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MRI of the knee region in leukemic children

Part I. Initial pattern in patients with untreated disease

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Abstract. The results of MRI studies performed on the medullary cavity in the knee region of 15 children with leukemia and 5 healthy children are reported. By the age of a few years the signal intensities and the relaxation times of bone marrow begin to resemble fat. Early leukemic infiltration can therefore be more easily recognised in the knee region than in the spine using simple T_1 weighted Spin-Echo images. We observed an abnormal signal pattern in all our patients which fell into three groups: (a) diffuse uniform (b) diffuse non-uniform and (c) patchy. We have not been able to correlate these into age, sex or the risk factor determined by clinical or laboratory methods. The diffuse patterns seem to dominate in cases of ALL, the patchy forms in AML. No correlation could be found between the blast levels established by the iliac crest biopsy and the results of MRI.

MRI presents a new, non-invasive method for judging bone marrow. Results so far prove it to be very sensitive in detecting changes within the medullary cavity. Several authors have already described their studies on MRI and diffuse bone marrow diseases [1-6].

The first systematic studies concerning MRI changes of the spine and proximal femur in leukemic children prior to therapy have been conducted [4, 6, 7]. This prospective study describes MRI performed on the medullary cavity in the knee region of leukemic children.

Material and methods

Fifteen children and adolescents with leukemia, ages ranging from 2 to 17 years, were subjected to a MRI examination of the knee region prior to treatment. Acute lymphoblastic leukemia (ALL) had been diagnosed in 9 cases, the other 6 patients had acute myeloid leukemia (AML). The diagnoses were based on clinical symptoms, laboratory values, blood counts and the results of iliac crest biopsies. One patient showed clinical and scintigraphic evidence of a circumscribed tumorous process in the left femur and biopsy led to the histological diagnosis of AML.

Equipment

Philips Gyroscan S 15 (Superconducting 1.5 T) Head Coil. 2D Fourier transformation (256 × 256), Slice thickness 5 mm, Spin-Echo Technique.

Coronal images of both the knee joints, proximal tibiae and distal femora were obtained. The left knee region was additionally examined using sagittal layers after angulation according to the position of the femur. Coronal T1 weighted images were created using a Multi-Slice technique (TR 500 msec, TE 30 msec), the sagittal images using a Single-Slice technique (TR 250 msec, TE 30 msec). Two measurements were performed in order to aquire the data.

To supplement the visual image evaluation the signal intensities were measured in 9 cases using the *R*egion-*o*f-*I*nterest (ROI)-method. The relative signal intensities of the following areas were measured: the epi-, meta-, and diaphyses of both the distal femur and proximal tibia, the subcutaneous fat, the popliteal fossa and the musculature.

Controls were obtained from the knee region 5 healthy children with ages ranging from 4 to 15 years. An additional "Mixed Sequence" (Spin-Echo Sequence, Inversion Recovery: TR 1000 msec, TRI 1500 msec, TE 50-200 msec, TI 400 msec) was used to determine the T_1 and T_2 relaxation times in a 4 year old child.

Results

Healthy children (Controls)

The bone marrow of the distal femur and proximal tibia produced strong, homogeneous signals on both T_1 and T_2 weighted images, in contrast to the cortical bone and the epiphyseal cartilage, which produced virtually no signals. Measurement of the signal intensities in T_1 weighted images from the controls confirmes that the signal from the bone marrow resembles fat at the age of 4 years (Table 1). The ratios of the relative signal intensities of fat (popliteal fossa) to bone marrow (epi- and metaphysis) lay between 0.96 and 1.3. The ratios of the relative signal intensities of fat to musculature were high in comparison, between 2.95 and 3.92. The signal intensities measured were confirmed by the T_1 and T_2 relaxation times of fat, bone marrow and muscle as measured in a 4 year old boy. The short T_1 relaxation times of 260

Table 1. Signal intensities of bone marrow, fat and musculature in the knee region of healthy children and adolescents. Spin-Echo Technique, TR 500 msec, TE 30 msec, Coronal planes, Slice thickness 5 mm. In brackets: standard deviation

