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Correlation between clinical, radiological and ultrasonographical image of knee joints in children with haemophilia

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Summary. The aims of the study were to evaluate the clinical, radiological and ultrasonographical images of knee joints in children with severe haemophilia and von Willebrand's disease, to determine the correlation between these images and to assess the usefulness of ultrasonography (USG) in evaluating the intensity of haemophilic arthropathy. Thirty-nine boys were included in the study, all of them with a past history of knee bleeds. The average age of the children was 10.02 ± 3.01 years. In patients with slight (1–3 points) and moderate (4–7 points) radiological changes in knee joint bones, an increase in synovial fluid, considerable hypertrophy and inflammation of the synovium were observed in USG. In haemophilic patients with severe (8–13 points) bone changes, the amount of fluid was usually normal and there was slight inflammation but considerable hypertrophy of the synovium. Radiological evaluation of haemophilic arthropathy was made according to the Pettersson classification. A good correlation between the degree of cartilage damage in USG and the progression of bone changes in radiographs was found. Cartilage and bone damage progressed with the increase in the number of intra-articular haemorrhages into the knee joint. In our opinion USG is useful in evaluating the fluid, synovium and cartilage of joints in haemophiliacs.

Keywords: chondromalacia, haemophilia, haemophilic arthropathy, knee joint, synovitis, ultrasonography.

Introduction

Joints are the most common sites of bleeds in haemophilic patients. Haemarthroses occur most frequently in the knees, elbows and ankles [1–4]. They can appear after trauma or spontaneously during normal daily activity and particularly in the severe type of the disease, when factor VIII or IX is below 1% of normal level [5,6].

Extravasated blood breaks down in the joint cavity and haemoglobin iron is absorbed by synovial macrophages and chondrocytes. If the synovium fails to recover fully between bleeding episodes, the excess of iron causes synoviocyte and chondrocyte disintegration with release of lysosomal enzymes, proteoglycan degradation and synovitis. The synovium stimulated by the blood becomes hypertrophic and its vascularity increases; such synovium is a ready source of additional bleeding. Hydrolytic enzymes, such as acid phosphatase and catepsin D, a high level of which is found in haemophilic joint fluid and the synovium, play a role in maintaining the inflammatory reaction of the synovium. These enzymes destroy not only free blood but also the synovium, cartilage and bone [6–12].

Synovitis causes hypertrophy of the epiphyses that may lead to leg length discrepancies and angular deformities in children [4,13]. Progressive cartilage damage causes narrowing of joint space and subchondral bone irregularity [5,14]. Defects in the superficial layer of bones, subchondral cysts, osteoporosis and

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joint surface incongruity occur [4,7,14–16]. The synovium is gradually converted from friable hyperaemic tissue to fibrotic scar tissue [12,17]. In advanced haemophilic arthropathy, fibrous changes of the synovium, joint space narrowing and joint surface incongruity lead to persistent limitations of joint motion [2,3,13,18,57].

The aims of the study were to evaluate the clinical, radiological and ultrasonographical images of knee joints in children with severe haemophilia and von Willebrand's disease, to determine the correlation between these images and to assess the usefulness of USG in evaluating the intensity of haemophilic arthropathy.

Materials and methods

Thirty-nine boys with severe haemophilia and von Willebrand's disease were included in the study. All of them had a past history of knee joint bleeds. There were 35 children with haemophilia A, three children with haemophilia B and one with von Willebrand's disease type III. In seven haemophilia A patients factor VIII inhibitor was detected, in five patients the inhibitor was still present and in two it was present in their past histories. The average age of the children was 10.02 ± 3.01 years, range 2 to 16 years.

From anamnesis, the frequency of haemarthroses into the examined knee joint was evaluated, i.e. the average number of bleeds per month during the previous year and the number of haemarthroses (approximately the total number of bleeds into the examined knee joint). During physical examination the range of motion of the knee joint was measured, defining an angle between maximal extension and flexion of the joint. Radiological evaluation of haemophilic arthropathy was performed based on the Pettersson classification [1]. According to this classification, the maximum possible score of points is 13, which reflects the most pronounced joint destruction.

