Bone marrow involvement is not manifest in the early stages of childhood acute lymphoblastic leukaemia

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ABSTRACT

INTRODUCTION: Acute lymphoblastic leukaemia (ALL) in children may have atypical presentations causing diagnostic delay. Guidelines for prompt referral have been published. The utility of the specified criteria is unknown.

MATERIAL AND METHODS: Symptoms, signs and laboratory findings at the time of diagnosis were reviewed in a consecutive series of 100 children with ALL in order to determine the frequency of atypical features and to evaluate the Danish referral guideline.

RESULTS: Only 36% had involvement of all three haematopoietic cell lines, and 23% presented with the classic clinical triad of pallor, fever and purpura. Symptoms of bone marrow insufficiency had been present in 77% for an average of two weeks as a late occurrence following musculoskeletal pains (in 49%, duration eight weeks) and constitutional symptoms (in 82%, duration four weeks). Organ infiltration was manifest in 71%. In 22%, only one or no cell count was abnormal; in this group, musculoskeletal symptoms were more frequent and symptom duration longer (two months versus one month). In 15%, lymphoblasts could not be detected in the blood. At the time of diagnosis, the Danish criteria for accelerated investigation were fulfilled in 98% of cases.

CONCLUSION: The clinical presentation of ALL is variable, and full-blown bone marrow insufficiency is a late occurrence as the disease progresses. Reduction of the diagnostic interval requires meticulous examination for organomegaly and attention to subtle haematologic changes.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood with an approximate annual incidence of 40 per million in the Nordic countries [1]. ALL incidence peaks between two and six years of age and occurs more frequently in boys than in girls. The survival rate has improved dramatically since the 1980s, and the overall long-term survival now exceeds 85% [2].

ALL may be a frequent diagnosis in paediatric oncology centres, but it is rarely encountered in general practice. Many cases are easily recognised, presenting with the well-known clinical triad of pallor, fever and purpura with corresponding anaemia, neutropenia and thrombocytopenia, reflecting lymphoblast infiltration of the bone marrow [3, 4]. Some children, however, have atypical presentations with non-specific symptoms and without characteristic signs and laboratory results [5-8]. Thus, referral may be delayed. It has been established that the delay is shorter for leukaemia than for other types of cancer, with a median of 10 days from presentation to the general practitioner to the date of diagnosis, but the time from onset of symptoms to treatment start was 25 days [9]. To reduce the delay, guidelines for rapid referral have been published in the United Kingdom and in Denmark [10, 11], and recently a German review defined "red flags" for recognition of ALL [8].

It has not been investigated whether the referral criteria are sufficiently sensitive to include children without the characteristic symptoms. In the present study, we review the clinical presentation in a cohort of 100 children with ALL in order to describe the clinical spectrum, determine the frequency of atypical cases, and evaluate the sensitivity of criteria for referral to accelerated investigation at a paediatric oncology unit. In addition, we explore the clinical differences between precursor B-cell ALL and the less frequent T-cell ALL.

MATERIAL AND METHODS

From 1 January 1986 to 30 June 2012, 114 children and adolescents were diagnosed with ALL at the Paediatric Oncology Unit, Aalborg University Hospital, Denmark. For the present analysis, 14 children were excluded: four infants aged < 1 year, five adolescents aged > 15 years, two children with Down's syndrome, two with mature B-cell leukaemia, and two with missing records. Thus, 100 children aged 1-15 years with pre-B ALL (n = 89) or T-ALL (n=11) were studied. The cohort included 50 boys and 50 girls, and there were 65 preschool children aged 1-5 years and 35 children aged > 5 years. All children were treated according to Nordic protocols (NOPHO-ALL 1986, 1992, 2000 and 2008) with stratification into standard, intermediate and high-risk treatment groups based on clinical, immunophenotypic and cytogenetic features [3].

