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REVIEW

Haemophilic arthritis

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Haemophilic arthritis is a relatively rare arthropathy, but several aspects of its management and pathogenesis are of interest to rheumatologists. Firstly, the number of haemophiliac patients has increased simultaneously with availability of clotting factor concentrates, and most severely affected patients are likely to have arthritis amenable to prevention or amelioration by approaches familiar to rheumatologists. Secondly, the pathogenesis is unclear, and a further understanding may provide insights into the responses of joint tissues to injury. Thirdly, the histopathology of haemophilic arthritis represents one extreme of changes seen in rheumatoid synovium, and thus haemophilic arthritis may highlight common mechanisms in joint destruction.

Why haemophiliac patients bleed into joints

Haemophilia describes two disorders—haemophilia A due to factor VIIIc deficiency and haemophilia B due to factor IX deficiency. Both factors are glycoproteins, encoded by X chromosome genes that form part of the intrinsic plasma clotting system. Specifically, factors VIIIc and IX activate factor X. The clinical manifestations of both disorders are therefore similar.

The predisposition to musculoskeletal bleeding in haemophilia compared with other congenital and acquired coagulation disorders cannot be entirely explained by a single cause. Mechanical factors are important as suggested by the onset of haemarthrosis with weight bearing; more frequent occurrence of bleeds into legs than arms; and the propensity of joints on the dominant side to be more severely affected. The inherent absence of tissue thromboplastin in synovium combined with an impaired intrinsic coagulation pathway may be another factor.[1]

Clinical manifestations

The frequency of bleeding episodes parallels plasma factor concentrations.[2] Severe defects (<1 IU/l) are characterised by spontaneous bleeding—the most common sites being joints, muscles, and renal tract. Factor concentrations between 1 and 5 IU/l result in bleeding after minor trauma. In mild deficiency (5–50 IU/l), bleeding occurs after severe trauma or surgery. Factor concentrations remain stable throughout life, except in rare variants.

Joint disease is the single most important cause of morbidity in haemophilia and up to 90% of severely affected patients have this complication.[2] Three stages are recognised: acute haemarthrosis, chronic synovitis, and degenerative arthritis.

Haemarthroses occur most commonly into knees, elbows, and ankles. Patients are often aware of a bleed before any clinical signs. Once a haemarthrosis is established the joint is tense, painful, and held in flexion. One joint often becomes a focus for recurrent bleeding.

Onset of the synovitic stage is often difficult to establish. The patient presents with persistent swelling in the absence of pain in a target joint. Swelling is due to synovial hypertrophy and usually refractory to clotting factor concentrate infusions. Joint aspiration may show an inflammatory exudate mixed with blood. Early degenerative arthritis is considered to be present if chronic synovitis persists for more than six months.[3]

Pathology

Acute joint bleeding produces a transient acute inflammatory synovitis, and resolution of these changes is often slow.[4] With repeated haemarthroses synoviocyte hypertrophy and hyperplasia supervene, which are supported by an intense neovascularisation of the synovial membrane. A characteristic feature is deposition of iron in superficial and subsynovial layers. A perivascular mononuclear cell infiltrate and fibrosis is also present. At the joint periphery the inflamed synovium is organised into a fibrous pannus, which is locally invasive. Cartilage loss also occurs in weightbearing areas, and at such sites chondrocytes contain haemosiderin. In the later stages there is complete loss of cartilage and subchondral bone is exposed with cyst formation. This is followed by collapse and sclerosis of the joint.

The early pathological features have been described in spontaneous haemophilia in dogs, and changes similar to haemophilic arthritis have been reproduced in experimental animals with injections of autologous blood.[5–10] Some aspects of haemophilic arthritis remain unclear, however. Firstly, the response of joint tissues to intra-articular blood is incompletely understood—changes include synovitis and subsynovial angiogenesis, but the component or components of blood that initiate and perpetuate synovitis are not known. Secondly, mediators participating in cartilage breakdown are uncertain. Thirdly, the way in which iron enters chondrocytes is not yet explained. An understanding of these mechanisms may

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provide insights into the pathogenesis of more common inflammatory arthropathies, such as rheumatoid arthritis.

