High incidence of ankle arthropathy in mild and moderate haemophilia A

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Summary
A clinical study of patients with mild haemophilia A to document the frequency and severity of arthropathy has not been previously published. We studied ankle arthropathy in 34 patients with mild/moderate haemophilia A. The patients were assessed for the presence and severity of pain, by and the physical and radiological scoring systems for the evaluation of haemophiliac arthropathy recommended by the World Federation of Haemophilia (WFH). Of the 34 patients, 16 (47%) had ankle pain, which was of moderate to severe degree in nine patients, and associated with limitation of physical activities in 13 patients. Of 33 patients examined by radiology 17 (52%) were positive for ankle arthropathy, and of these, 16 were also positive by the physical score. The presence and severity of ankle arthropathy was more common in patients with a one-stage factor VIII level of less than or equal to 11 IU/dl. There was a significant relationship between the presence of ankle arthropathy and a history of bleeds into the ankle joint as a child. We conclude that arthropathy of the ankle in these patients is common, is often severe and disabling, and is due to episodes of bleeding into the ankle joint during childhood.

Keywords
Mild haemophilia, moderate haemophilia, ankle arthropathy, factor VIII, Pettersson score

Introduction
Arthropathy due to recurrent haemarthrosis has been well studied in severe haemophilia A, and predominantly affects large joints such as knees, ankles, hips, elbows and shoulders (1, 2). However, there is only scant data on the prevalence and severity of chronic arthropathy in mild and moderate forms of the disease. In an early study published prior to the availability of specific factor VIII (FVIII) treatment, it was observed that “one-third” of the patients with moderate haemophilia A and only very few with mild haemophilia had ankle arthropathy (3). In a more recent study that was based only on a survey questionnaire concerning “bodily pain” in a life-quality survey, 43% of 100 patients with mild/moderate haemophilia A had chronic musculoskeletal pain (4). A third study showed that 51% of 35 patients with moderate haemophilia A had a positive Pettersson score in the combined radiological evaluation of three joints (ankle, knee and elbow), despite a third of them having received prophylaxis (5). However, this study did not give details of the degree of arthropathy in the different joints.

It is our experience that many patients with mild/moderate haemophilia have arthritis of one or both ankle joints, but do not have arthritis in the knee joints or the other joints that are often affected in severe haemophilia. A number of these patients suffer constant ankle pain, some to the extent of having to abandon long-term employment. This painful and disabling ankle arthropathy can cause significant medical and socioeconomic impact on the patient as well as the health system.

To understand the clinical picture of chronic ankle arthropathy in mild/moderate haemophilia, we examined ankle arthropathy in patients with mild and moderate haemophilia A in South Australia. We hypothesised that ankle arthropathy is common in patients with mild/moderate haemophilia A, that the presence of ankle arthropathy is associated with a relatively low FVIII level, and that a predisposing factor is recurrent bleeding into the ankle joint in early life.

The specific aims of this study were to determine the prevalence and severity of ankle arthropathy in mild/moderate haemophilia A, and to ascertain its relationship to FVIII level and to a history of haemarthrosis of the ankle joint during early life. We considered that the knowledge obtained in this study would form an initial understanding of the presence and extent of ankle arthropathy in mild/moderate haemophilia and that this knowledge may be helpful in preventing this complication.

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Materials and methods

Patients

This study was approved by the Research Ethics Committee of the Royal Adelaide Hospital (RAH), and informed consent from the patients studied was obtained. The patients are managed at the Haemophilia Centre for Adult Patients in South Australia, which is based at the Royal Adelaide Hospital (RAH) and the Institute of Medical and Veterinary Science (IMVS), Adelaide.

