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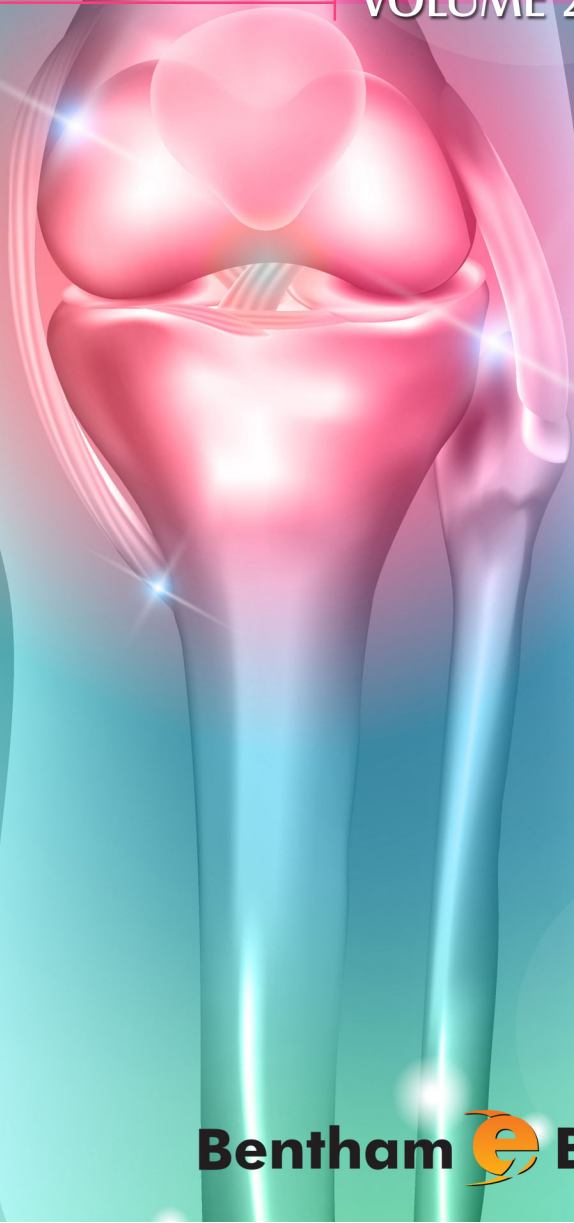
FRONTIERS IN ARTHRITIS

THE MANAGEMENT OF THE HAEMOPHILIC ARTHROPATHY

VOLUME 2



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(Volume 2)

(The Management of the Haemophilc Arthropathy)

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Frontiers in Arthritis

Volume # 2

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To Giulia and Alessia, my Masterpieces

FOREWORD

This book is the result of 20 years of clinical activity in the management of the haemophilic arthropathy. It is based on the personal experience and on the cultural and professional aspects shared with active scientists involved in the study and treatment of Haemophilia.

My personal experience started in the '90s as a consultant at the Florence Haemophilic Service, at that moment in the vanguard as a haematologic department; however, it lacked a modern orthopaedic approach to this disease, that was then introduced. Arthroscopic and prosthetic surgery were at the beginning focused on knees and hips; subsequently other surgeons in my hospital joined and shared with me their experience in elbow, hand, and ankle surgery. Moreover, I progressively and successfully applied in haemophilic patients several principles of the regenerative medicine when indicated, in particular in cases of important bone loss.

The high expertise of eminent haematologists as Dr. Morfini initially, and Dr. Castaman later with their equipes allowed us to safely perform complex surgical procedures without complications.

Subsequently, non-operative approaches as hyaluronic acid injections and chemical synoviorthesis were largely used, and physical therapy strategies increasingly promoted.

The local health service punctually granted financial resources, and enabled me to perform surgery in patients with inhibitors too.

In addition to clinical and surgical aspects, the book offers a detailed overview of the general aspects of Haemophilia and the haemophilic arthropathy: from the definition and features of the disease to the pathogenesis of arthropathy; from the pharmacokinetics of the most important drugs to the laboratory perspective. A chapter is dedicated to the radiological findings, lifestyle recommendations, and postoperative rehabilitation. A section on the nursing of such patients is also considered.

I think that anyone wishing to approach haemophilic patients and to treat the haemophilic arthropathy will find in this volume a useful and complete guide.

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PREFACE

Haemophilia is one of the most common rare diseases, characterized by bleedings and haemorrhages related to an inherited deficiency of coagulative factors. For decades it has been associated with higher rates of mortality and morbidity, until clotting factor concentrates were diffused, significantly limiting most of the complications. A dramatic raise of morbidity and mortality after blood transfusions was reported when HIV and Hepatitis infections were discovered. The development of recombinant concentrates, the modern prophylactic treatment, and the multidisciplinary approach to this disease lead over the years to the reduction of such complications and improvements in the management of the related clinical settings.

Then, why another book on the management of the haemophilic arthropathy? Simply because arthropathy may be to date considered the most frequent complication of Haemophilia.

Since childhood, the first falls in the physiological development of gait ability and the high frequency of impacts during games and sports activity may induce bleedings in muscles and joints. While a haematoma in muscles usually shows a self-resolution, blood in some joints, named “target joints”, may induce early negative effects, producing the so-called “arthropathy”. Such degenerative and inflammatory condition finally results in a mild to severe irreversible damage, that nowadays represents not a cause of mortality but rather a source of severe disability.

Even the powerful efficacy of bleeding prophylaxis, musculoskeletal alterations are still yet highly represented. Thus, the management of the haemophilic arthropathy has gained importance being to date one of the most essential goals of the modern approach to Haemophilia. Lifestyle modifications, selected sports activity, periodic evaluations by the multidisciplinary team (haematologist, orthopaedic surgeon, skilled nurse, radiologist, physiotherapist, lab personnel, and several other figures), and tailored prophylactic treatments represent the best way to prevent articular degenerative changes or to delay the progression of the arthropathy. In cases of fair results with this approach, it is possible to adopt conservative therapies, as braces, physical therapy, and articular injections with several substances and different indications. This would mean to avoid the early recourse to surgical procedures that until a decade ago was the only choice to ensure an acceptable quality of life in young symptomatic patients. On the other hand, a significant number of patients still now found no improvements with these strategies. In such cases, surgery is mandatory. With respect to the past, knee arthroplasty, ankle fusions, and arthroscopy are not the only orthopaedic procedures useful to address a joint arthropathy. Elbow and ankle arthroscopy, hip, ankle, and elbow arthroplasty are gaining popularity given the good outcomes and high reproducibility, simultaneously with the development of modern implants and devices, less invasive techniques, and biomaterials with better tribology and performance. Nowadays, it is possible to delay a joint replacement by a minimally invasive surgery, and also to achieve a long-term survival of implant after an arthroplasty. Joint fusions are unfrequently indicated, mostly after failure of the above mentioned procedures. Amputations are to date very uncommon, and proposed only in difficult cases when no limb salvage procedures are feasible. As expected, joint replacements in young haemophilic patients will fail, and revision arthroplasty often associated with reconstructive and plastic surgery will progressively arise. Thanks to modern modular revision implants, also such challenging conditions have been well addressed. Finally, no orthopaedic procedures may produce a good result without a valid and tailored rehabilitative protocol: specific approaches under control of the multidisciplinary team now ensure an effective functional recovery, and a better feeling referred by the operated patients.

Our future target will be the prevention of arthropathy by a multimodal and multidisciplinar approach, in order to make Haemophilia an early diagnosis but no more a source of disability. In specific challenging cases, as patients with inhibitors, the goal will eventually be the limitation of the natural history of arthropathy by all conservative or minimally invasive means that are now available, more than surgical procedures.

This textbook represents an updated overview on all aspects related to Haemophilia and its orthopaedic complications; it may be considered the most multidisciplinary textbook on this topic, focusing on this disease from the bench to the surgical room.

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CHAPTER 1

Pathogenesis of the Haemophilic Arthropathy

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Abstract: Joint damage due to recurrent bleedings in Haemophilia is the cause for long-term disabilities. The pathogenetic mechanism of haemophilic arthropathy is multifactorial and includes inflammatory synovium-mediated and degenerative cartilage-mediated phenomenons, in addition to neoangiogenesis and bone loss. Free blood in the joint has a direct effect on cartilage and synovium, and the deposit of iron appears to play a pivotal role. Iron may promote the apoptosis of chondrocytes by catalyzing the formation of oxygen metabolites. Iron may also act on the synovial membrane by favouring its proliferation through the induction of proto-oncogenes involved in cellular proliferation and stimulation of inflammatory cytokines. Such degenerative and inflammatory processes occur concomitantly, but also independently. A reduction of bone mineralization is usually present as a part of the articular damage associated to a multifactorial mechanism: it seems that the molecular triad (osteoprotegerin/Receptor activator of nuclear factor kB/Receptor activator of nuclear factor kB ligand) probably plays a major role, inducing osteoclastic differentiation and maturation. These processes finally result in a fibrotic and irreversible altered joint, feature of haemophilic arthropathy.

Keywords: Arthropathy, Haemophilia, Haemarthrosis, Haemosiderin, Neoangiogenesis, Osteoporosis, Synovitis.

INTRODUCTION

Haemophilia A and B are rare X-linked recessive bleeding disorders characterized by the absence or functional defect of clotting factor VIII (FVIII) or factor IX (FIX) respectively. The hallmark of such disease is represented by musculoskeletal bleedings, particularly haemarthrosis, leading to orthopaedic complications. Joint bleeding is the most common and potentially most disabling manifestation of severe Haemophilia (*i.e.* plasma FVIII or FIX <1U/dL) [1]. In

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nearly half of all children affected by severe Haemophilia, the initial haemartrosis occurs during the first year of life [2], and 90% of patients experience at least a joint bleeding before the age of 4.5 years [3]. Eighty per cent of joint bleedings involve knees, elbows, and ankles [4], and patients often develop multiple "target" joints. Although blood is rapidly cleared from the joint space also by the replacement with the missing factor, the pathologic process still continues, resulting in both clinical and radiographic changes. Recurrent bleedings cause an irreversible joint damage with progressive functional impairment [5], chronic pain [6], and heavy impact on quality of life [7]. Haemarthrosis can be prevented or controlled by the prophylactic administration of clotting factor concentrates. Compared with an on-demand treatment strategy, a primary prophylactic treatment (*i.e*. the regular continuous treatment initiated in the absence of documented osteochondral joint disease and started before the second clinically evident large joint bleed in children >3 years) leads to better musculoskeletal outcomes, as clearly established [8 - 11]. [8]. However despite such strategy, joint bleedings and related damages may recur and the haemophilic arthropathy (HA) may realize, as confirmed by the radiographic evidence by the age of 6 in some subjects who had no bleeding or few subclinical haemarthroses [11].

The mechanism of the progressive joint damage in patients with Haemophilia is still relatively unclear, but recurrence and persistence of blood into the joint cavity is the key factor responsible for synovial and cartilage changes [12, 13]. Increasing evidences of a close relationship between the type of mutation ("null" and/or "missense" mutations), bleeding, inflammatory process, and neoangiogenesis are emerging and suggesting that iron, cytokines, and neoangiogenic factors can initiate synovial and early cartilage damages with molecular changes and perpetuation of a chronic inflammatory condition [14].

From Bleeding to Synovial and Cartilage Damage

Bleeding into a joint exposes synovial cells to blood and its components including iron that plays a pivotal role in joint damage [15] (Fig. **1**). The progressive accumulation over time of iron as haemosiderin (normally removed from the by synovial macrophages) represents the trigger for synovial inflammation [16]. Haemosiderin deposits are crucial in the early stages of HA, triggering synoviocyte hypertrophy (resulting in "villi"), neoangiogenesis, and release of hydrolytic enzymes from synovial cells. Iron up-regulates the expression of proinflammatory cytokines, as interleukin-6 (IL-6), IL-1alpha, IL-1beta and tumor necrosis factor-alpha (TNF-alpha) in synovial cells and induces the regulator genes c-myc and MDM2 expression, resulting in synovial proliferation [17, 18]. Another effect of haemosiderin is the lymphocytes infiltration of the synovial membrane with subsequent inflammatory changes. Moreover, different

proinflammatory cytokines released by synovial cells may inhibit the formation of human cartilage matrix [15]. Synovitis is one of the earliest macroscopic effect of a target joint and it is not always easily distinguishable from a clinical point of view from haemarthrosis. Synovitis is an inflammatory process involving synovial tissue, characterized by hypertrophy, migration of inflammatory cells, and a high degree of neoangiogenesis [18 - 22].

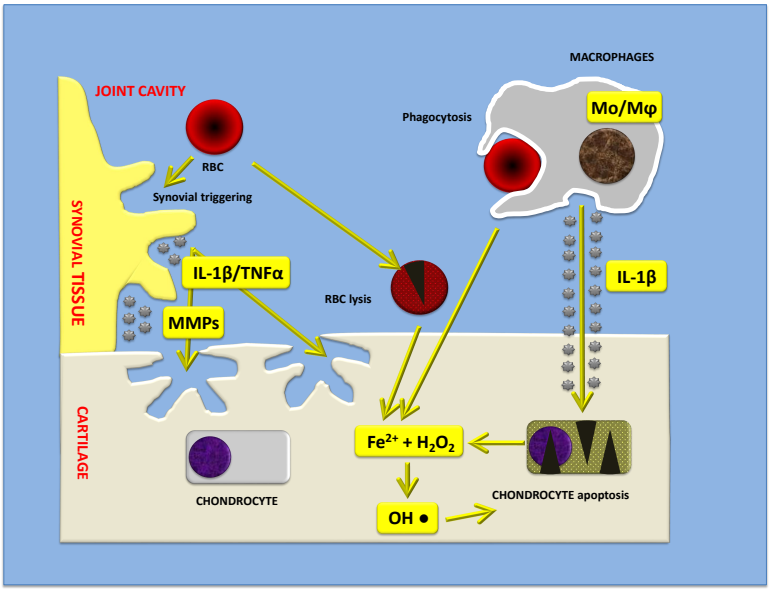

Fig. (1). Mechanisms of blood-induced joint damage in Haemophilia: the role of iron (Fe^{2+}) interacting with Hydrogen peroxide (H_20_2), macrophages'activation (Mo/Mö), matrix metalloproteinases (MMPs), and involvement of several cytokines.

Recurrent bleedings and synovitis rapidly evolving into joint damage can be considered two different aspects of HA. Intense, chronic effusion of the affected joint after one or several haemarthrosis typically occurs in the early stages of HA [23, 24]. Synovitis can lead to further bleedings with transformation of an acute process in a chronic disease.

Also the presence of free blood in a target joint has a direct harmful effect on cartilage, resulting in adverse changes in chondrocyte activity [25]. Moreover, these alterations may occur before the synovial inflammation becomes evident. Human articular cartilage consists of a relatively small number of chondrocytes embedded in a relatively large amount of extracellular matrix that consists mainly of collagen and proteoglycans. There is a continuous turnover of these components, with a delicate balance between synthesis and breakdown [26].

CHAPTER 2

Pharmacokinetic Approach to the Treatment of Haemophilia

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Abstract: Pharmacokinetic (PK) has improved our knowledge about the most appropriate dosing and timing of administration of FVIII/FIX concentrates in patients with Haemophilia. However, although several studies have recently addressed the relevance of PK of clotting factors, usual practice is still mostly based on empiric approaches since individual PK estimation is difficult to obtain unless the patient is formally enrolled in a study. In fact, several plasma samples collected over several hours and/or days are required to establish a half-life curve confidently and this may be a relevant problem, especially in children. Recently however population PKs has emerged as an important tool to overcome this drawback. Targeted prophylaxis could take advantage of knowing the individual response to factor concentrate administration. On the clinical ground, age and body weight (BW) are roughly used to guide dosing because usually *in vivo* recovery is lower and clearance is faster in children than in adults.

Keywords: Factor VIII, Factor IX, Haemophilia A, Haemophilia B, Pharmacokinetics.

INTRODUCTION

Replacement treatment with clotting factor concentrates (factor VIII – FVIII or factor IX – FIX) has dramatically improved Haemophilia care and prognosis [1]. In conjunction with the evolution of products and therapeutic regimens, the important role of pharmacokinetics (PK) has been also increasingly recognized. Methods for PK evaluation have been developed, progressively becoming more and more accurate. From the 1970s, it has been clearly shown that three times per week treatment was much better than once-weekly for prevention of bleeding [2, 3]. Subsequent careful PK studies showed the benefits of PK plotting and implementation in Haemophilia prophylaxis providing hints to a personalized

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prophylaxis in an attempt to strengthen efficacy without increasing the costs [4, 5]. Substitutive treatment for haemophilia is expensive, but inadequate treatment worsens quality of life by increasing morbidity and late sequelae and eventually increasing the associated costs. As in most fields of medical treatment, variability in response among patients is critical and thus tools to optimize clotting factor usage should be always pursued. The required dose should be administered according to the clinical setting (treatment of acute bleeding, surgical prophylaxis or regular prophylaxis), the degree of the factor deficiency, the site and severity of bleeding. On this basis the application of pharmacokinetic analysis would provide the clinicians with more accurate information to tailor patient treatment [6 - 9].