Haemophilic synovitis represents one extreme of the continuum of histological changes present in rheumatoid arthritis. In both rheumatoid and haemophilic arthritis it has been suggested that iron perpetuates synovitis and mediates tissue damage.[10–12] In both rheumatoid and haemophilic arthritis microbleeding is well recorded, and synovial iron deposition correlates closely with the extent of erosive disease and is associated with a poorer prognosis.[13 14] Differences include the relative absence of a chronic inflammatory response and the presence of iron with chondrocytes in haemophilic arthritis.[15] A possible sequence of events in haemophilic arthritis may be that intra-articular bleeding initially provokes a non-specific inflammatory response, and macrophages accumulate around synovial iron deposits, release monokines, and stimulate production of latent collagenases and prostanoids from synovium. With repeated haemarthroses the synovium proliferates, and the continued leak of red blood cells from the hypertrophied, vascular synovium produces a cycle of synovitis→bleeding→synovitis. The increased iron load results in further synoviocyte hyperplasia, pannus formation, and macrophage accumulation.

The cartilage loss is multifactorial, initiated by sequestered polymorphonuclear cells and the increased amounts of plasmin in the inflamed synovium,[16] and perpetuated by the synovial response, mediating damage directly in areas where pannus forms.[10] In areas free from pannus the deposition of iron within chrondrocytes may play an important part.[10 15]

Treatment

The aims in treating haemophilic arthritis are similar to those of any inflammatory arthropathy: symptom relief, prevention of the progression of the joint damage, and maintenance of function. In haemophilic arthritis these goals can be achieved by early treatment of haemarthrosis and by limiting the effects of chronic synovitis. In the subject with degenerative changes function is amenable to correction by surgical/physical methods with adequate haemostatic cover.

ACUTE HAEMARTHROSIS

Management of acute haemarthrosis is directed at stopping bleeding with replacement treatment and provision of adequate analgesia. Early treatment of bleeding can be achieved by the provision of clotting factor concentrates for home treatment.

Arthrocentesis is not generally recommended in the management of haemarthrosis. This procedure has not been shown to slow down the progression of haemophilic arthritis.[17] Joint aspiration should be considered in a large tense haemarthrosis for symptomatic relief or if joint sepsis is suspected. Septic arthritis was previously a rare complication of haemophilic arthritis, but the incidence has increased in patients with HIV-1 related immunodeficiency.[18]

Systemic corticosteroid treatment has been evaluated in dampening the intra-articular inflammatory response in acute haemarthrosis, but the benefits are short lived and because of frequent side effects their use is limited and not advocated.[19]

Although treatment for haemophilia has greatly improved, the influence of clotting factor replacement therapy on the progression of haemophilic arthritis is not known. Two uncontrolled studies reported that arthritis progresses despite adequate early treatment of haemarthrosis, and even patients receiving prophylactic infusions develop episodes of synovitis.[20 21] To determine further the influence of clotting factor on the outcome of arthritis in haemophilia an international cooperative study has been started. An interim analysis at four years showed that progression seems to be directly related to the frequency of joint bleeds. Treatment with dose regimens of greater than 1000 units/kg a year confers some advantage in progression, but more than 2000 units/kg a year offer no additional advantage. The early use of clotting factor concentrates, therefore, seems to delay rather than prevent haemophilic arthritis. A small subgroup of patients was identified in whom no joint disease was found. These patients had used significantly more clotting factor concentrate and had been receiving prophylactic treatment more often than those who had progressive disease (Aledort, personal communication).

