of care for these individuals is replacement treatment.

But, factor replacement therapy, like fresh frozen plasma (FFP), exposes the affected person to expanded risk of transfusion transmitted sicknesses for example HCV, HBV, and HIV infections and additionally end up in alloantibodies (inhibitor) formation against the lacking factor. These antibodies neutralize the procoagulant feature of therapeutically administered factor and in the end make the affected person resistant to conventional factor replacement therapy. Inhibitors expand with frequency of 20% to 30% in HA and 02% to 5% in HB [13, 14].

The inability of the body to regulate blood coagulation causes hemophilias, a group of genetic disorders that can occur spontaneously or in response to trauma. Four hundred thousand hemophiliacs are expected to exist worldwide. Haemophilia being X- linked recessive disorders, have an effect on males. Women are carriers which transmit the disorder to their sons. Clinically sufferers present with recurrent, spontaneous, and generally, posttraumatic haemorrhages which can also involve deep muscular tissues, resulting in hematoma formation, hemarthrosis, and easy bruising babies may additionally develop immoderate bleeding after circumcision [8, 15-17]. Bleeding in Haemophilia has a unique predilection for the joints which may be due to the synthesis of tissue factor pathway inhibitor (TFPI) in synovial tissue.

The low expression of tissue factor (TF) in synovial tissue is another plausible theory. The spontaneous bleeding into joints in individuals with significant hemophilia starts a vicious cycle of bleeding that is manifested by incomplete healing, cartilage degradation, and thickening of the synovium. It culminates in a string of episodes of acute and chronic synovitis and hemarthrosis, which lead to incapacitating arthropathy. The most frequent clinical sign of severe hemophilia (70–80%) is hemarthrosis, or intra-articular bleeding. Bleeds can occur in the wrist or shoulder joint, but generally speaking, hinge joints—such as the knees, elbows, and ankles—are most frequently impacted since they carry the most weight. It is rare for bleeding to occur into the hip joint.

With no outward coloring or bruising throughout the joint (ankylosis), the afflicted joint is swollen, heated, and kept in a flexional posture [18–21]. Preventing early joint bleeding, the subsequent synovial hypertrophy, and joint degeneration is crucial. All patients are managed through a team approach headed by the hematologist, with assistance from physiotherapists and orthopedic surgeons [22–26]. Factor replacement, cryoprecipitate, fresh frozen plasma, relaxation, ice, and supervised rehabilitation are all components of the most satisfying treatment. Joint aspiration may be considered under the guise of replacing the lacking component in positive situations [27, 28].

Radiation synovectomy is recommended in chronic situations. Patients with chronic knee and elbow synovitis that do not improve after a 3-month prophylactic factor replacement trial are given preference for radiation synovectomy. An open synovectomy is recommended if two or three successive synoviortheses spaced three to six months apart had failed or

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if the radiographic rating was more than two points [28]. Patients with severe hemophilia who started using clotting agents as a preventative measure between the ages of one and two may have normal joints and be able to go about their daily life [13, 29].

Because the articular cartilage is inclined and conservative therapy is difficult to adhere to, the objective ankle joint is a unique endeavor that frequently develops in very young children. It has been suggested that continuous prophylaxis between the ages of 2 and 18 reduces the risk of developing chronic hemophilic synovitis and joint damage [27].

Recurrent hemorrhages, such those seen in hemophilia, have been shown to cause serious joint degeneration [30–32]. Numerous writers have documented alterations in the cartilage and synovial membrane in chronic hemorrhage. The early joint alterations that result from this syndrome are still poorly understood. Haemarthrosis's "short-term" symptoms include muscular spasm, discomfort, edema, and warmth.

Recurrent joint bleeding has more severe "long-term" consequences. Frequent intra-articular bleeding events harm the joint, resulting in deformity and disability [32–37]. It is challenging to pinpoint the precise pathogenetic pathway because of the lag between joint bleeding and the ensuing joint injury.

Numerous joint conditions, including blood-induced ones like hemophilic arthropathy, inflammation-mediated ones like rheumatoid arthritis, and degenerative ones like osteoarthritis, cause cartilage destruction and alterations in synovial tissue. These alterations are believed to be caused by a number of mediators, including iron, cytokines, oxygen metabolites, and enzymes.

