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Treatment of Haemophilia A by Replacement Therapy using Factor VIII Inhibitors

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ABSTRACT

Haemophilia A is a very severe disease which is caused due to deficiency of a protein clotting factor VIII. Haemophilia A is X-linked recessive disorder which can be treated by the replacement therapy or by development of an inhibitors or antibodies against the FVIII. Hemarthroses is a disease in which bleeding in the joint spaces occur. This disease occurs approximately 70 to 80% in haemophilic patients. Then here we review about the epidimicity that deals with the transformation of haemophilia A. Then the process of inhibition stated, in which under the influence of some chemical substances the specific chemical process may inhibit. So, different replacement therapy may be ineffective when an inhibitor affect the factor VIII gene. In the end here stated different treatments for the management & control of disease, so among them the counselling between physician & patient is very effective.

Keywords : Hemarthroses, Haemophilia, Epidimicity, Epidemiology, DNA, AVD, IgG, TCR, Arthropathy, Prophylaxis

I. INTRODUCTION

There are many different types of bleeding disorders in which haemophilia A is known as a result of the deficiency of the protein clotting factor VIII and is genetically severe bleeding disorder. The deficiency of factor VIII in 1 in every 5000 male births without racial majority as X-linked recessive abnormality (Soucie *et al.*, 1998). Haemophilia A, as the most common disorder in patients, is intra-articular hemorrhages. The cure of haemophilia started from the last 40 years. In history, patients of haemophilia, including adults and children, had no ability of survival but now days this disease can be controlled and helps the patients to do their work activities in efficient way (DiMichele & Neufeld, 1998). Proper treatment of these patients requires deeply understanding of AHA path physiology by anaesthesiologists.

There are different therapeutic treatments for other bleeding disorders so that haemophilia A also cured by specific medication and blood products. At present the best treatment of haemophilia A is to replace the factor VIII by using the plasma or recombinant FVIII in order to stable its homeostasis. When a patient is develop an inhibitor against the factor VIII then the replacement therapy of haemophilia A becomes hopeless. Now a day's development of the inhibitor is the most important treatment of haemophilic patient (Fig. 1). Although there is decrease in death rate due to improvement in homeostatic agent but still there is another complication that is high rate of bleeding (Gringeri *et al.*, 2003; Darby *et al.*, 2004; Morfini *et al.*, 2007; Brown *et al.*, 2009; Di Minno *et al.*, 2010).

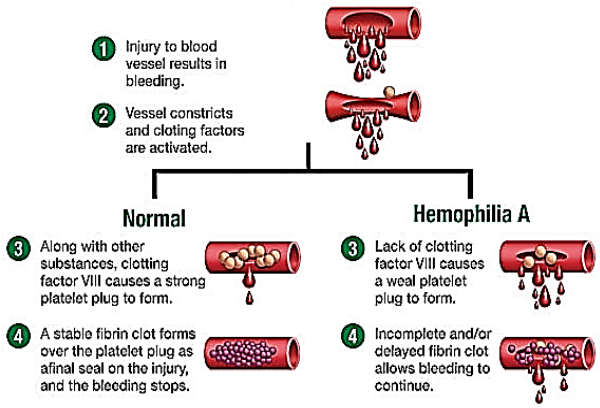

Figure 1. Difference between a normal and haemophilic blood vessel

II. METHODS AND MATERIAL

Epidemiology

The branch of medicines which deals with the transmission and control of diseases in population is known as Epidemiology. Haemophilia A is an x-linked medical disease which is triggered due to deficiency or deprivation of clotting FVIII. If we Talk about its epidemicity then we can see that Europe and some parts of North America is affected by Haemophilia A with the approximate ratio of 1:5000 male births. In other words, it prevails in 20.6 cases per 100,000 males, out of which 60% are severely affects by this disease. In other 40% of the cases, mutation occurs which includes transformation of Haemophilia A with FVIII gene. Other cases involve mutation in the DNA like deletions and insertion of genes (Tuddenham *et al.*, 1994; Ghosh & Shetty, 2009; Astermark 2010). Genetically haemophilia is usually identified during or soon after birth, may be possible during AVD (Assisted vaginal deliveries) and circumcisions (Chorba *et al*., 1994).

