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Review Article

A REVIEW ARTICLE ON HEMOPHILIA

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ABSTRACT

Hemophilia An and B are X chromosome-connected draining issue included among the uncommon infections and brought on by transformations in the element VIII (FVIII) and component IX (FIX) qualities. Dominant part of hemophiliacs, living in creating nations with poor to nonexistent administrations of hemophilia care, are as yet confronting the issue of seeping alongside its complexities and low quality of life. WFH with its central goal and vision is attempting to minimize the hole through extending its diverse program. However fruitful administration of the hemophiliacs in creating nations will to a great extent depend essentially on the state of mind of the taking an interest nations. With the achievement of quality treatment and accessibility of the new bioengineered items the possibility of the hemophiliacs will be brighter in not so distant future. In the previous three decades, hemophilia has moved from the status of a dismissed and regularly deadly innate hemorrhagic issue to that of a characterized gathering of all around portrayed sub-atomic elements. The ampleness of the example size is fundamental likewise for an uncommon malady such hemophilia and this objective can be accomplished just through cooperative multicenter contemplates. Also, it is important to keep up a high intrigue and ability in the field of hemophilia, particularly among more up to date eras of doctors, who seem, by all accounts, to be pulled in by the all the more engaging thrombotic side of hemostasis.

Keywords: Crucial coagulation factors, Signs and symptoms, Genetics, Epidemiology

INTRODUCTION

Hemophilia An and B are X chromosome-connected draining issue included among the uncommon ailments and brought about by transformations in the variable VIII (FVIII) and component IX (FIX) qualities [1]. Both components partake in the characteristic pathway of blood coagulation and influenced people have extreme, direct and mellow types of the sicknesses, characterized by element plasma levels of 1% or less, 2 to 5% and 6 to 40%, individually. The pervasiveness of hemophilia An is 1 in 5000 male live births, and that of hemophilia B is 1 in 30,000 .Hemophilia was perceived in old times. The Talmud, an accumulation of Jewish rabbinical compositions from the second century AD, expressed that male infants ought not be circumcised given two siblings had as of now kicked the bucket attributable to unreasonable seeping from the strategy. The Arabic doctor Albucasis, who lived

in the twelfth century, portrayed a family with guys who kicked the bucket from seeping after minor harm [3] .The main advanced depiction of hemophilia is from John Conrad Otto, a doctor from Philadelphia, who in 1803 distributed "A record of a hemorrhagic manner existing in specific families [4]." He obviously valued the cardinal elements of hemophilia, i.e., an acquired propensity of guys to bleed.However, the principal utilization of "hemophilia" shows up in an article written in 1828 by Hopff from the University of Zurich. Hemophilia B was recognized from the more normal hemophilia An in 1952, and was frequently alluded to as "Christmas sickness" after the last name of the principal youngster portrayed with this condition [4]. Hemophilia is at times alluded to as "the regal ailment", in light of the fact that few individuals from illustrious families in Europe were influenced by this scourge attributable to the way that Victoria, Queen of England from 1837 to 1901, was a hemophilia B transporter [5].

Her eighth child Leopold had hemophilia B, experienced regular hemorrhages and kicked the bucket of a cerebrum drain at 31 years old. Two Queen Victoria's girls, Alice and Beatrice, were transporters of hemophilia B and transmitted the malady on to the Spanish, German and Russian regal families [1,5].The draining inclination of hemophilia was initially accepted to be because of a delicacy of veins. In the 1930s deficient platelets were thought to be the in all probability cause. At that point, in 1937, Patek and Taylor from Harvard found that they could remedy the coagulation imperfection by including a substance extricated from plasma. This was called hostile to hemophilic globulin. In 1944, Pavlosky from Buenos Aires, demonstrated that blood from one hemophiliac could amend the coagulation deformity of another hemophiliac and the other way around. He had unearthed two patients with a lack in various proteins - calculate VIII and component IX [6]. These disclosures allowed a precise conclusion, and they additionally fabricated the reason for the current treatment of this acquired hemorrhagic issue