Pharmacokinetics: Basic Principles

The dose–response relationship for a drug is the result of dose, route of administration, patient characteristics and drug exposure that is defined by the PK of the drug. PK evaluates the rate of absorption, distribution, metabolism and excretion of a drug and its metabolite(s), commonly referred to as ADME. It can be broadly termed as what the body does to the drug and is essentially based on measurement of plasma concentrations. Pharmacodynamics (PD) is the other major component of the dose–response relationship and it can be defined as what the drug does to the body, that is the relationship between drug concentration at the site of action and a measurable effect. Jointly, pharmacokinetics and pharmacodynamics determine the necessary dose, dosing intervals and mode of administration [10, 11]. Typically, pharmacokinetic parameters are calculated on measurements of drug concentration serially taken over time or on measurable variations induced by the drug in plasma [6]. For coagulation products, PK differs from that of most pharmaceutical drugs since bioassays of coagulation factors are used to quantify the variation rather than on plasma immunological concentration [12]. Their concentrations in plasma are expressed as level of procoagulant activities of FVIII (FVIII:C) and FIX (FIX:C) in international units (IU) per milliliter or deciliter, rather than in molar units, as direct representations of the drug effects [10, 13].

Definitions and Applications of Pharmacokinetics

The pharmacokinetic parameters or definitions traditionally used in the study of coagulation products are summarized below together with how they are derived from the plasma concentration (or F:C) vs. time curve.

• *In vivo* recovery (IVR)

In vivo recovery (IVR) of a given clotting factor and its biological half-life, have

been the standards to compare different clotting factor concentrates [7]. The percentage IVR is the measured peak plasma level relative to the expected peak plasma level, where the latter is defined as the dose divided by the plasma volume of the patient and calculated on either body weight (BW) or plasma volume. Body weight is usually preferred to calculate recovery because of the variability of plasma volume calculations according to the different results obtained with the methods of estimating plasma volume, even in the same patient [6, 12, 14]. Nowadays incremental IVR is usually reported as peak level divided by dose in U/kg.

- **Half-life (T½)**

It can be loosely defined as the time required for plasma factor level to decrease by half during the elimination phase. Unlike the plasma clearance value, which expresses only the ability of the body to eliminate the drug, half-life expresses the overall rate of elimination process of a given factor concentrate. This overall rate of elimination depends not only on drug clearance but also on the extent of drug distribution.

- **Area under the plasma concentration *vs*. time curve (AUC)**

AUC (the area under the plasma concentration vs. time curve) is a measure of drug exposure and bioavailability. It is calculated as the product of plasma drug concentration and time. The AUC is used to derive many other pharmacokinetic parameters.

- **Maximum plasma concentration (Cmax)**

Cmax is the maximum ("peak") plasma concentration of a drug observed after its administration and before administration of a second dose. For an i.v. drug, this is usually assessed on plasma sample(s) taken very close to the end of infusion.

- **Clearance (CL)**

CL is the ability of the body to eliminate a substance and can be defined as the volume of plasma that is cleared of a drug in 1 min (or 1 hour). For an i.v. drug it is calculated as dose divided by AUC.

CHAPTER 3

Haematological Care of the Haemophilic Patient

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Abstract: Haemophilia A and B are X-linked recessive coagulation disorders resulting from the deficiency or abnormal function of either factor VIII or IX, respectively. Musculoskeletal bleedings, particularly joint bleeding, are the hallmark of severe Haemophilia. Recurrent joint bleedings lead to arthropathy and functional disability. Haemophilia can be treated either on demand to stop bleeding or with prophylaxis to prevent joint damage. A variety of high-quality clotting concentrates are available for patients with Haemophilia and long-acting concentrates are becoming available, with further improvements in the treatment of this potentially disabling disease. Also gene therapy is an impressive promise of cure for the patients, especially those with Haemophilia B. Currently, the development of alloantibodies directed against FVIII or FIX, able to neutralize their clotting activity, and making replacement therapy ineffective represents the most serious challenge of the treatment. A comprehensive care of patients with Haemophilia should be provided by a multidisciplinary team, offering the more appropriate and innovative therapies for Haemophilia and its complications.

Keywords: Factor VIII, Factor IX, Gene therapy, Haemophilia, Haemarthroses, infections, inhibitors, Prophylaxis, Replacement therapy, Target joint.

EPIDEMIOLOGY AND GENETICS

Haemophilia is the epitome of the inherited bleeding disorders, and is caused by the deficiency or functional defect of coagulation factor VIII in Haemophilia A (HA) or factor IX in Haemophilia B (HB). The incidence of HA and HB is respectively one in 5,000-10,000 and one in 30,000 – 50,000 male births regardless of ethnic and racial background [1].

The human *F8* gene comprises 186,000 base pairs while *F9* gene consists of 34,000 base pairs. These genes are located on particularly fragile portions of the X chromosome. The *F8* gene maps to the most distal band Xq28 on the long arm

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of the X chromosome and F9 gene is close to *F8* gene, on the tip of the long arm of the X chromosome at Xq27.1 [2]. Because of its greater size, *F8* gene is more susceptible to mutations resulting in the higher prevalence of HA *versus* HB (4:1).

F8 gene contains 26 exons and 25 introns, usually exon length ranges from 69 to 262 nucleotides apart from exon 14, 3,106 nucleotides long, and the last exon 26, which has 1,958 nucleotides. The spliced FVIII mRNA is approximately 9kb in length and predicts a precursor protein of 2351 amino acids. After removing peptide secretory leader sequence, mature FVIII comprises 2,332 amino acids with the domain structure A1-a1-A2-a2-B-a3-A3C1-C2 [3]. The liver appears to be the primary site of FVIII synthesis, although it is still unclear if the cells producing FVIII are hepatocytes or, more likely, liver sinusoidal endothelial cells [4]. FVIII circulates in plasma non covalently bound to von Willebrand factor (VWF), which represents 99% of the whole mass of the complex. VWF is the plasma carrier of FVIII, protecting it from proteolysis and rapid clearance. Unlike several other coagulation factors, FVIII does not have enzymatic activity, but as cofactor it accelerates the activation of FX by FIXa on a suitable phospholipid surface, thus amplifying coagulation reaction by several folds. Specific proteolytic cleavages between the domains both activate and inactivate the cofactor [5].

F8 gene mutations responsible for HA may be divided classically into several categories: gross gene rearrangements, insertions or deletions ranging from one base pair up to the entire gene, and single DNA base substitutions resulting in either amino acid replacement ("missense"), premature peptide chain termination ("nonsense" or stop mutations) or mRNA splicing defects [6]. At least 45% of severe HA cases are explained by the presence of the inversion of intron 22 in *F8* gene. The inversion occurs by the translocation and exchange of DNA between either of the two nonfunctional FVIII-related genes with intron 22 and areas of homologous DNA within the functional *F8* gene [7]. The recombination produces disjointed and inverted DNA sequences, preventing the transcription of a normal full-length FVIII molecule.

F9 gene contains 8 exons and 7 introns, the spliced FIX mRNA is about 2.8kb length and predicts a single chain glycoprotein of 415 amino acids. FIX is a vitamin-K-dependent coagulation factor; prior its secretion from hepatocytes, FIX undergoes gamma–carboxylation, O- and N-linked glycosylation, phosphorylation, sulfation, disulfide bond formation, and beta–hydroxylation, as well as cleavage of the signal peptide to propeptide. FIX plays a critical role in blood coagulation. When activated by FXI or FVII, FIX activates FX in presence of Ca^{2+}, membrane phospholipids, and FVIII as a cofactor [8].

Missense mutations are the most frequent cause of *F9* gene mutations in HB patients, but small insertions or deletions have also been identified [9]. As a consequence, frequently these patients have immunologically detectable FIX protein in plasma, but with discrepantly lower FIX activity (Cross-Reactin--Material positive, CRM+). Gross genetic abnormalities as complex gene rearrangements or deletions affecting the whole, or a large part, of the gene are much more rare than HA, and account for 7% of HB cases only.

Severity of Haemophilia

Severity of Haemophilia is defined according to the level of clotting factor activity in plasma, as compared to a reference standard that is assumed to have FVIII levels of 100% or to a FVIII activity of 1.0U/mL. The FVIII level in normal population ranges from 50 to 150% (0.50-1.5U/mL). Patients with factor levels <0.01 IU/mL are classified as severe haemophiliacs, those with factor levels between 0.01 and 0.05 IU/mL as moderate and those with >0.05 to 0.4 IU/mL as mild Haemophilia [1]. This classification is in good agreement with the severity and frequency of bleeding symptoms, although some phenotypic heterogeneity can occur [10, 11] (Table **1**).

Table 1. Clinical classification of Haemophilia A and B.

Classification	FVIII or FIX Activity	Clinical Manifestations
Severe	<1% of normal (0.1 U/mL)	Spontaneous hemorrhage from early infancy Frequent spontaneous haemarthroses and hemorrhages, requiring clotting factor replacement
Moderate	1-5% of normal (0.01-0.05 U/mL)	Hemorrhage secondary to trauma or surgery Occasional spontaneous haemarthroses
Mild	>5- 40% of normal (0.05-0.40 U/mL)	Hemorrhage secondary to trauma or surgery Rare spontaneous haemarthroses

Clinical Manifestations

Historically, severe HA and HB have been considered clinically indistinguishable, with musculoskeletal bleedings, particularly in joints, as hallmark of a severe Haemophilia. Recent evidences, however, suggest that patients with severe HB may have a less severe bleeding phenotype, a lower bleeding frequency and better long-term outcomes, compared to severe HA patients [12].

Repeated haemarthroses result in chronic, crippling haemophilic arthropathy. In decreasing incidence, the most commonly involved joints are knees, elbows, ankles, shoulders, wrists, and hips [13]. The first sign of a joint bleeding is a sensation of intraarticular burning, followed by fullness, tightness, swelling, and

CHAPTER 4

Laboratory Aspects

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Abstract: The haemostatic process is characterized by a series of biochemical reactions aiming at preventing blood loss through blood clot formation. This latter process is mediated by the interaction of platelets on the surface of the injured vessel wall which in turn induces the coagulative phase requiring the activation of inactive zymogen into active proteases.

Haemophilia A and B are rare disorders in which the coagulation cascade is affected due to the lack of blood clotting FVIII and FIX, respectively.

In order to provide the appropriate therapy for patients with these bleeding disorders, several laboratory tests have to be performed. The initial screening is conducted by screening global tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) but only this latter is prolonged in hemophilia. Next, the measurement of factor activity is required for the diagnostic assessment and classification of the disease severity. Three methods can be performed for evaluating FVIII activity including one-stage, two-stage and chromogenic assays.

Approximately 30% of severe Haemophilia patients develop FVIII inhibitors which neutralize the clotting activity. The most common assay employed for the detection of inhibitors is the Bethesda assay that combines plasma containing normal amount of FVIII with same volume of patient plasma.

Problems in Haemophilia diagnosis or inhibitor detection can occur at any stage in the clinical diagnosis/laboratory phase, from the pre-analytical to the analytical to post-analytical. Therefore, the aim of this chapter is to summarize the diagnostic approaches, pitfalls and interpretation of coagulation assay in Haemophilia.

Keywords: Clotting factor, Haemostasis, Haemophilia, Inhibitors assays, Laboratory test.

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INTRODUCTION

A sequence of biochemical and cellular reactions leads to haemostasis which is aimed to preventing blood leakage from the vascular lumen while maintaining blood within the vasculature in a fluid state, and protecting the integrity of vessels.

After injury to the integrity of vessel wall, the hemostatic process begins with an early vascular phase characterized by a vaso-constriction with reduction of the vessel lumen. This is followed by a platelet-subendothelium interaction mediated by von Willebrand factor (VWF) and subendothelial collagen and glycoprotein Ib on platelet surface. This interaction leads to the formation of a platelet plug (primary haemostasis). The simultaneous activation of clotting system eventually produces the formation of the fibrin clot (secondary haemostasis).

The coagulative or plasmatic phase, deficient in Haemophilia, comprises a series of proteolytic reactions, where an inactive precursor (zymogen) is converted into the active form (protease). This is in turn able to activate the next protease until fibrinogen, a soluble adhesive protein present in large amounts in the bloodstream, is transformed in a dense insoluble fibrin clot that completely covers the site of vessel injury.

In order to simplify and schematize the enzymatic activities of multiple molecules involved in the coagulation phase, a “cascade” model was developed. It is characterized by the sequence and by the specificity of events: for example, the first protein activates the second but can not instead activate the third, as showed in Fig. (**1**) and Table **1**.

Table 1. Nomenclature of coagulative factors.

Factor	Name	Pathway
Prekallikrein	Fletcher factor	Intrinsic
High molecular weight kininogen (HMWK)	Fitzgerald factor	Intrinsic
I	Fibrinogen	Common
II	Protrombin	Common
III	Tissue Factor	Extrinsic
IV	Calcium	Common
V	Proaccelerin	Common
VII	Proconvertin	Extrinsic
VIII	Antihemophilic factor A	Intrinsic
IX	Christmas-Factor Antihemophilic factor B	Intrinsic

(Table 1) contd.....

Factor	Name	Pathway
X	Stuart Factor	Common
XI	Plasma Thromboplastin Antecedent (PTA)	Intrinsic
XII	Hageman Factor	Intrinsic
XIII	Transglutaminase, fibrin stabilizing factor	Common

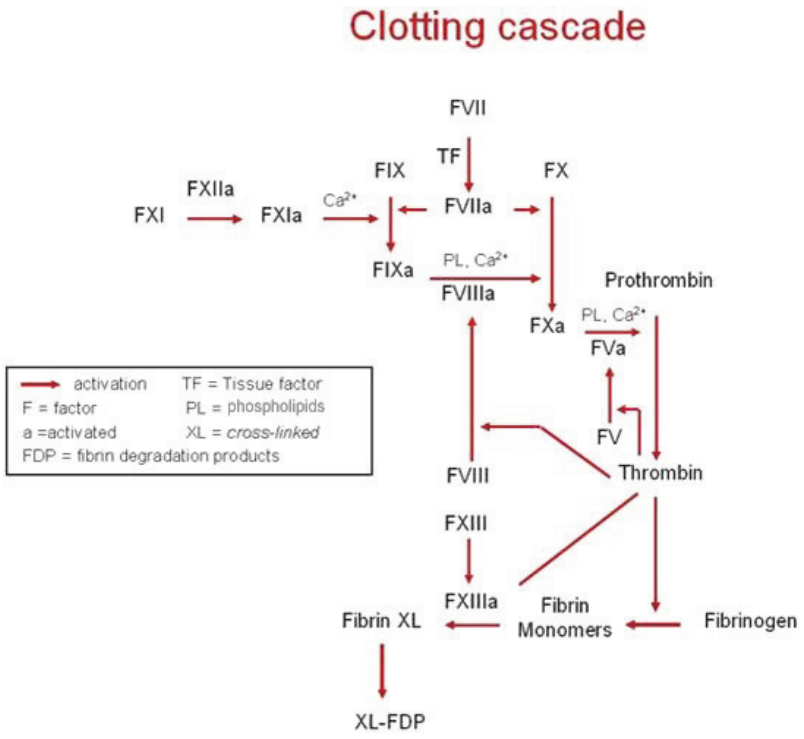

Fig. (1). Proposed mechanism of coagulation system (by courtesy of G.Castaman).

At variance with other coagulative factors, that are serine protease present in blood in the form of zymogens, tissue factor (TF), factor V and factor VIII (cofactors), and fibrinogen have no enzymatic activity. Within this sequence of events, also calcium ions and phospholipids of cell membranes, especially those of the platelet surface (PF3), critically intervene in the coagulation process, providing an appropriate cellular surface on which the coagulative process takes place.

Indeed, a series of complex events occurs to start, amplify, and propagate clotting response to the injury.

CHAPTER 5

Nursing of Patients with Haemophilia

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Abstract: The management of nursing consists in the performance of leadership functions of governance and decision-making within organizations employing nurses. It includes many processes common to all management as planning, organizing, directing, and controlling. In case of rare bleeding disorders, nurses may encounter patients who are experiencing acute bleedings or receiving treatments for another condition. In Haemophilia, the nurse is not only a professional figure but also a teacher of daily actions, as self-injections of substitutive factors, and a confidant reference point for patients and their family.

Keywords: Carrier, Caregiver, Haemophilia, Home treatment, Nursing, Replacement therapy.

INTRODUCTION

As nurses, we know that every patient is special for his past and present clinical history, and that management can be complicated by the association of several other conditions. As the general population ages, our patients will have longer lists of chronic disorders and related medications, and their nursing care will become even more complex. Moreover, life-long lasting genetic disorders are usually characterized by a multidisciplinary approach: nurses play a relevant role being the link between specialists involved in the management of all medical aspects related to the disease.

Haemophilia is an inherited bleeding disorder requiring specifically complex, life-long care [1]. At variance with the very frequent inherited thrombophilic syndromes, inherited bleeding disorders are uncommon, and most nurses have generally little experience and know-how to manage such patients. Unlike the diagnosis and treatment of thromboembolic disorders, which many nurses encounter on every shift, bleeding disorders rarely come up in shift report. Patients with Haemophilia

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and their parents are usually well informed and self-trained about their disorders, and able to quickly catch a caregivers' lack of knowledge. Such situation makes them uncomfortable, particularly in pediatric age. Thus, nurses should be trained and educated about all aspects of bleeding disorders. In this way, learning and teaching about bleeding disorders can vastly improve the provided care, thus increasing patients' trusting in the system of care.

Bleedings have multiple inherited and acquired causes. This chapter will discuss Haemophilia A and B related conditions and needs from the nurse perspective. Other coagulation factor deficiencies or platelet disorders, including von Willebrand disease which is the most common hereditary bleeding disorder, will not be dealt with for their milder bleeding tendency and pathophysiological complexity.