Inhibitors

A substance capable of stopping or slowing a specific chemical or biological process is known as inhibitor. Antibodies are also known as inhibitors for example immunoglobulin G (IgG) (Scandella *et al*., 1989). Immune system utilize antibody to determine and neutralize toxin objects for example viruses and bacteria. As we know that antibody is a large Y-shaped protein which is produced by the plasma cells (Fig. 2). There is an increase in risk of inhibitors developing in those chronic haemophilic patients which exposes about 10 to 20 days to FVIII concentrate. The treatment of haemophilic patients with inhibitions is difficult as that of prevention of orthopaedic complication. There is need of improvement in clinical outcomes in order to get a better result. With small exposure, chronic haemophilic patients in childhood about 20 to 30% will develop inhibitions to FVIII. Researchers tell us that there is a mutual relation between the inhibitions and low quality of life. When haemophilic patient is exposing to FVIII again & again then it develops in those patients and binds to inactivate FVIII. There are 2 types of inhibitors which are reversible inhibitors and irreversible inhibitors.

Figure 2. The antibodies working as inhibitors

Mechanism of the development of factor VIII inhibitors

This mechanism is indicated by various studies that FVIII is actually responsible for the activation of immune response. As we know that FVIII is mainly T helper cell-mediated and always present on the antigen presenting cells for example dendritic cells, B cells and macrophages (André *et al*., 2009; Astermark 2010). Whenever antibodies combines against FVIII then CAAs should incorporate FVIII and then after degeneration it is important that it should introduces to major histocompatibility complex molecules of Class II. After the attachment of FVIII peptides with MHC molecules this complex will accessible for the determination by the CD4+ T cells then in result CAAs will develop a plasma layer complex. Moreover, peptides located or occurring within the cells particles of FVIII, which incorporates in minute quantities in the patient, are introduced via MHC Class I molecular particles to CD8+ T cells which is accepted by antigen T cells receptors (TCRs) (Chaves & Rodrigues, 2009). For the arrangement of antigens to the TCRs in order to be well organized and systemic, a second indication takes place between CAAs and T cells which is the co-triggered CD80/86 molecules declared in CAAs attached to CD28 stated in T cells (Hoyer 1995; Wight & Paisley, 2003). T cells gets activated when both signals are there which can be the type-1 helper T cell (Th1) activation, in charge for the discharge of cytokines as that we know about the work of interferon gamma tumour necrosis factor alpha and interleukin 10 (IL-10), amid others that are significant in humeral resilience or immunity.

In addition to this, the declaration of CD2, CD30, CD40 and CD28 expands on the CD4+ T cell surface (Oldenburg & Pavlova, 2006; André *et al*., 2009; Ghosh & Shetty, 2009; Pratt & Thompson, 2009). When excreted by the Th1 or Th2 then these all cytokines induces the distinction or divergence of B cells, which alters the isotype of the immunoglobulin and yield

particular antibodies opposed to plasma VIII. Moreover, the B cells discharges the cytokine interleukin-12 (IL-12) which quicken the Th1- mediated growth of Interferon. The cytokines from Th1 evokes the progress of immunoglobulin G1 and immunoglobulin G4 (IgG4). The titters of highly responsive inhibitors are co-ordinated to IgG4 levels is shown in patients with haemophilia A, which proposes that the Th2-mediated immune reaction is strongly affiliated to the combination of anti-FVIII antibodies (Pratt & Thompson, 2009).