Patient records were reviewed and the following data extracted: age, sex, symptoms recorded at the time of admission, the duration of the symptoms (in most

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TABLE 1

Symptoms, signs and laboratory findings at the time of diagnosis in a cohort of 100 children with ALL, including comparison of features in children with precursor B-cell and T-cell acute lymphoblastic leukaemia.

	ALL, % (n = 100)	pre-B ALL, % (n = 89)	T ALL, % (n = 11)	Fisher's test, 2p < 0.10
Musculoskeletal pains	49	54	9	0.008
Leg pain (av.dur.)	34 (7 weeks)	37	9	0.09
Back pain (av.dur.)	15 (9 weeks)	17	0	–
Limp (av.dur.)	16 (9 weeks)	18	0	–
Joint pain (av.dur.)	17 (10 weeks)	19	0	–
Constitutional symptoms	83	83	83	–
Fatigue (av.dur.)	53 (5 weeks)	53	55	–
Anorexia (av.dur.)	43 (3 weeks)	44	36	–
Abdominal pain (av.dur.)	24 (3 weeks)	22	36	–
Headache (av.dur.)	10 (2 weeks)	8	27	–
Weight loss	11	10	18	–
Bone marrow insufficiency symptoms	77	80	55	–
Fever (av.dur.)	66 (2 weeks)	69	45	–
Bleeding (av.dur.)	35 (1 week)	37	18	–
Visible organomegaly	19	12	73	0.00004
Lymph gland enlargement (av.dur.)	16 (5 weeks)	11	54	0.002
Abdominal distension	5	3	18	0.09
Bone marrow insufficiency signs	90	92	73	0.08
Pallor	84	88	55	0.014
Fever: temp. > 37.5 °C	45	47	27	–
Purpura	44	46	27	–
All three findings	23	25	9	–
Organomegaly on examination	71	67	100	0.03
Hepatomegaly	51	51	55	–
Splenomegaly	42	37	82	0.007
Lymphadenopathy	26	22	55	0.03
Mediastinal tumour	1	0	9	–
Signs of joint or skeletal lesion	10	11	0	–
Arthritis	6	7	0	–
Vertebral lesion	4	5	0	–
Abnormal blood count	96	97	90	–
Hb < 6 mmol Fe/l	80	84	45	0.008
Platelet count < 100 × 10^9/l	67	72	27	0.005
Leukocyte count > 20 × 10^9/l	28	24	64	0.010
Leukocyte count < 4.0 × 10^9/l	35	36	27	–
2 or 3 cell lines affected	78	80	64	–
Neutrophil count < 1.0 × 10^9/l	68	73	27	0.004
Lymphoblasts in blood smear	85	84	91	–
Biochemical marker elevation	78	75	100	–
Lactate dehydrogenase conc. > 500 IU/l	68	64	100	0.015
Urate conc. > 0.35 mmol/l	24	24	27	–

ALL = acute lymphoblastic leukaemia; av.dur. = average duration; conc. = concentration; pre-B = precursor B-cell; T = T cell.

cases given as approximate number of weeks), clinical signs, initial laboratory results, percentage of blasts in the blood smear, and bone marrow findings. Quantitative data were categorised using the following definitions: leukopenia = leukocyte count < 4.0 × 10^9/l, leukocytosis = leukocyte count > 20.0 × 10^9/l, neutropenia = neutrophil count < 1.0 × 10^9/l, anaemia = haemoglobin (Hb) concentration < 6.0 mmol/l, and thrombocytopenia = platelet count < 100 × 10^9/l. The upper limit for normal serum lactate dehydrogenase (LD) concentration was 500 U/l and for serum urate concentration 0.35 mmol/l.

Data were transferred to an electronic database approved by the regional data authorities. Data analysis was mainly descriptive, explorative and retrospective and primarily focused on clinical evaluation of observed differences. Selected differences in frequencies were tested for significance using Fisher's exact test, and two-sided p-values < 0.10 were reported. Differences in median values were rank sum tested. The sensitivity of the published criteria for referral was assessed by determining their positive rates.

Trial registration: not relevant.

