Abstract
More than 90% of bleeding episodes in patients with haemophilia occur in the musculoskeletal system, of which most episodes occur in the joints. Haematoma formation in muscles, with the development of pseudotumours, may compromise neurovascular structures. The incidence of chronic compressive peripheral neuropathies due to extrinsic causes is low. Acute nerve compression due to intraneural bleeding in patients with haemophilia is a rare entity. We report on acute ulnar nerve compression due to intraneural bleeding, accompanied by median nerve symptoms and present a practical guide to the orthopaedic management of these patients.

Case report
A 23-year-old male patient, known to have severe haemophilia (factor VIII level <1%, with no inhibitors), presented at the Casualty unit with a one-week history of blunt trauma to his forearm. He reported that the size of the haematoma in the forearm compartment at presentation was half the size of the initial swelling.

The patient complained of a progressive deformity of his right hand, accompanied by absent sensation in the ulnar nerve distribution and weak hand function. On further enquiry, he also reported paraesthesia in the median nerve distribution of the hand. He had no bleeding in the elbow joint. On examination he had an ulnar claw hand, no sensation in the ulnar nerve distribution, weak intrinsic muscle function and a positive Froman’s sign. The elbow was normal. The volar aspect of the forearm was swollen but not tense.

Introduction
Haemophilia A and B are X-linked recessive diseases with a combined incidence of 1 in 5 000 live male births, of which approximately 80% have haemophilia A and 66% have severe disease. More than 90% of bleeding episodes in these patients occur in the musculoskeletal system, of which 80% occur in the joints. Haematoma formation, with the development of pseudotumours, can cause chronic compressive neuropathies due to extrinsic pressure on the neurovascular structures. This is well documented in the literature and it most often involves the quadriceps, iliotibial and forearm muscle compartments.

The incidence of chronic peripheral nerve lesions is estimated at 1.7–13.6%, of which the femoral nerve is the most commonly affected. Post-traumatic nerve compression due to intraneural bleeding has often been suspected. Only two cases are documented in the literature. We report on a case of post-traumatic ulnar nerve compression due to intraneural bleeding and present a practical orthopaedic guide to the management of patients with haemophilia.
He also had hypoaesthesia in the median nerve distribution of the hand. As this was a very recent bleeding episode, no muscle wasting was present.

Routine radiological findings, apart from the marked soft tissue swelling in the forearm, were negative. A magnetic resonance imaging (MRI) study revealed high signal intensity changes on both T1 and T2 images, suggestive of blood degradation products that surrounded the ulnar nerve in the forearm and extended from the level of the elbow in the flexor compartment to the carpal tunnel at the wrist (Figure 1).

Initial factor VIII levels on admission were suboptimal for surgery. Haemosolvate (FVIII) was administered according to the protocol suggested by the South African Haemophilia Foundation (discussed later), to reach levels of 100% pre-operatively. No improvement was noted 24 hours later and he was taken to theatre for an ulnar and median nerve decompression.

At the time of surgery, there was an intramuscular haematoma at different levels of the forearm flexor muscle compartment. More evident was the intraneural haematoma of the ulnar nerve, extending from the elbow to the wrist. There was also, to a lesser extent, a haematoma surrounding the median nerve in the carpal tunnel. A neurolysis of the ulnar nerve, including the Guyon and carpal tunnels, was done (Figure 2).

The tourniquet was released before closure of the wound, as suggested in the literature. The factor VIII levels were maintained in the immediate postoperative period (see Table I).

The loss of ulnar function did not improve on his five-month follow-up examination; however, the median nerve symptoms improved shortly after surgical decompression.

**Discussion**

Chronic neurological complications in haemophilia occur in 1.7–13.6% of patients. These symptoms may be due to compartment syndrome or entrapment neuropathies. Intraneuronal bleeding is a rare complication in these patients. Hayden and Cordingley and Crawford described the first two cases of acute nerve compression due to intraneuronal bleeding. Katz et al. reported on a large series of 81 haemophilia patients with compressive neuropathies. In this series, the most common cause of nerve palsy was intramuscular bleeding causing extrinsic pressure on neurovascular structures. There was no reported intraneural bleeding in their series over a 24-year period.