Treatment

For many years, blood or plasma transfusions were the main treatment for Haemophilia. In the 1970s, development of factor replacement products from plasma donations enlarged treatment options and changed the lives of such patients [2].

In this way, in order to stop bleedings, they could receive the required factor in a small fluid volume at home by a short infusion with a small butterfly needle Fig. (**1**).

Fig. (1). Example of recombinant factor infusion.

Until not long ago, many people with Haemophilia suffered a joint damage due to recurrent bleedings [3]. Because of the further risk of haemoartrosis during and after surgery, many orthopaedic procedures were addressed as very difficult. The large availability of factor replacement products now makes such type of surgery more feasible, improving the quality of life of haemophiliacs in terms of pain reduction and functional recovery.

Although replacement factors have brought Haemophilia one step closer to a cure, the promise of a definitive therapy was clouded in the '80s by the discovery of HIV and other blood-borne diseases. Unlikely, many people with Haemophilia contracted HIV, hepatitis C, or both from transfusions and first generation factor concentrates.

Given the critical concern on the safety of those concentrates, pharmaceutical companies soon developed virucidal methods that associated with safer blood donor screening procedures, virtually abolished the risk of infectious disease transmission [4]. Eventually, factor products without the use of human plasma were developed. Today, most factor products are recombinant and not processed from human plasma.

Recombinant Factor Products

Several recombinant factor VIII or factor IX products are now available. Dosing varies with the type of bleeding, and haematologists determine the right dosage. Each vial of concentrate is labeled with the total number of units expressed as International Units (IU). Vials range from 250 to 3000 units per bottle. Dose calculations can rarely be exact due to the variability in lot yields. It is not essential to administer exact doses; doses within 10% above the ordered number of units are usually acceptable.

Practical Nursing Recommendations

1. When administering factor products, make sure to give the right one for your patient's type of Haemophilia. Further, be aware that all factor products must be reconstituted immediately before administration. They are packaged in kits that include a vial of factor (powder), a vial of diluent, and a mixing device. Most mixing devices have a built-in filter. Swirl (do not shake) the medication when mixing.
2. Never waste factor concentrate by using a portion of a vial and discarding the rest. The full vial should be used, as overdosing is not an issue. A vial size that is as close as possible to the desired dose should be chosen, but it should be always round up to the nearest whole vial size.
3. Infuse the factor by slow intravenous push as soon as possible after

CHAPTER 6

Imaging of Haemophilic Arthropathy

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Abstract: Haemophilic arthropathy one of the most severe cause of disability in patients affected by severe Haemophilia. The identification of early signs of arthropathy and the assessment of osteochondral damage is fundamental in the management of such patients. Different imaging modalities can be useful to detect haemophilic arthropathy at various stages. Conventional radiography demonstrates bone alterations and indirectly osteochondral damages, and still remains the basis to plan a surgical treatment. Magnetic resonance imaging better detects soft tissues and cartilage abnormalities at every stages, while ultrasonography especially by the color-power Doppler modality has became crucial for the monitoring of underage subjects and for the clinical follow-up. Computed tomography is nowadays just used for the detection of invading pseudotumors, bone erosions, and some extra-musculoskeletal complications of Haemophilia.

Keywords: Computed tomography, Haemophilia, Haemophilic arthropathy, Imaging technique, Magnetic resonance imaging, Radiography, Ultrasonography.

INTRODUCTION

Haemophilia is characterized by recurrent haemorragic episodes in joints inducing an irreversible arthropathy, initially caused by inflammatory proliferation of synovial cells. Such changes may lead over several stages and in case of recurrent bleedings to cartilage and subchondral bone damages with final joint destruction, anatomical compromission, and ankyloses. A delayed haematological treatment increases the risk of arthropathy. The detection of early changes and stages of haemophilic arthropathy is thus crucial to avoid its natural history [1]. The identification of initial signs of haemophilic arthropathy is therefore fundamental and is carried out by various imaging techniques.

For over a century and until the end of 1970s conventional radiography has been used for diagnostic purposes; it still remains the standard tool of diagnosis for

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haemophilic arthropathy and has a central role for the planning of any orthopaedic treatment [1 - 9].

In the 1980s Magnetic Resonance Imaging (MRI) became a useful diagnostic technique for the assessment of several stages of arthropathy, and its importance progressively increased over the last years. This imaging modality has shown a considerable accuracy in assessing early soft tissues and cartilage changes, adding high levels of details with respect to x-rays [6 - 14].

Since the 1950s ultrasonography (US) was supposed to be an important technique for the clinical practice. In the last decades, its development by the use of linear high-resolution probes and dedicated software has enabled to visualize almost all musculoskeletal structures with less costs and an easier accessibility [1, 5, 12, 15, 16]. In addition, color and power Doppler modalities have been recently introduced in order to assess the synovial vascularity in case of arthropathy [17].

Finally, Computed Tomography (CT) commonly performed in the last decades and now progressively underused, is indicated to assess abnormal bone changes. It is very useful to evaluate alterations as erosions, cysts, and particularly indicated to characterize chronic encapsulated fluid structures as pseudotumors, or spontaneous or posttraumatic haemorragic episodes in other non-musculoskeletal sites [1, 16, 18 - 20].

The following is an overview of the diagnostic techniques useful to assess the diagnosis and the evolution of the haemophilic arthropathy and its related clinical issues.

CONVENTIONAL RADIOGRAPHY

For many decades the diagnosis of haemophilic arthropathy has been done by plain radiographs: radiography still nowadays represents the gold standard diagnostic tool for the clinical practice [1,13,21-23]. However, it is not properly indicated to detect early articular changes particularly in children. So, even if it represents the best examination in adults, especially before and after surgery it is often associated with US for the periodic assessment of target joints in underage patients and for follow-up evaluations after conservative treatments (see chapter 8)[15].

As mentioned in chapter 1, arthropathy usually starts from the first haemarthrosis in several target joints [1] Fig. (**1**). Knees are the most affected joints, given their high amount of synovial tissue. In children, x-rays may show the following common changes: epiphyseal overgrowth, widening of intercondylar notch, and squaring of the patella [5, 6] Fig. (**2**). Progressively, limb malalignment, and length

discrepancy may develop. In adults and later stages of haemophilic arthropathy conventional plain radiographs may demonstrate loss of joint space, bone erosions, osteophytes, subchondral cysts, and even ankyloses [2,23] Figs. (**3** and **4**).

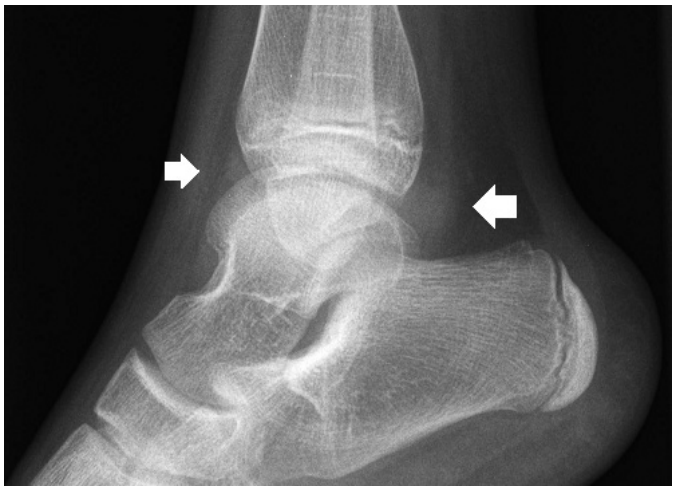

Fig. (1). Right ankle of a 11-years old child at his first episode of haemarthrosis. Note the slight swelling of articular soft tissue prevalent in the back seat due to bleeding (arrows).

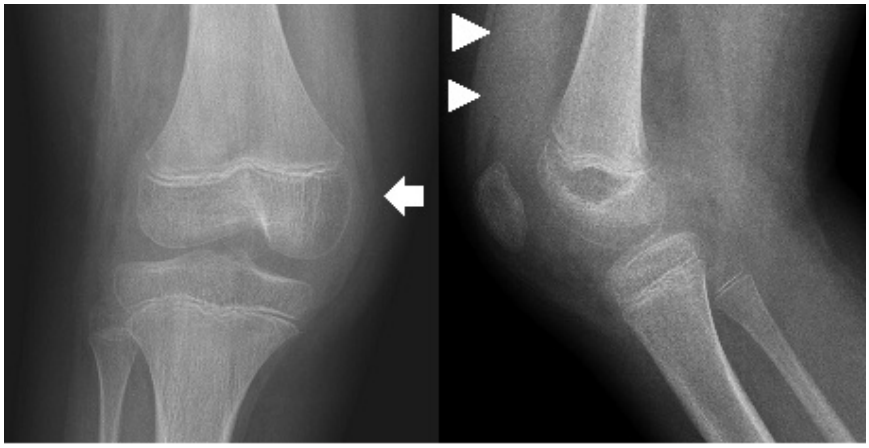

Fig. (2). Right knee of a 12-years old child with typical signs of the progression of the disease. Local osteoporosis at the medial condyle and growth of the trochlea femoral epiphysis with widening of the intercondylar notch (arrow), and effusion in the suprapatellar recess (arrow heads).

In order to quantify the severity of arthropathy, several x-rays based scores have been proposed. The most used classifications are the Arnold-Hilgartner (1977) and the Pettersson score (1980).

CHAPTER 7

Sonographic Findings and Scoring Method of Target Joints

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Abstract: In haemophilic arthropathy (HA), a spontaneous joint bleeding may trigger and perpetuate synovitis, and cartilage damage may follow even after a single exposure to blood, leading to a progressive and permanent joint damage. Ultrasonography (US) may detect articular and periarticular structures, muscles, tendons, tendon-sheats and enthesys. While power Doppler (PDUS) detects synovial inflammation and local blood flow. The US is based on technique, concepts and method widely accepted. We describe a US protocol to study the typical target joint (elbows, knees, and ankles). Knees, elbows, and ankles can be systematically and easily evaluated by means of conventional US machines, including portable machines, with a linear probe 13-4 MHz. The presence of haemarthrosis and the evidence of a synovial neoangiogenesis is assessed by PDUS in longitudinal scan. In the last decade, some scoring methods were proposed. Our scoring system requires a practice of US technique without necessarily being expert sonographers and allow to study all joints in static and dynamic position through nine items. This scoring method is applied to each target joint with a range from 0 to 21 and with cut off ≤ 5 or >5 useful to define the early stage of arthropathy.

Keywords: Haemophilic arthropathy, Power doppler, Scoring method, Target joint, Uultrasonography.

INTRODUCTION

Spontaneous joint bleeding in haemophilia A and B may trigger and perpetuate synovitis, and cartilage damage may follow even after a single exposure to blood [1 - 3], leading to a progressive and permanent joint damage, *i.e*. haemophilic arthropathy (HA). This results in loss of joint function and muscle hypotrophy, especially involving the larger joints (target joint) [4, 5].

Synovitis with synovial changes, cartilage, and bone damages with resulting disability may occur even after few bleeding episodes.

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The ultrasonographic examination (US) has shown its validity for the diagnosis of musculoskeletal diseases. It is easily available at any facility, results as a non-invasive evaluation, and allows for a quick and recurrent study of joint status. This relatively recent technique has been employed in Haemophilia starting from the pioneering work proposed by Wilson in 1987 [6] who first made a specific reference to the significance of the diagnosis by US in Haemophilia, and the routine control of bleeding in soft tissues.

US is an imaging method detecting joint structures, muscles, tendons, sheats, and entheses [9]. It is helpful to detect bone and cartilage alterations and synovitis [10]. It is also well known that power Doppler US (PDUS) may identify the synovial blood flow [11, 12]. The early diagnosis and evaluation of an acute haemarthrosis by US may optimize the Haemophilia treatment fostering the achievement of a satisfactory health condition of patients [7 - 10]. US is fast and effective, safe and widely available; it is a dynamic, real-time, comparative study that can confirm the clinical examination in haemophilic patients. This type of imaging evidences the presence of bleeding, its extension, exact location, relationships with adjacent anatomic structures, its evolution, and finally possible complications.

PDUS may identify bleeding also in asymptomatic joints and is able to show different types of haemarthrosis [11, 12].

Sonographic Findings

The US is based on technique, concepts and method widely accepted and described elsewhere [9, 11 - 14]. Here, we describe a US protocol to study the typical target joint (elbows, knees, and ankles).

Knees, elbows, and ankles can be systematically and easily evaluated by means of conventional US machines, including portable machines, with a linear probe 13-4 MHz.

The presence of haemarthrosis and the evidence of a synovial neoangiogenesis is assessed by PDUS in longitudinal scan.

The positioning of the probe and relevant US images for target joints are shown in the Figs. (**1-9**).

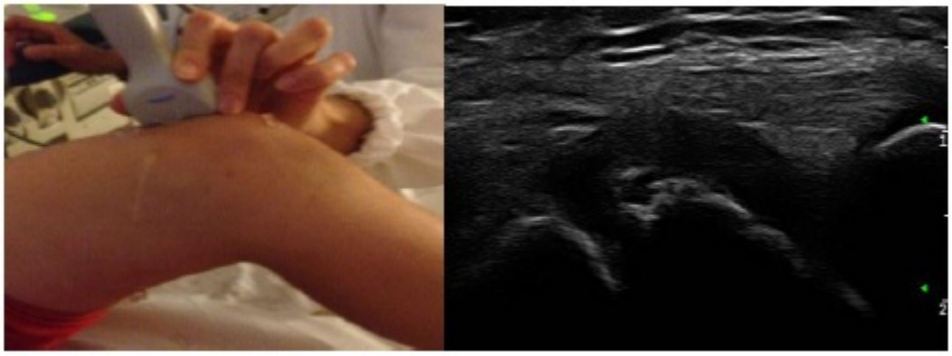

Fig. (1). Knee: the probe scans the joint in the longitudinal view in the supine position with the knee in full or moderate extension (30°-45°) to detect the superior (suprapatellar) recess and the presence of the joint effusion or haemarthrosis and thickening of synovial tissue.

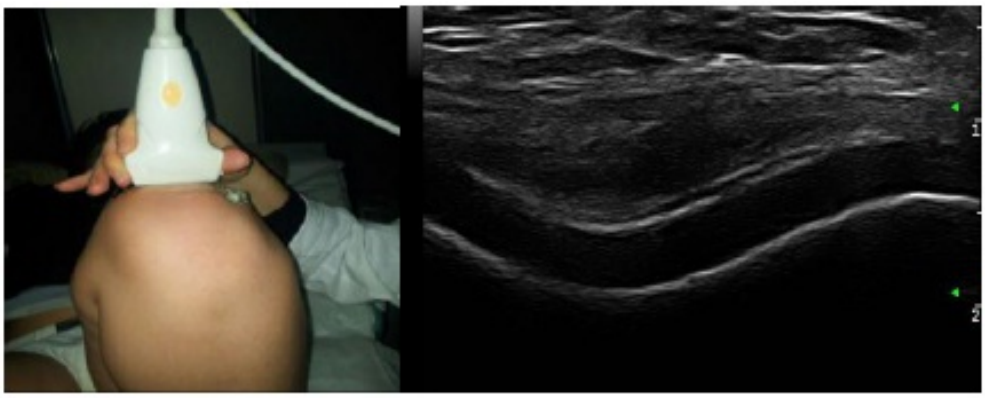

Fig. (2). Knee: the probe scans the joint in transverse view and supine position with maximal knee flexion to study the cartilage.

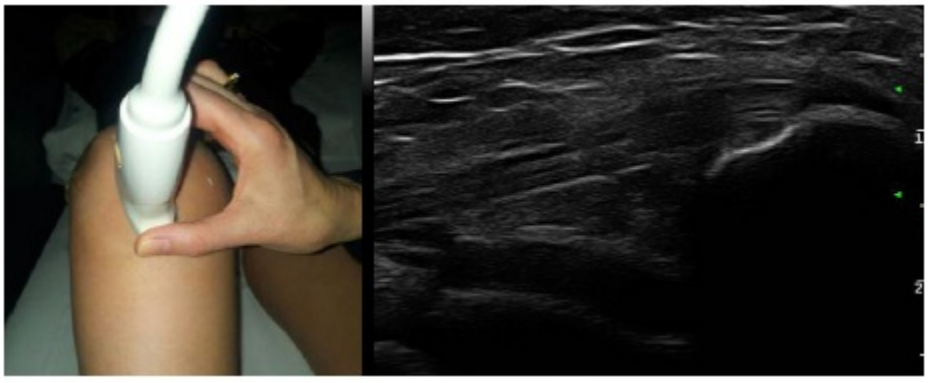

Fig. (3). Knee: in this view it is possible to detect the patellar tendon and Hoffa body.

CHAPTER 8

The Conservative Management of the Haemophilic Arthropathy

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Abstract: The combination of bleeding control strategies associated with lifestyle modifications, gentle physical activity, and the eventual use of ortheses are the basic principles to prevent the haemophilic arthropathy in its severe stages that represent the most common clinical manifestation of Haemophilia. Several conservative treatments may be also useful. Intraarticular injections of hyaluronic acid (viscosupplementation), Rifampicine (chemical synoviorthesis), and radioactive colloids (radiosynoviorthesis) with their different indications have been associated with good results. Other approaches as platelet-rich-plasma injections or synovial endovascular embolization have still to be validated and understood to ensure their safety or effectiveness.

Keywords: Chemical synoviorthesis, Endovascular embolization, Haemophilia, Haemophilic arthropathy, Hyaluronic acid, Platetet rich plasma, Physical synoviorthesis rifampicine Radiocolloids, Viscosupplementation.