Factors that helps to prompt patients for the development of factor VIII inhibitors

Ethnicity and family history of factor VIII inhibitors

Ethnicity and genealogy is well known with the respect to inclination for your real advancement connected with FVIII inhibitors. One study revealed that the Afro-Americans had very high danger of production of inhibitors (Gill 1999). In the Malmo international brother study the affiliation and genealogy of the advancement of inhibitors were seen. The results of this study shows the rate of inhibitors is a brilliant well spring of the sub group of individuals of African drops in correlation to Caucasians (55.6% contrasted with 27.4%). It's accepted that this real racial part will be based upon hereditary variations with all due respect system reaction determinants, essentially on the grounds that FVIII transformation range won't contrast in the middle of races (Astermark *et al*., 2001). Moreover, it was observed that the danger for the influencing of inhibitors increases specially in those patients which already had a family history of the improvement in inhibitors was 48% (95% certainty interim 95% CI :11-12%).

An alternate study by the same gathering surveyed the likelihood of hereditary changes affecting the arrangement of inhibitors relating to haemophilia in people of the same group. One hundred and thirteen primarily Caucasian families had two or more siblings with serious haemophilia were broke down. All siblings present in the 59 of the families created inhibitors from which 25 (42.4%) of the persons contained a family history of inhibitor improvement. It was discovered that the most widely recognized kind of transformation in the FVIII quality was reversal of intron. Inhibitors were distinguished in the 45 out of the 74 families (60.8%) with the help of transformation and in 18 (40%) out of these 45 different families all the siblings created inhibitors. On the behalf of this information, the impact of hereditary variables in the advancement of inhibitors is evident. Non hereditary components likewise seem to impact the invulnerable reaction and therefore change the danger of creating inhibitors in every crew. In any case it is impossible that these variables alone can clarify the similitudes reported. These perceptions propose that there is necessary need of changes in the invulnerable reaction that may be focused around both hereditary markers and non-hereditary factors.

Mutation occurs in the FVIII gene

The quality of factor VIII gene is spotted by the presence on the end of the lengthy arm of chromosomes X. it includes 186,000 base sets disseminated between the 26 exons and the 25 introns. The result of this quality of the factor VIII is a polypeptide containing 2332 amino acids (inactivated flowing master cofactor) and the enacted polypeptide is framed of six masterminded domains (Shen *et al*., 2008; Gitschier *et al*., 1984; Castaldo *et al*., 2007). The spaces of A2, A3 and C2 are the areas against which FVIII antibodies can respond and hinder the coagulation cascade (Scandella *et al*., 1989).It was demonstrated by complete study that the patients with the missense transformations are grouped in the areas of A2 and C2 then the danger of inhibitor arrangement is fourfold more noteworthy than in the patients having changes outside this area. This demonstrates that any progressions in the 3 dimensional structures then a piece of the FVIII atom may influence its immunogenicity. The opposition to A2 antibodies and at same time against C2 antibodies can connect with the A2 space and C2 area individually and kill the procoagulant action of FVIII (fig 3). The C2 space however influenced by against C2 antibodies counteract FVIII tying to phospholipids and von will brand factor and then hostile to A3 antibodies which then focus on the A3 area to keep the collaboration of the important FIX with the activation of FVIII gene which is responsible for the treatment of haemophilia (Lenting *et al*., 1996).

In the year 2012, 5243 sorts of transformations connected with this disease had been accounted for as

per the hamsters (test of mutation in haemophilia A and also site of resource search) electronic database. The gathering with the most astounding danger of delivering hostile to FVIII antibodies is unified with the finest variations in gene. One Meta investigation watched that the danger of inhibitor development in the patients with vast cancellations and babble changes is always greater than in those patients which have intron 22 reversals (pooled OR=3.6 as well as= 1.4, separately). The danger of patients with intron 1 reversals and join site changes is practically equivalent (pooled OR= 0.9 as well as=1.0 separately) and the danger of patients having small amount of cancellations and insertions and missense transformations are lower (pooled OR= 0.5 as well as= 0.3, respectively) (Gouw *et al*., 2012). Reversals in intron 22 (30 half) and intron 1 (0-5%) are generally connected with extreme haemophilia A phenotype and a middle person hazard for structuring inhibitors. In Brazil, an investigation of 86 Caucasian patients, examined the event of reversal transformations present in the 47 patients from which 33 (70%) had serious haemophilia and 14 (30%) with moderate or mellow haemophilia. An increment in the recurrence of reversal transformations (13/13; 39.4%) was seen in the subgroup named serious with the larger part (11/13; 86.4%) being changes in intron 22 (Soares *et al*., 2001).

