Advanced Medical Genetics

Task Requirement (Question)

Students will choose a specific genetic disorder from the list provided in class and available online and conduct a literature review of current genetic research into the genetic disorder. Factors to consider will include, but are not limited to, the genetic basis of the disorder, genetic diagnosis and screening, prevalence, inheritance patterns and clinical features of their chosen disorder. Students will also critically evaluate the current developments in the field applicable to their chosen disorder.

Answer

Introduction

Haemophilia is a bleeding condition affected by genetic incapability for the blood to clot properly. This may lead to bleeding on its own as well as bleeding after a wound or operation. Coagulation components are blood proteins that may assist to halt bleeding. People with haemophilia have small amounts of factor VIII (8) or factor IX (9) in their blood. The amount of a factor in a person's blood determines the seriousness of their haemophilia. The lesser the amount of the factor, the more probable bleeding will ensue, which might have an advantage to major health issues. A person may acquire haemophilia later in life in rare cases. Most victims are middle-aged or old people or young women who have just offered birth or are nearing the end of their pregnancy. With the right therapy, this issue may usually be resolved. Haemophilia is divided into two types: type A and type B. Hemophilia A is characterised by a dearth in coagulation factor VIII. This accounts for about 80% of all haemophilia cases. The severe type of haemophilia A affects around 70% of people (Franchini and Mannucci, 2013). The person with haemophilia B, sometimes known as "Christmas disease," lacks the clotting factor IX. Hemophilia affects around one out of every 20,000 men born across the globe (Donoso-Úbeda et al., 2018).

Varying on the extent of the coagulation component in the blood, A and B might be mild, normal, or severe. Moderate coagulation component levels vary from 5 to 40%, mild levels extend from 1 to 5%, and severe concentrations vary from less than 1%(Richards, 2014). While Hemophilia is primarily a hereditary disorder, procured Hemophilia is a uncommon autoimmune illness that may develop later in life, according to NORD. According to the Mayo Clinic, it occurs when your immune system targets blood-clotting components. Scientists think that this may develop as a result of an infection or underlying disorder and that it may also develop for no apparent reason. Hemophilia may strike at any age, though it is most frequent among the elderly. It's also linked to things like pregnancy, autoimmune diseases, cancer, and multiple sclerosis (Barnes et al., 2017).

General Background

People wrote about blood and bleeding issues in ancient times. Some people bled in unusual patterns, the researchers found. They had just the most basic understanding of how blood clots. Doctors didn't realise Hemophilia A was caused by a blood protein abnormality called

factor VIII until soon before World War II. In the 1950s, eleven new blood factors were found. To minimise misunderstandings, they were given Roman numeral names in 1961 (Yehuda Shoenfeld and M Eric Gershwin, 2005). Hemophilia is known as a "royal disease" since it affects royalty. This is because the Hemophilia gene was handed down via the reigning houses of Russia, Spain, and Germany by Queen Victoria, who became Queen of England in 1837. A spontaneous mutation in Queen Victoria's gene caused her to develop Hemophilia. One of her sons, Leopold, had Hemophilia, and two of her daughters, Alice, and Beatrice, were Hemophilia carriers. The daughter of Beatrice wedded to the Spanish royal family. She tossed the gene onto the Spanish throne's male successor (Ehsanbakhsh et al., 2020).

Alice, another of Queen Victoria's daughters, had a carrier daughter named Alix. Alix married Russia's Czar Nicholas in 1894 and come to be Empress Alexandra. Alexis, their son, was born in 1904 and acquired Hemophilia from his mother. The enigmatic Rasputin, considered a holy man with the capacity to cure, treated the young man Alexis for bleeds. Robert Massie's book Nicholas and Alexandra tells the interesting biography of this royal family. Hemophilia research has progressed significantly. Scientists discovered that human blood could be split into groups or kinds about 1900. Blood transfusions become substantially more effective as a result of this. In 1930, scientists figured out able to separate blood into its two major components, plasma and red cells. In the early 1960s, Dr Judith Graham Pool discovered a way of freezing and thawing plasma to form a level of factor-rich plasma (cryoprecipitate) (Glick et al., 2014). Cryoprecipitate was the most effective treatment for Hemophilia bleeds yet devised. The invention of factor concentrates, however, was the most significant advancement in Hemophilia treatment. The coagulation factor might be freeze-dried into a powder that would be convenient to store, transport, and use. People with Hemophilia may now be handled more swiftly than ever before because of factor concentrates. Factor focuses have allowed people to take care of their blood loss at home or work, allowing them to resume a more regular lifestyle (GOODEVE, 2010).