HISTORY OF HEMOPHILIA:-

i. Scientific disclosure

The principal restorative expert to portray the illness was Abulcasis. In the tenth century he portrayed families whose guys passed on of seeping after just minor injuries. (6-16) While numerous other such graphic and down to earth references to the ailment show up all through chronicled works, logical examination did not start until the begin of the nineteenth century.
In 1803, John Conrad Otto, a Philadelphian doctor, composed a record around "a hemorrhagic

manner existing in specific families" in which he called the influenced guys "bleeders". He perceived that the confusion was inherited and that it influenced for the most part guys and was passed around sound females. His paper was the second paper to depict vital qualities of a X-connected hereditary issue (the primary paper being a portrayal of partial blindness by John Dalton who contemplated his own particular family). Otto could follow the sickness back to a lady who settled close Plymouth, NH in 1720. The possibility that influenced guys could pass the characteristic onto their unaffected little girls was not portrayed until 1813 when John F. Roughage, distributed a record in The New England Journal of Medicine.(6-17). The expression "hemophilia" is gotten from the expression "haemorrhaphilia" which was utilized as a part of a depiction of the condition composed byFriedrich Hopff in 1828, while he was an understudy at the University of Zurich. In 1937, Patek and Taylor, two specialists from Harvard, found hostile

to haemophilic globulin. In 1924, a Finnish specialist found a genetic draining issue like Hemophilia confined in the "Åland Islands", southwest of Finland. [38] This draining issue is called "Von Willebrand Disease". In 1947, Pavlosky, a specialist from Buenos Aires, discovered hemophilia An and hemophilia B to be separate sicknesses by doing a lab test. This test was finished by exchanging the blood of one hemophiliac to another hemophiliac. The way this redressed the thickening issue demonstrated that there was more than one type of hemophilia.

ii. CONNECTION OF EUROPEAN ROYALTY:

Ruler Victoria passed hemophilia on to huge numbers of her relatives. Hemophilia has included unmistakably in European sovereignty and therefore is here and there known as 'the regal malady'. Ruler Victoria passed the transformation for Hemophilia B to her child Leopold and, through two of her girls, Alice and Beatrice, to different royals over the landmass, including the illustrious groups of Spain, Germany, and Russia. In Russia, Tsarevich Alexei Nikolaevich, child of Nicholas II, was a relative of Queen Victoria through his mother Empress Alexandra and experienced hemophilia. It was guaranteed that Rasputin was effective at treating Tsarevich Alexei's hemophilia. At the time, a typical treatment directed by expert specialists was to utilize ibuprofen, which intensified instead of diminished the issue. It is trusted that, by essentially prompting against the medicinal treatment, Rasputin could convey unmistakable and noteworthy change to the state of Tsarevich Alexei.

In Spain, Queen Victoria's most youthful little girl, Princess Beatrice, had a girl Victoria Eugenie of Battenberg, who later got to be Queen of Spain. Two of her children were hemophiliacs and both passed on from minor auto crashes. Her eldest child, Prince Alfonso of Spain, Prince of Asturias, kicked the bucket at 31 years old from inside seeping after his auto hit a pay phone. Her most youthful child, Infante Gonzalo, passed on at age 19 from stomach draining after a minor pile up where he and his sister hit a divider while maintaining a strategic distance from a cyclist. Neither seemed harmed or looked for quick medicinal care and Gonzalo kicked the bucket two days after the fact from inward dying (16).

iii. BLOOD CONTAMINATION ISSUES:-

Preceding 1985, there were no laws authorized inside the U.S. to screen blood. Accordingly, many individuals with hemophilia who got untested and unscreened thickening element preceding 1992 were at an extraordinary hazard for contracting HIV and hepatitis C through these blood items. It is evaluated that more than half of the hemophilia populace, i.e. more than 10,000 individuals, contracted HIV from the polluted blood supply in the United States alone .As an immediate consequence of the tainting of the blood supply in the late 1970s and early/mid-1980s with infections, for example, hepatitis and HIV, new strategies were created in the generation of coagulating element items. The underlying reaction was to warmth treat (sanitize) plasma-inferred figure think, trailed by the advancement of monoclonal variable concentrates, which utilize a mix of warmth treatment and proclivity chromatography to inactivate any popular specialists in the pooled plasma from which the component focus is determined. The Lindsay Tribunal in Ireland explored, in addition to other things, the moderate appropriation of the new techniques. [6, 7]

