Hemophilic Arthropathy

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abstract

The musculoskeletal manifestations of hemophilia A and B are some of the most common presenting symptoms and continue to be challenging to practitioners. Hemophilic arthropathy, if not initially adequately treated and managed, may lead to debilitating disease and eventually require the consideration of major surgery, including total joint arthroplasty. Thorough comprehension of the pathophysiology, diagnosis, and both medical and surgical interventions is critical in establishing an appropriate treatment regimen for these patients. Furthermore, a true multidisciplinary approach involving hematology, orthopedics, and physical therapy is essential for a patient with hemophilic arthropathy. The authors present a comprehensive review of hemophilic arthropathy from an orthopedist’s perspective. [Orthopedics. 201x; xx(x):xx-xx.]

Hemophilia A and B are X-linked recessive disorders caused by deficiencies or complete absence of coagulation factors VIII and IX, respectively.1 These are rare coagulation disorders with severe consequences. One orthopedic manifestation of hemophilia, known as hemophilic arthropathy, is characterized by joint deformities, synovial hypertrophy, and destruction of cartilage and bone often resulting in pain. These disease sequelae are a consequence of repetitive bleeding episodes into the joint. Hemophilic arthropathy causes significant morbidity and interference with a patient’s ability to perform daily activities. Early diagnosis, which can permit early factor replacement and increase the likelihood of avoiding permanent joint damage, is key. Overall management of these patients can be similar to that of nonhemophiliacs, depending on the severity of the deficiency. This may range from simple immobilization, nonsteroidal anti-inflammatory drugs, and rest for acute bleeds to more invasive procedures such as synovectomy or arthroplasty.

BACKGROUND AND GENETICS

Hemophilia A and B are hereditary X-linked recessive disorders predominantly found in males. Females are typically asymptomatic carriers; however, they can rarely present with moderate to severe phenotypes. Worldwide prevalence of hemophilia A and B is approximately 1 in 5000 males and 1 in 30,000 males, respectively.1 In severe hemophilia A, the most common genetic defect is a large inversion and translocation affecting the gene of factor VIII, which occurs almost exclusively in males. In hemophilia B, more than 2100 mutations in the factor IX gene have been documented, with most being point mutations.2 In approximately 30% of cases, de novo mutations occur without a family history.3

CLASSIFICATION

The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis classified hemophilia A and B as mild, moderate, and severe according to factor plasma levels rather than clinical bleeding symptoms.4 Mild is defined as a factor plasma level greater than 5% to less than 40% of normal. Moderate is defined as a plasma level between 1% and 5% of normal. Severe hemophilia is defined as a factor level less than 1% of normal.

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factor level 1% to 5% of normal. Severe is defined as a plasma factor level less than 1% of normal (Table 1).

**PATHOPHYSIOLOGY**

The pathomechanism underlying hemophilic arthropathy is complex, poorly understood, and the topic of much research. The basis for eventual joint destruction is the recurrent release of hemoglobin and iron deposits within the joint. Synovitis and secondary synovial hypertrophy are the initial manifestations of recurrent bleeding episodes. This is mediated by upregulation of local inflammatory cytokines and chemokines as the tissue is exposed to iron. Cytokines such as interleukin-1 beta and interleukin-6 are major contributors to cartilage destruction. In addition, an overall hypoxic environment promotes upregulation of vascular endothelial growth factor A, leading to a cycle of neoangiogenesis and enzymatic tissue destruction. This hypertrophic and hyperemic synovium is more susceptible to microtraumas; therefore, the cycle of recurrent hemorrhages is perpetuated. If left untreated, progressive intra-articular synovial and capsular fibrosis and cartilage destruction can eventually result in an ankylosed, dysfunctional joint.

**CLINICAL PRESENTATION**

The diagnosis of hemophilia is most commonly achieved secondary to a known family history or after recurrent bleeding episodes. Joint bleeding is a key clinical feature in severe deficiency, with approximately 90% of bleeding episodes occurring into joints, especially elbows, knees, and ankles. Development of target joints, defined as recurrent bleeding within the same joint 4 times during a span of 6 months, can lead to significant morbidity and eventually end-stage arthritis. Joint bleeding generally begins at walking age and, if left untreated, can progress to complete joint destruction by early adulthood.