Age (years)	4	6	9	10	15
Bone marrow					
Epiphysis (femur)	1467 (59)	1443 (34)	1681 (28)	1540 (62)	1458 (18)
Metaphysis (femur)	1461 (32)	1410 (61)	1674 (51)	1598 (37)	1432 (24)
Epiphysis (tibia)	1460 (32)	1503 (28)	1654 (43)	1631 (49)	1477 (15)
Metaphysis (tibia)	1449 (61)	1481 (35)	1703 (22)	1591 (53)	1402 (42)
Fat	1710 (61)	1643 (35)	1703 (22)	1640 (31)	1481 (18)
Muscle	438 (37)	483 (58)	565 (65)	505 (67)	433 (47)

Table 2. The pattern of signal reduction in the knee region in correlation to the blast percentage as determined by ilac crest biopsy ($N = 15$)

Leukemic subtype	MRI pattern	Biopsy findings		
		Blasts (%)	Infiltration pattern	Bone marrow insufficiency
ALL	diffuse-uniform	87%	diffuse	+
ALL	diffuse-uniform	83%	diffuse	+
ALL	diffuse-uniform	90,5%	diffuse	+
ALL	diffuse-uniform	99%	diffuse	+
ALL	diffuse-uniform	79%	diffuse	+
ALL	diffuse-nonuniform	96%	diffuse	+
ALL	diffuse-nonuniform	93%	diffuse	+
ALL	patchy	94,5%	diffuse	+
ALL	patchy (epiphysis normal)	94,5%	diffuse	+
AML	patchy (epiphysis normal)	62%	diffuse	(+)
AML	patchy	95%	diffuse and nidal	+
AML	patchy (epiphysis normal)	85%	diffuse	+
AML	diffuse-uniform	71,5%	diffuse	+
AML	diffuse-nonuniform	22% (left) 26% (right)	diffuse	–
AML	diffuse-nonuniform	82,5%	diffuse and nidal	+

(4) and 319 (12) msec of fat and bone marrow compared with 650 msec from muscle. The T_2 relaxation times of fat, bone marrow and from muscle were respectively 79 (2), 83 (3) and 50 (8) msec.

Patients with leukemia

Altered signal intensities in the medullary cavity in the knee region were seen in each of the 15 children and adolescents with leukemia. The signal intensities in T_1 weighted images were lower compared to the surrounding fat tissue and to the yet unaffected bone marrow. The iliac crest biopsies demonstrated that normal bone marrow had been displaced by diffuse or grouped leukemic cells (Table 2). Blast levels ranged from 22 to 99% (Table 2).

In the case of a 10 year old boy a bone tumor had been suspected. He had pain in his left thigh, increased scintigraphic activity in his left femur and had a reduced density on plain films of his left femur. MRI demonstrated zones of reduced signal intensity, circular in the axial layers and patchy in the coronal planes. These findings corresponded to a diffuse infiltration of the bone marrow, consistent with the diagnosis of leukemia but were not typical for a bone tumor (Fig. 1 a, b). Because the clinical symptoms still were in accordance with a circumscribed process and the peripheral blood showed no evidence of blasts, a biopsy was performed on the bone marrow of the left femur. There was an intramedullary nidal AML blast infiltration of 65%. The following iliac crest biopsy confirmed the presence of grouped leukemic blasts (62%).

The appearance of intramedullary intensity reductions differed from case to case. Three different patterns, however, could be recognized (Table 2):

- diffuse-uniform (Fig. 2)
- diffuse-nonuniform (Fig. 3)
- patchy (Figs. 1, 4)