There were 134 adult patients with inherited haemophilia A living in South Australia and registered on the clinical database in our Haemophilia Centre. This database is part of the Australian Bleeding Disorders Registry. Also, the families of all patients were identified in a genetic registry (South Australian Genetic Registry of Haemophilia A) at the IMVS. We were able to contact 92 of the 110 patients with mild/moderate haemophilia A on our database. This included 77 mild (one-stage FVIII 5 IU/dl) and 15 moderate cases (one-stage FVIII 2–5 IU/dl). For most patients a number of baseline FVIII levels had been recorded, and for the purpose of the study the median level was used. Of the 92 patients, 59 had equivalent haemophilia (defined as one-stage FVIII results equivalent to two-stage FVIII results) and 33 had discrepant haemophilia (one-stage FVIII more than double the two-stage results) (6–8).

A short survey on the symptom of ankle pain was posted to the 92 patients with mild/moderate haemophilia A. This enquired whether or not ankle pain was present and whether the patient was willing to participate in a clinical interview and assessment of the ankle joint. In addition, patients with ankle pain were asked to define whether the pain was “mild, moderate or severe”, according to the WFH criteria (9). Mild pain does not interfere with occupation or with activities of daily living (ADL), and may require occasional analgesics. Moderate pain causes partial or occasional interference with occupation or ADL, and requires use of analgesics. Severe pain interferes with occupation or ADL, and requires frequent use of analgesics, including narcotics.

Clinical interview and assessment of ankle arthropathy

Sixty-five of the 92 patients returned their answers and of these 34 (6 moderate haemophilia A and 28 mild) attended for the clinical interview and assessment of ankle arthropathy. None of the 34 patients had any recent events of acute or subacute joint bleeding or joint surgery, including their ankle joint. All except for one patient were on “treatment-on-demand” therapy. Three patients had inhibitors to FVIII. Twenty-three patients were hepatitis C antibody positive. The history of bleeding events during both early and adult life was collected during interview.

Evaluation of ankle arthropathy was by pain score, physical score and radiology score. To supplement the information on severity of pain by the WFH method obtained in the initial survey, the average degree of ankle pain in the preceding four weeks was indicated by each individual on a standard visual analogue scale (VAS) of 0 to 10 points (10, 11). We arbitrarily divided the VAS scores into four groups: zero, 0.5 – 3 (mild), 3.5 – 6.5 (moderate) and 7 – 10 (severe).

The physical ankle scores were obtained using the WFH guidelines recommended by its Orthopaedic Advisory Committee, for the evaluation of joints (9, 12). This included assessment of ankle swelling, calf muscle atrophy, axial deformity, crepitus, loss of range of motion (ROM), flexion contracture and instability. For each ankle joint, a score of 0 to 2 was assigned for each of the seven items. The combined score from both the left and right ankles was used to summarise the results for each individual.

An ankle joint was judged to have loss of ROM when the ROM was equal to or less than 63° as measured by a goniometer. This represents a loss of greater than 10% of the normal value (dorsiflexion plus plantar flexion = 70°). Loss of 10–33% of normal ROM (i.e. ROM 49–63°) was scored 1 while loss of > 33% (i.e. ROM < 49°) was scored 2.

We also adopted the WFH guidelines for the radiology assessment of haemophilic arthropathy based on the Pettersson scale (9, 13). The criteria assessed were osteoporosis, enlarged efflusion, irregular subchondral surface, narrowing of joint space, subchondral cyst formation, erosion of joint margins, gross incongruence of articulating bone ends and joint deformity. Each of the eight items was assigned a score of 0, 1 or 2. Two radiologists reviewed the films independently and the mean value of the two scores was taken as the final score for each joint. The combined score from both the left and right ankles was used to summarise the results for each patient.

One-stage FVIII assay

One-stage FVIII assays were carried out using an MLA Electra 1000C automatic coagulation analyser (Medical Laboratory Automation Inc, Pleasantville, NY, USA), as previously described (6, 7). The APTT reagent Actin FSL was from Dade-Behring (Marburg, Germany). Standards were calibrated against the International Reference Plasma for FVIII from the National Institute for Biological Standards and Control (NIBSC, Hertfordshire, UK).