INTRODUCTION

Modern bleeding-preventing drugs and tailored haematologic protocols have represented the milestones for the prevention of the complications of Haemophilia from the middle '90s in developed countries [1, 2]. To date, the musculoskeletal alterations represent the most common affection of haemophilic patients. The combination of the primary haematologic prophylaxis associated with medical therapy, lifestyle modifications, gentle physical activity, and the eventual use of ortheses have to be considered the historical basic principles to prevent the arthropathy or to limit its progression in case of early alterations. In cases of subjects not treated by a primary prophylaxis (patients >30years and middle aged), patients with poor bleeding control (particularly those with inhibitors), and in mild to advanced joint diseases such approaches may be associated to poor outcomes. In this population, the purposes of the treatment are the temporary

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modulation of symptoms or the delay of a surgical procedure [3]. On the other hand, surgery is mandatory to obtain adequate clinical results in cases of persistent symptoms or bleedings.

In the last years, new conservative or non-surgical therapies as injections of drugs with effect on synovial tissue and cartilage have been proposed. Recently, other minimally invasive treatments as Platelet-rich-plasma (PRP) and endovascular embolization have arised interest on the haemophilic population. These treatments, to be considered "modern" conservative strategies, have specific indications in Haemophilia: symptomatic early stages of arthropathy, acute or recurrent synovitis, and late stages of arthropathy in subjects with contrain-dications to surgery, waiting or just delaying a surgical procedure [3, 4].

The following is an overview of the historical and modern conservative orthopaedic treatments.

Viscosupplementation

Viscosupplementation is the intraarticular administration of hyaluronic acid (HA), and has been considered the treatment of choice of early knee Osteoarthitis with clinical results equal to or better than placebo and corticosteroids [5, 6]. Over the years, it has been hypothesized its efficacy in other arthritic joints even not reaching a full evidence but with good clinical outcomes, and an advantageous cost/benefit ratio [7, 8]. Moreover, given the substantially absence of complications, HA injections have been proposed also in other types of arthropathy as Rheumatoid Arthritis and Haemophilic Arthropathy with encouraging results in several target joints [3, 4, 9].

HA is a complex polysaccharide containing glucosamine and glucuronic acid produced by synovial cells, and highly represented in synovial fluid. It is involved in several biological mechanisms, such as joint lubrication, shock absorption, and viscoelasticity of synovial fluid. Theoretic effects of HA on inhibition of tissue nociceptors, stimulation of endogenous hyaluronan, direct anti-inflammatory effects, and inhibition of matrix metalloproteinase activity, have been demonstrated *in vitro* and *in vivo* over the years [6]. Degenerative joint diseases are related to modifications of HA concentration causing a reduced viscoelasticity of the synovial fluid. By inducing metabolic changes, intraarticular HA showed a certain efficacy principally related to the induction of effects as *disease modifying* more than *symptoms modifying drug*.

As widely known, haemophilic arthropathy is characterized by destructured joints, bone deformities, almost complete closure of intra-articular spaces, and significant malalignment. In most cases, typically in younger patients,

radiological aspects do not necessarily correspond to the clinical situation, thus involved joints are modestly painful, with little limitation in ROM, and fair flexion contractures. In these cases, surgery is usually not recommended. However, symptoms may be not tolerated, or poorly controlled with drugs and/or physical therapy, so further treatments are needed. Viscosupplementation may be considered one of the most indicated approaches given the ascertained improvements on pain reduction and functional abilities. Moreover, as mentioned before, it seems that this approach may ensure a delay for more invasive procedures even maintaining unmodified the joint from an anatomical and radiographic point of view [3, 4].

Fernandez-Palazzi *et al*. were the first authors to hypothesize the effectiveness and safety of HA in Haemophilia. In their latest report 25 subjects underwent viscosupplementation with a mean follow-up of about 2 years. The majority of patients reported satisfactory and persistent improvements, with only 10% requesting further treatments [10]. Wallny *et al*. reported their experience of viscosupplementation in knees of 20 haemophilic patients with good clinical results in 14 subjects and no complications at 2-years follow-up [11]. Athanassiou-Metaxa *et al*. reported only partial results in a population of eight children affected by haemophilic arthropathy treated with injections of HA and Rifampicine. In both groups, the authors noted several withdrawals related to low compliance, and complications not tolerated by too young patients particularly after rifampicine injections [12].

Carulli *et al*. reported the first prospective series of 46 haemophilic patients affected by arthropathy in elbows, knees, and ankles undergoing viscosupplementation and evaluated at a long-term follow-up [3]. More than 60% of them was in secondary prophylaxis and affected by severe stages of arthropathy (Petterson score>9). Administration protocols consisted in 3 to 5 injections of low molecular weight HA in sterile setting with 1–4 weeks intervals. All subjects were evaluated by the Visual Analogue Scale (VAS), the World Federation of Haemophilia score (WFH), and the Short Form-36 (SF-36). All patients completed at least two cycles of HA injections, 6 patients received three cycles. At a mean follow-up time of 6.3 years no adverse effect was recorded and almost all the patients reported significant improvements in pain control, joint function, and quality of life at 6 months follow-up. The best effects were achieved after the first HA cycle with respect to the others. At the long-term evaluation, 6 of the 24 patients with knee arthropathy needed surgery for persistent pain and functional impairment that injections temporarily limited in a period from 2 to 4 years after the first HA cycle (3 TKAs, 2 arthroscopies, 1 high tibial osteotomy). One patient among 22 affected by ankle arthropathy referred no effects requiring an ankle replacement, while the remainders reported satisfactory outcomes. All patients

CHAPTER 9

Lifestyle Strategies and Physical Therapy

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Abstract: Haemophilia is a condition that has to be kept under full control. A "3 M's" approach aiming to the patient's Mindfulness, Muscles and physical activity Maintenance is nowadays suggested. In association, an appropriate program of physical therapy with strategies fitting all needs and abilities of patients is mandatory and reasonable, particularly when acute or chronic musculoskeletal affections occur.

Keywords: Haemophilia, lifestyle strategies, Physical therapy.

LIFESTYLE STRATEGIES

In affective neuroscience it is common to quote an African proverb that says: "it only takes one woman to give birth to a child, but it takes a whole village to bring up that child". This same proverb can apply to hemophiliac children, who have the same need of friendship, emotions, incitements and childhood experiences than any other child in the world. Their only specific characteristic is their tendency to bleed. They will still grow, learn and have the same culture such as any other child, and they will become totally grown up adults only if they will have the opportunity to interact with their own environment just like any other child [1].

At some time in the '70s, for a month per year, the Olympic fields close to a Comprehensive Care Haemophilia Center, in Pisa, Italy, were opened to young Italian and European haemophiliacs. These teenagers had the opportunity to run, jump and test themselves in the most competitive sports in order to strengthen their body along with their self-esteem. This experience lasted almost one decade and allowed us to understand that Haemophilia requires understanding, adequate therapies, and commitment, but that it also allows a remarkable muscular

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development together with an outstanding social integration. Most of those teenagers, today, are active and graduated adults, many of which have become head of a family [2, 3].

So, which are the steps to take once the diagnosis of Haemophilia has been achieved? We suggest the 3 M's Approach to Haemophilia, as follows.

Mindfulness: "fully control the Haemophilia instead of letting it control you";

Muscles: "a harmonious physical development decreases the risk of haemorrhagic events whilst it increases self-esteem and socialization";

Maintenance: "an adequate physical activity needs to be pursued and maintained for the whole lifespan in order to enhance patients' lives and joints".

Mindfulness

In order to reach the first target of our program, it is important to deepen the knowledge of Haemophilia itself by speaking with the Reference Center doctors. This is due to be informed and have questions answered to, as well as obtaining a precise diagnosis (A or B, severe, moderate or mild Haemophilia). It is important to be aware that with the same level of factor, clinically milder forms exist, and these are detectable by careful observation of the child, the only person who will show us the clinical phenotype. It is also important to read about Haemophilia, bearing in mind that scientific literature is normally revised by many doctors and scientists who filter the many enthusiasms and take into consideration only demonstrated facts. On the other hand, the information found inside the web can be diffused by anybody, so it is important to read only official scientific organizations or patients associations websites in order to avoid unreliable sources [4, 5].

After obtaining appropriate medical information from the Haemophilia Center's health care staff members, the second - and sometimes amazing - step is understanding that you are not alone but that there is an international network ready to support you and provide you with very important information. The WFH (World Federation of Haemophilia) in Canada is committed to provide data, information, therapeutic guidelines or directions of Comprehensive Haemophilia Center of your own area or Nation. This makes possible to meet families of haemophilic children in order to obtain direct reports on the quality of life of their family, as well as to participate to a large number of social events such as summer camps, periodical meetings and even winter holidays! Nowadays haemophilic people rightfully belong to an international community [6 - 8].

Furthermore, it is important to consider that among congenital blood disorders Haemophilia has achieved a high standard of efficacious and safe treatments. As a consequence, also quality of life is definitely better compared to other inherited blood disorders. Over the recent years safer drugs for haemophiliacs have been developed and today long-acting recombinant drugs (rFVIII and rFIX) are available. So, now more than ever before, it is important to maintain a positive attitude towards this pathology and to understand that, with social and therapeutic efforts, it is possible to live a normal life. Comprehensive Care is a team aimed to approach the care and treatment of Haemophilia. The main target of this approach is to give the child the most normal life as possible [9, 10].

During the pre-scholar period we suggest to:

1. Build a solid relationship between the parents in order to take care, in the best possible way, of the characteristic of the child during the most delicate moment of his life, the early childhood;
2. Obtain an accurate and updated knowledge about Haemophilia, as previously said, referring to a Comprehensive Care Center, its members and to families;
3. Be aware that during this period (from the diagnosis to the beginning of primary school) three main difficulties will have to be dealt with:
    a. Avoiding the child's overprotection, in order to not interfere with his normal activities and to not limit his interaction with other children (for example, avoiding to take him to the nursery for fear of injuries or uncontrollable bleedings). Considering that we are next to commercialize second-generation long-lasting drugs, probably with non-intravenous injections, and we should certainly avoid provoking more damages with a wrong parents-child relationship than the pathology itself. It is then important to refer to Haemophilia experienced doctors in order to not fall in a harmful iatrogenic overprotection. Having a very clear idea of the family's function is really important during this age: that is, to support a person who is blossoming in order to have, one day, an autonomous individual who has his own family. Do not keep your child in the shade [11]!
    b. Learning how to distinguish intensity and location of traumas in order to decide if the child has to be infused or not. Remember that healthy children are full of energy and have often little accidents that cause bruises. When they start crawling they may hit their head against the coffee table or against its legs, they may get bruises on their bottoms when they fall down whilst trying to stand up. The most dangerous body parts are the inextensible ones, such as the spine and cranium. When the kinetic energy of the bump is strong enough to cause a bruise it is important to infuse the child and bring him immediately to the Hospital or to the Haemophilic

CHAPTER 10

Arthroscopy

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Abstract: Arthroscopy in haemophilic subjects is nowadays considered a procedure associated with good clinical outcomes and a low rate of complications. Once addressed as the minimally invasive way to obtain a synovectomy, to date it is performed for several other procedures, as loose bodies removal and joint debridement. It is also useful as assistance for a mini-open ankle fusion. The modern aim of an arthroscopy in a target joint is to delay a more aggressive surgical approach. Thus, critical are the indications: early to moderate or mild arthropathies, in adult or young subjects after failure of conservative treatments. Knees and ankles are the most arthroscopically treated joints, followed by elbows and shoulders.

Keywords: Arthroscopy, Ankle, Arthrolysis, Debridement, Elbow, Haemophilia, Knee, Loose bodies removal, Paediatric patients, Shoulder, Synovectomy.

INTRODUCTION

Arthroscopy is a minimally invasive procedure nowadays successfully performed in almost all joints, and associated with good outcomes and a very low rate of complications [1 - 5]. A-part from traumatic intraarticular lesions and sport-related injuries, in which arthroscopy is currently considered the gold standard of treatment, this procedure is also indicated in cases of degenerative joint alterations as Osteoarthritis to delay a more aggressive surgical treatment. In such cases, the arthroscopic treatment showed however variable short- to mid-term results [6 - 10]. Arthroscopy has been similarly advocated for the initial treatment of inflammatory diseases as Rheumatoid arthritis, mainly for synovial tissue removal and to provide a transitory relief from symptoms [11 - 14].

In haemophilic patients, over the decades, arthroscopy was used as a primary minimally invasive approach in order to delay a further aggressive surgery, specifically for the knee arthropathy [15 - 25]. It has been later indicated for ankles, and recently for shoulders and elbows, with satisfactory outcomes

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[26 - 36]. It is now debated if there is indication for a joint debridement in hips and wrists that on the other side represent very uncommon sites of haemophilic arthropathy.

The following is an overview of the indications, techniques, and complications of arthroscopic procedures in the main target joints affecting patients with Haemophilia.

INDICATIONS & CLINICAL SETTINGS

The most frequent indications are: joint debridement, synovectomy, removal of loose bodies (osteochondral or meniscal fragments), meniscal alterations, treatment of chondral lesions (Figs. **1** and **2**).

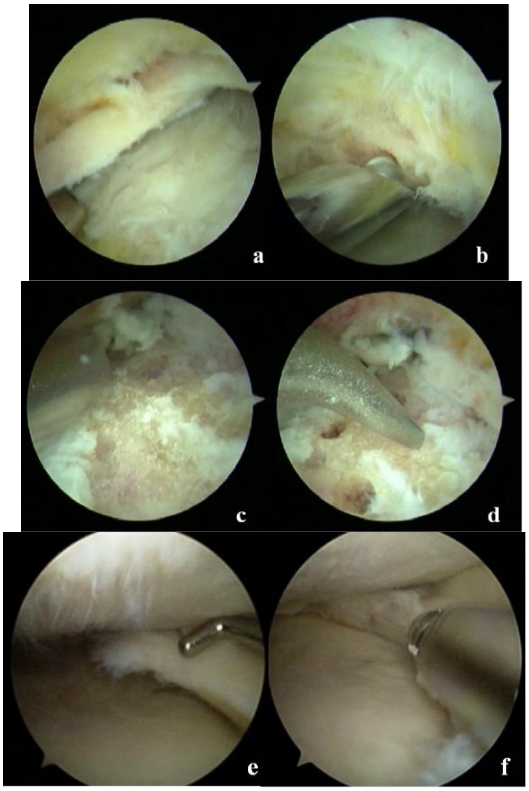

Fig. (1). Unstable ostechondral fragment of the anterior lip of the tibial side of an ankle of a 28-years old haemophilic patient with inhibitors (a) and its removal by a burr (b). Chondral lesion of a talar dome in an ankle of a 31-years old haemophilic subject affected by Haemophilia B (c) treated by shaving and microfractures (d). Global alterations in a knee of a severe Haemophilia A patient (e) managed by debridement (f).

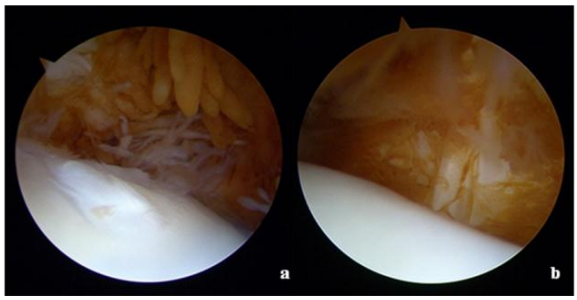

Fig. (2). Chronic hypertrophic synovitis in the lateral aspect of the ankle of a 20-years old patient affected by Haemophilia A (a). Synovectomy by shaver and radiofrequencies (b).

In ankles, arthroscopy is very useful to assist a mini-open joint fusion that represented a step forward in this surgical technique (See Chapter 13) [31, 33]. Moreover, also tendon release or repair, arthrolysis for flexion contractures after recurrent bleedings or related to previous fractures are in selected cases indicated [35, 37]. Paediatric patients with severe arthropathy or recalcitrant bleedings may be successfully treated by arthroscopic procedures associated with a very low psychological and physical impact [27, 28]. Finally, arthroscopy may find a role in the treatment of specific sequelae after joint replacements as stiff joints (typically after knee or ankle replacements), and for the management of its intraarticular complications as arteriovenous fistulae or portals haematoma [38, 39].

SURGICAL TECHNIQUE

As for other types of surgery in Haemophilia, the preparation of an arthroscopy requires a multidisciplinary planning, and specifically a tailored haematological prophylaxis. Perioperative doses of clotting factors are generally similar to other more aggressive procedures, as the high risk of bleeding associates particularly for synovectomy [35, 37]. General anaesthesia and standard antibiotic prophylaxis are required. Tourniquet is generally used to allow a better and clear visualization of the joint.

An arthroscopy with two (ankle, elbow) or three (shoulder, knee) portals is generally accepted as the standard approach to ensure a global visualization of joint space. However, accessory portals are required in case of loose bodies removal and synovectomy [35, 40 - 43].