RESULTS

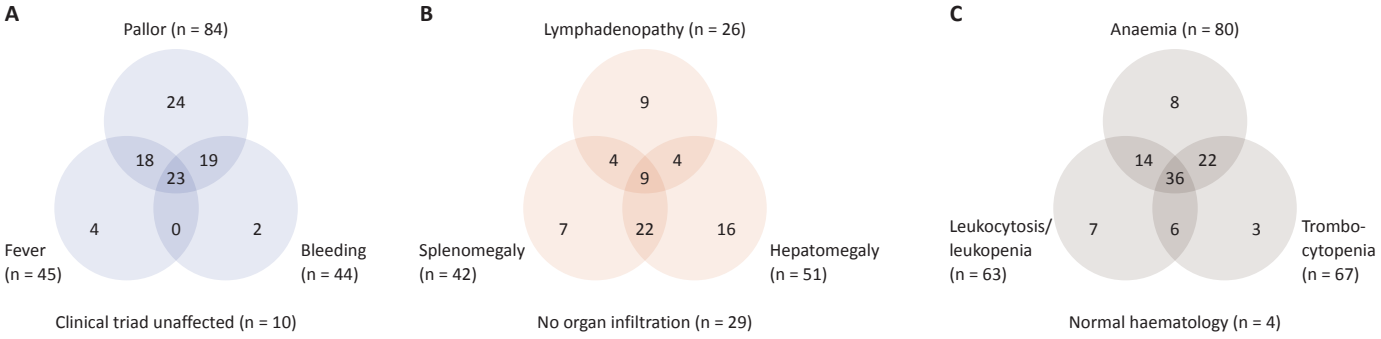
The frequencies of symptoms, clinical signs and laboratory findings are shown in **Table 1**. At the time of diagnosis, 49% had pain complaints with an average duration of 7-10 weeks, 83% had experienced constitutional symptoms for 3-5 weeks, and 77% reported symptoms referable to bone marrow insufficiency with a duration of approximately two weeks. Fever episodes, fatigue, and poor appetite were the most common symptoms, followed by leg pains and bleeding symptoms. In the subgroup with T-ALL, musculoskeletal pain was exceptional, bone marrow-related symptoms were less frequent, but enlarged glands were often present.

On admission, most children (84%) were pale, but fever and petechiae were less frequent, and only 23% presented with the complete clinical triad of pallor, fever and purpura (**Figure 1**A). On examination, organ enlargement was found in 71%, most frequently as hepatosplenomegaly; only nine children had enlargement of all three organs (Figure 1B). In children with T-ALL, splenomegaly and lymphadenopathy were frequent. Ten children, all with pre-B ALL, presented with joint or skeletal lesions demonstrable by ultrasound or radiological examination. A joint effusion was present in six cases. Among the children with back pain, four were found to have vertebral lesions, in two cases vertebral osteopenia with multiple fractures, in the other two a lesion resembling osteomyelitis.

Anaemia was the most frequent haematological abnormality (80%); thrombocytopenia and an abnormal leukocyte count were present in to thirds of the cases. All three lines were involved in 36%, but 18% presented with unilinear affection and 4% had normal values (Figure 1C). In T-ALL, leukocytosis was characteristic (64%) and LD was elevated in all cases. Serum urate concentration was raised in only 24%, independent of immunophenotype, and exceeded 0.5 mmol/l in only few