Genetic basis of Hemophilia

Hemophilia is a disease in which the body's capacity to form blood clots is impaired, leading people to bleed for longer periods than is typical. Hemophilia is a hereditary disease, which implies it is passed down from one generation to the next. Hemophilia A and B are the two most common kinds.

All living thing's characteristics are defined by the genetic code carried by DNA. A gene is a segment of DNA that contains instructions for producing a certain protein. Hemophilia A is caused by a mutation in the gene that delivers directions for making the protein factor VIII. The gene that delivers guidelines for getting protein factor IX has a mutation in Hemophilia B. In human cells, DNA is organised into chromosomes. Humans have 46 chromosomes, two of which, X and Y, are crucial for determining gender. Males have one X and one Y chromosome, while females have two X chromosomes (Grosse et al., 2011).

Hemophilia is a hereditary disease with an X-linked pattern, meaning the defective gene resides on the X chromosome. Because males only have one copy of the X chromosomes,

Hemophilia may be instigated by a single mutation. Females have two X chromosomes, and Hemophilia is caused by a mutation in both copies of the gene. A carrier is a female who has one mutant X chromosome and one healthy X chromosome. She may have Hemophilia symptoms, but it is unlikely that she would develop a severe form of the disease. She may pass the gene on to her offspring since she is a carrier (Harijadi et al., 2016).

Genetic diagnosis and screening

Individuals with Hemophilia A and Hemophilia B may have genetic testing for the element VIII and factor IX genes. Genetic testing examines the factor VIII or factor IX gene to find the genetic variation (i.e., change) that precludes the gene from properly manufacturing coagulation factor and, as a consequence, triggers Hemophilia. Taking a blood sample and submitting it to a facility that can do genetic testing is the first step in the testing. This information is crucial for many reasons:

For certain individuals with Hemophilia, this may give extra information regarding their chances of developing an inhibitor, which might change how they are treated. Once the disease-affecting variation in the element VIII or factor IX gene has been found in a person with Hemophilia, reliable carrier testing may be administered to his female relatives to see whether they are Hemophilia carriers (Iorio et al., 2019).

Carrier Testing

Carrier testing includes examining blood for coagulation factors. Women who have the Hemophilia A gene will have lower levels than normal, and some may have bleeding difficulties as a result. Despite its high accuracy rate of up to 79 per cent, carrier testing is inadequate to determine if a woman is a carrier. A woman's family history, in addition to testing, may show whether she has the Hemophilia A gene (Kazimova and Kadimova, 2017).

Women who are most likely to benefit from carrier testing are those who:

- Have sisters with Hemophilia A
- Have maternal aunts and first cousins with Hemophilia A on their mother's side, particularly female cousins.

Direct DNA Mutation Testing

DNA testing may be utilized to check for and detect mutations surrounded by genes. A blood test from a male family representative with Hemophilia A will be collected initially. The blood of the female being tested to determine whether she is a carrier is then analysed and examined for genetic alterations that are comparable. DNA mutation testing has a great amount of accuracy (Koc and Zulfikar, 2020).

Linkage Testing

Genetic mutations can't be discovered in certain cases of Hemophilia A. In these instances, linkage analysis, also known as indirect DNA analysis, may be used to monitor the family's gene mutation. Blood samples are gathered from a variety of family members, with a focus on men who are afflicted. Clinicians will next examine the person with Hemophilia A for patterns of linked DNA and compare them to the forms of other family members. Regrettably, linkage testing isn't as precise as other techniques of testing, particularly when the afflicted men are distant cousins (Lee et al., 2014).