Standard knee portals are the superomedial, anterolateral, and anteromedial. Posterolateral and posteromedial (transseptal) portals have been performed in haemophiliacs to ensure a full synovectomy [35, 40, 41]. The use of drainages are suggested but not always applied [35]. In the ankle the anteromedial and

CHAPTER 11

Total Knee Arthroplasty

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Abstract: Total Knee Arthroplasty is one of the most performed procedures in the haemophilic population. Several series have been released over the last decades: despite good clinical outcomes, high rates of complications such as infection and loosening have been reported. Such complications have been mainly related to co-infected patients (HIV-positive) and subjects with inhibitors frequently affected by uncontrolled bleedings. Moreover, almost all arthroplasties have been performed using standard cemented Cobalt-Chrome knee implants and generally high constraints to ensure the stability of the prostheses. Recently new biomaterials with a better tribology and implants with less constraints have been used in haemophiliacs with encouraging results. The present mean survivorship is more than 90% at a mid-term follow-up while it was about 82.5% (range: 68%-96%) in the period '70-'90s. Dedicated multidisciplinary teams, appropriate bleeding management, and modern modular implants may ensure even better outcomes than the last decades with rates of success and complications very close to those of the non-haemophilic population.

Keywords: Haemophilia, Knee arthropathy, Oxidized zirconium, Total knee arthroplasty, Tribology.

INTRODUCTION

Total Knee Arthroplasty (TKA) is the most common surgical procedure performed in haemophilic patients. Since the very first releases focused on the surgical treatment of haemophilic patients published in the late '70s, TKA demonstrated good clinical results with dramatic improvements in the functional ability and daily life activities [1, 2]. However high rates of complications were reported. The clinical success of TKA in Haemophilia has been related to several facts: the functional recovery of a joint normally submitted to high forces and torques, in particular in patients affected by simultaneous arthropathy of elbows, hips, and ankles; the correction of the typical malalignment between femur and tibia affecting the gait ability of these subjects; the significant reduction of

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bleedings of this target joint after the wide synovectomy usually performed during TKA [3, 4]. However, at a short follow-up, high percentages of complications and sequelae have been recorded [2, 3, 5 - 16]. Historically, the most common complications after primary TKA in Haemophilia have been represented by infections and aseptic loosening. Postoperative infections have been associated to co-infections, mainly to HIV, that was unfortunately very common after blood transfusions between ’80s and ‘90s in haemophilic subjects [3, 10, 13]. On the other hand, aseptic loosening of TKAs have been frequently reported after postsurgical haemarthroses mostly related to difficult or uncontrolled bleeding management and the presence of inhibitors [3, 8, 10, 12, 13].

During last decades, modern bleeding management and perioperative prophylactic strategies in combination with multidisciplinary teams dedicated to coagulative disorders, and advanced surgical techniques and knee systems have significantly improved the clinical outcomes and reduced the postoperative complications. The last series reported with a mid- to long-term follow-up witness these substantial improvements [2, 4, 17 - 29].

CLINICAL SETTINGS AND INDICATIONS

Most of haemophilic patients suffer of a knee arthropathy given its large amount of synovial tissue representing the main target of bleedings [30]. The clinical features of a knee arthropathy are generally: pain, swelling, haemarthrosis; deformity, progressive malalignment; flexion contractures and loss of range of motion (ROM); loss of muscular masses; alterations of gait and limitation of the daily life activities. The more the number of bleedings, faster is the progression of arthropathy; in a similar manner, earlier haemarthroses are associated to a more severe arthropathy. However, different stages of arthropathy may be treated differently on the basis of the severity of the disease. Presently, early detection of the arthropathy and strategies of prevention of its worsening have reduced the incidence of severe patterns of diseases. Thus, surgery and particularly TKA are not considered the only options of the modern treatment of the haemophilic arthropathy (see Chapter 8) [4, 31]. During the decades several classifications have been proposed to evaluate the severity of arthropathy in order to associate the better orthopaedic management. The most used clinical scores are the Gilbert score [32] and the Haemophilia joint Health score [33]. From a radiologic point of view, the most used are the Arnold-Hilgartner classification [34] and the Petterson score [35]. Other well-known and widely diffused scores as Short Form 36, WOMAC, and Knee Society Score have seldom been used but are not validated for Haemophilia [36 - 38]. Radiographic-based classifications are particularly useful to plan any strategy of treatment. Rather similar, they have been equally used in several series released over the years in literature. TKA is usually

indicated in advanced stages of disease corresponding to stages IV and V of the Arnold-Hilgartner classification, and with values from 9 to 13 of Petterson score [4]. Such stages usually correspond to the following clinical features: disabling pain unresponsive to medical treatments; severe deformity associated with flexion contractures (>15°), loss of ROM, and poor functional ability; tendency to bleedings even a close and tailored haematologic protocol; poor or unsatisfactory quality of life [3]. Actually, any of these features would represent a relative indication to TKA in a haemophilic patient; however, an association of various aspects may provide a strong basis to undergo a TKA. Nonetheless, it is mandatory to consider the very young age of patients affected by this arthropathy that may represent a reason to delay any invasive surgical procedure before an attempt of conservative approach [3, 4].

SURGICAL TECHNIQUE, CHOICE OF IMPLANTS, AND FIXATION

When approaching a case of haemophilic arthropathy of the knee, it is necessary to keep in mind that surgery is not a standard procedure. On the contrary, as for other specific diseases like rheumatoid arthritis, TKA in Haemophilia is a technically demanding surgery. Preoperative settings has to be carefully prepared by dedicated figures, as anaesthesiologists, haematologists, infective disease specialists, and skilled nurses. Haematologic protocols and storage of adequate quantities of recombinant or clotting factors have to be planned days before surgery. TKA should be scheduled in the morning and not in the afternoon. A central venous catheter is necessarily needed for the continuous infusion of FVII in patients with inhibitors. Prevision of blood bags for transfusion, urinary bladder catheter, and general anaesthesia are generally required. Furthermore, it is mandatory in our opinion for a modern management of such cases, a second-level antibiotic prophylaxis, strongly suggested both for the high risk of infections in Haemophilia and the high frequency of co-infections. Aminoglycosides and glycopeptides are efficient, wide spectrum, and diffused antibiotics useful to cover the extensive bacterial variety related to these cases [4]. Pneumatic ischemia of the leg is generally obtained after antibiotic administration. However, several series have been released reporting knee replacements conducted without tourniquet but with brilliant outcomes and rates of complications similar to other experiences [22, 26]. Both options have advantages and disadvantages, thus the use or not of the pneumatic tourniquet is a choice of the surgeon and his team depending on their experience.

Preoperative planning is usually difficult to be performed in haemophilic patients given the severe deformity and shape of bones, and the presence of adhesions and pseudocysts (Fig. **1**). The level of bone cuts, sizing of components, use of wedges, cones, offsets, and stems, and the level of constraint are generally intraoperative

CHAPTER 12

Hip Arthroplasty

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Abstract: Hip arthropathy in patients with Haemophilia may be disabling. In early stages a conservative treatment may be useful, as in late stages a Total Hip Arthroplasty is indicated. During the '80s and '90s clinical outcomes after a hip arthroplasty were variable given the use of first generation cemented implants, and the significantly high rates of complications, as for other types of surgery. In the last decades modern cementless implants with high performing materials and less invasive surgical techniques have been introduced with expected improved results. Recently several series have been reported with very satisfactory outcomes, and longer survival rates of implants with respect to the past. A combination of multidisciplinary teams dedicated to haemophilic subjects, the use of modern cementless implants, and less invasive surgical approaches may represent the key to achieve good outcomes, fewer complications, and better prosthetic survivorship in such difficult patients.

Keywords: Ceramics, Ceramic on polyethylene coupling, Cementless arthroplasty, Total hip arthroplasty.

INTRODUCTION

Hips are not typical target joints of bleedings induced by Haemophilia, given the paucity of synovial tissue. However, the involvement of the hip induces a significant impairment in haemophilic subjects similarly to other joints affected by arthropathy. Several conservative approaches have been reported during recent years with high rates of clinical success before surgery (see chapter 8). Most of these approaches are indicated for the early stages of arthropathy of knees, elbows, and ankles: the main target of treatment in such joints is effectively the synovial tissue [1 - 3]. Unfortunately, these strategies have not shown similar effects in the hip, thus only a Total Hip Arthroplasty (THA) is considered useful, as reported by several series [4 - 6]. Historically, outcomes of hip surgery in haemophilic patients have shown acceptable rates of success, despite the high risk of complications related to comorbidities, mostly coinfections (HCV, HIV), liver

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disease, and septic or aseptic loosening [7 - 10]. Such undefined results have been mostly related to the type of available implants (first-generation cemented implants), and to the difficult management of haemophilic patients before the introduction of the modern substitutive haematological therapy. Moreover, the lack of an actual multidisciplinary approach to such rare disease in those years implicated a further risk of failure.

In the recent years, several larger series of haemophiliacs undergoing THA with modern implants and followed by dedicated teams have been reported: excellent outcomes and transcurable rates of complications have underlined the crucial steps to achieve an ideal balance between clinical results and such demanding surgery in haemophilic patients.

INDICATIONS, CLINICAL SETTINGS, AND SURGICAL TECHNIQUE

As before mentioned, late stages of hip arthropathy in Haemophilia have to be treated by THA. A very little room is left to the conservative (medical) treatment: this has to be reserved to early stages [11]. THA may be addressed and planned as other major surgical procedures. General anaesthesia, antibiotic prophylaxis with appropriate antibiotics, tailored substitutive haematological prophylaxis, and close multidisciplinary perioperative evaluation are the basic procedures (see chapter 11).

Over the years, THA in haemophiliacs was performed by two main surgical approaches: lateral and posterolateral approach. As for hip Osteoarthritis, both have advantages and drawbacks, but the most important factor is surely the surgeon's experience. It is well known that the lateral approach is easier and safer for the lower risk of postoperative instability with respect to the posterolateral access. On the other side, the posterolateral approach is more conservative and no muscular impairment is left after surgery compared to the lateral access, where a limp due to abductor muscles deficiency may be present [12, 13].

The other key element is the choice of implant. For decades all THAs were cemented and with metal small-diameter heads, coupled with PolyEthylene (PE). Also in Haemophilia this represented for years the main option [4 - 10]. Later, few experiences with Metal-on-Metal (MOM) cementless THAs were reported with variable results [14]. Recently, series with cementless Metal-on-PE (MOP) or Ceramic-on-PE (COP) have been reported with consistent follow-up periods and satisfactory outcomes [15 - 19]. Given the young age of haemophilic patients (often <50years) it is nowadays reasonable to use cementless MOP or COP implants, for two main reasons: first of all, a young patient has higher functional requests, and an implant with a more favourable tribology and an expected low wear is desirable. Moreover, young subjects will surely undergo a revision for any

reason in the future: a cementless THA will be easier to be removed with respect to cemented components [11].

Several series with modern short stems in Osteoarthritis have been reported, whereas no similar experience was presented in Haemophilia. A single series with such type of stems was successfully published at a medium-term follow-up with comparable results to standard femoral components [11].

Some technical aspects of THA in Haemophilia deserve a detailed analysis. Easy is to ensure an adequate limb length in modern THA: however, rarely a haemophilic patient shows an isolated hip arthropathy without any other involvement of target joints. Generally hard is to obtain such results when a multiple joints involvement is present. Flexion contractures of both knees, secondary scoliosis due to chronic postural changes, stiffness of ankles, and compensatory pelvis tilting are frequently present, creating an objective impossibility to realize an adequate length and an ideal hip centre restoration. Nevertheless, rarely a relative limb length discrepancy is source of pain or complaint by haemophiliacs [11].

Drains are generally used and removed between 12 and 24 hours after surgery. Laboratory samplings of deficient factor are usually performed every day for the first days and after a week in case of actual necessity to progressively diminish the doses of the haematologic drugs. Tailored rehabilitative protocols and dedicated physical therapy are mandatory to achieve an early recovery and muscular tone after THA. An *in-patient* rehabilitative period should be considered in order to allow a close monitoring by the dedicated multidisciplinary team. Specific principles of rehabilitation after THA in haemophilic patients will be discussed in another section (see chapter 16). As for TKA (see chapter 11), basic rehabilitation protocols after a hip replacement in haemophiliacs are: tailored pain management over all the postoperative period; exercises sessions after the infusion of deficient factor; early rehabilitation by passive mobilization without adduction and excessive intra and extrarotation of the hip; isometrics exercises; progressive recovery of weight bearing and gait exercises with canes or crutches respecting the postoperative pain.

Methods of objective evaluation of THAs in haemophiliacs do not differ from other type of patients. DeLee's and Charnley's criteria for cups positioning [20], Gruen's method for the analysis of radiolucency lines and osteolysis [21], and Brooker's classification for postoperative periarticular calcifications [22] are the main tools to evaluate the follow-up and the long-term survival of a hip replacement. The only subjective method applicable for haemophilic subjects is the Haemophilia Joint Health Score (HJHS) [23], that represents the most used

CHAPTER 13

The Management of Foot and Ankle Arthropathy

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Abstract: The primary prophylaxis is the best way to protect haemophilic patients from synovitis and arthropathy in foot and ankle. By the replacement of the deficient factor, haemophiliacs requiring orthopedic surgery of the foot and ankle may successfully and safely undergo such type of surgery. Radiosynovectomy is a very effective procedure able to induce the decrease of frequency and intensity of bleedings related to synovitis. On average, the number of haemarthroses may diminishes up to 65%. If three consecutive radiosynovectomy procedures, repeated at six-month intervals, fail to lessen the synovitis, arthroscopy should be performed. In such cases, large osteophytes may develop on the anterior aspect of distal, causing severe pain and impingement. Open or arthroscopic osteophyte removal (queilectomy) should be considered. Achilles tendon lengthening in cases of fixed equinus deformity represents another common procedure in haemophilic subjects. In the case of advanced haemophilic arthropathy of the ankle, the first option is the arthroscopic debridement. In severe cases three further options are available: ankle distraction by means of external fixation (arthrodiastasis), ankle fusion (tibiotalar and/or subtalar), and total ankle replacement.

Keywords: Ankle fusion, Arthropathy, Arthroscopic synovectomy, Conservative treatment, Chemical synovectomy, Foot and ankle, Haemophilia, Rehabilitation, Radiosynovectomy, Removal of osteophytes, Surgical treatment, Total ankle replacement.

INTRODUCTION

In haemophilic patients, the foot (mainly the subtalar joint) and the ankle (tibiotalar joint) are prone to bleedings starting from the age of 2 years, resulting in foot and ankle haemophilic arthropathy [1](Figs. **1** and **2**).

Several deformities affect the tibiotalar and subtalar joints: fixed plantar flexion, related to alteration of the anterior region of the ankle; varus hindfoot, due to a malalignment of the subtalar joint; and ankle valgus rotation, caused by an

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overgrowth of the distal tibial epyphisis during adolescence or progressive arthropathy during maturity [1 - 4]. These conditions may start after a single or recurrent hemarthroses, and are often extremely painful: adequate treatments may induce a full correction of the affected joint. The result of this progression is an antalgic position in equinus or plantar flexion, that eventually becomes fixed.

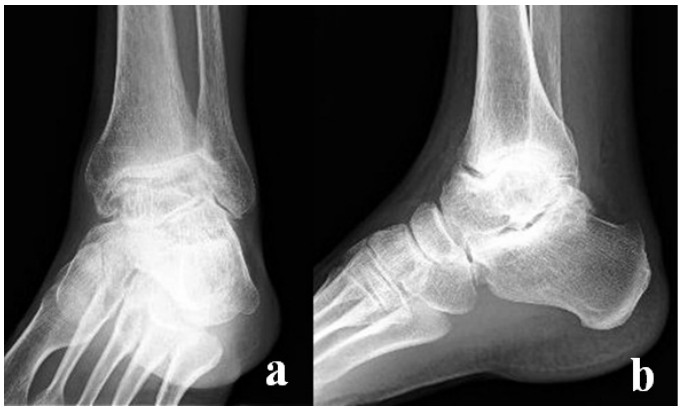

Fig. (1). Radiographs of a haemophilic patient showing severe arthropathy (narrowing of the joint space) of the tibiotalar and subtalar joints: (a) anteroposterior view, (b) lateral view.

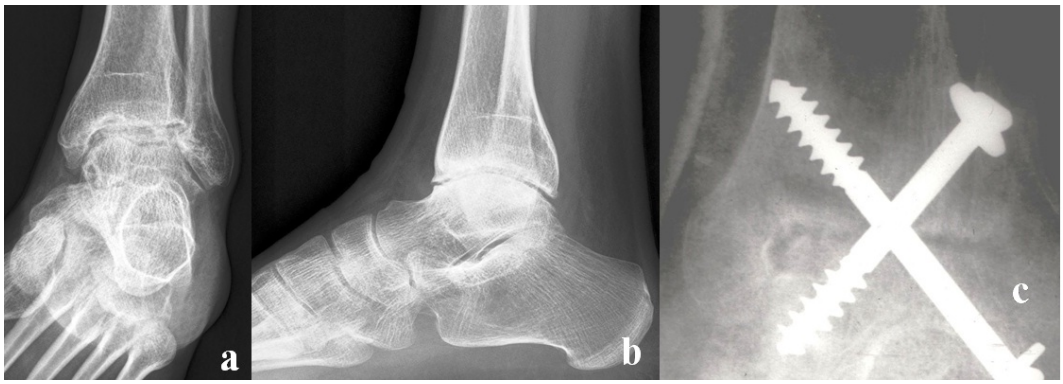

Fig. (2). Radiographs of a haemophilic patient showing severe arthropathy (narrowing of the joint space) of the tibiotalar joint. A tibiotalar fusion by means of two crossed screws was performed due to intense ankle pain: (a) anteroposterior and (b) lateral preoperative radiograph, (c) anteroposterior postoperative view.