SIGNS & SYMPTOMS:-

Trademark indications fluctuate with seriousness. As a rule indications are inner or outside draining scenes, which are called "bleeds"[16].People with more extreme hemophilia endure more serious and more regular drains, while individuals with gentle hemophilia for the most part endure more minor side effects aside from after surgery or genuine injury. In instances of direct hemophilia side effects are variable which show along a range amongst serious and mellow forms. In both hemophilia An and B, there is unconstrained draining yet a typical draining time, ordinary prothrombin time, ordinary thrombin time, yet drawn out halfway thromboplastin time. Interior draining is basic in individuals with serious hemophilia and a few people with direct hemophilia. The most trademark kind of inward drain is a joint drain where blood goes into the joint spaces. Kids with mellow to direct hemophilia might not have any signs or manifestations during childbirth particularly on the off chance that they don't experience circumcision. Their first manifestations are regularly incessant and huge wounds and haematomas from successive knocks and falls as they figure out how to walk. Swelling and wounding from seeping in the joints, delicate tissue, and muscles may likewise happen. Kids with gentle hemophilia might not have observable indications for a long time. Regularly, the main sign in exceptionally mellow hemophiliacs is substantial seeping from a dental strategy, a mishap, or surgery. Females who are bearers for the most part have enough coagulating elements from their one ordinary quality to counteract genuine draining issues, however some may present as mellow hemophiliacs. [16]

DEFINITION AND TYPES :

Hemophilias are the hereditary bleeding disorder due to absence or deficiency of plasma clotting factors, resulting in prolong and uncontrolled bleeding either spontaneously or following trauma

Two most common forms of hemophilia are Hemophilia A (HA) and

Hemophilia B (HB) and are caused by deficiency of factors VIII and IX respectively. HA accounts for 80-85% of cases and HB in 15-20% of cases. [19, 20] Both types are inherited as X linked recessive pattern characterized by prolonged bleeding and hemorrhages typically in joints and soft tissues.An uncommon type, Hemophilia C is an autosomal recessive defect that results in deficiency of factors XI and is characterized by bleeding in mucous membrane, the pattern of bleeding similar to Von Willebrand disease rather that hemophilia A and B[22-24]

6. GENETICS

Females have two X-chromosomes, guys have one X and one Y-chromosome. Since the changes bringing about the infection are X-connected latent, a female conveying the deformity on one of her X-chromosomes may not be influenced by it, as the equal allele on her other chromosome ought to communicate to create the fundamental thickening variables, because of X inactivation. In any case, the Y-chromosome in the male has no quality for variables VIII or IX. In the event that the qualities in charge of generation of component VIII or element IX exhibit on a male's X-chromosome are lacking there is no proportionate on the Y-chromosome to offset it, so the inadequate quality is not covered and the confusion will create.

Since a male gets his single X-chromosome from his mom, the child of a solid female quietly conveying the insufficient quality will have a half possibility of acquiring that quality from her and with it the malady; and if his mom is influenced with hemophilia, he will have a 100% shot

of being a hemophiliac. Conversely, for a female to acquire the malady, she should get two inadequate X-chromosomes, one from her mom and the other from her dad (who should along these lines be a hemophiliac himself). Subsequently hemophilia is much more normal among guys than females. In any case, it is workable for female transporters to end up gentle hemophiliacs because of lyonisation (inactivation) of the X-chromosomes.

EPIDEMIOLOGY:

Hemophilia is pervasive worldwide and happens in all racial and financial gatherings (22). The rate of HA and HB is around 15-20 for every 100 000 male conceived around the world. HA is otherwise called 'Traditional hemophilia' and record around 80% of instances of hemophilia and happens 1 in 10,000 male births 8. HB otherwise called 'Christmas ailment' happens in around 1 in 25,000 male births.

