The Role of Coagulation Factor VIII Substutution Therapy in the Management of Type A Hemophilia Complications

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Hemophilia is a pathologycharacterized by a disturbance in the normal clotting process of the blood, as a result of a functional deficit of clotting factor VIII or IX.There are two types of hemophilia: type A and type B, the former expressing a deficit of factor VIII, while the latter a deficit of factor IX.C.L., a 43 years old male, was diagnosed at the age of 8 months with a severe form of type A hemophilia. From that time, the patient presentedhemorrhagic episodes, resulting either from trauma or appearing spontaneously and requiring factor VIII substitution therapy and hemostatic treatment.Bloodwork show a prolonged aPTT, as well as microcytic anemia with a low iron serum level, as a result of chronic blood loss.The particularity of this case consists in the high degree of development and recurrence of hemophilia associated complications, leading to superior and inferior limb motor deficits and chronic pain which is currently managed with opioid medication. Also,the patient suffers from chronic hepatitis due to infection with B and C hepatitis viruses as a result of previous lifesaving plasma substitution therapy.Even though the clinical manifestations of hemophilia excert a high cost on the patient's life as well as the medical system, timely prophylactic factor VIII substitution therapy from the moment of diagnosis until the age of 18 can reduce both the toll on the patient's health and quality of life and also on the medical costs. Thus, we stress the fact that prophylactic therapy can have a beneficial effect both on patient's life and also on the health system.

Key words:Hemophilia, clottingfactor VIII, hemostatic treatment, chronic pain

Hemophilia is congenital coagulopathy caused by a coagulation factor VIII or IX deficit.

Congenital hemophilia is the result of the mutations, deletions or inversions affecting the genes responsible for the coagulation factors VIII or IX. These genes are located on the long arm of chromosome X both in type A hemophilia and in type B hemophilia. Due to this topography, hemophilia is virtually an exclusive male condition. The daughters of hemophilic men are sure carriers, but their sons are normal.

Both types of hemophilia may have three forms: severe, mild and light. Severe hemophilia is characterized by hemarthrosis and multiple hemorrhagiparous episodes in the different tissues, which eventually lead to chronic severe arthropathies, which may be prevented by prophylactic therapy using factor VIII or IX concentrates. The two forms of coagulopathies are similar from the phenotypic point of view and determine coagulation factor VIII or IX deficits, which will lead to thrombin and fibrin generation incapacity[1].

Type A hemophilia is a heterogeneous condition caused by the decrease of the coagulation factor VIII levels in the plasma. The incidence of this type of hemophilia is 1:5000 or 1:7000 in male newborns, and does not show any preference for a particular ethnic group[2].

Experimental part

Material and Methods

The 43-year-old patient named C.L., diagnosed at the age of 8 months with type A hemophilia-severe form (factor VIII<1%), has benefitted over time of substitution therapy consisting of freshly frozen plasma and coagulation factor VIII concentrates. In addition to his main disease, the patient has suffered many hemophilia complications, which have set in at an early age: multiple hemophilic arthropathies, which caused motor deficiencies in both his lower and upper limbs and for which he underwent total right elbow and right hip replacement procedures. He was also diagnosed with hepatitis B and C virus infection, due to his past plasma transfusions.

In March 2012, the patient comes to the emergency room of our hospital with multiple hemorrhagiparous episodes in his joints. The physical examination reveals the presence of a 7/5 cm tumor mass located under his left sternum-clavicle, painful on and in the absence of palpation, with congested superjacent teguments. The paraclinical data reveal a 55.1 sec. aPTT. Therefore, factor VIII substitution therapy is administered. After the therapy, the aPTT becomes normal (39.2 s). Pain killers and antibiotics are also administered.

The surgical examination requires a chest CT scan to be performed. This imaging examination reveals the pseudotumoral nature of this lesion, which is the consequence of a previous hematoma that occurred at this level in the past. Moreover, the examination reveals aspects of bone lysis and the extension of the pseudotumor towards the back of the chest, namely in the prevascular mediastinal space, pressing on the right venous brachiocephalic trunk. Pseudotumor puncture is

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subsequently carried out, and the specimen sampled from the lesion turns out to be sterile.

About two months later, the patient comes back to the hospital with impaired general condition, pain in the area around the pseudotumor and recurrent hemorrhagiparous episodes. As the aPTT is 57.1 sec. we start the factor VIII substitution therapy, further to which we achieve aPTT correction. The surgical examination reveals pseudotumor superinfection and tendency to fistula formation, for which reason he is referred to the Surgery Department where tumor mass incision is carried out accompanied by debridement and washing. The delivery of factor VIII is recommended throughout the surgery. After the performance of this surgical procedure, he is transferred back to the Hematology Clinic, where he experienced persistent hemorrhagiparous episodes improved after the delivery of factor VIII substitution therapy. His evolution after hospital discharge is partly positive, as the fistula closes.

In November 2012 he comes to the emergency room again complaining of joint pain and hemarthrosis in his right elbow and hip. The hemarthrosis required broad-spectrum antibiotic therapy during his hospitalizations in January, February and March 2013, the patient's evolution being partly positive.

During the following years and up to date, the patient required repeated hospitalizations for hemorrhagiparous phenomena in his right elbow and hip. These phenomena were generally accompanied by hemopurulent content in which we sampled different bacterial agents like Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii. During these hospitalizations, the patient receives coagulation factor VIII substitution therapy, antibiotic therapy, pain suppression therapy and wound cleaning in the Surgery Department, and the patient's evolution is slow but positive, as the aPTT gets normal and the right elbow and hip bleedings cease.