Tibiotalar joint is often the first target joint in Haemophilia, with onset of joint bleedings as children start to stand and walk. Advanced ankle arthropathy is common in patients affected by severe Haemophilia since the early adulthood [4 - 8]. Abutting anterior exostoses on the distal tibia and talus usually develop and are associated with equinus deformity [7]. Growth asymmetry can result in a lateral tilt of the distal tibia and valgus malalignment. Patients complaining mild to moderate pain are successfully treated by ankle orthoses (e.g., stirrup air

splint). Symptomatic and incapacitated patients, on the other hand, may require further procedures as arthroscopic debridement, arthrodesis, or total ankle replacement (TAR) [1, 5, 9].

In this chapter, the most important therapeutic approaches for the management of haemophilic arthropathy of foot and ankle are reviewed.

CONSERVATIVE TREATMENTS

Conservative treatments are represented by: radiosynovectomy (RS), chemical synovectomy, and rehabilitation (physiotherapy, splints, braces, wedge insoles). Such options should always be attempted prior to surgery [1 - 6, 10 - 17].

Radiosynovectomy

RS associated to primary prophylaxis can help to halt haemophilic synovitis. RS is a relatively simple, virtually painless and inexpensive treatment in case of chronic haemophilic synovitis, even in patients with inhibitors. RS finds its rationale in the necrotic effect on synovial tissue induced by intraarticular injections of a radioactive agent (usually Rhenium-186) (Fig. **3**). Radioactive substances have been for many years used for the treatment of chronic synovitis.

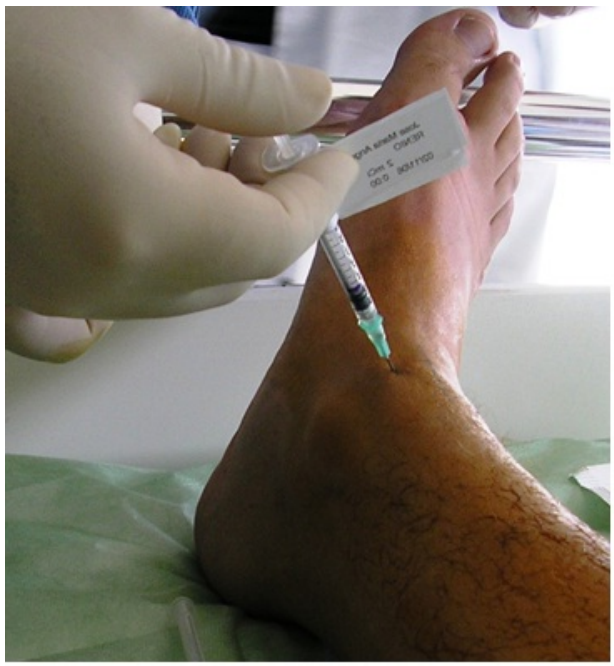

Fig. (3). Clinical view of a radiosynovectomy in a patient with Haemophilia.

CHAPTER 14

Elbow Arthroplasty

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Abstract: The elbow is the second most commonly affected joint in haemophilic patients. As for other target joints, the strategy of treatment starts from a medical management, and in case of failure, more specific approaches have to be chosen. Radioactive or chemical synovectomy represent valid options but may not be adequate in moderate arthropathies. In such cases, surgical procedures as arthroscopic or open synovectomy are useful. Advanced haemophilic arthropathy of the elbow may be severely disabling, particularly for younger patients. In these conditions, a total elbow replacement may be a good option. Thanks to modern implant designs and materials, this procedure has shown excellent clinical outcomes and an acceptable survival rate. Nevertheless, it remains a complex surgery and considering the postoperative restrictions and risks, it requires a careful selection of patients.

Keywords: Elbow arthritis, Elbow arthroplasty, Haemophilia, Haemophilic elbow, Stiff elbow, Total elbow replacement.

INTRODUCTION

The elbow is the second most commonly affected joint in haemophilic patients and the most frequent target joint in the upper extremity [1]. Its involvement can be particularly disabling due to its physiological role in positioning the hand in space. In contrast to knees and ankles, however there are limited informations regarding the arthropathy of the elbow in Haemophilia. Longitudinal studies suggest that the arthropathy of elbows may induce severe functional impairments in children since 5 years of age [2]. There is a strong debate on the frequency of the involvement of dominant or non-dominant elbow, even if about half of the patients have a bilateral disease [1, 3 - 5]. The pathophysiology of haemophilic arthropathy starts with recurrent intraarticular bleedings [4], but little is known about the length of the process, frequency, and number of haemarthroses needed to induce the joint compromission [6]. The elbow is exposed to haemathrosis

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firstly due to its anatomical characteristics: it is a diarthrodial hinged joint, as the knee and ankle, with a large amount of synovial tissue, main target of the blood [3, 7, 8]. A concomitant involvement of a joint in the lower legs makes elbow arthropathy more prone to develop disability and symptoms: the use of crutches shifts the elbow from a non-bearing to a bearing one.

CLINICAL SETTINGS AND INDICATIONS

In the acute setting of a haemarthrosis, the joint is swollen, painful, and warm, with limited range of motion (ROM) and strength. The first approach is typically the factor replacement, crucial to induce a partial to full remission. Ice, rest, and pain control are useful to let the elbow returning to a normal condition in days or weeks [9].

Subacute phases of arthropathy are characterized by a persistent joint swelling with decreased motion due to proliferative synovitis. Synovial hyperplasia results in recurrent bleedings. The reduction of such condition is thus the key to prevent recurrence of intraarticular haemorrhages, and the consequent worsening of chondral damage

In chronic stages, haemophilic arthropathy shows osteoarticular changes, cartilage loss, and juxta-articular cysts: ligamentous and capsular fibrosis also develop [10] (Fig. **1**).

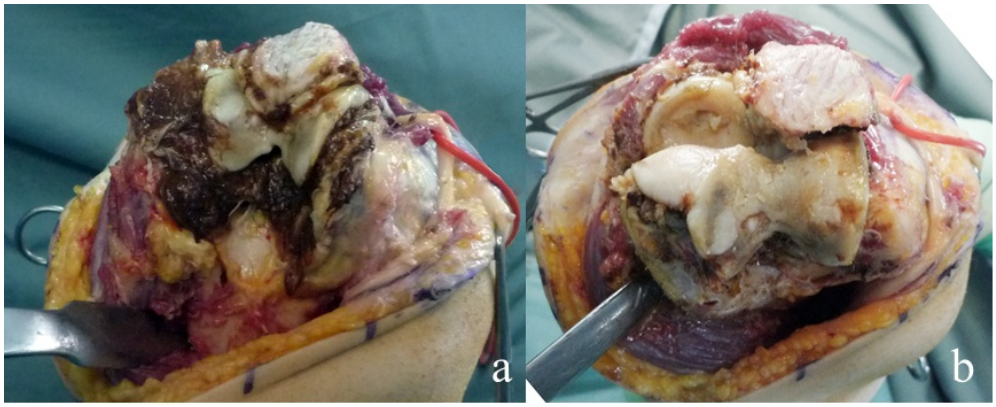

Fig. (1). Intraoperative aspect of the right elbow of a 30-years old haemophilic patient. Synovial proliferation (a) and cartilage erosions (b).

The physical examination of the haemophilic elbow may lead to suspect the presence of synovitis, while deformity and malalignment are evident. Palpation maneuvers help to assess effusion and tenderness. Active and passive ROM is measured and recorded taking care to detect whether limitations are due to a soft

tissue interposition or bony impingement. Typically, the first motion to decrease is pronation and supination due to a radio-capitellum involvement, although an extension gap shows a significant reduction related to flexion contractures [11, 12].

Neurologic and vascular examination should be carefully carried out. Peripheral nerve entrapments are relatively frequent in patients with Haemophilia with rates ranging from 4% to 19% [13, 14]. These conditions are generally caused by an extrinsic compression due to intramuscular, intraneural, or intraarticular haemorrhages or pseudotumor.

From a radiological point of view, joint changes in the elbow vary from 25% to 87% [3, 15]. Findings include enlargement of the epiphysis, osteoporosis, and subchondral irregularities. Radial head enlargement or splaying is commonly observed [16] (Fig. **2**).

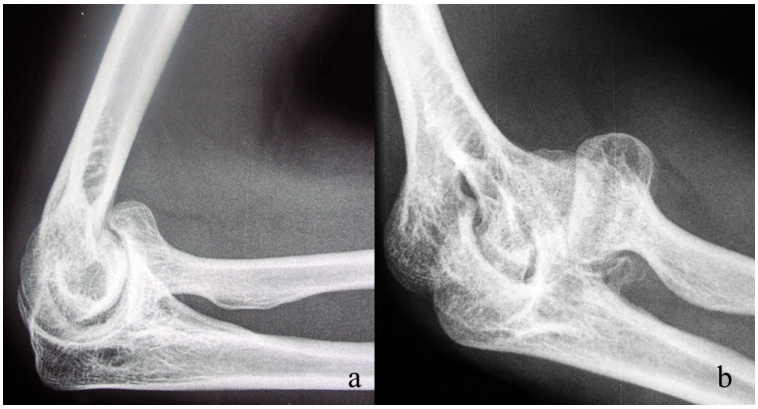

Fig. (2). Radiological signs of haemophilic arthropathy of the elbow: radial head splaying, narrowing of the joint space, articular erosions with chondral irregularity, and subchondral cysts (a). Oblique radial head view showing the predominant involvement of radial side (b).

Obliteration of the capitello-condylar groove, widening of the olecranon fossa, narrowing of the joint, and erosions with cysts are other common radiological signs. Joint deformity, major erosions, and bone fusion develop as advanced findings.

A radiologic study should be obtained, providing AP, lateral, and 45° oblique views MRI is useful to detect early joint changes and synovitis, although it is not routinely necessary. CT scans are helpful for the assessment of bony hypertrophic changes and for the surgical planning (see chapter 6).

CHAPTER 15

Revision Surgery in the Lower Limb of Haemophilic Patients

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Abstract: The management of a failed orthopaedic implant is potentially complex in haemophilic patients. Several critical aspects have to be considered ranging from a tailored haematological care and rehabilitative period to high technically demanding surgical procedures and type of implants needed for the management of the compromised joint. Hip and knee are the most involved joints needing a substitution after a prosthetic failure. All these interventions are delicate and expensive, particularly when the failure is not a simple aseptic loosening but it is represented by an infection or a case with severe bone defects, pseudotumours, and soft tissue mortification. Only specific facilities and specialized teams may be able to manage such these conditions in a safe manner.

Keywords: Ankle arthroplasty, Aseptic loosening, Haemophilia, Hip arthroplasty, Infection, Knee arthroplasty, Revision, Salvage surgery.

INTRODUCTION

A *revision* is defined as the substitution of one or more components of a failed orthopaedic implant. Several mechanisms may induce a failure of a prosthesis, and then needing a revision. The most frequent causes of failure are: aseptic loosening and wear, infection, and instability. Lower more than upper limbs are affected by these clinical issues [1 - 5]. During last decades, given the increasing mean age of the population and the consequent more active general way of life, we are assisting to a worsening of chronic diseases. This is particularly true for degenerative articular pathologies as Osteoarthritis, specifically in hips and knees. The result is that a larger number of surgical procedures (primary total hip and knee arthroplasties) have been recently performed worldwide with respect to the past [1, 4 - 6]. The more the number of procedures, the more the rate of complications: an increasing number of failures are consequently expected [6, 7].

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In the haemophilic population, a joint replacement is generally performed in very young patients, often less than 40 years old. In this setting and differently from adult-elderly subjects affected by Osteoarthritis, the main mechanism of failure of an orthopaedic implant has been considered the septic loosening [8 - 13] (Fig. **1**).

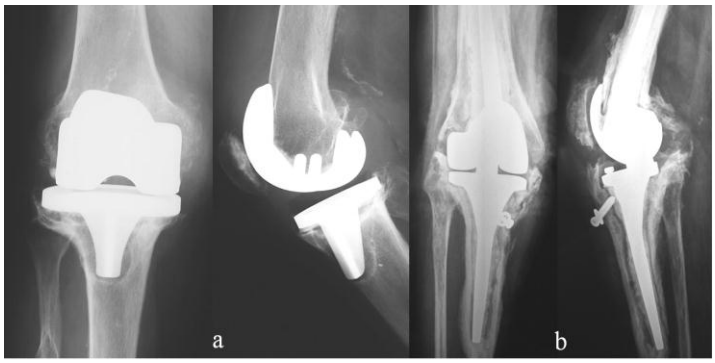

Fig. (1). Comparison between the classic radiologic aspect of a failure of primary cemented knee implants in patients affected by Osteoarthritis (a: aseptic loosening in a 74 years-old female) and Haemophilic arthropathy (b: septic loosening in a 53-years old male).

Several generations of haemophiliacs suffered for infections after orthopaedic procedures with dramatic rates of incidence reported in different series [8, 9, 11, 12]. The second common cause of failures is represented by the aseptic loosening related to bleedings after surgery [8, 9, 11, 12, 14 - 17](Fig. **2**).

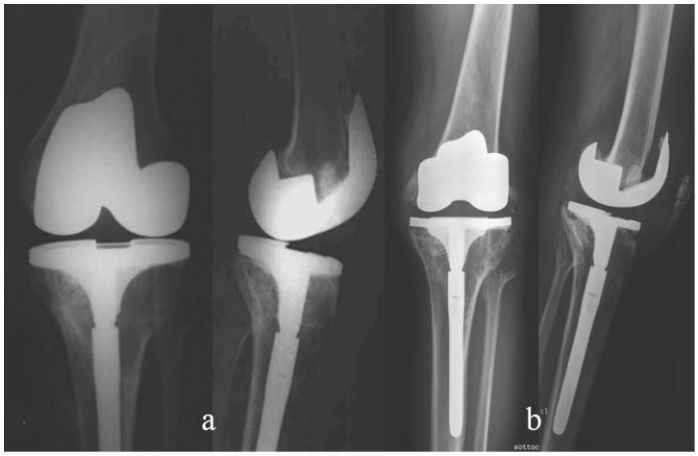

Fig. (2). Typical radiologic aspect of a TKA in a 42 years-old haemophilic patient **(a)** failed after recurrent bleedings 4 years after the index operation **(b)** . Of noting, the cemented femoral component and tibial baseplate, and the cementless tibial keel and stem. This is the modern ideal fixation of components in young haemophilic patients.

No clear data are reported regarding wear and pure mechanical failures. Differently from the past, the modern evaluation of clinical results is based not only on relief from symptoms and restoration of functional ability but also on the longest survivorship of the implants. Thus, it would be necessary to consider also the survival rates of orthopaedic implants in very young patients [18].

RISK FACTORS & CLINICAL SETTINGS

As mentioned, most failures in Haemophilia are related to infections more than aseptic loosening or instability. Several factors are likely involved: a higher prevalence of pre-existing joint damage due to recurrent haemarthrosis before surgery; the consistent risk of subclinical haemarthroses in subjects after a joint replacement; and the growing number of joint replacements performed in this population in the last decades. Historically, co-infections in haemophilic patients have been addressed as important risk factors [19 - 27]. Most failures have been related to co-infections in patients treated by clotting factor products before 1990. The main co-infections have been represented by hepatitis B and C, and HIV.

Hepatitis B and C seem nowadays not to be significant as potential infectious risks, despite the prevalence of hepatitis C has been reported as 80–100% in the haemophilic population and in about 80% of these subjects a chronic hepatitis developed [20 - 23]. HIV infection is considered a strong risk factor for septic sequelae in Haemophilia. Ragni *et al.* reported a survey on the US haemophilia centers to determine the incidence of postoperative infections in HIV-positive haemophiliacs with CD4 counts of $\leq$200 mm^3 undergoing orthopaedic surgery. Among 115 centers a postoperative infection occurred in 10 (15.1%) of 66 patients undergoing 74 orthopaedic procedures within 6 months following surgery [24]. Joint arthroplasty has shown a 10 times higher risk of postoperative infection with respect to other forms of surgery (arthroscopy, osteotomy, joint fusion) with a percentage of 26.5% *vs.* 2.5%. Phillips *et al.* similarly reported a higher risk of postoperative bacterial and opportunistic infections in HIV-positive haemophilic patients undergoing orthopaedic surgery: however no significant difference between the number of CD4 lymphocyte in HIV-positive patients undergoing surgery was found when compared to HIV-positive subjects not undergoing surgery [25]. Moreover, the overall rate of prosthetic joint infection after arthroplasty in haemophiliacs especially if HIV-positive has been reported as higher than the non-haemophilic population [23, 26 - 29]. Thomason *et al.* published a series of 15 HIV-positive haemophiliacs undergoing 23 TKAs with 4 infective failures (2 early, 2 late) at a mean follow-up of 7.5 years [26]. Rodriguez-Merchan and Wiedel reported their series of 26 HIV-positive patients (37 TKAs) with at least 200mm^3 CD4 count at a mean follow-up of 9.6 years. They recorded a total of 28 complications, with 5 failures related to infections

CHAPTER 16

Postoperative Rehabilitation

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Abstract: The proposal of a comprehensive rehabilitation program after major orthopaedic surgery, specifically Total Hip Arthroplasty (THA) and Total Knee arthroplasty (TKA), is a key event in the management of patients affected by haemophilia arthropathy. Rehabilitative protocols should be carried out by a multidisciplinary team. This is a modern approach consists of three main stages: preoperative evaluation and education, in-hospital rehabilitation, and out-patient rehabilitation. The primary purposes are the control of pain, the recovery and maintenance of range of movement, and the muscle strengthening. In-hospital rehabilitation usually starts the day after surgery, using specific protocols in order to gradually counteract joint stiffness and pain. After the discharge haemophilic patients should improve their training with task-oriented exercises. An adequate and individually-tailored rehabilitation program could optimize the result of major orthopaedic surgery, improving the functional ability of haemophiliacs, and resulting in a better quality of life.