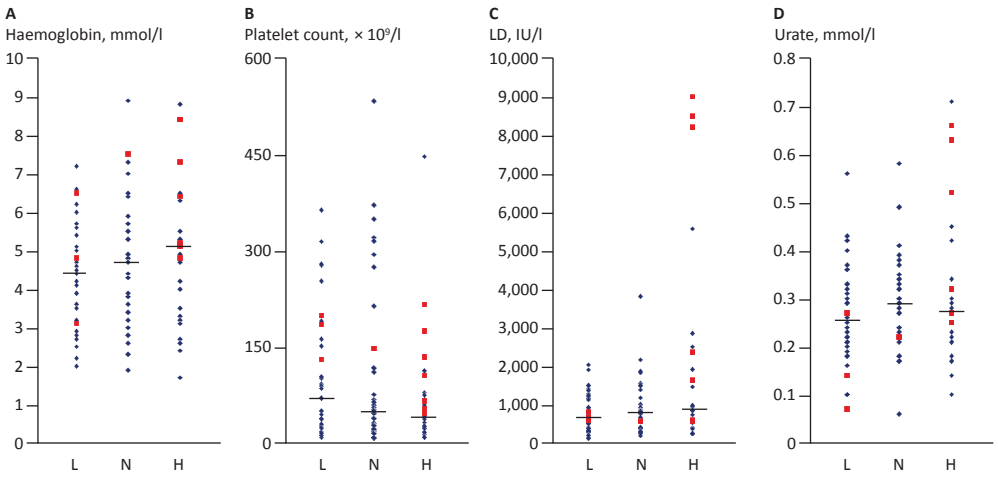
FIGURE 1

Venn diagrams showing the combination of (**A**) general clinical signs, (**B**) organ infiltration and (**C**) haematologic findings in 100 children admitted to hospital with acute lymphoblastic leukaemia[a].



a) Anaemia: haemoglobin concentration < 6.0 mmol/l; leukopenia: leukocyte count < 4.0 × 10^9/l; leukocytosis: leukocyte count > 20.0 × 10^9/l; thrombocytopenia: platelet count < 100 × 10^9/l.

FIGURE 2



Dot plot comparison of haematologic (**A** and **B**) and biochemical (**C** and **D**) values in children with acute lymphoblastic leukaemia with leukopenia, normal leukocyte count or leukocytosis.

ALL = acute lymphoblastic leukaemia; LD = lactate dehydrogenase. L = children with low counts: < 4.0 × 10^9/l (n = 35).
N = children with normal counts: 4-20 × 10^9/l (n = 37). H = children with high counts: > 20 × 10^9/l (n = 28).
Blue dots = children with precursor B-cell ALL (n = 89). Red dots = children with T-cell ALL (n = 11). Black bars = median values[a].
a) The median serum LD value is significantly higher in the H group than in the L group (2p = 0.05, rank sum test); other differences do not reach statistical significance.

cases. On blood smear examination, lymphoblasts were detectable in 85%.

The leukocyte count was normal (37%) or low (35%) in most cases; leukocytosis was present in only 28 cases. Children with leukocytosis had higher LD values and tended to have lower platelet counts but to be less anaemic (**Figure 2**). Peripheral lymphoblasts were always present in cases with leukocytosis, whereas one third (12/35) of the leukopenic cases were aleukaemic.

The haematologically typical (multilinear) and atypical groups are compared in **Table 2**. As expected, manifestations of bone marrow insufficiency were less frequent in the atypical group. Hepato/splenomegaly and marker elevation were also less frequent. Symptom duration was longer, and the frequency of pain and skeletal lesions was higher. Risk group assignment, however, did not differ significantly. Lymphoblasts were equally frequently present in peripheral blood in the two groups.

The Danish guidelines for accelerated investigation specify a list of symptoms that should elicit referral of children with only one abnormal haematological value (Table 2). Even though the symptoms were less frequent than in the group with multilinear involvement, at least one of the criteria was fulfilled in all 18 cases. Adding

TABLE 2

Comparison of clinical features in children with acute lymphoblastic leukaemia with typical or atypical blood counts, defined as involvement of 2-3 or 0-1 cell lines, with evaluation of the Danish Health and Medicines Authority criteria for referral.