USG examinations were carried out using ATL HDI 3000, 3500 and 5000 machines with wideband high frequency (5–10 and 5–12 MHz) linear probes or Siemens Elegra with a wideband high frequency (5–9 MHz) linear probe.

The following were defined in examination:

1 Amount of synovial fluid according to the scale: 0 = normal, 1 = slight increase, 2 = moderate increase, 3 = considerable increase;
2 Hypertrophy of the synovium according to the scale: 0 = no hypertrophy, 1 = moderate hypertrophy, 2 = considerable hypertrophy, 3 = severe hypertrophy;
3 Inflammatory reaction of the synovium as a degree of hyperaemia: 0 = no hyperaemia, 1 = slight hyperaemia, 2 = considerable hyperaemia, 3 = severe hyperaemia with numerous vascular conglomerates;
4 Degree of cartilage damage according to Outerbridge's scale [19]: 0 = normal-thickness cartilage with smooth surface, I° chondromalacia = normal-thickness cartilage, heterogeneous, locally increased echogenicity, II° chondromalacia = blurred cartilage surface, normal or slightly decreased thickness, hyperechogenicity, III° chondromalacia = irregular cartilage surface, decreased thickness, IV° chondromalacia = extensive cartilage erosions, irregular subchondral layer, subchondral cysts.

The synovial fluid and the synovium were evaluated in suprapatellar recess, while cartilage was assessed on femoral condyles.

All patients were divided into four groups depending on the intensity of radiological changes in haemophilic arthropathy: group I, normal joint (0 points); group II, slight changes in joint bones (1–3 points); group III, moderate changes in joint bones (4–7 points); group IV, severe changes in joint bones (8–13 points).

The correlation coefficient between respective parameters from clinical, radiological and USG examination was calculated in statistical analysis [20]. For comparison of data in respective groups of patients the term 'median' was used for parameters expressed in the ordinal scale and less frequently, the term 'arithmetic mean' was used for parameters expressed in the interval scale [21].

Results

Among 39 examined patients, there were six boys in group I, 16 boys in group II, seven boys in group III and 10 boys in group IV.

The mean age of the children was 6.83 ± 4.02 years in group I (range 2 to 11 years), 9.5 ± 2.36 years in group II (range 4–15 years), 10.42 ± 2.14 years (range 7–14 years) and 12.5 ± 1.84 years (range 0–16 years) in groups III and IV, respectively.

There were no boys with a maximal radiological score in group IV. The most damaged joint was evaluated as 12 points in one boy, 11 points in another and 10 points in two other boys. The median was 9 in this group.

The average frequency of bleeds into the examined knee joint was 0.17 ± 0.09 (range 0.1–0.33) in group I, 1.85 ± 1.35 (range 0.1–6) in group II,

Table 1. Radiological image (rtg) of knee joint and frequency of haemarthroses in haemophiliacs.

Group number	Rtg points[1]	Rtg median of points[1]	Number of patients (%)	Mean age of patients (%)	Mean frequency of haemarthroses per month (range)	Number of haemarthroses [median (range)]	Mean motion in degrees (range)
I	0	0	6 (15)	6.83 ± 4.02 (2–11)	0.17 ± 0.09 (0.1–0.33)	1.5 (1–2)	135 ± 0
II	1–3	3	16 (41)	9.5 ± 2.36 (4–15)	1.85 ± 1.35 (0.1–6)	30 (1–50)	114 ± 18.45 (75–135)
III	4–7	5	7 (18)	10.42 ± 2.14 (7–14)	2 ± 0.5 (1.5–3)	50 (40–100)	92.8 ± 20.7 (60–120)
IV	8–13	9	10 (26)	12.5 ± 1 84 (10–16)	2.2 ± 0.58 (1.5 –3)	50 (50–150)	63 ± 43.9 (10–115)

[1]According to Pettersson's scale.

Table 2. Radiological picture (rtg) and USG of knee joint in haemophiliacs.