Keywords: Continuous passive motion, Haemophilia, Proprioception, Rehabilitation, Total knee arthroplasty, Total hip arthroplasty.

INTRODUCTION

Orthopaedic surgery in haemophilic patients (HP) showed significant advancements after the introduction of factor concentrates [1]. Another key event in the management of such patients was the improvement of a comprehensive rehabilitation program after major orthopaedic surgery, particularly Total Hip Arthroplasty (THA) and Total Knee arthroplasty (TKA) [2]. Some considerations in the postoperative management of HP are mandatory:

- Generally, HP are young and affected by more severe joint alterations than non haemophiliacs [3]. Similarly, in the postoperative setting, HP have more functional requests with respect to the general population undergoing major orthopaedic surgery;

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- Postoperative physiotherapy has several purposes: early recovery of range of motion (ROM), muscle strength, and proprioception [4];
- Reconditioning of motor patterns has to be as much as possible complete in order to improve the functional ability minimizing the risk of future bleeding episodes;
- Postoperative recovery of HP is often limited due to the involvement of several other target joints, particularly in the lower limb [5];
- The best result is achieved by close communication and cooperation between physiatrists, physical therapists, and surgeons, coupled with the generally high motivations of patients The concept of the multidisciplinary team (MT) is crucial [6];
- Also a preoperative relationship between MT and the patient may improve the feeling and influence the outcomes. By this knowledge, the MT has the opportunity to evaluate the functional status, bleeding pattern, and the muscles conditions of the patient [7];
- Treatment goals, timelines, and all aspects of rehabilitation should be discussed before surgery [8].

Postoperative rehabilitative protocols after major orthopaedic procedures in HP have been rarely investigated, due to the fact that Haemophilia is a rare disease, and few centres usually deal with such conditions. The few reported protocols vary from one centre to another [9, 10]. Moreover, rehabilitative protocols have to be specific and tailored for each HP.

The following is the overview of the rehabilitative aspects related to Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA).

TOTAL KNEE ARTHROPLASTY

The knee is the most involved target joint and TKA is a valid treatment for severe, end-stage cases of arthropathy [11, 12]. The medical community agrees on the brilliant outcomes of TKA in terms of pain relief, functional recovery, deformity correction, and patient’s quality of life (QoL) [13 - 15].

The ideal indications for TKA in a patient affected by Haemophilia are persistent pain and impaired function as a result of extensive erosion of the joint surfaces, and a severely restricted range of motion [16](See Chapter 11). Functional impairment, often subjectively referred as 'joint stiffness', is objectively measured by the loss of ROM. Stiffness is defined as an inadequate ROM that results in functional limitations in activities of daily life [17, 18]. Despite all the advancements in surgical techniques, implant design, haematological care, and postoperative management, stiffness continues to be a relatively common complication for haemophilic patients after TKA.

Preoperative ROM is the most important variable influencing the postoperative ROM. Thus, the presence of a significant flexion contracture and/or poor passive flexion is highly correlated with a poor postoperative ROM. Also a preoperative physical and muscular conditioning may improve the functional recovery or, if not performed, predict some limits in the postoperative rehabilitation. As well, an early knee mobilization after TKA is as soon as possible encouraged both in flexion and in extension [19].

It is possible to underline different stages in rehabilitation after TKA in HP: pre-operative evaluation and education; in-hospital rehabilitation; out-patient rehabilitation.

Preoperative Evaluation and Education

During the preoperative assessment, the MT should perform a complete evaluation of all target joints (ROM, muscular strength, local conditions, evaluation scales), discussing the patient's expectations after surgery [2, 20]. In some reviews [21 - 23] several authors concluded that preoperative physiotherapy may not be effective for the outcomes. In other studies, however, individually tailored, multidisciplinary preoperative rehabilitation was suggested to reduce the hospital stay in selected patients with comorbidities or limited social supports [21].

In-Hospital Rehabilitation

After surgery, the first stage of rehabilitation is started directly in the orthopedic ward (Table **1**). The primary objectives are: control of pain, recovery of ROM, and muscle strengthening [19]. In selected cases and depending on the pain, the day of surgery patient could immediately turn on his side and move actively the knee. The patient should also start with ankle flexion/extension exercises. In order to guarantee a correct postural alignment, the horizontal decubitus in the bed is alternated with the semi-sitting position, tilting the head of the bed up to 45°. Pain could be controlled by the use of cryotherapy or painkillers. To prevent bleeding complications, each session of physiotherapy should be preceded by an infusion of the deficient clotting factor.

On the first day after surgery, passive flexion and extension exercises can be performed by the physiotherapist; autonomous active and continuous passive mobilization (CPM) exercises may be realized manually or by dedicated devices. Knee mobilization should start from a limited ROM (10°- 40°) and gradually increased to 0°- 90° in the first week [24]. After TKA, the flexion improves quickly and reaches a plateau within a few months, while the extension requires more time to be achieved [25]. It is crucial that patients understand the importance

CHAPTER 17

Complications of the Orthopaedic Surgery in Haemophilia

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Abstract: The knowledge regarding the management of complications related to orthopaedic surgery in Haemophilia is still limited due to the lack of published data and several concerns about the possible catastrophic damage to patients. A quote of 12% to 17% of haemophilic patients need a hospital admission to undergo orthopaedic surgery and more than one procedure is often needed for some subjects. Complications in haemophilic patients occur from 2% to 66% and are strictly related to the severity of disease, type of orthopaedic procedure, and patient comorbidities.

Bleeding, haematoma, wound complications, infection, inhibitors development, deep venous thromboembolism, and intraoperative fractures are the most frequently reported complications. The management of complications of the orthopaedic surgery in haemophiliacs is a challenging task, requiring complex treatment performed in a highly specialized centre by a multidisciplinary team.

Keywords: Bleeding, Complications, Fractures Haemophilia, Haematoma, Infection, Inhibitors, Orthopaedic surgery.

INTRODUCTION

In recent decades, the availability of safe and effective clotting factors concentrates had a strong impact on the natural history of Haemophilia, reducing the incidence of arthropathy and allowing surgeons to perform a greater number of orthopaedic procedures. Despite the use of the replacement therapy, surgery in patients with Haemophilia remains challenging. Clinical guidance on treatment during orthopaedic procedures in this population are strongly recommended to prevent or minimize any related complications [1]. Many orthopaedic surgeons still hesitate to perform surgeries for haemophilic arthropathy because of the higher risk of complications. However, orthopaedic surgery should be restricted to

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patients with severe joint damage and when conservative treatments have failed [2].

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV), have been mediated by unheated plasma-derived factor concentrates, and discouraged most of the orthopaedic surgeons from performing surgery. Moreover, antiretroviral therapies increased the risk of metabolic syndrome, diabetes, renal insufficiency, and cardiovascular disease exposing patients to additional generic complications [3].

Nevertheless, 12% to 17% of haemophilic patients usually need a hospital admission to perform orthopaedic surgery, and more than one procedure is often requested by several subjects.

Complications in haemophiliacs occur from 2% to 66% and are strictly related to several factors: severity of disease, type of orthopaedic procedure, and patient comorbidities [4, 5].

The management of complications of orthopaedic surgery in Haemophilia is still debated due to the lack of published data and several concerns about the possible catastrophic damages to patients.

The knowledge of preoperative factors affecting the incidence of perioperative complications is crucial to safely perform surgery in such patients.

Surgery must be performed by an experienced surgeon, under a tailored haematological prophylaxis, and in a specialized center, in order to manage the proper daily replacement therapy. This multidisciplinary approach is essential to ensure a surgical success [2].

SPECIFIC COMPLICATIONS OF THE ORTHOPAEDIC SURGERY IN HEMOPHILIA

Bleeding

Bleeding is the most common complication during orthopaedic surgery in haemophilic patients.

A satisfactory control of haemostasis is achieved in most patients but bleeding complications are observed in 3% to 20% of treated patients and it is more frequent in case of major orthopaedic procedures [6 - 8], and in inhibitor than non-inhibitor patients. Published data have demonstrated that a proper replacement therapy can provide an adequate and well-tolerated perioperative and postoperative haemostatic coverage for a variety of major orthopaedic procedures

in patients with Haemophilia. Although a surgical haemostasis can be achieved by the use of tourniquet and infusion of factor concentrates at the adequate dose, our recommendation for surgeons is always to have availability of local intraoperative haemostatic agents (*i.e.* fibrin glue, absorbable hemostatic sponge) [9].

Blood Loss

The decline in haemoglobin levels and transfusion requirement tend to be greater in haemophiliacs than in the general population [7].

Blood loss is often associated with total hip and knee replacements. The median blood loss, and postoperative drainage is reported to be respectively 1350 mL and 500 mL in Total Hip Arthroplasty (THA) and 625 mL and 600 mL in Total Knee Arthroplasty (TKA). The median red blood cell transfusion volume in THA is reported to be 5 U (0-14), and 2 U (0-18) in TKA [10].

The success rate for haemostasis response during and after surgery is very high and the reported results are “excellent” or “good” in major and minor surgical procedures [11].

Haematoma

Haematoma related to arthroscopic surgery has been described in two papers and is considered as a rare event. Arthroscopic surgery may be certainly considered as a low risk procedure associated with satisfactory outcomes. The only relative disadvantage is the poor management of postoperative bleedings and the risk of additional haemarthroses [12]. In 1998, Heim reported two expansive haematomas at the arthroscopic portal and in 1992, he described an arterovenous fistula following a knee arthroscopy [13].

In order to avoid these complications, we recommend to highlight all the arterials, venous, and nervous landmarks by a dermographic marker pen before performing the standard arthroscopic portals.

On the other hand, the incidence of postoperative intraarticular haematoma following a joint replacement is higher (up to 7.7%) than in non-haemophilic population. This complication is usually managed by additional doses of coagulative factors replacement, and a delayed beginning of the rehabilitation. A surgical evacuation is rarely necessary and not always recommended. An accurate monitoring of the evolution of haematoma is necessary to early identify local signs of infection.

CHAPTER 18

Microsurgery and Plastic Surgery in Haemophilia

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Abstract: Microsurgery is increasing popularity among plastic surgeons, creating new alternative solutions for patients that until few years ago only had amputation as final option. Muscles are supplied by several vascular pedicles and the knowledge of their anatomy may allow the use of myocutaneos islands and a rotation on its axis (propeller flap), or a complete detaching from the rest of the body (free flap) and its anastomosis with a recipient vessel to cover soft tissue defects. These procedures are very similar in patients affected by Haemophilia: the only specific issue in such patients is the attention paid to the maintenance of an adequate vascularization that represents the key for the survival of any type of flap.

Keywords: free flaps, Haemophilia, Microsurgery, plastic surgery, propeller flaps.

INTRODUCTION

Patients with haematological disorders usually represent a significant challenge of unappreciated complexity for plastic and reconstructive surgeons. The key for a successful outcome is a close cooperation between plastic surgeon, orthopedic surgeon, haematologist, and infectious disease specialist for a strict follow-up of patients' before and after surgery. This section focuses on the general principles of surgical management of haemophilic patients, pointing out indications, new successful microsurgery techniques, and tip and tricks for such patients. To date, there are no published studies investigating the correct management of haemophilic patients in order to reduce complications and maximize outcomes.

PRINCIPLES IN PLASTIC SURGERY

Regardless of defect's area, size, and shape, the surgeon's task is to choose the correct method for its closure or reconstruction in a single stage. Following the

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so-called "reconstructive ladder", surgeons have to deserve the best repair technique, starting from the simplest reconstructive method, as skin grafts or local tissue transfer, then progressing to more complex strategies, such as pedicled or free flaps. In particular, free tissue transfers can improve patient's expectancy for a normal daily routine by ensuring a full-thickness cover of damaged tissues by transferring well-vascularized tissues, without loss of function from the donator site. In addition, patients very often show a recovery of daily life activities, such as the gait or legs functional ability in the perioperative period, if compared with delayed or no reconstructions.

HISTORY OF FLAPS IN PLASTIC SURGERY

The history of plastic surgery corresponds to the evolution of flaps. Because of the limited knowledge of specific patterns of reliability of blood supply, historically surgeons started to harvest random flap based on strict length-to-width ratios to avoid necrosis, but limiting dimensions and mobility especially for wound coverage in the lower leg. Firstly described by McGregor and Jackson in 1972 [1], axial pattern flap entails the detriment of a main artery to gain better results [2 - 6]. Muscolocutaneous flaps increased their popularity since first description by Ger in 1966 [7] and Orticochea in 1972 [8] because of their reliability [9]. Fasciocutaneous flaps, because of their lack of extension for distal third of the leg coverage [10 - 13], were suggested in selected cases although Ponten in 1981 proved that by including the deep fascia in a cutaneous flap, they could be raised without respecting the length-to-width ratio, even if anatomical basis were investigated later [14 - 17].

The unreliability of fasciocutaneous flap for wound coverage of the lower third of the leg is reported by Chatre and Quaba, with an elevated incidence of necrosis (about 25% of cases) [13].

New impulse to flap design was given by the discovery of *angiosomes*, defined as a well-defined anatomical territory with a complete vascular network supplied by a main artery and vein, partly linked by anastomosis to the surrounding angiosomes [18 - 20].

Taylor and Pan [21] set the first milestone for the use of perforator flaps in the lower leg by proving that a damage to deep fascia creates a new vascular network in all directions. Later works by Koshima and Soeda [22] and Kroll and Rosenfield [23] set the starting point for perforator flaps-based reconstruction.

To reconstruct lower leg and foot, free perforators flap taken from different anatomical regions (such as anterolateral thigh perforator flap [11, 24, 25], tensor fasciae latae muscle perforator flap [11, 26], inferior epigastric artery perforator

flap [27], thoracodorsal artery perforator flap [28 - 30], medial sural artery perforator flap [11, 31]) were considered as first surgical option since reliability and safety of local perforator flaps was proven, as showed in literature.

Perforasomes, firstly identified by Saint-Cyr and his coworkers and later discussed by Geddes *et al*. [32], increased the interest for harvesting new or improving perforator flaps, exploiting their dynamic potential in lower leg [33 - 36]. Due to a strictly connected vessel network [35], the harvest of a single perforator flap stimulates a hyperperfusion, as described by Rubino *et al* [37], allowing larger dimension flaps because of new enrollment of interconnected vessels.

Perforator flaps have many advantages such as: less donor site morbidity, a satisfying blood flow for musculocutaneous flap, restore of the anatomy with like-to-like reconstruction, primary closure (in most of the cases), faster and easier technique compared to free flaps harvest [6, 10, 13, 34, 36, 38 - 41].

Hyakusoku *et al*. [42], in 1991, was the first to develop the concept of propeller flap by using a subcutaneous pedicled flap with a rotation of 90°. Hallock [43], instead, was the first one who defined the term of propeller flap with a perforator flap with a skeletonized pedicle rotated of 180°. Only in 2009, at the First Tokyo Meeting on Perforator and Propeller Flaps [44] was reached the last definition of propeller flap as a perforator flap designed as a skin island with two paddles of various dimensions (equal or different) based on the permitted rotation of the pedicle for at least 90 to 180 degrees. Teo [45] in 2006 meticulously described the proper technique to harvest propeller flaps in lower leg reconstruction.

After first works have been published in literature [11 - 13, 17 - 21, 26, 46 - 50], an increasing number of microsurgeons became interested in pedicled perforator flap, by evaluating perforator arteries, to reconstruct lower leg [6, 10 - 13, 25 - 28, 31, 33 - 37, 39, 41, 44, 45, 51 - 56]. Despite many advantages are present, complication rates of propeller perforator flap and free flaps are similar, mostly due to partial or total necrosis for venous congestion [10, 13, 36, 44, 52, 53, 55]. This problem is partly solved by supercharging the venous network with the suture of a concomitant subcutaneous vein [36, 38, 44, 57].

To improve the chance of an efficient mobility of the flap, Teo suggested to add 1cm to the distance between the distal edge of the defect and the flap [45] and 0,5cm to the width, with the pedicle released from muscular branches for 2cms at least (also around the venae comitantes). To assess the proper vascularization, flap must rest in its original position for fifteen minutes after tourniquet is released.

CHAPTER 19

Haematological Care in Patients with Haemophilia and Inhibitors Candidate to Orthopaedic Surgery

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Abstract: A standard replacement treatment by FVIII or FIX concentrates is in most cases ineffective in haemophilic patients with inhibitors. To overcome this problem, the so-called bypassing agents (BPAs) have been introduced in the market and patients may be efficaciously treated also in the orthopaedic setting. However not all patients with inhibitors need to be treated at the same manner. In a proportion of patients a standard replacement therapy by FVIII and FIX concentrates may be useful for the postoperative period or just for a part of it. Ancillary therapy by tranexamic acid may significantly contribute to the bleeding control while anti-thrombotic drugs seem unnecessary differently from non haemophilic patients. Brand new drugs are now being studied representing a potential actual revolution in the treatment of patients with haemophilia and inhibitors.

Keywords: Haemophilia, Inhibitors, Orthopaedic surgery.

INTRODUCTION

During the last decades, joint replacement has become the gold standard for end stage haemophilic arthropathy. One of the limitation or concern about approaching a surgical procedure in a proportion of haemophiliacs is the presence of "inhibitors", that prevent the efficacy of the standard replacement treatment by FVIII or FIX concentrates (see Chapters 2 and 3).