	0-1 cell line	1 cell line	2-3 cell lines	Fisher's test
Clinical characteristics				2p < 0.10
n	22	–	78	–
Pre-B ALL, %	82	–	91	–
High risk stratification, %	14	–	22	–
Symptom duration, average, weeks	10	–	5	–
Pain, %	59	–	46	–
Constitutional symptoms, %	73	–	86	–
Fever, %	45	–	72	0.04
The clinical triad[a], %	0	–	29	0.003
Lymphadenopathy, %	27	–	26	–
Hepato/splenomegaly, %	45	–	65	–
Joint/bone lesions, %	27	–	5	0.10
LDH conc. > 500 IU/l, %	50	–	73	0.07
Urate conc. > 0.35 mmol/l, %	9	–	28	–
Lymphoblasts in blood smear, %	86	–	85	–
Referral criteria[b]				p < 0.10
n	–	18	78	–
Bone/joint pain, %	–	61	46	–
Constitutional symptoms, %	–	72	86	–
Hepato/splenomegaly, %	–	50	65	–
Lymphadenopathy, %	–	33	26	–
Elevation of LDH- or urate conc., %	–	56	77	0.08
≥ 1 of the above, %	–	100	100	–

conc. = concentration; LDH = lactate dehydrogenase; pre-B = precursor B-cell.

a) Pale with fever and petechiae.

b) Each criterion should raise suspicion of leukaemia and consideration of referral to a paediatric department. Referral to a paediatric oncology unit for accelerated investigation is indicated 1) if 2-3 cell lines are involved, 2) if 1 cell line is involved combined with bone pain for > 1 week, unexplained hepatosplenomegaly, unexplained lymphadenopathy, constitutional symptoms, or raised lactate dehydrogenase or urate or 3) if presence of lymphoblasts in the blood is suspected.

the presence of peripheral blasts in 2/4 cases with normal values, the sensitivity of the criteria was therefore 98%. In comparison, the sensitivity was 86% with the National Institute for Health and Care Excellence (NICE) criteria which specify a similar list of symptoms that should elicit immediate referral or a full blood count with blood smear examination.

DISCUSSION

When assessing whether a child may have leukaemia, most physicians look for clinical evidence of bone marrow destruction. In this descriptive review of 100 children with ALL, 78 had involvement of two or three haematopoietic cell lines and only 23 presented with the classic clinical triad. In addition, the analysis of symptom duration established that evidence of bone marrow involvement is a late occurrence in the progression of the disease, being preceded in most patients by a phase with constitutional symptoms, and in half of the patients an even longer phase with musculoskeletal pain. Thus, the timely recognition of ALL requires awareness of a range of symptoms and signs.

Our study describes an almost complete consecutive series of children with ALL admitted to a single institution, but as the study is retrospective, its findings must be interpreted with some caution. Symptoms and their duration are subject to biases in parental recall, and physical signs have been elicited by multiple doctors and may therefore also be subject to error. The laboratory data are accurate, but the categorical transformation is arbitrary although used previously [8]. Referral practices may have changed over the 16-year study period. Furthermore, a series of 100 cases with small subgroups is not large enough to estimate all relevant differences in clinical features at a level of statistical significance. Thus, the description of ALL is not as accurate as it would be in a large prospective and systematic study, but it probably still reflects the disease as it manifests itself in daily clinical practice.

The haematologic symptoms and signs occurred with the same frequency as in previously published series with bleeding as the least common symptom, but enlargement of the liver, spleen or lymph nodes was less frequent [5-8]. Skeletal pain was reported in half of our patients, which is more than the 25% expected from descriptions of Nordic children [4] and from a recent Danish patient cohort [9, 12], but this level does not much exceed the 40% incidence reported in reviews with special focus on musculoskeletal complaints [6, 13-15]. "Red flags" were defined by Bernbeck et al who found that bone marrow insufficiency was clinically obvious in less than half of the children, but that organ infiltration was detectable in > 95% and that the smear was positive for lymphoblasts with few exceptions [8]. Our findings, however, do not confirm that these features are highly sensitive.