As indicated by the Report of the yearly worldwide overview 2009, the eleventh review by World alliance of Hemophilia (WFH) with a taking part 105 nations, add up to number of hemophiliac is 153,253 of which 115,209 is HA and 24,038 is HB9. Number of HA and HB patients with clinically recognized inhibitors was 5013 and 363, Reported number of Hemophiliacs contaminated with HIV and HCV was 5,665 and 24,340 (25-26). Be that as it may, these figures are a think little of than genuine ones. Since according to estimation of WFH, with a pervasiveness of HA and HB of 135 for every million male youngster (total populace being 6 billion), there would have been 399,000 hemophilia around the world. So larger part of the patients stays under analyzed and the reality of the matter is that the greater part of them are living in the creating nations (26-27).

CLINICAL MANIFESTATION:

The Clinical manifestation of HA and HB are identical, however HB is relatively milder disease so often diagnosed relatively in later life Hemophiliacs have the heterogenous phenotypic presentation depending upon its severity described in the table.

Table 1:- Level of severity

TYPES	% CLOTTING FACTOR 8&9	TYPE OF HEMORRHAGE
Severe	1	Spontaneous; hemarthroses and deep tissue hemorrhage
Moderate	1-5	Gross bleeding following mild to moderate trauma,; some hemarthroses; seldom spontaneous haemorrhages
Mild	5-40	Severe hemorrhages only following moderate to severe trauma, spontaneous bleeding is rare

Severe hemophilia usually present in neonatal period and early infancy, while moderate hemophilia in toddlers and mild hemophilia in late childhood or adolescent and adult often incidental or following major trauma Bleeding is the hallmark of hemophilia, sites and pattern of bleeding varies over life time [25-30]

DAIGNOSIS OF HEMOPHILIA:

- At birth: Hemophilia is diagnosed either due to known family history or after presentation with bleeding. Collection of blood sample: Arrangement of collection of blood sample from fetal side of placenta should be done if there is possible family history or mother of a male fetus is known or possible carrier. If any newborn /child presents with unusual / prolonged bleeding is subjected for basic screening test.
- Screening tests: Complete blood count- remains normal other than anemia.
- Bleeding time: remains normal.
- Prothrombin time (PT): also normal in hemophilia.
- Activated partial thromboplastin time (APTT): usually increased by one and half fold to more than 2 fold. Normal hemogram, bleeding time and PT with prolonged APTT leads to the suspicion of hemophilia which warrants specific factor analysis.[31]

TREATMENT OF HEMOPHILIA:

Hemophilia is managed through a combination of education, clotting factor replacement and comprehensive care. Proper exercise and nutrition help control bleeding and maintain health. Primary aims are- Prevention of bleeding and treatment of acute bleeding, Provide comprehensive care by multidisciplinary care team, Home therapy, Attention for psychosocial health and Rehabilitation [32].

Treatment of acute bleeding:

Factor replacement and other pharmaceutical therapy:

Replacement therapy is the breakthrough in the treatment of hemophilia which started with fractionated human plasma (FFP) in 1930's which reduces mortality and gave hope for the unfortunate hemophiliacs and to the treating physicians as well. But because of low content of factors large volume is needed for replacement. However it is still in use in acute bleeding where specific cause is not identified and also in resource poor country where availability of clotting factors are limited. Cryoprecipitate, first available in 1960's provide concentrated FVIII (100 unit in 5-15 ml bag). It is also in use in many countries because of its availability and low cost. Unfortunately both the FFP and cryoprecipitate are not heat treated and not recommended for specific therapy as they contain many other factors and they must be kept frozen until use (33). FVIII and FIX concentrate developed during 1960's and 1970's, by additional purification technique, provides specific replacement therapy for specific hemophilia. Plasma derived concentrate are made from as many as 20000-30000 donors and risk of transmission of blood borne diseases like hepatitis and HIV was improved by donor screening and viral inactivation and purification process. Recombinant factor VIII developed in 1984 through sequencing of

human factor VIII gene by genetically modified cells and is purified by MAB (monoclonal antibody) chromatography technique that render the potential of unlimited supply and virtually devoid of risk of blood born infectious agents. Only disadvantage is its high cost.