Soft tissue hematomas are common additional manifestations of hemophilia occurring within or outside fascial compartments or even within muscles. Muscles most affected in the lower extremity include the gastrocnemius–soleus complex, psoas, and quadriceps. In the upper extremity, the forearm flexors and deltoid are the muscles most commonly affected. Intramuscular bleeds generally resolve spontaneously; however, patients must be monitored closely for the development of compartment syndrome, which is considered a surgical emergency. Other, less commonly reported complications include myositis ossificans, nerve palsies, and even soft tissue pseudotumors. Recurrent hemorrhages in the hip have been reported to cause hip dislocation and Legg-Calvé-Perthes disease–like changes secondary to increased intracapsular pressure.

**EVALUATION**

**Radiographs**

Plain radiographs have been historically successful in evaluating and staging hemophilic arthropathy. Common findings representing late arthropathic changes include osteonecrosis, osteopenia, subchondral cysts, joint space narrowing, angular deformities, and ankylosis (Figure). In 1981, the World Federation of Hemophilia recommended the Pettersson score for universal use of staging. The Pettersson score involves an additive scale in which each abnormality is graded from 0 to 2.
Magnetic Resonance Imaging Versus Ultrasound

With the goal to diagnose potential joint involvement early on, research has focused on several imaging modalities. Magnetic resonance imaging (MRI) can detect the early development of pathology such as joint effusions, synovitis, bony edema, and cartilage involvement. However, limitations of MRI, such as cost, availability, and often the need to sedate children, have led to the recent use of musculoskeletal ultrasound to evaluate hemophilic joints. Ultrasound advances have provided higher-resolution images, allowing for adequate visualization of tendons, muscles, ligaments, and fluid. Soft tissue visualization may be even greater than with MRI. Multiple studies have shown musculoskeletal ultrasound to be as effective as MRI in detecting joint bleeds, synovial hyperplasia, and joint erosions. The addition of a power Doppler permits identification of active synovial flow that allows differentiation between synovitis and joint fluid. On the contrary, MRI cannot adequately detect a difference without the addition of contrast. Other advantages include cost, speed, and not needing to administer contrast when compared with MRI. The consistent major limitation of musculoskeletal ultrasound is operator and radiology experience.

TREATMENT
Nonoperative Treatment of Hemarthrosis

The key to successful management of hemophilic arthropathy is to begin treatment early, before the hemarthrosis progresses to chronic synovitis and articular erosion. Aspiration of the hemarthrosis, appropriate factor replacement, and physical therapy should be implemented early. Close clinical follow-up is necessary to assess resolution of symptoms. Temporary splinting for several days can reduce the risk of a recurrent hemarthrosis and expedit the time to synovitis resolution with full joint range of motion. Ice may be applied to enhance vasoconstriction and relieve pain. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided because of the risk of bleeding. Cyclooxygenase-2 inhibitors, which have the advantage of not provoking disturbance of primary hemostasis, may be used for acute episodes. Indications for aspiration of patients with grades III and IV arthropathy are limited to impairment and pain because articular damage is already present. Steroid injection along with cast immobilization for up to 2 weeks has been shown to be effective for some patients with chronic synovitis.

Fracture Care

Secondary to advancements in treatment for hemophilic patients, fracture care does not significantly differ from that for nonhemophilic patients. Secondary to risk of compression and compartment syndrome, acute nonoperative fractures should be splinted for approximately 4 to 7 days and should not be acutely casted. After the initial inflammatory stage has subsided, patients can be transitioned to casting. Factor should be provided to keep blood levels between 70% and 100%, ensuring they do not drop below 30%. If the fracture is deemed operative, then the standard principles should apply to prevent deformity and restore function to the injured extremity.

Management of Pseudotumors

Pseudotumors are essentially encapsulated hematomas with a thick, fibrous capsule and varying states of organization. These may become calcified and even ossified over time. A progressively slow growing mass in a limb of a patient with hemophilia should raise suspicion for a pseudotumor. Most are seen in adults, occurring in long bones, with eventual erosion of adjacent bones. These can cross joints and limit range of motion. Pseudotumors typically are painless until a pathological fracture occurs. Radiographically, they present as a large soft tissue mass with adjacent bony destruction and commonly have calcification within the mass.