On the other hand, the lifelong dependence on blood products has placed patients with haemophilia at increased risk of blood borne viral infections. Hepatitis due to hepatitis B and the non A, non B agents is invariably found in regularly treated haemophiliac patients, and chronic liver disease is an increasingly common cause of morbidity.[22 23] HIV-1 induced immunodeficiency is now the most common cause of death in patients with severe haemophilia.[24] The risk of infections with these agents in the future has been significantly reduced, however, with newer methods of fractionating and sterilising clotting factor concentrates. The recent availability of screening tests for hepatitis C should further reduce the incidence of hepatitis.

CHRONIC SYNOVITIS

The aim in treating haemophilic synovitis is to prevent further cartilage damage. At present treatment remains empirical and is directed at interrupting the cycle of bleeding→synovitis→bleeding. Further haemarthrosis may be prevented by prophylactic replacement treatment. The synovitis, however, is more difficult to suppress, and both surgical and radiochemical synovectomy have been tried.[25–31] The immediate to short term benefits of surgical synovectomy in reducing bleeds are encouraging, but, unfortunately, the procedure is associated with stiffness and loss of motion. Few long term results have been published.[32] More

Surgical treatment options in haemophilic arthritis

Joint affected	*Synovectomy*	*Arthrodesis*	*Arthroplasty*
Shoulder	Rarely indicated	Good pain relief	Little experience
Elbow	Good pain relief. Often combined with radial head excision	Rarely indicated	Little experience with newer prosthesis
Hip			Results comparable with other inflammatory arthropathies
Knee	Reduces frequency of haemarthrosis/ associated with loss of function	Consider if arthoplasty fails	Procedure of choice
Ankle/subtalar	Rarely indicated	Procedure of choice	Results unsatisfactory

recently, arthroscopic synovectomy has been attempted, but in both surgical and arthroscopic synovectomy[33] postoperative bleeding has been a problem.

Radiocolloids reduce the frequency of subsequent bleeds but seem not to confer any additional advantages.[30] We have often used intra-articular corticosteroid treatment and found that the subsequent use of clotting factor concentrate was reduced and the subjective intensity and duration of synovitis was diminished. Favourable results have also been reported with osmic acid (York, personal communication). If intra-articular treatment is to be used our policy is to perform the procedure under prophylactic clotting factor concentrate cover, and patients remain non-weight-bearing for at least 24 hours. In patients positive for antibody to HIV-1 the increased risk of joint sepsis should be borne in mind. Surgical synovectomy should be considered if synovitis persists for six months.

D-Penicillamine has been shown to reduce the mononuclear cell infiltrate in an animal model of haemophilic arthritis.[34] Anecdotal experience in four patients treated with D-penicillamine for a median of 10 weeks showed promising results in three.[34]

DEGENERATIVE ARTHRITIS

Degeneration of the joint in haemophiliac patients results in pain and progressive impairment of function. Adequate analgesia in such patients can be difficult to provide and is often influenced by previous drug habituation. The efficacy and safety of non-steroidal anti-inflammatory agents has been evaluated.[35–39] Ibuprofen has the advantage of a short half life and flexible dosage regimen; its effect on the gastrointestinal tract is a limiting factor, however. Its cautious use in selected patients may be beneficial.

Corrective orthopaedic surgery, including replacement arthroplasties of hips,[40] knees,[41] and elbows,[42] has been successfully undertaken in patients with haemophilia. It requires intensive monitoring to maintain haemostasis, however, and should be undertaken only in centres where facilities and experience are available. The table shows possible surgical options. The only haemostatic contraindication is the presence of a high titre inhibitor.

In conclusion, several aspects of haemophilic arthritis are amenable to treatment. Management of chronic haemophilic synovitis remains a problem, but approaches familiar to rheumatologists may be helpful. The best treatment remains prevention, and the availability of monoclonal antibody purified and recombinant factor concentrates free of infectious agents combined with a comprehensive approach to treatment make this goal attainable. Further studies of the pathogenesis of haemophilic arthritis may clarify mechanisms of joint damage in the more common arthropathies.

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