Results and discussions

Most type A hemophilia patients are diagnosed towards the end of their first year of life, when they start to walk and when they hit themselves against things while trying to learn to walk and they undergo various injuries. This was also the case of our patient, who was diagnosed with this coagulopathy at the age of 8 months. The paraclinical data reveal that his aPTT values generally range between 39.2 and 59.2 seconds, and they tend to become normal after the delivery of the coagulation factor VIII substitution therapy. Our patient's early diagnosis setting is an advantage, and his clinical evolution would have been positive, if it had been associated with its adequate and thorough management.

The life quality of hemophilic patients has constantly improved over the last 50 years. Given the increased availability of coagulation factor VIII concentrates, the main goal of the clinical management of the disease is the long-term prevention of the complications of this disease. Recurrent bleeding may cause over time chronic potentially invalidating arthropathies, which require total joint replacement. This complication (chronic arthropathy) is accompanied by others, such as viral infections, pseudotumors, intracranial hemorrhage and inhibitor occurrence, their occurrence rate being directly proportional to old age.

Hemarthrosis make up about 75% of the din hemorrhagiparous episodes in patients with severe type A hemophilia. The synovial membrane has a low number of cells, and any mechanical injury or the normal joint wear in time destroys many capillaries. Hemarthrosis is characterized, at first, by mild yet progressive discomfort, which may become extremely painful. After the pain has set in, the area around the impaired joint becomes swollen, the teguments become warm and the movements limited. Functional joint disability is a complication of repeated hemarthrosis, being due both to muscular atrophy, and to the morphological changes in the synovial membrane, which thickens and limits the mobility of the joint. Another hemarthrosis complication is joint infection, and it occurs in patients with fever, leukocytosis and other systemic symptoms. Diagnosis setting is compulsory since an infection at this level may eventually lead to functional disability. Also, a painful and deformed joint requires both substitution therapy and orthopedic care[3].

Factor VIII substitution therapy has significantly improved the clinical symptoms by reducing the number of hemorrhagiparous episodes and functional disability. Substitution therapy consists of factor VIII concentrates, which may be[4]: recombined products, products from monoclonal purified antibodies and intermediate products and high purity products. An adequate activity rate of factor VIII should be reached before any surgical procedure. Large surgical procedures like the orthopedic ones require a factor VIII rate of 100%[5].

In case of severe arthropathy, orthopedic surgical procedures are the only alternative. In most cases, they are total joint replacements procedures, the purpose of which is to alleviate pain and prevent hemophilic arthropathy complications. Total joint replacement recovers joint mobility by creating a new articular space. Total joint replacement is recommended in case of hemophilic arthropathies with pain and functional impairment, which have a significant impact on the quality of the patient's life. The most common joint replacement procedures are done in the knees, hips and elbows, and their long-term functional results are very good[6].

The clinical management of hemophilia is dominated by the complication risks of this coagulopathy, in which viral infections play a major role. Before 1985, the most common complications of most hemophilia patients were hepatitis B and C virus infection, due to the blood transfusions they had to undergo [7]. At that time, almost 100% of the patients who had had repeated plasma transfusions containing coagulation factor VIII had hepatitis C virus infections.

Another specific complication of this condition, the incidence rate of which is only 1-2% though, is represented by pseudotumors. They are a cluster of blood cysts occurring preponderantly in tissues and bones.

Tumors represents one of the most important pathological manifestation at worldwide level, being characterized by an extremely complex etiology, inducing highly diverse associated complications of physiological, metabolic or biochemical nature. [8-11] The paradox of immunology is that, often, the immunitary system favourstumoral development rather than its inhibition [12,13].

In most cases, the pseudotumor is not painful, except when the mass grows fast or when it applies pressure on a nerve. As the pseudotumor grows, it starts to apply pressure on and destroy the underlying muscles, nerves and bones. Pseudotumors tend to expand with time and they may located anywhere in the body. Unfortunately, some pseudotumors may grow extensively and invade many anatomical structures, which makes them virtually inoperable. Most pseudotumors are located in the lower part of the body, but their occurrence in the upper part of

the body is not unusual either. The management of this complication consists of a CT or MRI scan, as these imaging methods may provide useful information about the existence of a pseudotumor. Nevertheless, pseudotumor biopsy is not recommended as this procedure involves high infection and hemorrhage risks[14]. In the absence of adequate care and therapy, the pseudotumor may lead to the compression and necrosis of the structures around it. Its specificity consists of the absence of specialized therapy, pseudotumor management consisting of factor VIII substitution therapy, which precedes any surgical procedure, and progressive injury excision.

From the point of view of the therapy used, our patient received cryoprecipitate therapy, freshly frozen plasma and coagulation factor VIII. Cryoprecipitate is a preparation made of freshly frozen plasma and includes factor VIII concentrate, factor IX, fibrinogen, factor von Willebrand and fibronectin. Its viral transmission risks are lower than those of freshly frozen plasma. Factor VIII may be delivered as concentrates. Factor VIII concentrate undergoes viral inactivation, but it does not eliminate the virus. Another alternative is recombinant factor VIII, a factor which is virus-free, but its costs are high and it may run a high risk of inducing isoantibodies.

The particular character of our case resides in the patient's multitude of chronic complications (hepatitis B, hepatitis C, pseudotumor, multiple chronic arthropathies), plus the numerous hemorrhagiparous episodes that occurred between 2012 and 2018.

Conclusions

To conclude with, mode of transmission of the disease, the severity of the clinical manifestations and the therapeutic management are representative aspects of both type A hemophilia and our patient. From the clinical point of view, even minor haemorrhages can endanger the lives of haemophiliac patients, and a correct management of management can lead to an increase in quality of life and a pseudonormal life.

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