Table 2

<table>
<thead>
<tr>
<th>Radiographic Finding</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Enlarged epiphysis</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Irregular subchondral surface</td>
<td>0</td>
</tr>
<tr>
<td>Partially involved</td>
<td>1</td>
</tr>
<tr>
<td>Totally involved</td>
<td>2</td>
</tr>
<tr>
<td>Narrowing of joint space</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1 mm</td>
<td>1</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>2</td>
</tr>
<tr>
<td>Subchondral cyst formation</td>
<td>0</td>
</tr>
<tr>
<td>1 cyst</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 cyst</td>
<td>2</td>
</tr>
<tr>
<td>Erosion of joint margins</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Gross incongruence of articulating bones</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>1</td>
</tr>
<tr>
<td>Pronounced</td>
<td>2</td>
</tr>
<tr>
<td>Joint deformity (angulation, displacement, or both between articulating bones)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Slight</td>
<td>1</td>
</tr>
<tr>
<td>Pronounced</td>
<td>2</td>
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</tbody>
</table>
Although rare, pseudotumors in children and adolescents are more commonly the result of direct trauma. They develop rapidly secondary to intraosseous hemorrhage. These often present in smaller bones, such as the talus, calcaneus, and metatarsals, and rarely in the carpus.

The acute and smaller forms can typically be treated with factor replacement and immobilization, especially in children. Often larger forms in adults may need to be treated surgically. If amendable, certain cases may be aspirated percutaneously and their cavities filled with fibrin glue or bone graft. In more advanced cases, open surgery is indicated, which requires extensive planning, involving advanced imaging and even angiography to allow for preoperative arterial embolization. Overall, pseudotumors can be difficult to diagnose and treat; however, the availability of maintenance therapy has fortunately made them a less common entity.

**Factor Replacement**

**Prophylaxis**

The goal of prophylactic therapy is to reduce factor VIII or factor IX deficiency and decrease spontaneous bleeding episodes. It can be administered as on demand or long term. Results of prospective randomized controlled trials have shown better musculoskeletal outcomes with long-term prophylactic treatment rather than on-demand treatment in children. The most appropriate regimen is debatable and varies worldwide. When to initiate prophylaxis and the most effective interval of administration depend heavily on the severity of the deficiency. It is general consensus that, when economically available, initiation in early childhood is the most beneficial in avoiding the later development of joint arthropathy. The determined regimen is typically based on an individualized, tailored approach. Methods may include evaluating individual pharmacokinetics with computer-simulated doses and intervals to achieve a predetermined trough activity level.

**Inhibitors**

Inhibitors are antibodies that develop against epitopes of the deficient coagulation factor. They significantly change the pharmacokinetics and are present in up to 30% of patients with hemophilia A and 5% of patients with hemophilia B. Many factors play a role in the development of inhibitors, including the severity of the deficiency, genetic makeup, type of replacement therapy used, and age at therapy initiation. Inhibitor treatment includes immune tolerance induction. There are both low-dose and high-dose protocols, with the most used regimen being the Bonn protocol. Outcome studies are currently lacking. The first randomized induction study, which began in 2002, was prematurely stopped in 2009 because the international hemophilia community was slow to embrace the multicenter trial.

**Acute Bleeds**

Treatment of acute bleeding episodes depends on the presence of inhibitors and the severity of the episodes. Those with low-responding inhibitors are generally treated with high doses of factor, and those with high-responding inhibitors are treated with products designed to bypass the inhibitor presence to ultimately achieve hemostasis. The 2 main bypassing agents are recombinant factor VIIa and activated prothrombin complex concentrates. Single dosing regimens of factor VIIa have been shown to be effective and preferable secondary to convenience as reported by Santagostino et al.

**Major Surgery**

Effective treatment of patients facing major orthopedic surgery, especially those with high inhibitor titers, can be challenging for both the surgeon and the hematologist. In a study by Rodríguez-Merchán et al, 20 patients undergoing major surgery, including total knee and hip arthroplasties, fracture fixation, and even hip osteotomy, were treated with either recombinant factor VIIa or factor VIII anti-inhibitor product (factor 8 inhibitor bypass activity). Overall, 16 of 20 patients were considered to have good outcomes, while 3 patients experienced postoperative bleeding complications. This study showed that, even in the face of high-titer inhibitors (5 Bethesda units/mL), such procedures can be performed relatively safely, especially with the use of recombinant factor VIIa. The standard dosing that was used in this study was, on average, 150 µg · kg⁻¹ (range, 90-200 µg · kg⁻¹) prior to surgery. The same dose was then given every 2 hours for 24 to 48 hours postoperatively. On postoperative days 3 to 7, a continuous infusion of 45 µg · kg⁻¹ · h⁻¹ was administered.

