

Osteoporosis in haemophilic patient, rehabilitative aspects

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Summary

The continuous improvement of substitution and antiviral treatments available to date (at least in countries with greater economic and social development) allow better survival of patients with haemophilia, both as regards the duration and quality of life, to the point that the haemophilic arthropathy, that is the co-morbidity almost always present and extremely debilitating, come to be treated successfully using prosthetic joint replacement surgery. This has further highlighted other aspects of disease such as osteopenia or osteoporosis, which frequently occurs in these patients, and in recent years has aroused the interest of research.

Rehabilitation plays a vital role in helping to tackle the different risk factors in young patients, in containing the consequences of the disease on the skeletal and muscle apparatus such as on the recovery after surgery and prosthetic.

KEY WORDS: haemophilia; arthritis; osteoporosis; rehabilitation.

Introduction

Haemophilia is an uncommon genetic disorder, inherited in a recessive trait, X-linked, characterized by abnormalities of blood coagulation, leading to an increased tendency to bleeding. We recognize two forms known as haemophilia A and B. Haemophilia A is characterized by deficiency of coagulation factor VIII (the so-called "antihemophilic globulin") and affects about 80% of patients, while haemophilia B is characterized by deficiency of factor IX and it is the least frequent. In fact in the Haemophilia A it is deficient or absent just the portion of low molecular weight complex called factor VIII factor VIIIc. The lack of factor VIII coagulant function results in a reduction in the activation of factor X, the decrease in the formation of activated factor X does not allow the complete and rapid conversion of prothrombin to thrombin: it means that there is formed less quantity of thrombin and slowly than in the normal subject.

Haemophilia B, or "Christmas disease" after the first patient in whom it was diagnosed, is rarer than haemophilia A, with a ratio of about 1 case of haemophilia B every 10 cases of haemophilia A, but it has a higher incidence in some regions. The clinical picture is similar as well as treatment, even if the haemophilia B patient with the pace of infusions of factor IX is a bit less intense than haemophilia A because the factor IX has a longer half-life.

Haemophilia can be caused by a gene mutation: point mutations involving a single nucleotide deletions of all or parts of the gene mutations that affect gene regulation. About 50% of cases of severe haemophilia is derived from an inversion of a major section of the X chromosome.

Since the genes of factor VIII and IX are located on the X chromosome, haemophilia affects males almost exclusively. The daughters of haemophiliacs are carriers required, while the boys are healthy. Each son of a carrier will have 50% probability of being haemophilic and each daughter has a 50% probability of being a carrier. In the female, the combination of homozygous, derived from the combination of a carrier with a patient, it is unlikely that an occurrence and it is considered life-threatening and does not allow the development of the embryo. Moreover, in a carrier, rarely, the random inactivation of one or two X chromosomes in early embryonic life, means that the levels of factor VIII or IX are so low as to cause abnormal bleeding tendency.

Clinically, haemophilia varies from mild to severe depending on the degree of deficiency of coagulation factor involved. Patients with less than 1% of plasma factor VIII or IX clotting have a severe form, where there is frequent spontaneous bleeding, which may persist despite administration of massive replacement therapy.

Patients with levels of factor VIII or IX included in the normal range of 5% have mild haemophilia. Rarely bleeding undergo "spontaneous", but if not treated properly can have serious bleeding (including fatal) during surgery (1).

There are also occasional forms of haemophilia even less in relation to a serious level of factor VIII or IX between 10 and 30% of the normal range. These patients may present profuse bleeding after tooth extraction or surgery (4-6).

The symptomatology is dominated by the bleeding and the consequences of bleeding in the different organs and systems. The bleeding is usually secondary to trauma, even minor, sometimes, at least apparently spontaneous. Most of the time we can have a slow bleeding, prolonged (may continue for weeks), uncontrollable, it can continue even after a period of shutdown due to the absence of inefficient clots. It often recurs in the same location. The bleeding symptoms appear early in life. Sometimes the parents aware of the first bleeding at the beginning of gait or at the first dentition.

Then the causes of bleeding can be quite different: bleeding skin wounds, bites, injuries.

Subcutaneous hematomas may occur in even insignificant trauma, when they are formed in the subfascial layers or the thickness of the muscles can provoke serious consequences such as compression of the nerve trunks or arterial segments, with residual paralysis, muscular atrophy, muscular retractions and/or tendon; frequently joints may be deviated because of the thigh popliteal hematoma, paralysis of the ulnar nerve in the elbow bruises. Ossified subperiosteal hematomas may cause dull and tenacious pain. Intra-connectival hematomas can be extremely dangerous, most

of all if they are located in peri-laryngeal tissues because can cause suffocation by compression of the airways, otherwise if they are retro orbital hematomas can cause blindness.