Prenatal Testing

If an individual has a family history of Hemophilia then she should consider having their unborn child checked. Chorionic villus sampling may be done as early as 10 weeks into pregnancy. This requires taking a small sample of the placenta and testing the DNA for genetic changes. An amniocentesis is a test that is done later in pregnancy, usually between 15 and 20 weeks. A small needle is introduced into the uterus via the abdomen to acquire a sample of amniotic fluid. Hemophilia is a blood disorder that affects people. The cells found in the fluid are then examined for a gene (Lim and Pruthi, 2011).

Prevalence

The worldwide number of Hemophilia patients is three times bigger than previously thought. Patient registry data from Australia, Canada, France, Italy, New Zealand, and the United Kingdom—the nations with the most comprehensive Hemophilia registries—were employed by an international team of researchers led by McMaster University. Hemophilia A is affected by a flaw in the F8 gene, whereas Hemophilia B is instigated by a fault in the F9 gene; both variants mainly afflict males (Melchiorre et al., 2016).

According to the meta-analysis, more than 1,125,000 males worldwide have an inherited bleeding problem, with 418,000 of them having a severe form of the disease that is generally undetected. Previously, the condition was thought to affect just 400,000 people worldwide. For the first time, the pervasiveness of Hemophilia in newborns at birth was determined in this study. The researchers determined that people with Hemophilia had a smaller life expectation than the general population, especially in low-income countries where treatment is scarce. The chronic and severe joint disease results from a lack of treatment while bleeding into organs and brain haemorrhages may lead to paralysis and fatality. Clotting factor replacement therapy is the standard treatment for Hemophilia, although it may not be accessible in countries with inadequate health resources. Patients, carers, and the healthcare system as a whole sometimes bear a tremendous financial and psychological cost as a consequence of severe Hemophilia (MONAHAN, 2010).

According to the study, for every 100,000 men, there were, for all severities of Hemophilia A, 17.1 cases. The study had 6.0 cases of severe Hemophilia A. *While, on the other hand* severities of Hemophilia B, there were 3.8 cases and there were 1.1 cases of severe Hemophilia B (Qu et al., 2012a). In upper-middle-income countries, the odds of enjoying a normal-length and quality life are lowered by 64%, 77 per cent in medium-income countries, and up to 93 percent in low-income countries for children born with Hemophilia(Lyonnet, 2014).

Inheritance patterns and clinical features of Hemophilia' disorder

X-linked inheritance is present in both Hemophilia A and B. The X chromosome contains the genes that produce specific types of haemophilia, which explains why. At birth, humans have two sets of sex chromosomes. A single X chromosome egg is born to a mother with two X chromosomes. In his sperm cells, the father, who possesses both an X and a Y chromosome, generates either an X or a Y chromosome. When a father donates his X chromosome, a female is devised. If a man underwrites his Y chromosome, a boy is conceived. The sex chromosomes are one of the 23 pairs of human chromosomes present in every bodily cell (Buchlis et al., 2012).

Because a male child has only one X chromosome, he will develop the disease if he receives an X chromosome from his mother holding a disorder-triggering gene. Since women have two copies of the X chromosome, they must get two copies of the disease-affecting mutation, which makes them less likely to develop the disease (one from each parent). Therefore, there are fewer women with Hemophilia than men. However, at times, the situation may get more difficult. Despite the fact that females have two copies of the X chromosome, one is typically deactivated throughout expansion to reduce the number of active genes on the chromosome. A girl may get the disease even if she only has one copy of the disease-causing mutation, varying on which X chromosome is inactive (Raabe, 2008).

A woman with one mutant copy of the gene is known as a carrier. The right extent of clot factor, which is essential for normal blood clotting, is commonly present in the blood of these women. A small percentage of female carriers, however, have less than half the normal amount of coagulation factor, placing them at risk for irregular bleeding, especially after an accident, surgery, or tooth removal. Hemophilia C is also predominantly hereditary, although it is not X-linked since the causing mutation disturbs a gene on chromosome 4. As a result, both men and women are affected equally by Hemophilia C. People with one faulty copy of the Hemophilia C gene are often asymptomatic and unaware that they have the gene. When two carriers create a child, there is a 25% risk that the child will inherit one faulty copy of the gene from each parent and build the disease. There is also a 50% probability that any infant will inherit a copy of the disease-causing mutation from his or her parents and a 25% likelihood that the child will not receive a copy of the illness-triggering mutation and hence will not build on the illness or become a carrier (Scharf, 2017).