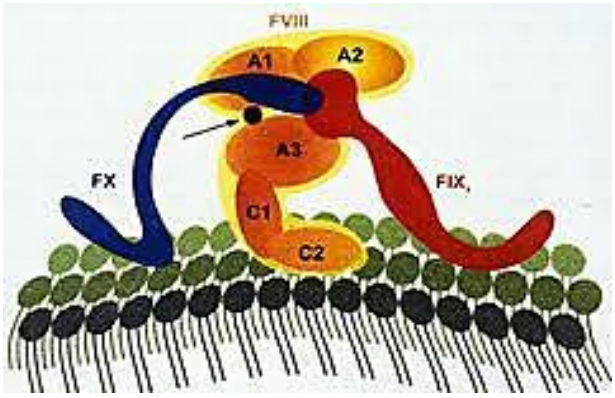

Figure 3: Mutation in factor VIII gene

Arthropathy

Arthropathy is the term which is used for the diseases and abnormalities of joints (ex. hemarthroses). Hemarthroses is a condition in which there is bleeding in the joint spaces and this condition occurs in haemophilic patients about 70 to 80% (Parameswaran *et al*., 2005). There are different causes of this disease like injury, knee joint arthroplasty and inflammation in the joints (DiMichele & Neufeld, 1998). This disease can be treated by the administration of clotting factor. Arthtropathy is most commonly occurs in haemophilic patients. This condition occurs during the twenty to thirty series of life. The condition can be quite painful and they usually require treatment to inhibit further degeneration of the joint. Uncontrolled bleeding is the cause of severe arthropathy in haemophilic patients usually in young patients. The symptoms of arthropathy depend on the root cause. The risk of joint diseases and other sicknesses can be reduced by staying active and eating a balanced.

III. RESULT AND DISCUSSION

Treatment

Concentrated FVIII was first produced using a cry precipitation method in 1965 that was simply duplicated by blood banks to make use of it for routine analysis and treating joint and muscle haemorrhage (Tullis *et al*., 1965; DiMichele & Neufeld, 1998). In spite of the fact that this method provided immense clinical advantages to patients of haemophilia, it also caused rise in risk of blood borne aggressive viral infectious disease. Aggressive transmission of HIV and HCV happened in the haemophilia group via contaminated human plasma products (Tencer *et al*., 2007). It was estimated in 2004 that minimum one third of victims who got affected by haemophilia were also affected with HIV and 80% with HCV (Fig. 4).

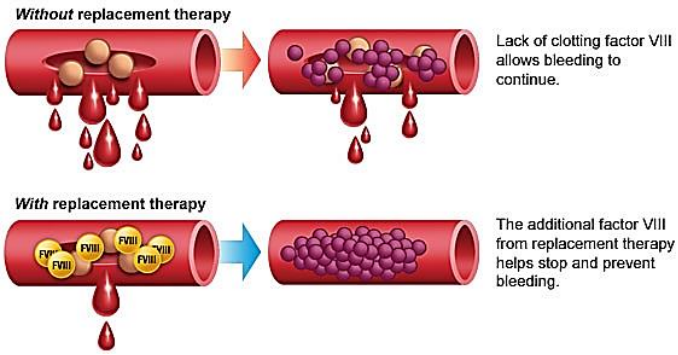

Figure 4. Replacement therapy through additional factor VIII

This calamity for the haemophilia group not only caused the application of screening but also viral inactivation procedures by using heat methodologies. In spite of the fact that products obtained from plasma are more

secured it normally faces infectious instruments that might be against the current procedures for viral, chemical or even physical inactivation (non-lipid enveloped diseases). There may not have been announced cases of HIV or HCV transferrable congealing factor since 1986 and 1997 (National Haemophilia Foundation 2012). Recently, a HIV transferred case from the exchange of fresh frozen plasma in USA highlights the possibility of transferable wrapped up diseases from human derived blood products is not zero (Centers for disease control and prevention, 2010).