All these collections can lead to hemorrhagic symptoms, generally associated features include fever, anemia, jaundice and sub-urobilinuria resorption. They lead not very commonly to gastrointestinal bleeding, easier to haematuria – sometimes with clots – rather rarely – but extremely dangerously – to bleeding and meningeal encephalitis (2-6).

Bleeding can occur in any organ or tissue as well as the thickness of the skeletal muscle, a frequent site are the joints. This is because the synovial membrane is physiologically deficient in tissue coagulation factor, so the addition of plasma coagulation factor deficiencies, characteristic of haemophilia makes joints with synovial capsule exposed to severe bleeding. Recurrent hemarthrosis and chronic arthropathy are the major causes of co-morbidity in haemophilia. In severe forms the articular bleeding can occur when the child begins to crawl or walk. The most commonly affected joints are knees, ankles, elbows, shoulders and hips.

The hemarthrosis usually occurs very quickly, and in a short time makes the joint swollen, hot, painful; functional impotence is significant and fever can appear.

The persistence of bleeding, the deposition of iron-rich pigment, the frequency of relapses cause the appearance of a true arthritis. The synovium thickens and forms numerous villi highly vascularized, articular cartilage undergoes regression and subsequent wear phenomena of the sub-chondral bone, periosteal reaction, secondary osteophytes, and capsular fibrosis. The joint movements become more limited, until ankylosis, muscle atrophy. Radiologically the changes are complex, sometimes remind severe osteoarthritis, a frequent observation are opaque flanges due to hemosiderin deposits, they can appear as rounded areas in the sub-chondral hyperlucency due to bone hematoma (7-9).

In recent years there have been, in various countries of the world, several studies linking haemophilia and osteoporosis. These two diseases have a significant socio-economic cost as well as both have an important impact on the quality of life for patients. The connections between the two diseases are not yet completely understood but several studies seem to suggest its existence (10). Osteoporosis is a disease characterized by low mechanical strength of the bone, due to alterations in both bone mass and structural integrity of the bone so that fractures can occur even during everyday activities, and there are many factors that can cause this condition (1).

The bone strength reflects the integration of bone density and bone quality. Bone mineral density is the most important factor weighing for 60-80% in determining the mechanical strength of bone. Bone mineral density is determined in each individual, from the peak bone mass and bone loss share. Peak bone mass is reached between 20 and 30 years of age and is determined by many factors such as genetic factors, the degree of nutrition, body weight, physical activity, and under load, etc.

Earning a good bone mass during the early part of life is a good factor for osteoporosis prevention (10-13).

In haemophilic patients there are many factors that determine a low peak bone mass during adolescence and then, osteoporosis in adulthood: first of all, the reduced physical activity, due both to the risk of hemarthrosis, as well as to the same hemarthrosis, which causes long periods of immobility and joint stiffness, and an increased osteoclast-mediated bone resorption. As a result of excessive activation of osteoclasts, responsible for bone resorption, bone trabeculae become thinner and are more brittle as the thickness of the cortical and porous bone is reduced, thereby reducing resistance and increasing the risk of fracture. In addition, other important factors are: prolonged immobility, poor exposure to sunlight, viral infections, particularly hepatitis C, which have a prevalence in patients with haemophilia, which varies from 10 to 60%, as well as the activation of osteoclast-mediated bone resorption (14-16).

Since 1994 several studies of haemophilic patients have shown abnormalities of liver function associated with hypogonadism, abnormalities in vitamin D metabolism and hyperbilirubinemia elements which induce a reduced formation and increased bone resorption (10-15).

Studies of young patients have small differences in the results but the comparison is not easy because it is a relatively rare disease with a wide variation in treatment, especially among countries with different socio-economic development (due to high costs of prophylaxis), and also equipment for evaluation of bone density (BMD) are created and calibrated for adult women (osteoporosis as a disease more common in women), while haemophilia is a disease present in males. Studies in adult patients all seem to confirm a certain degree of osteopenia/osteoporosis in patients with haemophilia. Two elements seem to unite the different studies, however: the haemophilic patient probably does not reach optimal peak bone mass (which predisposes to the development of the disease osteoporosis in adulthood), that might be encountered in osteoporosis in older adults with hemophilia and is closely related to the degree and the number of joints involved into arthropathy (17-20).

In some subjects additional feedback of infection with HCV and HIV have suggested that both direct influences on immune-mediated effect on osteocytes and bone turnover (15, 16).