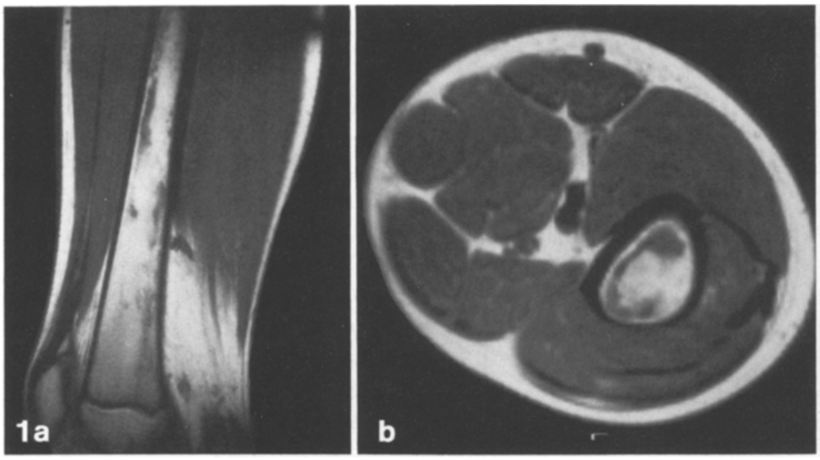
Patchy patterns were found in 5 out of 15 cases (Tables 2, 3). Three of the five had epiphyses showing normal signal behavior and distinctly higher than the signal intensities in the metaphyses. The *diffuse-nonuniform* pattern in 4 children was combined with a normal epiphysis and a diffuse signal reduction in the metaphysis. The area of signal reduction had no clear demarkation from the much lighter diaphysis (Fig. 3). In the cases of *diffuse-uniform* patterns of invasion ($N = 6$) there was a homogeneous reduction of signal intensities in the meta-, dia- and epiphysis. Four of these cases additionally showed uniformly reduced signal intensities in the patella.

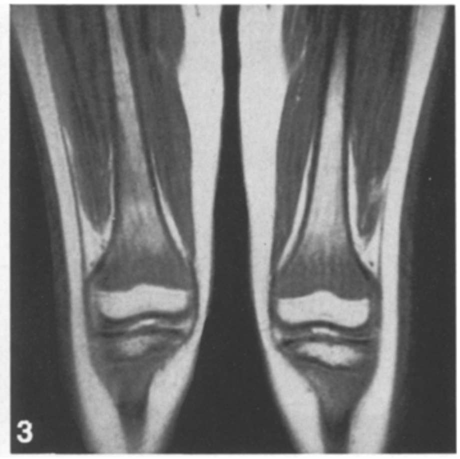
A definitive correlation between the signal pattern of the medullary cavity, sex, age or risk factor of the children could not be established. Neither did the blast level as found by iliac crest biopsy show any sign of correlation to the invasion pattern found in MRI (Table 2). The diffuse patterns seemed to

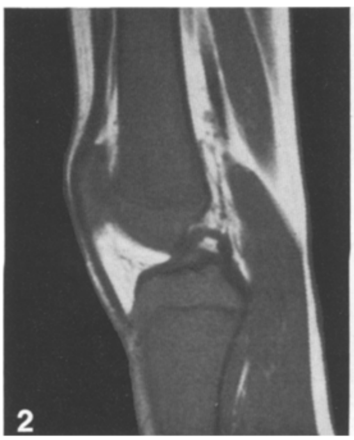
Table 3. Signal intensity pattern of the bone marrow of the knee region after the first manifestation of leukemia prior to therapy ($N = 15$). Correlation of infiltration pattern, leucemic subtype, risk factor, age and sex

Diffuse						Patchy		
Uniform			Non-uniform					
Subtype	Age	M/F	Subtype	Age	M/F	Subtype	Age	M/F
C-ALL/LR	4	M	C-ALL/LR	7	F	T-ALL/HR	7	M
C-ALL/HR	9	M	C-ALL/LR	9	F	AML	10	M
O-ALL/MR	12	F	AML	3	M	AML	11	M
C-ALL/HR	15	M	AML	17	M	AML	14	F
C-ALL/MR	3	M				C-ALL/LR	14	F
AML	2	M						