Two-stage FVIII assay

Two-stage FVIII assays were measured by a semi-automated clotting method, using a Coag-a-Mate X2 (Organon Teknika, Oss, The Netherlands) and the Diagen Two-Stage Factor VIII Assay Kit (Diagnostic Reagents, Oxon, UK) as previously described (6, 7). In preparation for the assay, standards and samples were adsorbed with aluminium hydroxide – citrated plasma was mixed with 1/100th volume of 2% Al(OH)3, (Alhydrogel, Superfos Biosector A/S, Frederikssund, Denmark), incubated for 5 minutes (min) at 37°C, centrifuged and the supernatant taken for assay.
Chromogenic FVIII assay

Chromogenic FVIII assay was performed on an STA-Compact or STA-R instrument (Diagnostica Stago, Anieres, France), using Biophen Factor VIII:C kit (Hyphen BioMed, Neuville-sur-Oise, France), according to the manufacturer’s instructions, but with an incubation time of 450 seconds (sec) instead of 300 sec (14).

Statistics

A non-parametric Spearman rank correlation was used to analyse associations between two groups of non-parametric data. A Fisher’s exact test was used to analyse data of contingency tables. Analysis of receiver-operator characteristic (ROC) curves was performed to calculate sensitivities and specificities for different cut-off values of FVIII, using software Prism 4 (GraphPad software, CA, USA).

Results

Ankle pain

Of the 65 patients with mild or moderate haemophilia A, who responded to our initial survey, 27 (42%) had ankle pain (unilateral or bilateral) of various degrees of severity on a regular basis. Of the 34 patients interviewed, a similar proportion, 16 (47%) had ankle pain. Age distribution and FVIII levels were also similar in the survey and interview populations (data not shown): hence the interview population was a reasonable representation of the survey population.

Of the 16 patients with ankle pain, 10 (63%) had bilateral ankle involvement. When the severity of ankle pain in the 34 patients interviewed was analysed by the WFH method, of the 16 patients with ankle pain, eight were mild, four moderate and four severe. This was in strong agreement with the analysis by the VAS pain score, where seven were mild, five moderate and four severe.

Ankle arthropathy had a significant effect on the general mobility of the 34 patients. Of the 16 patients with ankle pain, 10 had difficulties climbing (up and/or down) stairs and six were only able to walk for less than 30 min (four for less than 10 min). Five patients attributed lack of regular exercise to their ankle pain. Only three patients had ankle pain but without noticeable limitation on physical activities. Four patients required long-term analgesics including medications with a narcotic component. Although the majority of these patients do not use walking aids regularly, five have to wear modified shoes.

Physical ankle score

Of the 34 patients interviewed, 27 (79%) had a positive ankle score (median score 2, range 1–6) by the WFH physical scoring system: 19 had both ankles affected, seven right ankle only and one left ankle only.

Table 1: Physical scoring system to assess ankle arthropathy in the 27 patients with a positive physical ankle score.

<table>
<thead>
<tr>
<th>Physical signs</th>
<th>Number of patients</th>
<th>Total ankles affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sides</td>
<td>Right side only</td>
</tr>
<tr>
<td>1) Swelling</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2) Calf muscle atrophy</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3) Axial deformity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4) Crepitus on motion</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5) Range of motion</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>6) Flexion contracture</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7) Instability</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>At least one of above</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

Physical ankle score (median score 2, range 1–6) by the WFH physical scoring system: 19 had both ankles affected, seven right ankle only and one left ankle only.

Radiological ankle score

Thirty-three of the 34 patients had ankle radiographs taken. Of these, 17 (52%) had various degrees of haemophilic arthropathy (median score 3, range 0.5–12). The most frequent signs detected were irregular subchondral surface, narrowing of joint space, subchondral cyst formation and enlarged epiphysis (Table 2). There...
were 28 ankles with a positive radiology score. In 16 of these two or more of the parameters were affected (data not shown).

About two-thirds of the patients (11/17 = 65%) with a positive radiology score had both ankles affected. This frequency was similar to the findings for bilateral ankle involvement by the VAS pain score and physical ankle score (63% and 70%, respectively).