Current theories, which are supported by experimental in vitro research and clinical experience, maintain that excessive exposure to blood components causes the synovium to become catabolically active, which in turn causes cartilage breakdown. According to recent research, iron stimulates the expression of genes related to cell division [37–40]. The degree of hemophilic arthropathy may be indicated by synovial iron accumulation, which is readily seen on magnetic resonance imaging. According to other research, chondrocyte activity and cartilage matrix integrity alter when articular cartilage is exposed to blood [32]. These ideas, however, are based on a small number of investigations.

The processes behind cartilage deterioration in hemophilic arthropathy are poorly understood in contrast to our understanding of osteoarthritis and rheumatoid arthritis. The pathogenesis may have a complex origin and involve both inflammatory synovium-mediated and degenerative cartilage-mediated components.

A lack of blood coagulation factors VIII or IX causes hemophilia, a hereditary condition [41]. The most typical sign of hemophilia is bleeding into the joints [42]. Hemophilic synovitis (HS), an inflammatory and proliferative illness, is the result of hemarthrosis [25]. Over time, hemophilic arthropathy, a painful and devastating form of arthritis, develops [25]. Clinical activity such as arthropathy, synovitis, and joint hemorrhage are well described [43].

Following a few joint bleeding episodes, synovial fibroblasts and vascular cells proliferate, and hemosiderin is deposited in both the superficial and deeper layers of the synovial membrane [44]. The underlying bone and cartilage deteriorate over the ensuing years [45]. Ankylosis and fibrosis appear [46]. The pathogenesis of and molecular modifications leading to blood-triggered HS are poorly understood [47]. The gross [48], radiologic [49], microscopic [50], and ultrastructural [51] modifications that arise within the synovial membrane of human and experimental hemarthrosis are paying homage to modifications described in malignant tissues.

Villous hypertrophy may be caused by a merchandising of cellular growth and/or abrogation of cellular dying. The element or elements in blood that cause these changes are unknown, but iron is frequently suggested as one possibility [52–54]. Iron plays a role in tumor progression, local invasion, and malignant cell growth [55, 56], likely due to changes in oncogene expression [52]. We hypothesized that iron plays a similar role in HS. To support this theory, Wen et al. confirmed that in vitro iron will increase the proliferation of human synovial fibroblast cells (HSFC) and induce the expression of the c-myc oncogene [52].

Here, we used normal human and murine synovial cells to evaluate iron-induced mdm2 gene expression in vitro and blood-induced synovitis and mdm2 expression in vivo in a mouse model of human hemophilia.

In Pakistan, the government does not provide assistance for managing hemophilia. There is no infrastructure available to treat this chronic bleeding illness. Only teaching health centers in larger cities like Rawalpindi, Islamabad, Lahore, and Karachi are able to do laboratory hemophilia diagnosis. The majority of patients receive FFP or occasionally cryoprecipitate.

Only individuals who are registered with hemophilia societies receive appropriate care at public hospitals located in major cities.

Most patients cannot afford excessive-purity or intermediate-purity factor concentrates that have been virally inactivated. Patients in small towns, cities, and villages are ignorant and do not know how to receive a diagnosis. Even with modest diagnostic centers in remote parts of the nation, medical professionals cannot diagnose hemophilia because they do not know enough about the condition. This might result in a high prevalence of sickness and mortality among residents of underdeveloped regions.

With the assistance of the Armed Forces Institute of Pathology (AFIP) and the Haemophilia Patients Welfare Society (HPWS), this study was created to determine the prevalence of bleeding disorders in the Rawalpindi and Islamabad areas as well as in patients who come from neighboring cities. It also aimed to evaluate the severity of complications and the available treatment options for these

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patients. Updating knowledge and skills in the prognosis of bleeding problems and preventing consequences related to the condition and its treatment was the secondary goal of the study [28].

Objectives:

- Additionally, setting up comprehensive clinics for hemophilia care, raising awareness of transmission, and providing prenatal and postpartum counseling.
- This study set out to assess and describe hemophilia (A and B) and ascertain the relationship between hemophilia and cousin marriages.

MATERIALS AND METHODS

Study design:
Hemophilia A and B, rural and urban areas, and the family histories of cousin and non-cousin marriages were all compared in this study.

Study setting:
The study was carried out between July 30, 2022, and September 30, 2022.