Principles for factor replacement (34)

• Factor replacement in acute bleeding should be prompt and within 2 hours and if in doubt about the bleeding treatment should be started before assessment is complete.

• Whenever possible specific deficiency should be corrected by specific factors

• Adjuvant therapy can be used to control bleeding in the absence of clotting factor concentrate

• If bleeding does not resolve despite adequate treatment, clotting factor should be assayed and inhibitors should be assayed if the clotting factors level are unexpectedly low.

• Home therapy can be encouraged in case of mild to moderate bleeding.

FUTURE PROSPECTS:

In the last two decades the fore mentioned advances on the efficacy and safety of the treatment of hemophiliacs have been obtained and implemented quasi exclusively in western countries. Thus, the first goal for the next future is to obtain wider treatment availability. There are a number of emerging and densely populated countries, such as India and China, where the level of hemophilia care is far from being satisfactory.

For these countries, which are rapidly developing a high level of technological competence, it is probably more appropriate to foster DNA technology with the goal to produce recombinant factors and develop gene transfer rather than programmes based on plasma fractionation.

On the other hand, the industrial production of plasma-derived factors should continue and expand, to meet the increasing needs and demands of those countries (especially in South America and Eastern Europe) that are rapidly improving their programmes of health care delivery to persons with hemophilia and that cannot afford the higher cost of recombinant factors. Although the extension of programmes of hemophilia care to developing countries is the main goal for the immediate future, there are also a number of objectives for high-income countries. First of all, to maintain the current excellent levels of treatment that risks to be jeopardized owing to the global economic crisis. It must be emphasized that the costs of hemophilia are truly a tiny part of the whole budget for health care in any country, and that cost effectiveness of hemophilia care is well proven. In addition, richer countries should support the needs of factor replacement therapy of low-income countries of Africa, where an adequate production of plasma-derived or recombinant factor concentrates cannot be foreseen for the next future.[35]

13. CONCLUSION:-

The hemophilia is the commonest inherited bleeding disorder which can lead to chronic disorder and lifelong disabilities if not properly managed. Over the past decades, its management has improved markedly and the life expectancy of a newborn with hemophilia would be close to normal healthy child and the hemophiliacs could pursue life with vigor of any normal population. But this is materialized only for those who live in developed countries where dedicated comprehensive care for hemophiliacs are available. Vast majority of hemophiliacs, living in developing countries with poor to nonexistent services of hemophilia care, are still facing the problem of bleeding along with its complications and poor quality of life. WFH with its mission and vision is trying to minimize the gap through expanding its different program. However successful management of the hemophiliacs in developing countries will largely depend primarily on the attitude of the participating countries. With the success of gene therapy and availability of the new bioengineered products the prospect of the hemophiliacs will be brighter in near future.

In the past three decades, hemophilia has moved from the status of a neglected and often fatal hereditary hemorrhagic disorder to that of a defined group of well-characterized molecular entities. There is little doubt at the moment that, among the most prevalent monogenic disorders (cystic fibrosis, thalassemia, muscular dystrophy), hemophilia enjoys the most efficacious and safe treatment. Indeed, after the dramatic events of widespread blood-borne virus transmission in the 1970s–1980s, there has been a strong drive towards a continuous improvement in the efficacy and safety of replacement therapy and towards the cure of the disease through gene therapy.

To maintain this high level of health care and research two elements are essential. First, there is a need of international collaboration in clinical research on hemophilia. Indeed, very few of the aforementioned cogent unsolved questions can be tackled by studies done in single, albeit large, hemophilia centers. The adequacy of the sample size is essential also for a rare disease such hemophilia and this goal can be achieved only through collaborative multicenter studies. Secondly, it is necessary to maintain a high interest and expertise in the field of hemophilia, especially among newer generations of physicians, who appear to be attracted by the more appealing thrombotic side of hemostasis.

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