Group number	Rtg median of points[1]	Fluid amount [median] (range)[2]	Hypertrophy of synovium [median](range)[2]	Inflammatory [median] (range)[2]	Chondromalacia (range)[3]
I	0	1 (0–1)	1 (0–2)	0 (0–2)	0 (0–I0)
II	3	2 (0–3)	2 (0–3)	2 (0–3)	II0 (0–IV0)
III	5	1 (0–2)	2 (0–3)	2.5 (0–3)	III/IV0 (I/II–IV0)
IV	9	0 (0–2)	2 (0–3)	0.75 (0–3)	IV0 (I/II–IV0)

[1]According to Pettersson's scale; [2]according to own scale from 0 to 3; [3]according to Outerbridge's scale.

2 ± 0.5 (range 1.5–3) in group III, and 2.2 ± 0.58 (range 1.5–3) in group IV.

The number of bleeds into the examined joint ranged from 1–2 (median 1.5), 1–50 (median 30), 40–100 (median 50) and 50–150 (median 50), respectively, in groups I, II, III and IV.

Normal motion of examined knee joint (135°) was found in all boys in group I. In group II the average range of motion was 114 ± 18.45° (range 75° to 135°), in group III it was 92.8 ± 20.7° (range 60° to 120°) and 63 ± 43.9° (range 10° to 115°) in group IV. The results are presented in Table 1.

In group I a normal (0) or slightly increased (1) amount of synovial fluid in USG (median 2) was found, in group II the amount of fluid ranged from normal to considerably increased (3, median 2) and in group III and IV it ranged from 0–2. The median in group III was 1 and in group IV it was 0.

The hypertrophy of synovium was expressed in numbers from 0–2 (median 1) in group I, and 0–3 (median 2) in the other three groups.

The inflammatory reaction of synovium was defined in numbers from 0–2 (median 2) in group I, and 0–3 in the other three groups with median 2, 2.5, and 0.75, respectively, in groups II, III and IV. In five boys from group IV an increased inflammatory reaction of the synovium was not found and in three of them there were signs of fibrosis.

Normal or slightly changed cartilage (I°, median 0) was detected in group I, cartilage damage from 0–IV° in group II (median II°) and I/II°–IV° in groups III and IV (median III/IV° and IV° in groups III and IV, respectively). The results are presented in Table 2.

The correlation coefficient between the radiological score of the knee joint and the degree of chondromalacia in USG was 0.71 in the whole examined group. A similar correlation coefficient was found between the radiological score and the number of bleeds (0.67) and between the degree of chondromalacia and the number of bleeds (0.73).

The correlation coefficient between the radiological score and the inflammatory reaction of the synovium, and between the degree of chondromalacia and the inflammatory reaction was 0.269 and 0.469, respectively.

A negative correlation coefficient between the radiological score and joint motion (−0.70) and

between the degree of chondromalacia and the motion of the examined knee joint (−0.46) was obtained.

Discussion

On the basis of radiological examination the boys with severe haemophilia or von Willebrand's disease were divided into four groups depending on the intensity of bone changes. The group with slight changes in the radiological image of joint bones (group II–41% of patients) was the most strongly represented. The median of radiological scores was 3 in this group. A normal joint image was found in a few patients, because only those who had undergone knee joint bleeding were included in the study.

Intensity of radiological changes increased with the age of the patients, which is in accordance with previous findings in numerous publications [5,22,23]. The wide range of age in the groups was notable. On several occasions a normal radiological image of the knee joint was observed in the 11-year-old patients, while slight or even moderate bone changes were found in 4- and 7-year-old boys. Therefore, the disease may take a different course in spite of FVIII (or FIX) deficiency indicating a severe type of haemophilia [24]. Not infrequently young children suffer from recurrent joint bleeds with signs of haemophilic arthropathy, whereas teenagers present normal joints. There are without doubt other reasons for this apart from the level of deficient coagulation factors, such as defects of stature, structure of the myoligamentous system, circumstances and dimension of the first intra-articular bleeding, the method of treatment, the time of recurrence of bleeding into the same joint and proper physiotherapy [13,25].