Table 3 shows the comparison of physical and radiological scoring systems in the assessment of ankle arthropathy in 33 patients with mild/moderate haemophilia A. Also shown are the numbers of patients with ankle pain in each group. There was a strong relationship between the two scoring systems and also with the presence of ankle pain. Sixteen of the patients (48%) were positive by both scoring systems and 14 of these had ankle pain. Only six patients (age 22–51 years) were free of ankle arthropathy by both systems. There were 10 patients with a normal ankle X-ray but a positive physical ankle score (median score 1, range 1–4) and of these only one had ankle pain.

Relationship of ankle scores to age

There was an increase in both physical and radiological ankle scores with increase in age (Fig. 1), especially for the radiological score (Fig. 1B). The figure shows that many patients have a positive physical score but a negative radiological score, which tended to occur in patients of younger age.

FVIII level and presence and severity of ankle arthropathy

In the 33 patients studied for ankle arthropathy by both physical and radiology scoring systems, 27 patients had equivalent FVIII levels by one- and two-stage FVIII assays, while six had discrepant FVIII levels.

The relationship between the radiological ankle score and the FVIII levels is shown in Figure 2. There is a significant negative correlation between the radiology ankle score and the one-stage FVIII (R = −0.49). By visual inspection, there appeared to be a threshold effect of the one-stage FVIII on the presence of ankle arthropathy. When the one-stage FVIII was equal to or less than 11 IU/dl (n = 16), there was an increase in the occurrence and severity of ankle arthropathy (n = 12) (Fig. 2A).

For FVIII levels by the two-stage assay (Fig. 2B) or chromogenic assay (Fig. 2C), there was also a statistically significant correlation between the FVIII level and the radiology score (R = −0.55 and −0.43, respectively). The observed threshold level of FVIII to predict ankle arthropathy by radiology assessment appeared to be 6 IU/dl for the two-stage assay and 8 IU/dl for chromogenic assay. The two discrepant patients who did have arthropathy had a two-stage FVIII below threshold (≤6 IU/dl), whereas using one-stage or chromogenic results, they were above threshold.

A ROC curve analysis was also used to examine the effect of one-stage FVIII on predicting arthropathy (Fig. 3). There is an inflexion of the ROC curve at a FVIII level of approximately 11.5 IU/dl (sensitivity 75% and specificity 71%). This agrees well with the cut-off level of 11 IU/dl determined by visual inspection of the cut-off levels of 6 and 8 IU/dl for the two-stage and chromogenic assays respectively (data not shown).
Bleeding history and presence of ankle arthropathy

Table 4 shows that ankle arthropathy was associated with a history of ankle bleeding and multiple episodes of ankle bleeding. Fifteen of 16 patients with ankle arthropathy had a history of ankle bleeding, compared with 9 of 17 without ankle arthropathy (p = 0.02, Fisher’s exact test). In contrast to ankle bleeding, equal numbers of patients with (11 of 16) and without (11 of 17) ankle arthropathy had a history of bleeding into other joints (data not shown). Also, 11 of 16 patients with ankle arthropathy had a history of muscle bleeding, while a similar number (13 of 17) of pa-

Figure 1: The relationship between age and physical or radiology ankle score in 33 patients. ◆ patients (n = 27) with equivalent FVIII levels by one- and two-stage FVIII assays; ○ patients (n = 6) with discrepant FVIII levels by one- and two-stage FVIII assays. Non-parametric (Spearman) rank correlation for: A) Age and physical ankle score: R = 0.36, p = 0.04; B) Age and radiology ankle score: R = 0.56, p = 0.0008.

Figure 2: The relationship between FVIII level and radiology ankle score in 33 patients. ◆ patients (n = 27) with equivalent FVIII levels by one- and two-stage FVIII assays; ○ patients (n = 6) with discrepant FVIII levels by one- and two-stage FVIII assays. Spearman rank correlation coefficient for one-stage assay: R = –0.49, p = 0.004, for two-stage assay: R = –0.55, p = 0.001 and for chromogenic assay: R = –0.43, p = 0.01.
Figure 3: ROC curve for one-stage FVIII level and ankle arthropathy. AUC, area under the curve.