The initial lesions of arthritis haemophilia A at histological level are poorly documented, but probably the alterations begin already at the first episode of hemarthrosis leading to the proliferation of synovial cells, because of the stimulus caused by irritation from hemosiderin deposits from red blood cells. The iron deposited within the synovial cells also causes an inflammatory reaction with perivascular acute inflammation calling local typical cells (macrophages, granulocytes, T lymphocytes) and the production of chemical mediators of inflammation (interleukin 1-3-6-11-17, TNF, TNF γ , TGF β , etc.) that also support the inflammatory reaction, have an effect on bone by stimulating the proliferation and differentiation of osteoclast precursors, osteoclast activation, apoptosis by inhibiting their apoptosis. These cytokines, through their interference with the RANKL / OPG system, lead to increased bone resorption resulting in sub-chondral bone damage, and possibly also to increased bone fragility that is observed in the general haemophilic patient (17-19).

RANKL / OPG System

RANKL (receptor activator of nuclear factor KB ligand) is a family of cytokine TNF-ligands normally expressed on the cell membrane of osteoblasts that binds to its receptor RANK present on osteoclast hematopoietic precursors of the membrane. The stimulation of RANKL results in activation of nuclear factors that increase the number and activity of cells of bone resorption.

The OPG (osteoprotegerin) is a soluble glycoprotein, belonging to the TNF receptor family that acts as a natural inhibitor of RANKL, that is, acting in competition with the RANK RANKL binds to RANK-RANKL, preventing the connection. Osteoprotegerin biological effects are inhibiting RANKL in the last stages of osteoclastogenesis, preventing the activation of mature osteoclasts and inducing apoptosis.

The effectiveness with which the osteoprotegerin system can compete with RANKL / RANK would seem of great importance for the control of skeletal complications of several diseases characterized by inflammatory reactions in important joints such as haemophilia or rheumatoid arthritis.

The skeletal damage occurs first as a focal bone loss affecting the sub-chondral bone, periarticular osteopenia, involving later the adjacent bones and then can turn into a generalized osteopenia/osteoporosis increasing bone fragility and risk of fracture of long bones and/or vertebrae.

Following repeated episodes of hemarthrosis the synovial membrane becomes hypertrophic and intensely vascularized villi with loose joints that protrude into the cavity. At this stage, microscopically it is observed a significant accumulation of hemosiderin within macrophages localized in the synovial and sub-synovial tissues such as scarcity of other cells typical of inflammatory reactions. In the peripheral joints they form a "cloth" mainly composed of dense fibrous tissue, not vascularized, acellular strictly adherent to the cartilage (17).

The final stage is characterized by progressive degeneration of articular cartilage, with hemosiderin also evident in chondrocytes, degeneration of synovial tissue that becomes fibrotic and secondary osteoarthritis. The pathogenesis of joint disorders is not fully elucidated, probably responsible are: a nonspecific synovial reaction, the subsequent cartilage damage, leading to degenerative arthropathy, repeated hemarthroses, but also direct toxic factors on cartilage, as well as synovitic specific immune-mediated reactions (17-19).

Rehabilitation

Historically, patients with haemophilia have always been instructed to avoid physical activity with the exception of walking and swimming, patients tend to show, however, reluctant to engage in physical activity especially if they already suffered for hemarthrosis episodes. A recent study conducted in Sweden showed how the regular administration of prophylaxis from an early age, combined with rehabilitation therapy, can limit the damage or at least can contain the damage possibly delaying the use of surgical therapy (16).

Often, those who undergo surgery are young and have clinical features of extreme gravity.

The rehabilitation of these patients requires a good knowledge of the underlying disease, haemophilia, and possible consequences of an incorrect therapeutic approach.

The physiatrist must take into account several factors, first of all: the clinical form of the underlying disease and the type of prophylaxis, as well as age and medical history are other important elements to take into consideration.

In young patients, the role of physiotherapy is to promote physical activity in times and ways permitted by the underlying disease, in order to maintain proper joint range, adequate muscle tone, best musculoskeletal activity, encourage correct posture and avoid articular defects.

Even in recent years young people with haemophilia are encouraged in sports activities because of the undoubted benefits that derive from them. There are many ventures in which even haemophilic patients are admitted to practice competitive sports.

Rehabilitation in haemophilic patient after arthroplasty

In the adult patient physical activity and/or sports continues to maintain its key role, nevertheless joint suffering still remains a frequent entity in haemophilia which, thanks to improved prophylaxis and surgical techniques, can also tackle a possible replacement surgery.

It is very important to know the therapy at the time of the rehabilitation phase and in particular the determination of the deficient clotting factor, and this allows the physiatrist a correct and constant modulation of rehabilitation by avoiding, or at least limiting, the risk of bleeding.

