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The History, Implications, Recent Advancements and Role of Genetic Counselling Pertained to Haemophilia.

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Abstract

The present article discusses the history, implications, advancements focussing on haemophilia and the role of genetic counselling in genetic disorders in general.

The article, firstly looks into the history of haemophilia, symptoms and the evolution of treatment. It was noted that continuous research and trails has been able to introduce satisfactory treatment techniques. Secondly, the article discusses on genetic counselling, which, on the other hand has been able to uplift the psychological well-being of individuals suffering from genetic disorders. It was understood that the effectiveness of genetic counselling relied on the counsellor, the client's intellect, the culture and the family's influence, finance and geographic factors.

Keywords: *Haemophilia, genetic disorders, genetic counselling*

Introduction

Genetic research had been constantly studying on new developments in the field. As at October 2020, Geneticists had identified a number of 4339 variant causing genes. The recorded number of diseases caused by genetic mutations, as at September 2020, were 7800 (Bick et al., 2021). Genetic mutations are defined as a change that occurs in the structure of the chromosome or the base composition of the DNA (Zeiger, 2010). These mutations cause various types of disorders and are congenital or acquired. A congenital disorder may occur by inheritance which is present at birth and an acquired genetic disorder occurs due to an environmental cause (O'Malley & Hutcheon, 2007). These genetic disorders are categorised into 3 groups, namely monogenic disorders, which occur due to a single mutation in the gene, chromosomal disorders, which occur as a damage caused to the

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structure of the chromosome and multi-factorial disorders, which occur due to multiple mutations in the gene (Mahdieh & Rabbani, 2013).

Haemophilia is defined as a bleeding disorder which is inherited and is relatively rare, caused by an abnormality in the X chromosome. As a result the coagulation of blood does not happen properly, leading to excessive bleeding which may occur internally or externally (Plug et al., 2006). Mentioning on the history of haemophilia, in the second century Jewish records mentioned on the disease. Another similar description had been found in the writings of a physician named Al Zahrawi between 936 and 1013 CE (Kaadan & Angrini, 2022). Focussing on the recent era, it is recorded that in 1803, John Otto, a physician from America, discovered haemophilia as a hereditary disorder. Further, Otto had described that the disorder only affected males and the transmission was done by females who were unaffected (Kaadan & Angrini, 2022). However, much later it was discovered that females were also affected by haemophilia, although the occurrences were comparatively rare (Nance, 2013). In 1886 it was identified that in rare instances, females were affected by haemophilia. Throughout the time period from 1770 until now, continuous discoveries were recorded. The factor VIII and factor IX were discovered in the years of 1937 and 1952 respectively, which resulted a division as haemophilia A and haemophilia B (Sidharthan & Sudevan, 2020).

Noting on the pathophiciology, haemophilia A occurs due to clotting factor VIII dysfunction and Haemophilia B occurs due to clotting factor IX dysfunction (Mannuccio, 2020). Factor VIII is located on the X chromosome's long arm end and the factor IX is located close to the centromere of the X chromosome's long arm (Castaman & Matino, 2019). Haemophilia is identified as an X linked recessive disorder (Schrader et al., 2015). Unlike in dominant inheritance, in recessive inheritance, in order for the disorder to occur, abnormality should occur in both genes. With only one muted gene, the symptoms does not appear or will be mild. However, individuals having one abnormal gene has the tendency to be carriers and pass it to the next generation (National library of medicine, 2022). It is identified that 25% of haemophilia A is caused by gross gene arrangements, 20% due to of a segment and 5% due to deletion that occur in the factor VIII (Nance, 2013). In haemophilia B, 2% is caused by re-arrangements of the factor IX. Base substitutions and minor insertions or deletions may also contribute (Nance, 2013). Most common type is haemophila A which has a prevalence ratio of 1 to 5000, whereas haemophila B records a ratio of 1 to 30000 (Castaman & Matino, 2019). It has been discovered that haemophilia B is 8 to 9 times higher in male germline (Nance, 2013). Mentioning on the severity levels, if the clotting factors are less than 1%, it is considered as severe haemophilia. Moderate state is diagnosed when the clotting factor availanility is 1% to 5%, and the mild state results a clotting factor availability of 5% to 40% (Schrader, 2015).