Table 4: Ankle bleeding and arthropathy.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Episodes of ankle bleeding</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1–4</td>
</tr>
<tr>
<td>Ankle arthropathy*</td>
<td>+ve</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>−ve</td>
<td>8</td>
</tr>
<tr>
<td>Subtotal</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

* Ankle arthropathy defined as positive for both physical and radiology scores.

The prevalence of ankle arthropathy in our group of 34 patients with mild/moderate haemophilia A was: 16 of 34 by pain score, 26 of 34 by physical score and 17 of 33 by radiology score. There was a good agreement between pain score and radiology score with 15 patients being positive by both pain score and radiology score (R = 0.79, p < 0.0001). On the other hand, the physical scoring system was more sensitive than the radiology scoring system and the pain score. There were 10 patients who had a positive physical score but a negative radiological score, and these were of younger age. Only one of them had ankle pain. A positive physical score in the absence of positive radiology score may be an indication of impending arthropathy. However, a longitudinal study of a cohort of patients would be required to confirm or refute this.

We consider the most objective evaluation of ankle arthropathy in mild and moderate haemophilia is the radiology assessment. In the current study, the most frequent radiology findings were irregular subchondral surface, subchondral cyst formation and narrowing of joint space. There were similarly frequent findings of loss of ankle ROM (predominant loss of dorsiflexion) on physical examination. This observation was consistent with an earlier study, which concluded that the loss of cartilage articular space was the single most important roentgenographic finding related to reduced ROM in haemophilic arthropathy (15).

There is a significant correlation between FVIII level and radiology score, consistent with ankle arthropathy being related to a low FVIII level. In addition, there appears to be a threshold effect of FVIII level on the presence of arthropathy: a FVIII level of equal to or less than 11 (one-stage), 6 (two-stage) and 8 (chromogenic) IU/dl is associated with an increase in the frequency and severity of patients without ankle arthropathy had muscle bleeding. Similarly there were approximately equal numbers of patients with a history of haematuria, epistaxis and mouth bleeding in those with or without ankle arthropathy (data not shown).

Of the 24 patients who had a history of ankle bleeding, 18 had ankle bleeding in childhood/adolescence, while six had ankle bleeding only in adulthood. Of the 18 patients with ankle bleeding early in life, 14 had ankle arthropathy, whereas in the 15 patients without bleeding in childhood/adolescence, only two had ankle arthropathy (data not shown). There is a strong relationship between ankle arthropathy and history of bleeding early in life (p = 0.001, Fisher’s exact test).

## Discussion

The results of this study confirmed our hypothesis that there is a high prevalence of ankle arthropathy in patients with mild and moderate haemophilia A. Of the 33 patients, half (n = 16) had ankle arthropathy by both physical and radiological scoring systems. This included four of the six patients with moderate haemophilia A and 12 of the 27 patients with mild haemophilia A. In those with ankle arthropathy, approximately two-thirds were affected in both ankles.

The only recent published data on arthritis in mild/moderate haemophilia is a study on 46 patients with moderate haemophilia (5). In this study, 51% of the 35 patients with moderate haemophilia A (1/3 were on prophylaxis) were found to have a positive Pettersson score. However the scores were based on the combined assessment of six joints (ankles, knees and elbows). The scores for the individual joints were not published (5). The median Pettersson score was 1 point (maximum score in the group: of 78 points) at the age of 25 years. Hence the authors considered that the arthritis in these patients was only “mild”. However, it was acknowledged that some patients did experience severe joint pathology: five patients had chronic synovitis and eight patients underwent a total of 11 orthopaedic surgeries, including three arthrodeses of the ankle (5).

The presence of ankle arthropathy was characterised not only by its high frequency, but also by its disabling consequences. There was a significant impact of arthritis on the patients’ general mobility including difficulty in climbing stairs and limitation of walking distance. In addition, ankle arthropathy was highly associated with the symptom of pain. Nearly all of the 16 patients with ankle arthropathy (14/16) had ankle pain on a regular basis, and some required long-term analgesics.