In the present study, 22 children had not developed the typical multilinear bone marrow involvement. They were distinguished by a lower frequency of constitutional symptoms, hepatosplenomegaly and biochemical marker elevations. Musculoskeletal manifestations, on the other hand, were more frequent. Seemingly, ALL was diagnosed at an earlier stage, but symptom duration was much longer, averaging two months. Thus, the group may represent a subset with slowly progressing leukaemia. Importantly, even if only one haematologic count is definitely abnormal, an underlying leukaemia may be indicated by low normal values in other cell lines. It may also be noted that blood smear examin-

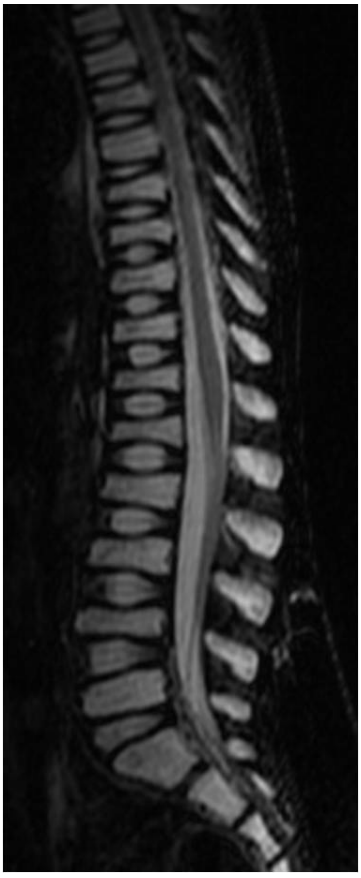
ation for lymphoblasts was as sensitive in the atypical as in the typical group. Flowcytometric analysis of a peripheral blast population may not be more sensitive, but it can usually determine the leukaemia subtype before bone marrow investigation.

Our series included 11 cases of T-cell leukaemia (10-15%). This subgroup occurs mainly in older children, and it is associated with an increased risk of induction failure, central nervous system infiltration and early relapse [3, 4, 16]. The differences in clinical manifestations from pre-B leukaemia are sparsely reported in the literature. In our small series, organomegaly was always present, skeletal involvement always absent, leucocytosis was usually present and LD always elevated.

Among children with pre-B ALL, musculoskeletal pain was reported by more than half, and in 10% a manifest joint or bone lesion resembling arthritis or osteomyelitis had developed. It is known that ALL can present as orthopaedic or rheumatologic problems with subtle haematologic manifestations [13, 17], that radiographic abnormalities can be found in more than half at the time of diagnosis [6, 14, 15], and that bone or joint pain is a prominent or presenting symptom in 20% [5, 13] of cases. Children with skeletal lesions have a longer diagnostic interval with slower disease progression which is associated with favourable features and may have a good prognosis unless diagnosis is much delayed [14, 15]. An earlier diagnosis of these cases is warranted. A case-control study has shown that early ALL may be distinguished from rheumatoid arthritis by the presence of night-time pain, a platelet count in the lower part of the normal range, and a low leukocyte count [18].

More than one third of the children had symptoms for more than one month before the diagnosis was made and thus did not have “acute” leukaemia. In the early stages with non-specific symptoms, diagnosis is difficult [19]. Once symptoms referable to bone marrow dysfunction develop, the children appear to be referred with little delay, with bleeding as the symptom with the shortest time interval to admission. Strategies to shorten the diagnostic interval are needed. Health authorities have specified guidelines for referral and timelines for rapid investigation. We found that the Danish criteria for referral were fulfilled in 98% of cases, a seemingly satisfactory sensitivity. It should be noted, however, that the sensitivity is probably lower in the earlier stages of the disease. In addition, their lack of complete specificity means that alert symptoms have a very low positive predictive value [20]. Referral guidelines, therefore, may have only a limited value. In the first two years after fast-track pathways were established, they were used in only 2% of cancer patients, but long diagnostic intervals were less frequent [12].