Haemophilia symptoms might appear in later stages of life, if the effect is mild. However, in the event of severe haemophilia, symptoms appear soon after birth (Schrader, 2015). Hemarthrosis is a common manifestation, which results bleeding into the joints. Symptoms include tingling sensation, joint cavity inflation and restricted movements. Mostly, joint bleeds occur in the knee, ankle, wrist or elbow (Mansouritorghabeh, 2015). bleeding in the central nervous system is another manifestation, which individuals experience neck pains, headaches, vomiting repeatedly, double vision, difficulty in arm movements and walking. Further, muscle bleeds occur and cause pain and swelling, which also leads to less movement of the affected organ (Blanchette et al., 2014). muscle bleeding is experienced by over 75% of haemophilia patients (Mansourritorghabeh, 2015). A condition called new bleed may occur, which is an episode of re-bleeding that happens in the same organ after 72 hours of ceasing treatment (Blanchette et al., 2014). Apart from main manifestations, excessive bleeding on tooth extraction, bone density reduction, bleeding in the vertebra and gums, spontaneous gestrointestinal bleeding, hematuris, which is an abdominal pain caused suddenly and hemorrhagic episodes, which is loss of blood from a damaged blood vessel may occur (Mansouritorghabeh, 2015; Merchan et al., 2021).

Common screening methoods used are prothrombin time tests and activated partial thromboplastin time tests (Capoor et al., 2015). Muscle bleeds are identified through clinical testing and imaging (Blanchette et al, 2014). Fibrinogen tests are also used in screening (Huisman & Crighton, 2021). Further, Prenatal screening, direct DNA-based analysis, Linkage Analysis are carried out (Pruthi, 2005).

Haemophilia treatment has a long history. However, it had been identified that only about 25% of the affected individuals receive treatment worldwide (Ohmori, 2020). The first successful blood transfusion was recorded in 1840 which was carried out by a physician named Lane (Escobar & Nguyen, 2014). In the beginning of the 20th century, blood clotting due to haemophilia was treated using a donor's normal plasma. The possibility of isolating plasma from blood was discovered in the 1950s, and it was used to treat patients with excessive bleeding (Escobar & Nguyen, 2014). Standard therapy method uses Antihemophilic factor VIII agent in order to replace clotting factor VIII, while antihemopilic factor IX agent replaces clotting factor IX. In order to control the bleeding and support clotting in both haemophilia A and haemophilia B, Recombinant factor VII is utilised (Schrader, 2007). Gene transduction is another method used in gene therapy. It involves inserting the gene which expresses the sequence, into the cells (Ohmori, 2020). Genome editing method focuses on the abnormal gene at the level of DNA by attempting to repair the gene. Tools such as zinc finger nucleases or transcription activator like effector nucleases, are used in gene editing (Merchan et al.,2021). At present, tissue engineering, regenerative medication, gene therapy and cell therapy are used (Merchan et al., 2021).

Continuous research had been carried out on haemophilia treatment. One treatment method is injecting adeno associated virus. Clinical trails carried out on 10 patients having haemophilia B, reported that there was an increase in clotting activity by 4% to 7%. Another clinical trail carried out on 9 patients having severe haemophilia A, reported an increase of factor VIII over 12% (Ohmori, 2020). Presently, researchers are focusing on avoiding replacement methods by utilising antibodies. As an example, emicizumab antibody is used to treat haemophilia A. Further, according to research, emicizumab can be used without an inhibitor. Trails recorded an 87% success rate in reducing bleeding episodes (Merchan et al., 2021).

At present, the involvement of genetic counselling in assisting individuals with genetic disorders is considered indispensable. The concept of genetic counselling was initially proposed in 1947 (Alabek et al., 2015). However, it is noted that genetic counselling was first introduced as a post graduate programme in 1969 at Sarah Lawrence College, New York, and genetic counselling established

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as a profession towards the end of the 1980s (Ormond et al., 2018). Genetic counselling is defined as the process which helps individuals to understand as well as adapt to the medical and psychological, as well as the familial implications which arise as a result of the disease (Resta et al., 2006). Mainly the process of genetic counselling involves in assessing family history and interpreting chances of disorder occurrence, educating individuals and families on inheritance and prevention methods, testing and management of the relevant disorder and providing counselling support in order to assist and promote adaptation (Alabek et al., 2015).