**Minor Surgery**

Patients undergoing minor orthopedic surgery are at less risk for serious postoperative bleeding episodes; however, they still require close monitoring, and an overall stringent protocol must be in place. The aforementioned study by Rodríguez-Merchán et al also included 88 patients undergoing radiosynoviorthesis in various joints, which was considered a minor procedure. Most patients were treated with 1 dose of recombinant factor VIIa (150 µg/kg before the procedure, followed by 3 doses of 150 µg/kg at 2-hour intervals after surgery) or factor 8 inhibitor bypass agents (100 U before surgery, 100 U 6 hours later, and 50 U at 12-hour intervals for 4 to 5 days after surgery). Of these 88 procedures, 66 had good results with no postoperative complications. In another study, Quintana-Molina et al found that they had greater success using large doses of recombinant factor VIIa in minor procedures likely secondary to the shorter half-life of this factor. They also found good results for those patients administered factor 8 inhibitor bypass agents.

**Surgical Treatments**

The first line of treatment for hemophilic arthropathy is physiotherapy with a factor replacement regimen to prevent
Reduction in bleeding episodes and joint damage. Steroid and hyaluronic acid injections can be trialed before considering more invasive management, although long-term benefits of these injections are questionable. Often the next line of treatment is synoviorthesis, also known as radionuclide synovium ablation. When injections and other conservative measures fail to improve pain and function, surgical options may be considered, including arthroscopic synovectomy, open synovectomy, and total joint arthroplasty.\(^{35}\)

The goal of synovectomy, either chemically or surgically, is to remove inflamed and hypertrophic synovium to prevent the onset of hemophilic arthropathy. However, for treatment of chronic hemophilic synovitis, synoviorthesis should always be indicated as the first procedure. Intra-articular injection of a radionuclide induces fibrosis of the synovium, decreasing bleeding episodes. Yttrium-90 and rifampin synoviortheses have shown an 85% or higher success rate.

Synovectomy (open or arthroscopic) can then be considered after 3 failed synoviortheses in a 3-month period.\(^{34}\) When surgical synovectomy is indicated, arthroscopic synovectomy is the gold standard secondary to open synovectomy, given the reported decrease in complication rates and improved early mobilization.\(^{36}\)

Open and arthroscopic synovectomy and radionuclide injection have reported success rates ranging from 70% to 100%.\(^{37,38}\)

Total joint replacement is the treatment of choice for end-stage arthropathy. Goals of the procedure include resolution of pain, correction of deformity, and return of limb function. However, total joint replacement procedures can be complicated because of the presence of intra-articular fibrosis, contractures, and severe joint deformity. Arthrofibrosis is a common complication after total joint replacement, especially in total knee replacement. However, the literature reports good outcomes overall. Goddard et al\(^{39}\) performed a retrospective study of 70 primary total knee replacements in 57 patients. They reported an 80% implant survivorship at 20 years. Patients reported a 95% good or excellent outcome on the Hospital for Special Surgery score system.\(^{39}\) Westberg et al\(^{40}\) retrospectively reviewed the results of 107 primary total knee replacements in patients with hemophilic arthropathy. Five- and 10-year survival rates were 92% and 88%, respectively. The most common causes of failure were aseptic loosening (14 knees) and infection (7 knees). The infection rate for all patients was 6.5%. The mean blood loss was 4.3 g/dL.\(^{30}\) These results compare favorably with those of patients without hemophilia, as recent studies have shown an overall 92% 10-year survivorship in primary total knee arthroplasty.\(^{41}\)

A tailored long-term rehabilitation course and a regular factor replacement schedule should be implemented. Lobet et al\(^{42}\) proposed an algorithm for a physical therapy regimen following total joint replacement. Although not vastly different from postoperative treatments in the general population, the Lobet et al\(^{42}\) regimen calls for implementation of several modalities, including cryotherapies, auto-posture exercises, early continuous passive motion, muscular strengthening, hydrotherapy, ergotherapy, and isometric exercises, for an extended period to prevent the common complication of loss of motion due to arthrofibrosis.\(^{42}\)

Elbow arthropathy may occur in this patient population as well. Surgical resection of the radial head in conjunction with synovectomy and joint lavage can be proposed in cases of severe elbow arthropathy in which a block to motion exists.\(^{38}\) Immediate improvements in pronation and supination can be achieved. In end-stage arthropathy, a total elbow replacement may be indicated in low-demand patients. Marshall Brooks et al\(^{43}\) reported improvement in range of motion and pain relief at an average of 19.2 months postoperatively in 6 of 7 patients.