Sampling technique:
To gather data, a non-probability sampling approach was used. Clotting time (CT), activated partial thromboplastin time (APTT), bleeding time (BT), thrombin time (TT), prothrombin time (PT), platelet count, and factor level estimation were used to establish the diagnosis. Adsorbed plasma (normal plasma adsorbed by barium sulphate) and aged serum (24-hour-old serum stored at 37°C) were used in mixing experiments. A 1:1 ratio of the patient's plasma with aged serum and adsorbed plasma, respectively, was then used to calculate the activated partial thromboplastin time (APTT).

Commercially available deficient plasmas were used to assess factor levels. Records were kept of the kind and location of bleeding, the causes of the bleeding, and other relevant information. Clinical features such as impairment, functional loss, and joint involvement were noted. A record of the treatments administered and the results obtained was kept.

Sample size:
A non-random selection of 100 – 200 patients.

Data collection procedure:
Data was collected from Hemophilia Patient's Welfare Society and Armed Forces Institute of Pathology.

Data Analysis:
Data was analysed through the SPSS.

Data Presentation:
Data was presented in tabular form.

Inclusion criteria:
Patients having haemophilia and deficient in factors VIII and IX.

Exclusion criteria:
Patients having blood abnormalities and bleeding have no deficiency of factors VIII and IX i.e., Von Willebrand Disease, or others factor deficiencies.

Possible Outcomes:
This data might be utilized to assess and describe hemophilia (A & B) based on lab reports from patients in Islamabad and Rawalpindi, as well as to emphasize the necessity of ongoing, individualized patient education and care. Additionally, to assess the family history of hemophiliac patients who have cousin weddings and to educate the public about the possibility of blood-relative marriages spreading this hereditary illness.

RESULTS

The study included patients who reported to AFIP and the Hemophilia Patients Welfare Society. Tables 1 and 2 show that of the 163 instances with hereditary bleeding disorders, 13 (3.68%) had hemophilia B and 104 (63.8%) had hemophilia A.

Table 1: Break up of Cases with Inherited Bleeding Disorders

Disorder	No of Pts (163)	Percentage (%)
Haemophilia A (FactorVIII Deficiency)	104	63.8%
Von Willebrand Disease	27	16.56%
Haemophilia B (Factor IXDeficiency)	13	7.97%
Glanzmann Thrombasthenia	06	3.68%
Factor X Deficiency	03	1.84%
Factor V Deficiency	02	1.22%
Bernard Soulier Syndrome	01	0.61%
Factor XIII Deficiency	01	0.61%
Factor XI Deficiency	01	0.61%

Table 2: Haemophilia: Break up of Cases

Factor VIII Deficiency (Haemophilia A)	104/117 (88.88%)
Factor IX Deficiency	13/117 (11.11%)

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(Haemophilia B)	

Only 10 patients (8.5%) were less than two years of age while 5 patients (4.27%) were in age group more than 40 years. Rural to Urban ratio was 1.2:1. In 66/117 patients (56.41%) haemophilia was found in brothers, maternal uncles and maternal cousins (Table 3).

Table 3: Haemophilia: Demographic Details

Sex:	Males	100%
Age:	Up to 2 years:	10 (8.5%)
	3 – 10 years:	42 (35.89%)
	11 – 20 years:	45 (38.46%)
	21 – 30 years:	03 (2.56%)
	> 40 years:	05 (4.27%)
Rural:	64 (54.7%)	
Urban:	53 (45.3%)	
Family History of Haemophilia (Maternal uncles, brothers, maternal cousins)		
Positive:	66/117 (56.41%)	
Negative:	37/117 (31.62%)	
Not known:	14/117 (11.96%)	

In the initial tests all the cases revealed normal ThrombinTime (TT) and Prothrombin Time (PT), while Activated Partial thromboplastin time (APTT) was prolonged in all cases (Table 4).

Table 4: Haemophilia – Lab Diagnosis

	PT	APTT	TT	BT	CT	Mixing Studies Correction by aged serum	Mixing studies Corrected by adsorbed plasma	Factor VIII assay	Factor IX assay
HA	Normal	Prolonged	Normal	Normal	Prolonged	Corrected	Not corrected	Deficient	Normal
HB	Normal	Prolonged	Normal	Normal	Prolonged	Not corrected	Corrected	Normal	Deficient

Mixing research causes hemophilia. Aged serum was shown to enhance APTT. Adsorbed plasma showed no improvement, although hemophilia B showed the opposite effect. Reduced factor levels were revealed using factor level estimation.