Clinical features of their chosen disorder

Depending on the kind of mutation, the severity of Hemophilia might vary. The seriousness of signs is decided on the impaired coagulation factor's levels. 1% factor activity is considered a severe disease, 1% to 5% factor activity is considered a mild disease, and higher than 5% factor activity is considered a moderate disease (Theodoraki, 2013). The severity determines the degree of bleeding, which is identical for Hemophilia A and B. Severe Hemophilia (A or B) causes bleeding to start at a young age and may arise suddenly (Shetty and Ghosh, 2016). Mild Hemophiliacs may only bleed heavily when they are injured or traumatised. Female Hemophilia carriers have varying levels of factor action; some have near-normal levels and do not bleed, while others have less than the anticipated 50% decline and bleed more often than non-carrier females. Bleeding episodes often start in the first two

years of life in people with severe haemophilia. The initial symptom of the disease in males is often severe bleeding following circumcision. In individuals with moderate or mild disease, symptoms may develop later. Hemophilia may occur bleeding in any part of the body. The joints, muscles, and gastrointestinal tract are all common places for bleeding (Sharathkumar and Carcao, 2011).

Hemophilia is characterised by hemarthrosis (bleeding into the joints). The knees and ankles are the most often afflicted areas (Srivaths, 2020). The bleeding produces joint swelling, severe pain, and the possibility of scarring over time. Over moment in time, joint degeneration occurs, needing joint replacement surgery. In the development of a hematoma, complications such as bleeding into the muscles (compartment syndrome) may arise. Mouth bleeding or nosebleeds are potential adverse effects. After dental practices, bleeding is typical, and dripping blood from the gums may happen in young newborns as their teeth develop. Blood in the stool might lead to bleeding in the gastrointestinal tract. Urinary tract bleeding might lead to blood in the urine. Acute intracranial haemorrhage may result in nausea, vomiting, or lethargy, as well as death. Hemophilia is defined by characteristic bleeding following surgery or trauma (TAGLIAFERRI et al., 2012).

Current developments and future in Hemophilia

For the treatment of bleeding problems, various novel medicines or therapies are presently being investigated. Because they use unique methodologies, these treatments are generally referred to as "new" therapies. Until recently, all therapies for Hemophilia and other bleeding disorders relied on human blood products (called plasma-derived) or a synthetic protein to replace the missing clotting factor protein (typically factor VIII (8) or factor IX (9)). (called recombinant.) "Factor replacement" therapy is the name for this form of treatment. Not all of the new therapies being researched today aim to replace the missing factor. Some people try to stop bleeding in unconventional ways(Xu et al., 2009). The way these items are through clinical trials, which are testing conducted by researchers to make that medicines operate as intended. All new medicines must first be tested in clinical trials and then authorised by the FDA before they can be recommended by a doctor. Gene therapy is a method of treating a genetic disease or disorder by giving people functioning copies of the gene that may be used to remedy the problem. Gene therapy may be accomplished in a variety of ways, including gene transfer, cell therapy, and CRISPR gene editing. The National Human Genome Research Institute (NHF) includes several materials that might assist you in learning more about gene therapy(Gir et al., 2012).

Advanced therapies like as gene therapy, targeted therapies, and tissue engineering, as well as the more recently developed induced pluripotent stem cell (iPSC) technologies, may have a plethora of therapeutic uses for the treatment of monogenic illnesses like haemophilia. Although haemophilia is well appropriate to progressive therapy conventions due to its monogenic nature and the fact that a modest upsurge in coagulation factor levels is enough to change a severe to a reasonable phenotype, it must be remembered that research in this field is still in its early stages, and significant exertions will be required earlier such treatments can

be implemented. Safety concerns must be considered extremely seriously, especially in this group of patients who appear with certain medical features that are almost always the outcome of their previous and current treatment. The occurrence of inhibitors or a susceptibility to utilize them, the patients' particular immunological condition, and the occurrence of pathological co-infections (HIV/HCV) are among these features. For these reasons, while enthusiasm is appropriate, vigilance is required to prevent instilling misleading prospects in both clinicians and patients (Tribuzi et al., 2017).

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