The haemophilic patients undergoing arthroplasty, often need explanation of the therapeutic method.

In the post-operative period patients are often afraid to use their new joint, and implement a series of patterns and attitudes, already used before surgery in order to preserve the limb.

At this stage the educational role of the therapist is essential because it educates the patient about what should be done to improve the motor performance and to correct the bad posture.

The patient must be motivated to functional recovery he has to participate in rehabilitation and not suffer it. In the normal course of rehabilitation the person undergoes a prosthetic treatment, begins physiotherapy as early as the second day.

In the fourth and fifth day, the rehabilitation program consists of several stages: preparatory maneuvers, stretching and skimming massage of the limb, active-assisted mobilization of the segment, muscle strengthening, proprioceptive re-education – in order to improve the stability and strengthening the trunk and Glutei muscles – re-education step in order to reduce imbalances and spoiled attitudes along the way.

Whenever possible, it is useful to set up an Hydrokinesis therapy programme. Therapy in water, performed at around 34°-36°, brings great benefits: it performs an action on pain and relaxes the muscles, allows the support limb prosthesis and walk if you can not start immediately distributing the entire load, allows the strengthening of muscles due to the resistance offered by water, it also obtains benefits on the psychological sphere.

The rehabilitation treatment should always aim to obtain the best functional recovery specific to each subject.

However, several are the adverse events that may elapse during the rehabilitation process and influence the final result:

- pain;
- wound infection;
- scar adhesions;
- joint locking resistant to all facilitation maneuvers;
- concomitant secondary infections.

Maintenance therapy

After the immediate post-surgical rehabilitation treatment, the patient is advised to continue to make a maintenance therapy to prevent relapse and possibly preventing further damages.

The concept of maintenance therapy also provides the opportunity to pursue a sport activity at low speeds.

Some countries have made a list of sports that the haemophilic patient can practise according with the severity of the disease. The rehabilitative and conservative surgery in many cases provide the opportunity to recover a good quality of life in all its areas.

Treatment of haemophilic patient with osteoporosis

Of course, even in the haemophilic patient prevention is crucial and certainly the improvement of prevention allows young patients to perform physical activity (sports, even competitions) which was denied in the past; physical activity is essential for achieving an optimal bone peak mass through direct stimulation of exercise on the osteoarticular apparatus, and exposure to sun radiation. When it should be necessary it will be possible to suggest dietary supplementation with calcium and vitamin D.

As for the adult subject, the drug therapy of haemophilic patient does not differ from that indicated by international guidelines. Since haemophilia is a disease that concerns only male subjects, the only drugs currently permitted in Italy to treat osteoporosis in males are bisphosphonates, coupled with possible integration of calcium and vitamin D, while keeping in mind that bisphosphonates do not act by forming new bone or increase the peak bone mass, but only by reducing the reabsorption by osteoclasts (15).

Recently, attention has been centered on other drugs such as denosumab, which, unlike bisphosphonates, acts in the extracellular environment by preventing RANK Ligand from binding to its receptor, thus inhibiting the development, activation and survival of osteoclasts and favoring the almost complete elimination.

In postmenopausal women, administration of denosumab showed a dose-dependent response with a half-life of 26 days. The effects related to this drug are rapidly depleted with the suspension of the same. In contrast, the effects related to the administration of bisphosphonates remain within weeks, months and years after stopping treatment. In people with haemophilia, in which the risk of bleeding is high, considering the adverse effect of bisphosphonates on stomach, the treatment with denosumab appears to be a better therapeutic strategy.

Conclusions

The improvement of the currently available drug therapies have allowed patients with haemophilia, a marked increase in quality and length of life, asking doctors to cope with additional co-morbidities such as osteoporosis. Several studies conducted in various countries have highlighted how different factors contribute to a condition of increased bone fragility, including the hemarthrosis and arthropathy resulting in haemophilia seem to have a prominent role in the activation of both mechanisms of local bone resorption, and because due to prolonged periods of immobility that are responsible for the phenomena of increased bone resorption and generalized failure to achieve peak bone mass during adolescence. Furthermore the effect of concurrent infection with hepatitis C virus or HIV, that are often present in patients with haemophilia and probably contribute to immune-mediated mechanisms to further increase bone resorption.

So in the haemophilic patient is fundamental the start of replacement therapy early, depending on the severity of the clinical aspects, in order to prevent the phenomena of hemarthrosis and the consequent arthropathy, and limit the periods of immobility and its consequences. Rehabilitation has therefore a key role in helping to tackle the different risk factors in young patients, in containing the consequences of the disease on the skeletal and muscular apparatus, in recovering after surgery and prosthetic treatments.

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