Significantly more severe arthropathies have been reported in patients with inhibitors [1] and the burden of orthopedic implications on the impact on QoL is more severe in haemophilic patients who have developed inhibitors than in those without inhibitors [2]. This justifies such type of surgery in those patients to

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restore an articular function and improve their quality of life, otherwise very compromised.

Until recent years, major surgery in such patients was seldom performed due to the inefficacy of standard replacement by FVIII or FIX concentrates. Fortunately patients with inhibitors may now be treated by efficacious therapies using the so-called “bypassing” agents (BPAs) [3, 4].

The treatment by BPAs pones further concerns related to the high costs as stated by the COCIS study where it was demonstrated that the management of inhibitor patients was significantly more expensive when compared to the use of rFVIIa either in orthopedic surgery or in severe bleeding episodes [5].

In this chapter we would like to address the medical approach in this sub group of patients with inhibitors candidate to major orthopaedic surgery.

CURRENT CONCEPTS

In the last two decades many surgeries have been performed worldwide mostly using recombinant activated FVII (rFVIIa, Novoseven, Novonordisk, Denmark). More recently also activated prothrombin complex concentrates (aPCC, FEIBA, Baxter Healthcare, Vienna, Austria) have demonstrated good clinical effects. Moreover, both agents have been tested in a sequential manner with positive outcomes [3, 4].

In the recent past, There was a greater concern in planning surgery in patients with inhibitors. The reason was related to the dramatic severity of the arthropathy needing difficult and long reconstructions and the higher risk of bleeding. This strategy was then associated to severe sequelae given the slow but inexorable joint deterioration related to the haemophilic arthropathy in such patients: the late the surgical procedure, the more challenging intraoperative theatre, and the worst the clinical outcome.

To date, nearly 400 procedures using rFVIIa have been reported [3], and more than 200 using aPCC [4]. The first experience of major surgery in patients with inhibitors with BPAs was reported in 1989 by Ula Hedner [6]. Since then the introduction of activated recombinant factor VIIa has allowed a safer elective surgery in subjects with inhibitors. Several pitfalls associated with its use have been however reported: the short half-life, necessitating frequent intravenous injections, and its very high costs. In fact, the administration of rFVIIa is recommended by bolus injection (BI) at short intervals of two hours at the dosage of 90-120ng/kg/bw for the first 24-48 hours after surgery. Progressively, the intervals may become longer and doses reduced. A possible option to avoid such

these aspects may be the use of rFVIIa in continuous infusion (CI) as this way of administration may warrant the same efficacy saving nearly 30% of the product and consequently reducing costs. This approach has been efficaciously tested in several centers, including our institution [7 - 10].

A prerequisite for CI is the stability of the product and the safety of the diluted drug. This has been clearly demonstrated for rFVIIa in previous reports and CI has already been shown to be effective [7, 8]. CI with coagulative factors has demonstrated to provide further advantages: it avoids peaks and troughs; it is cheaper due to lower usage of clotting factor; finally, in the specific case of rFVIIa, it may avoid too frequent administrations. Other advantages are the possibility to associate the antiphibrinolitic drug (tranexamic acid), and to prevent an anamnestic response to FVIII or FIX, which may occur with the other alternative treatments.

Major orthopaedic surgery in Haemophilia is represented mostly by Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA), as mentioned in Chapters 11 and 12. In our personal experience we have reported a THA in two patients with severe Haemophilia A and high titre inhibitors to FVIII using rFVIIa therapy by CI. In one case a failure was reported because of recurrent bleedings, while in the second patient the procedure was successful. Of noting that the total amount of rFVIIa administrated was similar in the two patients (9.93 mg $kg^{-1}$and 9.32 mg kg^{-1}, respectively), but the way of administration was substantially different. The first patient received the therapy for a longer period, but with a lower dosage, while the second was treated intensively for 12 days only. In both subjects, the level of plasma FVII:C was for most of the time above 10 U mL^{-1} (Figs. **1a** & **1b**), which was at that time considered to be the target for optimal rFVIIa efficacy. In our opinion, the crucial point is to obtain a full haemostatic control during the early perioperative phase. For this reason, we usually used high amounts of rFVIIa at the beginning of the operation in the second patient [10]. Starting from this experience we do recommend a maintenance of the FVII:C level well above 10 U mL-1, particularly if there is a significant involvement of soft tissues as usually for standard THA. Saline infusions are useful to avoid local thrombophlebitis at the site of the vascular access. Furthermore tranexamic acid administration seems to produce a better result if given by CI, helping the bleeding control without thrombogenic effects.

In 2003 we have described for the first time a simultaneous THA and TKA in a haemophiliac with inhibitors. The amount of rFVIIa concentrate used (8.57 mg) was similar to that normally used for a single joint replacement. Also in this case the use of continuous infusions allowed an easier administration, and further contributed to the reduction of related costs [11].

CHAPTER 20

Miscellaneous

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Abstract: Haemophilia as other complex diseases deserves several peculiar orthopaedic conditions that may not be classified in specific routinary categories. A multidisciplinary approach and a full information of the patients may be useful to treat such usually difficult cases. An overview of unusual clinical settings regarding joints, bones, and muscles are reported. Finally, a brief summary of the gene therapies and novel approaches is presented.

Keywords: Antithrombin, Adeno-associated virus, Bilateral joint replacement, Gene therapy, Haemophilia, Haematoma, Iliopsoas, Periarticular ossifications, Pseudotumours, Simultaneous bilateral joint replacement, Surgical treatment.

INTRODUCTION

As for other complex diseases, Haemophilia offers several uncommon orthopaedic conditions that may involve joints, bones, and muscles, and not belonging to specific categories. Such conditions may be sometimes challenging and no help is usually found in literature. Thus, only a dedicated and experienced multidisciplinary team may decide with the patient to undergo a novel type of treatment.

Moreover, the future direction of the treatment of Haemophilia and its complications (as arthropathy and musculoskeletal alterations) will surely be its complete prevention. This goal will be achieved by novel approaches as gene therapy and non-factor solutions that in the last two decades have been studied by preclinical experiments and translational researches. Encouraging outcomes are emerging, confirming their theoretical validity.

The following is an overview of several rare conditions and their related treatment, and a brief summary of the gene and other novel therapies recently proposed.

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JOINTS

Multiple Joint Replacements

Some decades ago, it was unimaginable to think about a simultaneous bilateral Total Knee or Total Hip Arthroplasty (TKA, THA) in patients affected by Osteoarthritis. Similarly, it was considered unsafe to perform a combined TKA and THA in such subjects. Later, multiple replacements have however become safe and feasible in selected cases given the gross improvements in surgical and anaesthesiologic techniques, tailored substitutive therapies, and closer perioperative care of patients [1 - 3]. Many osteoarthritic patients may be efficiently treated with rates of complications and functional outcomes similar to unilateral or staged procedures, but with lesser costs [3].

In Haemophilia, this type of experience has been faced in very few cases and in specific centers, but associated with a significant rate of complications and variable clinical results [4, 5]. Reichel and colleagues reported about 6 cases treated by a one-stage bilateral TKA: they finally suggested strict indications due to high risk of intra and postoperative complications [4]. Frauchiger and colleagues reported a single case of a simultaneous bilateral TKA in a 40-years old haemophilic patient with inhibitors who developed, after surgery, an aneurysm of the popliteal artery that requested a further surgical procedure [5].

A better knowledge of the coagulative profile of patients, a strong motivation showed by some subjects (asking the faster resolution for their orthopaedic problems), a rigorous selection of candidates to such procedures, and a full information about risks and benefits have led to the opportunity to perform multiple arthroplasties (Fig. **1**). Even if these procedures do not represent the rule and may be realized only in selected subjects, a step forward in the management of haemophilic patients has been made. Just few years ago, such attempts in rather larger series have been reported with better outcome [6, 7]. Mortazavi *et al* presented a series of 8 haemophiliacs safely undergoing bilateral TKAs with half the costs of a staged procedure [6]. Thès *et al* reported a cost-effectiveness analysis related to 5 patients candidate to a simultaneous bilateral TKA compared to 12 patients undergoing a staged bilateral TKA: similar outcomes but lesser costs were recorded for the bilateral cases [7]. In a single case, a simultaneous TKA and THA has been reported with clinical success in a haemophilic patient with high titer of inhibitors [8].

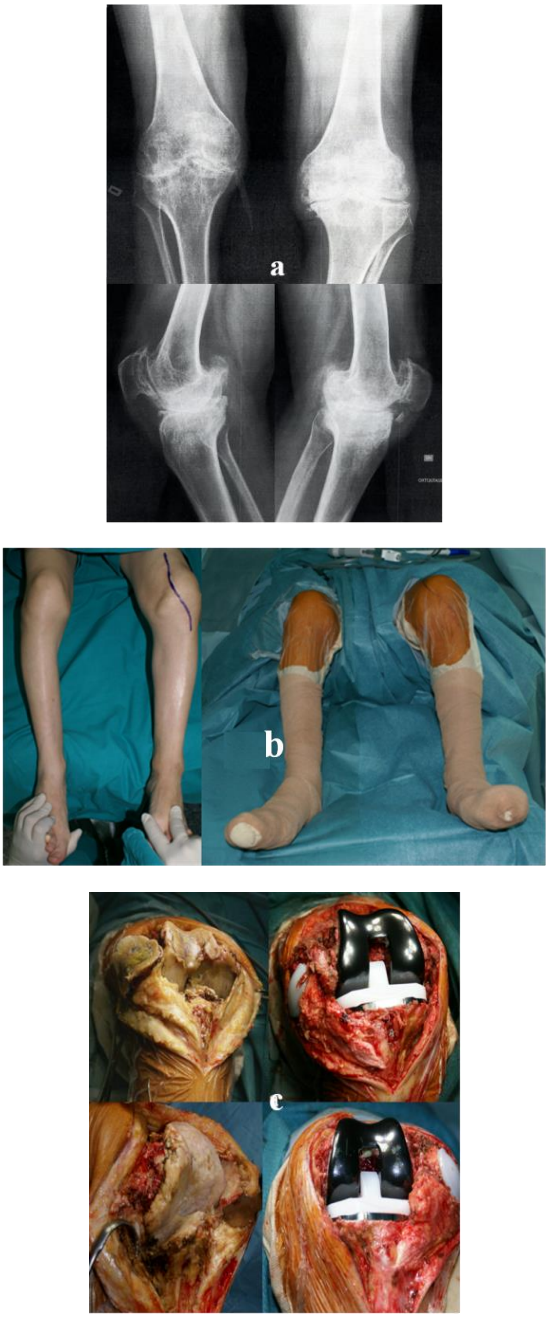

Fig. (1). Simultaneous bilateral TKA in a 51-years old haemophiliac affected by severe Haemophilia A. X-rays (a) and clinical (b) aspect of his knee (Petterson score 12 and 13). Intraoperative pictures before and after the implant of a modern high-tribologic properties TKA (c).

CHAPTER 21

Final Considerations

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INTRODUCTION

Despite significant improvements in Haemophilia care, joint disease remains an issue for many patients. Most bleeding episodes occur in the musculoskeletal system and recurrent joint bleeds result in progressive joint damage leading to haemophilic arthropathy. Early identification and treatment of musculoskeletal bleeding episodes is crucial to prevent dysfunction. The routine use of prophylactic clotting factor concentrate has resulted in significant improvement in the quality of life and life expectancy of haemophilic individuals.

PATHOGENESIS OF JOINT DISEASE

The severity of bleeding experienced by persons with Haemophilia is generally correlated with the baseline clotting factor level, although considerable heterogeneity in bleeding pattern exists [1, 2]. Approximately 80-90% of bleeding episodes in Haemophilia occur in the musculoskeletal system [3]. Joint bleeding is associated with acute pain, swelling, tenderness and reduced mobility, resulting primarily from the intraarticular presence of blood, which is degraded and gradually resorbed by the synovial tissue [4].

The ability of the synovium to resorb the blood is compromised by rebleeding into the same joint, which results in synovitis and more bleeding [5 - 7]. The development of progressive joint destruction includes several processes involving the joint synovium, cartilage and bone. Furthermore, prolonged exposure of cartilage to blood in a target joint causes cartilage damage with bone remodelling occuring as joint disease progresses. Each of these aspects contributes to the development of the progressive degenerative arthropathy. To prevent the development of chronic synovitis, degenerative arthritis and haemophilic

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Christian Carulli (Ed.)

arthropathy, this cycle of recurrent joint bleeds needs to be broken. Evidence from research into the pathophysiology of Osteoarthritis and Rheumatoid arthritis, aspects of which resemble haemophilic arthropathy, suggests that several mediators in blood, including iron, cytokines and pro-angiogenic factors, may be involved in the initiation of the synovial changes [5, 6]. However, the mechanisms of cartilage and bone destruction after bleeding remain undefined, and more research is needed to fully elucidate the pathogenesis of haemophilic arthropathy. A more detailed account of the molecular aspects of the pathogenesis of haemophilic arthropathy is given by Melchiorre and colleagues in chapter 1 of this book.

Interestingly Melchiorre *et al* also propose that there are molecular explanations for the less severe arthropathy that has been reported in Haemophilia B. This issue was first reported by a group of Italian Haemophilia treaters led by Tagariello in 2009 [8]. Despite initial scepticism among the Haemophilia community this has now been confirmed by a number of other studies. The underlying reason for the milder arthropathy in Haemophilia B appears to be the less frequent presence of null mutations in Haemophilia B [9]. Thus in contrast to Haemophilia A, Haemophilia B patients appear to express some residual factor that is below the sensitivity of the current laboratory tests to detect.

THE MULTIDISCIPLINARY TEAM APPROACH

Increasingly it is recognized that the management of all patients with Haemophilia and those with haemophilic arthropathy in particular require the services of the multidisciplinary team. The different roles of the members of the team in the management of haemophilic arthropathy are outlined at the start of this book by a haematologist (chapter 2), a nurse (chapter 5), a laboratory technician/scientist (chapter 4), a physical therapist (chapter 9) as well as the orthopedic surgeons whose role is obviously critical as addressed by the majority of the remaining chapters.

The value of the physical therapist in the multidisciplinary team in managing arthropathy is critical and so obvious to any Haemophilia treater, that we remain surprised by the many Haemophilia centres in Europe which lack specialized physiotherapy. The value of the physical therapist is well described in chapters 9 and 16. The first explains the role of physical therapy in the treatment of acute bleeds as well as in the management of chronic arthropathy. It is unfortunately common for clinicians to treat arthropathy with increasing doses of concentrate rather than using physical therapy and appropriate analgesia.

The role of post-operative physical therapy and rehabilitation are outlined in considerable detail in chapter 16 by Pasquetti and colleagues. Although they

largely tackle Total Knee and Total Hip replacement, it is likely that their recommendations will be appropriate in the management of other joint replacements which are less frequently tackled. The described management is detailed and clearly gained through years of experience. This is an area where randomized studies are very difficult to do and Haemophilia centres with very experienced physical therapists are very fortunate in managing in having these facilities to manage these patients.

CLINICAL EVALUATION OF THE HAEMOPHILIC JOINT

The first assessment by clinician of structural and functional joint damage is through physical joint assessment. The main tools commonly used are the Gilbert score [10] and more recently the HJHS 2.1 [11]. The HJHS has several advantages over the Gilbert Score: it is more sensitive to the smaller and earlier signs of joint changes, is better designed for use in children, and has undergone rigorous reliability and validation testing [11 - 13]. However, the data on the application of HJHS refers to a population of children with or without mild joint impairment, usually on prophylaxis. Consequently, further studies in adults and in patients with advanced joint disease are needed for the validation of this tool in these setting.

Because of the possibility of sub-clinical microhemorrhage, imaging continues to be required for the exhaustive evaluation of joint status, besides being an important complementary tool for the evaluation of complications, diagnostic confirmation and therapeutic follow-up of haemophilic arthropathy.

IMAGING THE STATE OF JOINTS

Any clinician managing patients with Haemophilia needs to know the status of the joints even if a patient does not complain of any problems. Traditionally this involved x-rays which have the limitation of exposure of patients to radiation and only show abnormalities when arthropathy is well established. Roselli and colleagues in chapter 6 report on the historical value of conventional radiological investigation and describe the radiological scoring systems of Arnold-Hilgartner and Pettersson. Whilst the Pettersson score is the more widely used one of the two, it has fallen out of favour and its value remains for research studies.

Over the last decade the use of ultrasound has been shown to be valuable in detecting early arthropathy but the major advance has been the realization that members of the Haemophilia team can use this technique. In chapter 7, Melchiorre and Matucci-Cerinic in a highly illustrated chapter take the reader through the way haemophilic joints can be systematically assessed using this technique. The details of the most widely used HEAD-US protocol [14] are

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Christian Carulli

Christian Carulli graduated at the School of Medicine, University of Rome – Tor Vergata in 2000. He completed the residency program in Hand Surgery in 2003, and in Orthopaedics and Traumatology in 2008 at the University of Florence.

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He is author and co-author of more than 60 papers and books, with a current Impact Factor of more than 50.

His main clinical and surgical fields of interest are: management of the haemophilic arthropathy and coagulative disorders; avascular necrosis of bones; hypersensitivity to orthopaedic implants; lower limb traumatology; hip and knee arthroplasty; hip, knee, and ankle arthroscopy; orthopaedic treatments of rheumatologic and neurologic diseases.