The average frequency of knee joint bleeds in the year preceding examination of the joint and the total number of haemarthroses into the joint considerably influenced the radiological image of the joint. This was particularly observed in group I, with no bone changes in the knee joint, in which one or two bleeds at most occurred in each child (mean frequency 0.17 ± 0.09). In the other groups frequency of bleeds into the knee joint considerably increased with the intensification of bone changes. However, the differences in frequency of bleeds between these groups were much smaller (from 1.85 ± 1.35 in group II to 2.2 ± 0.58 in group IV).

Slight changes in joint bones were caused by fewer bleeds (median 30) than moderate and intensive changes. The number of bleeds was the same in groups III and IV (median 50), which indicates that a large number of bleeds always causes radiological changes in the joint but these changes are of different intensity. The degree of intensity of joint changes is also dependent on the length of time that blood is retained in the joint, the chronicity of synovitis, the time of bleeding recurrence in relation to the phase of previous bleeding absorption, the dimension of haemarthrosis and the time of starting haemostatic treatment [26]. The high correlation coefficient (0.67) between radiological scores of the knee joint and the number of bleeds undergone confirms the general positive correlation between these parameters.

Even the first long-lasting bleeding can lead to the appearance of joint bone changes, which was shown by our patient with factor VIII inhibitor from group II. The knee joint of this boy was evaluated at 3 points after 1 month of persistent bleeding. However, it usually takes several days for blood to be absorbed and the joint returns to normal when proper treatment is given if there are no additional negative factors, for example the presence of factor VIII (IX) inhibitors [4,13].

Slight bone changes of the joint, up to 3 points in the radiological image, can regress completely after treatment resulting in no further joint bleeds [5]. The treatment can be based on prophylactic infusions of coagulant factor concentrates or, if this proves ineffective, synovectomy [27,28].

In USG of the knee joint a slight increase in the fluid amount, a moderately hypertrophic synovium without inflammatory reaction and normal cartilage were found in group I. While it is not possible to differentiate between the blood and synovial fluid in the USG image, one can expect that it was blood and not synovial fluid in group I due to the acute phase of bleeding and lack of inflammatory reaction. In groups II and III considerable hypertrophy and hyperaemia of the synovium were dominant, but hyperaemia was more extensive in group III. The amount of fluid slightly or moderately increased in patients from these groups, which indicates intensive synovitis. Joint synovitis, usually chronic, is manifested by an increase in joint size, which is most often painless, and also by a floating patella and raised temperature of skin in the area of the joint [14,17,29]. In group IV the USG image of the knee joint changed considerably, the amount of fluid normalized and inflammatory reaction decreased below the values described as slight hyperaemia of the synovium, with considerable hypertrophy as before. Fibrosis of the synovium was observed in several cases. Deformation of joint bones without increase of soft tissue and no floating patella, intensive muscle atrophy and limitation of joint

motion were noted in clinical examination. This stage corresponds with pronounced bone changes in the development of haemophilic arthropathy, which progresses even without further bleeds, leading to increasing degradation of joint function and to disability [1–3,14].

The cartilage image changed with the increase of bone changes in the radiological image. Normal-thickness cartilage with a smooth surface was found in group I. In group II the thickness of cartilage was normal or decreased, the cartilage surface was blurred and echogenicity increased. In group III the cartilage thickness decreased and there was an irregular cartilage surface with erosions. In group IV the extensiveness of erosions was much greater and, in addition, irregularity of the subchondral layer and subchondral cysts were observed.

The relation between the cartilage image in USG and joint bone changes in the radiological image is shown by the high correlation coefficient (0.71).

A high correlation coefficient (0.73) between the degree of chondromalacia and the number of knee joint bleeds was found as well. It confirms the known fact that blood is the main factor destroying the cartilage [8,30].

The limitation of knee joint motion increased together with intensification of bone changes in the radiological image. In group IV knee joint motion was the worst, while the range of results was the greatest (from 10° to 115°), which proves that good joint function is possible, despite very intensive joint changes. The highly negative correlation coefficient (−0.70) between the radiological score and the range of joint motion reflects the tendency for joint motion to decrease together with a progression of joint destruction. This is connected with the narrowing of joint space, incongruence between joint surfaces, fibrosis of the synovium, weakness of extensor muscles and contracture of hamstring tendons [4,7,17].