Substantial developments have been witnessed in haemophilic victims without inhibitors. Patients with serious haemophilia had an expected life of 11 years in 1960 and it grew to 50 years in 1980s (Strine et al., 1994; Chorba *et al*., 2001). Latest advancement in treatment of haemophilia focuses to lessen the mortality rate and upgrade the life standard of haemophilic patients. Patients with inhibitors have less medical treatment options compared with those without one. The focus is to stop critical bleeding spells in patients with inhibitors and maintain homeostasis. In these days, there are two bypassing agents accessible ways for nursing haemophilia A patients with inhibitors. Recombinant factor 7a is approved to sustain homeostasis in haemophilic patients with inhibitors. ITT is composed by managing repeat high doses of F7. This method later enables substituting F7 to restarting usage effectively. ITT was victorious in more than 80% of the patients with inhibitors according to international immune tolerance registry. By comparing high dosage and low dosage, only 69% patients were successful but bleeding spells were considerably reduced in high dosage community but unfortunately, these findings didn't affect the outcome significantly.

Prophylaxis and Episodic Treatment of Bleeding Disorders

Patients of Chronic haemophilia suffer from continuous bleeding in joints. The result of chronic haemophilia is severe pain and weak joints. Prophylaxis is the prevention of disease and control of its possible spread over the society. Prophylactic treatment is the preventive treatment of hemarthrosis and musculoskeletal disorders which are common in haemophilic patients. If we talk about the levels of prevention so in primary prevention we can see that it is the method to avoid occurrence of disease by removing disease agents and increases the resistance to disease. For example by immunization, by maintaining healthy diet, exercise and by avoid smoking. The secondary level of prevention is the method which is used to detect an existing disease before its symptoms will appear. The treatment of hypertension by cancer screening is one of the examples. Then the tertiary prevention is the method which is used to reduce all the negative impacts of disease, whose symptoms are known, such as disability or death by the rehabilitation and treatment e.g., by surgical procedures. When prophylactic treatment begins before the age of three years, best results are achieved.

Episodic treatment of haemophilic patients is also an effective method. Episodic treatment is a pattern of medical & nursing in which services are provided to a particular patient, without an ongoing relationship being established between person and health professionals. For example in emergency department there are many advantages of this type of treatment like orthopaedic function becomes better and it also improves overall quality of life. It also helps in rapid bleed control (Lusher 1998). In USA 251u/kg to 40u/kg of FVIII three times weak of haemophilia.

Primary Care and Haemophilia Treatment Centres

In the treatment of haemophilia A, interaction with a physician is very important for patients and their families. The relationship of patient with physician is very critical for the long time treatment with the respect to prophylaxis. In some cases, patients are responsible for their own care (Geraghty *et al*., 2006). Recently, by the studies of treatment centres it proves that increase in only one physician per 10,000 individual populations was associated with an average reduced in death rate of 49 per 100,000 people per year. These studies also showed that a patient which is treated at HTCS has death rate only 40% but in comparison with a patient which is treated by local hospitals carries towards more severe sickness (Soucie *et al*., 2000).

IV. CONCLUSION

Haemophilia A can by treated by the replacement of FVIII and it may also treated by introducing an inhibitor. This disease can be treated by complete contact with consultant and by proper care. This may also be treated by giving people awareness at each level starting from schools. Episodic treatment is also very affective for haemophilic patient.

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