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arthropathy. Two discrepant patients with two-stage FVIII below the threshold did have a mildly positive radiological ankle score, but their one-stage or chromogenic FVIII results were above the threshold. However the numbers were much too small to determine whether or not for the discrepant patients, the two-stage FVIII level (in contrast to the one-stage or chromogenic results) is more predictive of ankle arthropathy.

It is of interest that there is such a high occurrence of arthritis of the ankle joint in patients with FVIII levels up to 11 IU/dl (one-stage) when patients with severe haemophilia are treated with prophylactic FVIII to keep the trough FVIII level above 1 IU/dl. There is data to show that whereas prior to the introduction of prophylaxis in severe haemophilia the knee joint was the most frequently affected by bleeding, it is now the ankle joint that is most often involved (16). Hence the ankle joint may not be adequately protected by current prophylaxis regimens. It is suggested that prophylaxis has led to higher levels of activity including participation “in higher impact sports” and that this may lead to more injury of the ankle joint than the knee (16). In addition, a higher level of FVIII may be required to prevent bleeding after ankle sprains. To lessen the risk of ankle bleeding in severe haemophilia A it may be appropriate to consider aiming for a FVIII trough level higher than 1 IU/dl. Alternatively, the risk may be lessened by timing prophylaxis to be given on the day(s) of increased activity thus ensuring a higher level of FVIII at these times. Similarly patients with mild/moderate haemophilia may benefit from a dose of prophylaxis prior to higher level sports activities.

In the present study, the history of bleeding shows that patients who had ankle arthropathy had significantly more bleeding episodes in the ankle joints than in patients who did not have ankle arthropathy, and this mostly occurred early in life. In contrast, other bleeding manifestations, such as bleeding into other major joints or haematuria, were equally frequent in the two groups. The results are consistent with our hypothesis that in mild and moderate haemophilia A, ankle arthropathy is prevalent and is due to frequent episodes of ankle joint haemorrhage, especially in childhood and/or adolescence.

It is of interest whether sports activities predispose to arthritis. Many of the patients gave a history of taking part in sports activities, in some cases including contact sports such as Australian rules football, rugby, soccer, basketball, boxing. However, we could not demonstrate any relationship between participation in sports and the prevalence of ankle joint arthropathy (data not shown). A more detailed and prospective study would be required to resolve this.

There are limitations of the current study. The sample size was relatively small. To overcome this, a multi-centre study would be desirable. This would also provide further evidence concerning the FVIII cut-off level. Another possible limitation is that bias may arise from the recruitment of patients, because those with symptoms might be more likely to agree to participate in the study. Nevertheless, the 34 patients in our study had a similar distribution of age and FVIII level to the 92 patients of the database cohort (data not shown).

An important implication of our study is that in the treatment of mild and moderate haemophilia A, strategies aimed at prevention of arthritis of the ankle joint should be developed. Guidelines should advocate prompt and adequate treatment of ankle joint trauma, which in practice is often an ankle joint sprain. Adequate treatment should include the infusion of FVIII concentrate and appropriate physiotherapy. It is important that patients and parents of children with mild/moderate haemophilia A should be warned of the dangers of untreated ankle bleeding, and of the necessity that any sprain of the ankle joint should be evaluated at the Haemophilia Treatment Centre as soon as possible. Pending results of further studies, we recommend that special attention should be paid to patients with a FVIII level below about 11 IU/dl.

This study is the first to document the scale of chronic ankle arthropathy in mild and moderate haemophilia A, a seemingly under-studied and infrequently reported complication. We identified that ankle arthropathy is prevalent and disabling in our group of adult patients with mild and moderate haemophilia A. We also demonstrated that the presence and severity of ankle arthropathy is positively correlated to a lower FVIII level. The presence of ankle arthropathy is also associated with a history of ankle haemorrhage. Further studies are indicated to document frequency and to evaluate protocols aimed at prevention of this complication.

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References