LR = Low risk, MR = Medium risk, HR = High risk







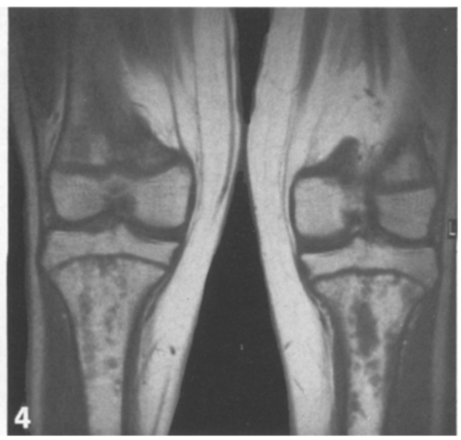


Fig. 1 a and b. AML, male, 10 years old. Confirmation of the diagnosis by femur biopsy. Percentage of blasts in the biopsy material: 62%. SE, TR 500 ms, TE 30 msec. **a** patchy and oblong zones of signal reduction in the metaphysis and diaphysis of the left femur. Sagittal plane **b** an axial layer in the area of the femur diaphysis showing the circular orientation of the infiltration

Fig. 2. ALL, female, 12 years old. *Diffuse-uniform* signal reduction in all medullary cavities, including the patella. SE, TR 500 ms, TE 30 ms. Coronal plane

Fig. 3. ALL, female, 9 years old. *Diffuse-nonuniform* pattern of signal reduction with emphasis on the metaphysis. The epiphysis shows a normal intensity, the left diaphysis is hardly involved. SE, TR 500 ms, TE 30 ms. Coronal plane

Fig. 4. ALL, Female, 14 years old. *Patchy* pattern of signal reduction. SE, TR 500 ms, TE 30 ms. Coronal plane

dominate in cases of ALL, the patchy pattern in cases of AML (Tables 2, 3).

The signal intensities of the medullary cavity were measured in order to verify the visual evaluation, using the ROI method on the epi-, meta-, and diaphysis of the distal femur. In 6 out of 9 cases the values were comparable after considering the standard deviation; any reduction of the signal intensity affected all three regions. This was found in the diffuse-uniform and patchy pattern as well. In 3 patients, however, there was a marked reduction of the signal intensities of the metaphysis in comparison to the epiphysis. If meta- and diaphysis were not equally affected, then the metaphysis showed the stronger reduction of signal intensity (Fig. 5).

Discussion

There are two reasons for imaging the knee region, distal femur and proximal tibia when trying to examine the medullary cavity.

1. One of the most common skeletal changes in cases of leukemia is the classical metaphyseal translucent band. This change is usually best seen in the metaphyses of the proximal tibia and distal femur [8, 9]. It seemed obvious to examine those skeletal regions which show the first changes in conventional radiography. Pathological studies have proved that the marrow infiltration involves the whole skeletal system, including both long and short tubular bones [10].

2. The transformation of the red, blood producing marrow to yellow, fatty marrow is a steady process, beginning at birth in the hand and foot bones [11]. The change starts distally and progresses continuously towards proximal [12]. The final adult distribution is eventually reached by the age of 25 years, the red marrow in long tubular bones is then limited to the proximal third in healthy individuals [13].

On the basis of pathological-anatomical studies performed by Custer and Ahlfeldt [14], Cristy [15] was able to calculate the ratio of yellow marrow in the tibia: 43% in 5 and 77% in 10 year olds. The ra-