The most common cause of nerve palsy was intramuscular bleeding causing extrinsic pressure on neurovascular structures.
Intraneural bleeding has often been suspected but not often documented. Bleeding into a muscle with a tight enveloping fascia can lead to compartment syndrome, causing increased intracompartmental pressure and subsequent decrease in nutrient blood flow to the muscles and nerves, resulting in ischaemia. If the pressure within the compartment is not decompressed, irreversible nerve and muscle damage may occur, which may cause paralysis, anaesthesia, muscle contracture and, in growing children, growth retardation.

The femoral nerve is the most commonly involved, and the incidence of co-existing median and ulnar nerve compression in patients known with haemophilia is estimated at 3.4%.

The case presented here had a pronounced ulnar nerve neuropathy due to intraneural bleeding, associated with mild median nerve compressive symptoms.

**Practical guide to the orthopaedic management**

Management of patients with haemophilia remains a challenge to orthopaedic surgeons, be it on an elective or emergency basis. Severity usually relates to the plasma levels of the coagulation factor in question.

Many patients with haemophilia will present to an orthopaedic surgeon necessitating a practical approach to manage these patients.

**Establishing a diagnosis**

**History**

The majority of patients diagnosed with haemophilia have a positive family history and up to 25% of affected children have bleeding episodes prior to diagnosis. Investigation for haemophilia should be prompted in patients presenting with:
- male distribution family history of bleeding tendency
- consistent (lifelong) history of bleeding.

**Clinical picture**

Haemophilia patients typically present with:
- spontaneous bleeding into joints, soft tissue or mucosal surfaces
- excessive bleeding on haemostatic challenge.

**Laboratory diagnosis**

The diagnosis is easily made with routine investigation: full blood count, partial prothrombin time (aPTT), factor VIII / factor IX levels. According to the International Society on Thrombosis and Haemostasis, severe disease is classified as levels below 1% and is associated with spontaneous haemorrhage. In moderate disease, factor levels vary between 1% and 5%, with haemorrhage usually associated with trauma, surgery or dental work. Mild disease (FVIII>5%) only presents with severe trauma or surgery.

Once the diagnosis has been made, the presence of inhibitor formation should be checked. Inhibitors are antibodies formed as a complication of replacement therapy. These antibodies inhibit the biological activity of infused factor VIII or factor IX, rendering the patient refractory to treatment. It occurs more frequently in haemophilia A (10–30% vs 2–5% in haemophilia B) and more often in patients with severe disease. It is, however, also seen in mild to moderate haemophilia A.

<table>
<thead>
<tr>
<th>Table I: Recommended plasma factor levels and duration of administration</th>
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<tr>
<td><strong>Haemophilia A</strong></td>
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<td>Desired level</td>
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*Haemosolvate® (factor VIII) has a half-life of 8–12 hours, necessitating twice-daily dosing

**Haemosolvex® (factor IX) has a half-life of 16–24 hours, necessitating daily dosing*
Consider the presence of inhibiting antibodies (inhibitors) in:
• patients with mild to moderate severity disease presenting with a marked increase in bleeding frequency (i.e. conversion to severe haemophilia)
• patients with bleeding episodes refractory to usual therapy.

Patients should be screened for inhibitors 3–6-monthly, especially in black patients, as the presence of inhibitors is more common in this population group.

The inhibitory titres are measured in Bethesda units (BU) – low-titre levels classified as <5BU and high-titre levels that exceed 5BU. Patients are further classified as being high or low responders, based on the titre response following factor replacement/treatment. If titre levels remain low (≤5BU), it classifies as a low responder but levels exceeding 5BU are classified as high responders.

Management
The aims of management of haemophilia are:
• prevention of intramuscular haemorrhage and haemarthrosis
• limiting the extent of the bleed
• prevention of the development of chronic synovitis in target joints and subsequent haemophilic arthropathy.17

Acute haemorrhage
Acute haemorrhage represents 80–85% of all bleeding episodes of haemophilia encountered in orthopaedic practice.