In conclusion, this review of clinical findings in children with ALL shows that the disease covers a broad spectrum and that there are several subgroups with atypical features. Importantly, there seems to be a diagnostic delay in many cases where referral is postponed until the tell-tale haematological signs become apparent. Awareness of atypical presentations is important for general practitioners. There is no single “red flag” which can be relied on for recognising the disease; rather, a constellation of features must be sought and attention must be paid to subtle haematologic changes. Hopefully, the information presented here may promote early recognition so that fewer children have undue diagnostic delays and so that the children are in a better clinical condition when treatment is initiated.



Magnetic resonance image showing collapse of multiple vertebral bodies at the time of diagnosis in a child with acute lymphoblastic leukaemia.

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LITERATURE

1. Hjalgrim L et al. Age- and sex-specific incidence of childhood leukemia by immunophenotype in Nordic countries. J Nat Cancer Inst 2003;95:1539-44.
2. Schmiegelow K, Forestier E, Hellebostad M et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukaemia. Leukemia 2010;24:345-54.
3. Ritter J, Schrappe M. Clinical features and therapy of lymphoblastic leukemia. In: Lilleyman JS et al, ed. Paediatric haematology. 2nd ed. London: Churchill Livingstone, 1999.
4. Schmiegelow K, Gustafsson G. Acute lymphoblastic leukemia. In: Voute et al (Ed.) Cancer in children: Clinical management. 5th ed. New York: Oxford University Press Inc, 2005.

5. Ma SK, Chan GC, Ha SY et al. Clinical presentation, hematologic features and treatment outcome of childhood acute lymphoblastic leukemia: a review of 73 cases in Hong Kong. Hematol Oncol 1997;15:141-9.
6. Sinigaglia R, Gigante C, Bisinella G et al. Musculoskeletal manifestations in pediatric acute leukemia. J Pediatr Orthop 2008;28:20-8.
7. Biswas S, Chakrabarti S, Chakraborty J et al. Childhood acute leukemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pacif J Cancer Prev 2009;10:903-6.
8. Bernbeck B, Wüller D, Janssen G et al. Symptoms of childhood acute lymphoblastic leukemia: red flags to recognize leukemia in daily practice. Klin Pädiatrie 2012;221:369-73.
9. Ahrensberg JM, Schrøder H, Hansen RP et al. The initial cancer pathway for children – one-fourth wait more than 3 months. Acta Pædiatr 2012;101:655-62.
10. National Institute for health and Clinical Excellence. NICE clinical guideline, June 2005. www.nice.org.uk/CG027 (29 May 2014).
11. Danish Health and Medicines Authority. Pakkeforløb for børn med kræft. Integrated pathway, Copenhagen: Danish Health and Medicines Authority, 2012.
12. Ahrensberg JM, Olesen F, Hansen RP et al. Childhood cancer and factors related to prolonged diagnostic intervals: a Danish population-based study. Br J Cancer 2013;108:1280-7.
13. Jonsson OG, Sartain P, Ducore JM et al. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. J Pediatr 1990;117:233-7.
14. Heinrich SD, Gallagher D, Warner R et al. The prognostic significance of the skeletal manifestations of acute lymphoblastic leukemia of childhood. J Pediatr Othop 1994;14:105-11.
15. Müller HL, Horwitz AE, Kühl J. Acute lymphoblastic leukemia with severe skeletal involvement: A subset of childhood leukemia with a good prognosis. Ped Hematol Oncol 1998;15:121-33.
16. Goldberg JM, Silverman LB, Levy DE et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. J Clin Oncol 2003;21:3616-22.
17. Ostrov BE, Goldsmith DP, Athreya BH. Differentiation of systemic juvenile rheumatoid arthritis from acute leukemia near the onset of disease. J Pediatr 1993;122:595-8.
18. Jones OY, Spencer CH, Bowyer SL et al. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics 2006;117:e840-4.
19. Raab CP, Gartner JC. Diagnosis of childhood cancer. Primary care 2009;36:671-84.
20. Dommett RM, Redaniel MT, Stevens MCG et al. Features of childhood cancer in primary care: a population-based case-control study. Br J Cancer 2012;106:982-7.