A much lower negative correlation coefficient (−0.46), between the degree of chondromalacia and joint motion was noted, because cartilage damage precedes the appearance of joint bone changes and the range of motion can still be close to normal, despite extensive cartilage damage.

The relative low correlation coefficient (0.469) between the degree of chondromalacia and the intensity of inflammatory reaction of the synovium is surprising. It is generally known that joint damage induced by extravasated blood is followed by synovitis and articular cartilage destruction [7,8,11,12]. These processes are strictly connected to one another but it is not clear which comes first. The concept of the leading role of synovial changes is in contrast to the observations suggesting the primary role of articular cartilage damage [8,30]. The disappearance of inflammatory reaction together with synovial fibrosis in group IV, despite intensive cartilage destruction, probably particularly influenced the relatively low correlation coefficient between the intensity of chondromalacia and inflammatory reaction in our study. An even lower correlation coefficient (0.269) between the progression of bone changes in the radiological image and the intensity of inflammatory reaction was found, which shows a lack of linear correlation between these parameters. Intensive synovitis was observed in slight bone changes and also in considerable bone changes.

Early perception of intra-articular changes and monitoring of their progress is extremely important. Radiological examination does not show any abnormalities at this stage. USG examination shows the amount of synovial fluid, the degree of hypertrophy and hyperaemia of the synovium, as well as cartilage damage. USG makes it possible to differentiate synovial hypertrophy from effusion at the knee joint [13]. After blood absorption from the joint cavity, USG determines whether the amount of fluid and the synovial image return to normal. If not, it is necessary to prolong haemostatic treatment until the joint image is normal. This treatment is based on prophylactic transfusions of factor VIII (IX) concentrates 2–3 times a week [31,32].

If recurrent joint bleeds are observed earlier, USG enables us to evaluate abnormalities in the structure of soft tissues and articular cartilage. The detection of chronic synovitis is a signal to start intensive haemostatic treatment with several months prophylaxis and, if this proves ineffective, synovectomy should be performed [33–36].

Information about cartilage damage in haemophilic joints was for a long time gathered exclusively from observations made during surgical procedures, and therefore particularly concerned joints with pronounced arthropathy [8,9,37].

Magnetic resonance imaging used in haemophilic arthropathy evaluation made it possible to expose even early changes in cartilage and the synovium, but because of the expense of this examination, it is difficult to recommend it in routine, frequent control of the intensity of intra-articular changes [38–40].

USG examination, which is convenient, inexpensive and easily available, is mainly recommended in diagnosis of soft tissue haemorrhages, for example, abdominal bleeds, haemorrhages into the illiopsoas muscle and pseudotumours [38,41]. In the past joints were rarely evaluated by this method [39]. Together with the advancement of USG techniques, mainly

with the development of digital and Doppler technology (Power Doppler) it appears that USG can provide more details about synovial fluid, the synovium and articular cartilage. USG can often be repeated and it can be used for monitoring treatment.

Conclusions

The increases in the amount of synovial fluid, intensive hypertrophy and synovitis in USG examination were observed in haemophilic children with slight and moderate changes in knee joint bones.

In haemophiliacs with considerable bone changes, the amount of synovial fluid is normal and inflammatory reaction is slight with considerable hypertrophy of the synovium.

The degree of articular cartilage damage noticeable in the USG image of the joint is in good correlation with the intensity of bone changes in radiological examination.

A high correlation coefficient between the number of joint bleeds and the intensity of bone changes (0.67), as well as between the number of joint bleeds and the degree of chondromalacia (0.73) was found.

The range of motion in the knee joint decreases together with the progression of bone changes in haemophiliacs, from normal motion in the group with a normal radiological image of the joint to average motion of $63 \pm 43.9°$ in the group with considerable bone changes.

Ultrasonographical examination is useful in evaluating fluid, synovium and articular cartilage in haemophiliacs.

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