The shoulder is another common joint affected by hemophilic arthropathy that can be effectively treated with arthroplasty for end-stage disease. Wendt et al\(^{44}\) performed a retrospective review examining 7 shoulder arthroplasties performed in 6 patients. The average blood loss was 475 mL, with 2 patients requiring intraoperative transfusion. These patients were followed clinically for an average of 13.8 years. Four patients underwent a total shoulder arthroplasty, and 3 patients underwent a shoulder hemiarthroplasty. Pain relief was achieved in 5 patients (6 shoulders). Based on the modified Neer score, there were 2 excellent results, 4 satisfactory results, and 1 unsatisfactory result. There were no postoperative hematomas, and none of these patients required revision or reoperation.\(^{44}\) Additional studies are needed to determine the true long-term outcomes in the hemophilic population, although the results of Wendt et al\(^{44}\) are promising.

The ankle is often the first joint affected by hemophilic arthropathy, with pain and swelling presenting when children begin to walk. Severe ankle arthropathy commonly presents by early adulthood.\(^{37}\)

Ankle arthrodesis is the gold standard treatment for end-stage ankle arthropathy; it is reliable but can have many drawbacks in young populations. Ankle arthrodesis accelerates adjacent joint disease and arthritis, which later in life may require further treatment, including additional joint fusions. Total ankle arthroplasties are reasonable options in older low-demand patients, as successful long-term outcomes decrease with increased patient activity demands.\(^{45}\) Strauss et al\(^{46}\) retrospectively reviewed 10 patients with 11 total ankle arthroplasties. Five patients had human immunodeficiency virus and 2 had hepatitis C. Two patients developed deep infection requiring removal of the implants. The remaining 8 patients had improvement of average American Orthopaedic Foot and Ankle Society scores from 21.5 preoperatively to 68 at final follow-up.\(^{46}\) Aside from arthroscopy with synovectomy and ankle arthrodesis, there...
has recently been interest in regenerative procedures. Buda et al\textsuperscript{47} retrospectively reviewed 5 patients who received bone marrow–derived cell transplantation, synovectomy, arthroscopic debridement, and autologous platelet-rich fibrin. The mean American Orthopaedic Foot and Ankle Society score improved from 35 preoperatively to 81 after a mean postoperative follow-up of 2 years.\textsuperscript{47}

The hip is much less commonly affected in hemophilic arthropathy compared with the ankle, knee, elbow, and shoulder. The radiographic appearance of hip hemophilic arthropathy can take the form of adult osteoarthritis, or more commonly juvenile arthritis. Although patients may be young, they may develop osteonecrosis secondary to treatment of human immunodeficiency virus with protease inhibitors or corticosteroids.\textsuperscript{48} As with other joints, end-stage disease is often treated with a total joint arthroplasty. Hip arthropathy is contraindicated, as the knee is also commonly affected. Cemented components have not been reported to be as reliable as those within the knee. Kelley et al\textsuperscript{11} reported a failure rate of 21% for cemented femoral components and 23% for acetalubar components at 8-year follow-up. Some data have suggested that press-fit components may have better outcomes, but other data suggest similar loosening rates for press-fit and cemented components.\textsuperscript{37} Range of motion is more often improved postoperatively in contrast to total knee arthroplasty, which is more prone to have arthrofibrosis.\textsuperscript{37}

**Conclusion**

Hemophilic arthropathy can be an extremely debilitating orthopedic entity experienced by patients with severe hemophilia. Fortunately, with the advent of early prophylactic administration of factor replacement, effective prevention has been shown. Much research has been dedicated to the early diagnosis and prevention of late-stage arthropathy. Unfortunately, despite treatment, a subset of patients will have joint destruction possibly requiring joint arthroplasty. The care of these patients can be complex and requires a multidisciplinary approach including hematologists, orthopedists, and therapists to achieve success. Future areas of research and treatment include regenerative interventions, gene therapy, the development of new immune tolerance induction therapies, and affordable global access.

**References**