Application of genetic counselling in haemophilia focuses on helping affected individuals and families to understand the process of diagnosis and the implications of the disorder, thereby supporting adaptation to live with the disorder and especially, guiding on re-production due to the risk of passing the disease causing gene on to the next generation (Alabek et al., 2015). Further, genetic counselling can be stated as one section of a collaborative activity, which engages in the treatment and management process of haemophilia. Apart from the genetic counsellors, nursing personal, haematologists, psychologists and social workers involve in the activity (Alebek et al., 2015).

Genetic counselling is a process consisting of 6 stages which begins with contracting. In the contracting stage, the client and the counsellor share the expectations and come to an agreement on the process. During this stage, introductions are made and assessing client's understanding is done by the counsellor. Prior to the discussion arrangements, topics are proposed to the client for selection. The second stage focuses on gathering information. Both clinical as well as non-clinical information are collected. Details on tests undertaken, details of planed tests and treatments undertaken are recorded during the clinical information collection (Alebek et al., 2015). Documenting of pedigree form is also considered an important action, which is undertaken during the second stage. Patient's awareness on the implications and psychosocial issues are recorded as non-clinical information. Thirdly, a risk assessment is carried out. The counsellor's subject knowledge is applied on the gathered information and the risks on both the client and the family are assessed. It is recommended that the assessment details are conveyed to the client. The fourth stage is on educating the client, and may include the family members where applicable. Information about the history of the disorder, inheritance patterns and risks are suggested to be discussed. Counsellor's awareness on the client's level of understanding is considered crucial. This enables the counsellor to more effectively educate the client. A considerable amount of time of the counselling session is spent on the educating stage (Alebek et al., 2015).

Next, psychosocial assessment is carried out followed by counselling. This stage focuses on supporting the client to adapt, as new tests carried out may disclose sensitive information which may cause new emotions that were not present before. Such emotions might not be direct expressions. Recognising the psychosocial impact caused by any advances, is important to the genetic counsellor to provide additional support where it is necessary. It is also recommended that counsellors have a proper understanding of their limitations and thereby reaching out for additional resources depending on the requirement (Alebek et al., 2015). Although considered as the final stage, case management should be implemented throughout the entire counselling process. This practice is suggested as it results overall effectiveness and enhance efficacy. Apart from recording standard details such as family history, medical records are reviewed to have a proper understanding of the present situation, prior to the session. Counsellors are encouraged to facilitate tests. Further, documentation on session details and progression should be undertaken. Follow-up on the client's adaptation, coordinating and arranging tests when necessary are also considered components of case management (Alebek, 2015).

Progression of the client might be influenced by global, individual or culture specific factors. A main factor is the severity of the disorder. The individual as well as the family might place higher importance to counselling if the severity is high and, thereby the importance is felt. Individual's perception and the understanding on genetic counselling is also an influencing factor. An individual who is unfamiliar with genetic counselling will be reluctant to take counselling support. Further, unwilling participation might lead to develop anxiety. Especially, in countries where the priority is directed towards other diseases and health issues, less attention will be paid on genetic counselling. Practical issues such as availability, access to services and cost issues may also affect counselling. Arranged marriages in certain cultures might prevent carrier identification. Certain cultures may refrain from disclosing information or religious beliefs may prevent seeking counselling support (Alebek, 2015).

At present genetic counselling is an expanding field. According to records, there were around 7000 genetic counsellors globally at the beginning of 2018 (Ormond, 2018). Mentioning on Asian countries, at the beginning of 2018, the number of genetic counsellors were estimated to be around 350. The Asian countries practising genetic counselling were identified as Japan, Philippines, Indonesia, Malaysia, India, Singapore, and South Korea (Ormond, 2018). Rapid expansion of genetic counselling will result better services to individuals, affected with not only haemophilia but also other genetic disorders. The service of genetic counselling combined with medical services will enable better living through support and care.

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