• General measures: Include immobilisation, ice packs, elevation, and pain management. It is important that anti-platelet therapy (non-steroidal anti-inflammatorlies like aspirin, ibuprofen, etc.) be avoided and if intramuscular medication is warranted, it should be administered under full factor coverage. Early consultation with a physiotherapist will ensure sensible rehabilitation.
• Specific measures: FVIII/FIX administration and frequency:
The following formula should be used to determine the dose of administration:

\[
dose = \frac{(\text{required factor level } \%) \times \text{(factor level at presentation)} \times \text{weight}}{2}
\]

As a practical example, the above patient can be used:
Patient weight: 60 kg
Desired FVIII level: 100%
Increase needed: 100% - 38% = 62%

Therefore, \((100\% - 38\%) \times 60 \text{ kg} \)
\[
= 1 \times 660 \text{ IU stat dose}
\]

Uncomplicated
Early recognition and diagnosis with effective treatment is very important. The factor VIII level is raised to 60–100% (80–100% for iliopsoas bleeds and 60–80% for other muscle bleeds). The level is kept at 50% until symptoms resolve and the patient regains function. It is important to prevent further bleeding during mobilisation and rehabilitation.

Elective procedures of patients known with haemophilia should be planned meticulously. Desired factor levels throughout the peri-operative period has been stipulated by the World Federation of Haemophilia, based in Canada, and makes a distinction between situations with and without resource constraints20

| Complicated |

In bleeding haemophilic patients with inhibitors, the main treatment aim remains to stop the haemorrhage. Treatment options are considered based on patient response to factor replacement:
• Low-responder inhibitors:
  • Plasma-derived factor VIII at two to three times normal dose
  • High-responder inhibitors:
  • Activated prothrombin complex concentrates (aPCC) or FEIBA®
  • Recombinant activated factor VII (NovoSeven®)

Rehabilitation
Physiotherapy should be initiated early in the rehabilitation process. Various treatment options can be utilised including cold packs, isometric and isotonic exercises, passive range of motion exercises, strengthening, proprioceptive and flexibility exercises, etc. Other physical modalities currently under investigation include diathermy and ultrasound. It is best to consult a physiotherapist established in the field of haemophilic treatment mobilisation, as various modalities are indicated in various clinical settings. Once invasive physiotherapeutic interventions are used, factor should be administered prophylactically.

Follow-up
Prophylactic therapy is indicated in specific patients in this population group, and can be subdivided into primary and secondary therapy. Primary prophylaxis involves factor infusions administered to prevent bleeding and its consequences – considered in infants with severe haemophilia at risk of developing haemophilic arthropathy. This practice constitutes the continuous administration of factor in patients before 2 years of age in divided dosages (25 to 40 units/kg factor VIII three times weekly in haemophilia A, and 25 to 40 units/kg factor IX twice weekly in haemophilia B). This has obvious cost implications, and is mainly only used in developed countries.
Chronic complications
Synovial hypertrophy with neo-vascularisation renders the joints more prone to haemorrhage.
Secondary prophylaxis is defined as intermittent factor infusions and aims to increase the factor level to above 1%. The administration of prophylactic factor concentrate limits the requirement for on-demand treatment. Regular administration may also prevent re-bleeds into target joints, especially where chronic synovitis has developed. It may also be given prior to activities likely to cause bleeding. It is administered as a single dose prior to the high risk event. Patients with established inhibitors should be considered for eradication therapy. Various regimens exist, and should best be embarked on by an expert in the field. The risk of thromboembolic events seems to be increased on long-term use of aPCC, but has not been demonstrated in the use of recombinant-activated factor VIIa. The risk of this complication should however be recognised, and as patients receiving any of these products should be monitored, it may be prudent to refer or manage these patients in close consultation with specialists in the field of complicated haemophilia.

Patients with established inhibitors should be considered for eradication therapy

Once the patient’s factor requirements have been determined, the administration method needs to be established. Two approaches have been used:
- **Continuous infusion of factor concentrate** has been thoroughly evaluated since first described in the 1950s. The factor concentrate is administered as a continuous infusion over 24 hours and is effective to reduce factor usage by up to 30%. The advantage is stable factor levels without peak and trough variation. The product remains stable and is not prone to bacterial contamination. This method requires close monitoring by staff and equipment – a less attractive option in a resource-restricted setting.
- **Bolus infusions** – the administration of factor supplementation in divided doses – may be given according to various existing protocols. This method does require less monitoring, but raises the issue of trough levels and possible bleeding complications.

Conclusion
Management of haemophilic patients remains a challenge for most orthopaedic surgeons. It is therefore prudent to define clear management guidelines to not only standardise treatment modalities, but also to optimise patient care, by basing these protocols on established evidence-based medicine.

References

* SAOJ