Of those diagnosed, 53% were younger than one year old (Table 5). According to clinical classification, 55.55%, 18.8%, and 25.64 percent of patients had severe, moderate, or mild hemophilia, respectively (Table 6). 75.21% of patients had joint involvement. 31.62% of patients had persistent impairment (Table 7).

Table 5: Age at Diagnosis

Up to 1 year:	62 (53%)
1-5 years:	23 (20%)
> 5 years:	32 (27%)

Table 6: Haemophilia – Patients Stratification on the Basis of Clinical Severity

	Bleeding Tendency	Sample size (n=117)
Severe Haemophilia (Expected factor levels: < 2 U/dl)	Regular spontaneous bleeding into the muscles, Joints, and internal organs.	65 (55.55%)
Moderately Severe (Expected factor levels: < 2-10 U/dl	Certain spontaneous bleeds; bleeding after injury.	22 (18.8%)
Mild Haemophilia	Bleeding only after prominent injury	30

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Expected factor levels: > 10-30 U/dl	or surgery.	(25.64%)

Table 7: Disability and Arthropathy

Permanent disability present:	37/117 (31.62%)
No permanent disability present:	80/117 (68.37%)
Arthropathy present:	88/117 (75.21%)
No arthropathy seen:	29/117 (24.78%)

Table 8: Bleeding Pattern

Bleeding episodes/year	Percentage (n = 117)
Up to 3	57/117 (48.61%)
4 – 10	32/117 (27.35%)
11 – 20	16/117 (13.67%)
> 20	12/117 (10.25%)
Spontaneous bleeding	87/117 (74.35 %)
Bleeding after trauma	30/117 (25.64)

Majority of the patients were treated with factor concentrates and majority (72%) responded to a single infusion (Table 9)

Table 9: Treatment Given

Product used	Episodes (%)
Fresh Frozen Plasma	15%
Cryoprecipitate	11%
Factor Concentrates	62%
DDAVP	3%
Combination*	9%

***Infusion of factor concentrate, FFP & Cryoprecipitate

DISCUSSION

In Pakistan, people have lived together for a very long period. Cataclysms, migrations, and the pursuit of better socioeconomic prospects have all contributed to the introduction of new alleles into these groups. Nevertheless, these groups persisted in coexisting and maintained their distinct geographic and genetic makeup. By keeping their gene pool intact across social borders, the high rate of first- and second-cousin marriages may have contributed to the establishment of this mixing, but it can also result in the transfer of inherited genetic illnesses to the next population. Scientists claim that intermarriages result in a large number of genetic mutations throughout Pakistan, which causes problems in the offspring.

Regardless of heritage or race, every family can be impacted by genetic and congenital defects.

One-third of birth abnormalities are the result of cousin marriages. The rate of consanguinity is rising as a result of these communities' ability to marry within families in order to maintain their familial and cultural structure due to convenient communication, religious concerns, and cultural heritages. Consanguineous couples may be more compatible and have a lower divorce rate, according to many Egyptians. However, this may make future generations more susceptible to genetic problems [57]. Pakistan is the most consanguineous country in the world, with over half of all marriages being between cousins [58].

According to this study, autosomal recessive illnesses had the greatest consanguinity rate (56.41%). Nearly identical outcomes have previously been shown for sensorineural deafness [61], mucopolysaccharidosis [59], and neurodegenerative diseases [60].

Eighty-five percent of parents with autosomal recessive disorders in Jordan were consanguineous [62]. According to several other studies, children of consanguineous couples were more likely than those of non-consanguineous couples to have diabetes, mental retardation, asthma, and epilepsy [63]. There have been several reports of an increase in the death rate among offspring of consanguineous marriages from all over the world [64].

Intermarriages have resulted in increased similarities among the members of these communities. Every evidence review including DNA profiles should evaluate and take into account these similarities between the individuals.

CONCLUSIONS AND RECOMMENDATION

This study provides basic information about the heredity of rare bleeding disorders and discusses the hazards associated with consanguinity, which might be useful in developing a public and health sector awareness campaign. Additionally, creating comprehensive clinics for hemophilia care, raising knowledge of the disease's transmission, providing prenatal and postpartum counseling, and treating it. Numerous additional hereditary bleeding illnesses, such as Von Willebrand Disease, Thalassemia, and missing Factor V or X diseases, Glanzmann Thrombasthenia, and others, are similar to hemophilia. A potential future viewpoint and suggestion may be the investigation of such illnesses in this context.

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