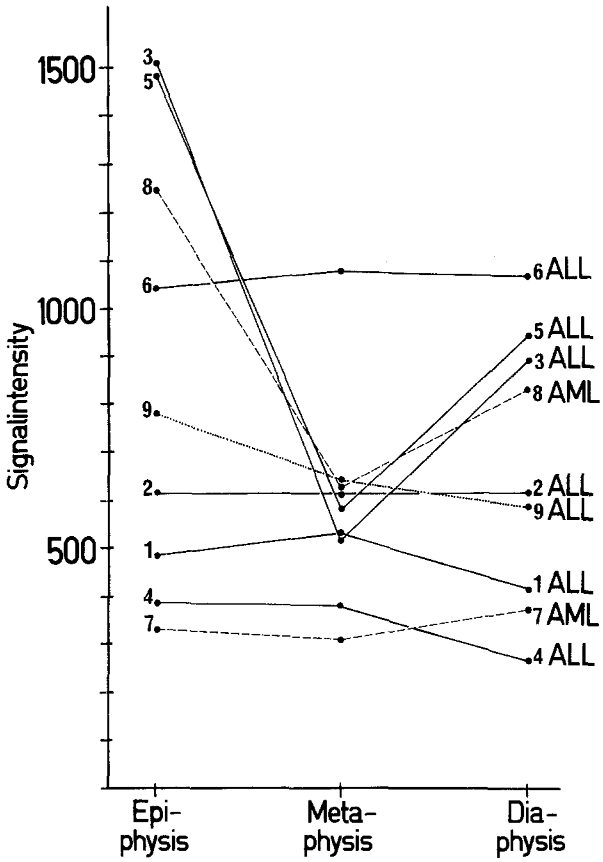


Fig. 5. Signal intensities of the epi-, meta- and diaphysis of the distal femur in leukemic children prior to therapy. Determination of signal intensities using the ROI technique. SE, TR 500 msec, TE 30 msec

tios of the femur were 29% and 61% respectively. According to our studies it is possible to estimate the ratio of yellow marrow in the proximal tibia and distal femur in this age group on the basis of MR signal intensities and relaxation times. These results confirm the assumption that signal intensities and relaxation times of the bone marrow in the knee region begin to resemble those of fat already by the age of 4 years. This causes leukemic infiltrations of the marrow with low signal intensities in MR images to be rich in contrast on T_1 weighted Spin-Echo images and therefore earlier and easier recognized. As has been confirmed by other studies [4, 5], the large physiological amount of blood producing cells in the spines of children and adolescents make it possible to overlook a diffuse infiltration by leukemic cells in normal Spin-Echo images. The same applies to the use of fat/water separated images [3].

The pathological-anatomical studies by Hashimoto [16] and Uehlinger [10] described the displacement of fat cells by leukemic cells. This seems to be the cause of the reduction of the signal intensity and rise of the T_1 relaxation time of the medullary cavity in patients with leukemia, and biopsy of the distal femur of one of our patients with AML confirmed this. Both blood producing and leukemia cells have a longer T_1 relaxation time then fat [17]. On the other hand, follow-up studies reveal that there is no simple correlation between decreased signal intensity and cellular content of the bone marraow [6, 18].

Present studies on the medullary cavity of leukemic children prior to therapy have been limited to the measurements of T_1 relaxation times of the spine [2, 7]. The proof of pathological signal behavior in the distal femur and proximal tibia in every patient with juvenile leukemia examined by us confirms the high sensitivity of MRI in this region. The coronal and sagittal layers made possible by MRI showed to be of great advantage. It made it possible to judge the longitudinal extension of the disease and the involvement of the epiphysis. We were able to recognize three signal intensity patterns prior to therapy:

- diffuse-uniform
- diffuse-nonuniform
- patchy

The presence of both leukemic infiltrations and normal marrow with a high percentage of fat in the distal femur and proximal tibia [19] is the most probable explanation for the patchy MRI pattern. The evidence of signal reduction of the epiphysis even in patients with patchy patterns of the meta- and diaphysis makes it seem unlikely that the involvement of the epiphysis in children is primarily a problem of "space reserves". This had been suspected by Olson et al. [5] in cases of leukemia in adults where the proximal femur had been affected. On the other hand the metaphysis, as opposed to the epiphysis, was not only involved in every case, but was also more strongly affected on the whole. One must assume that the severity of the infiltration is coincident with the normal pattern of hematopoiesis. This would exempt the epiphysis prior to the metaphysis [13].

The described variance of both involved areas of the skeleton and in pattern of invasion makes it possible to correlate the MRI findings with the clinical data. The results do not yet show any connection between the infiltration pattern and age, sex, and especially the risk factor as determined clinically and by laboratory tests. Neither could the involvement of the epiphysis be connected to the risk factor. Apart from the small number of observations there are difficulties in determining when the first clinical symptoms set in. This makes it impossible to clearly correlate the length of the illness to the invasion pattern.

Moore et al. [7] have reported about children with suspected leukemia who were false-negative in iliac crest biopsy but who showed signs of diffuse bone marrow processes in MRI examinations. The authors have also observed a child with uncharacteristic clinical symptoms and a normal blood count, in which MRI was the first method to diagnose a diffuse bone marrow process, consistent with the diagnosis of leukemia. Even though, in clinical routine MRI will surely be used only exceptionally as a diagnostic method when leukemia is suspected.

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