Abstract

Objective: to study the frequency, the clinical features and laboratory exams of patients with musculoskeletal symptoms at the onset of acute leukemia.

Methods: retrospective, descriptive study including patients diagnosed with acute leukemia, and treated at the Institute of Pediatric Oncology of UNIFESP, carried out from November 1999 to February 2000. The data on musculoskeletal complaints were obtained from a questionnaire. The medical records were revised in order to get data on the clinical examination and laboratory tests at the beginning of the illness.

Results: sixty-one children were included in this trial, 93% with acute lymphoid leukemia, and 7% with acute myeloid leukemia. Thirty-eight patients (62%) had musculoskeletal pain at the onset. Arthritis was observed in 8 patients. The mean number of involved joints was 2.5 (1-6). The most frequently involved joints were the knees, ankles and elbows. Three patients (4.9%) had normal blood count. Low hemoglobin was reported in 54 patients (88%) (in six patients it was the only hematological abnormality), leukopenia in 14 (22%), leukocytosis in 26 (42%) and low platelet count in 46 (75%).

Conclusions: the musculoskeletal symptoms are common at the onset of acute leukemia so, malignancy should always be ruled out in patients presenting chronic or acute arthritis or benign limb pain. The laboratory tests may be normal at the onset of the illness, making differential diagnosis more difficult.


Introduction

Joint and limb pains are very common complaints within the pediatric population, affecting between 10 and 20% of school-age children. Its differential diagnosis, however, can very often be difficult. While we know that the majority of cases of limb pain are of benign origin,2 organic causes should nevertheless be investigated. A worrying possibility which should always be taken into consideration is that of neoplastic disease, especially leukemia. Recently, Trapani et al.3 studied the incidence of occult cancer in 1,254
children presenting musculoskeletal symptoms, following them for ten years, and found an incidence of neoplasms of less than 1%, with acute lymphoblastic leukemia (ALL) being the most frequent type.

Acute lymphoblastic leukemia (ALL) is the most common type of cancer during childhood, corresponding to 25% of neoplasms between 0 and 14 years of age and constitutes 85% of juvenile leukemia cases. Its peak incidence occurs between two and five years of age, discreetly more frequent in males and in white individuals.

The clinical presentation is highly heterogenic and varies according to the extent of bone marrow and extramedullary involvement. Fatigue, lethargy and weight loss are common symptoms and 53% of cases present fever. Around 40% of patients exhibit bone pain (diffused or localized) which is initially intermittent tending to become persistent, and/or arthralgia and/or arthritis, the pattern of which is highly variable. According to extant literature, arthritis occurs with a frequency of 13.5%, being more common with ALL. Patients with this manifestation frequently have normal initial hemograms, which can contribute to late diagnosis. It is possible that a physical examination will find nothing more than arthritis. Pallor, and/or the presence of mucocutaneous bleeding may be observed. Liver, spleen and lymph nodes are enlarged in more than half of these patients.

As the disease evolves, involvement of the eyes and testicles, subcutaneous nodules, enlarged salivary glands, priapism and medullary compression can occur.

Leukemia, therefore, presents nonspecific signs and symptoms which may simulate the clinical presentation of many other pathologies, including juvenile rheumatoid arthritis (JRA), rheumatic fever (RF), systemic lupus erytematosus (SLE), idiopathic thrombocytopenic purpura (ITP), bone marrow aplasia and infectious mononucleosis.

Certain works have described the rheumatic manifestations of leukemia, since musculoskeletal complaints may be the initial manifestations of leukemia. The arthritis in leukemia can be chronic or recurrent and generally presents in an asymmetrical pauciarticular form, normally additive but sometimes migratory too, and its onset may be either insidious or sudden.

Laboratory tests show various alterations reflecting the degree of marrow infiltration. Anemia, usually normochromic and normocytic with a low reticulocyte count, occurs in more than 75% of the cases. The leukocyte count may vary from 100 to 1 million leukocytes/mm³; 53% present less than 10,000, 30% from 10,000 to 49,000 and 17% more than 50,000 leukocytes/mm³. Although thrombocytopenia is a frequent finding, 46% of leukemia patients with musculoskeletal manifestations present normal initial counts. The identification of blasts in peripheral blood is possible in one third of the patients.

Due to nonspecific clinical findings and to the delay in the appearance of hematologic alterations diagnosis can be late by periods of between two weeks and 13 months as described in literature. Thus, serial hemograms are indicated for the early detection of any alterations in suspected leukemia cases.

As early diagnosis is a decisive factor in the treatment and evolution of leukemia, our objective is to alert pediatricians and rheumatologists to its possible existence in patients with joint complaints and/or limb pain, and to verify the factors which, in association, can lead us to this diagnosis.

Objectives

To study the prevalence and clinical and laboratory characteristics of patients with musculoskeletal manifestations during the initial presentation of acute leukemia.

Patients and Methods

Sixty-one patients diagnosed with leukemia, being treated at the Institute of Pediatric Oncology (IOP) - UNIFESP - between November 1999 and February 2000, were evaluated.

Once informed consent had been given, the patients and their parents were interviewed by a pediatric rheumatologist in order to complete the questionnaire. The interviews took place on the days of consultation at the IOP, on which occasion their medical charts were also reviewed, and historical data and physical examinations were checked. The laboratory exams considered were those that had been performed at the onset of the disease.

Results

Of the 61 patients diagnosed with leukemia, 54% were male, and 55.7% were Caucasian. The age at the onset of symptoms varied from 10 months to 15 years and 6 months with an average of 8.1 years. The most common type of leukemia was ALL (93.4%). The time between the appearance of symptoms and the diagnosis ranged from five days to seven months, with an average of 2 months. Of the 61 patients, seven were being followed up for other reasons: one with benign limb pain, one with SLE, two with JRA, one with ITP and two diagnosed with leishmaniasis; three of them were using corticosteroids.

Table 1 shows the musculoskeletal signs and symptoms at presentation of leukemia. Thirty-eight patients (62%) had limb pain and/or joint pain. Arthritis detected by physical examination occurred in around 13% of the patients and was predominantly pauciarticular (75%): the number of joints involved ranged from one to six with an average of 2.5. The main joints affected were knees, ankles and elbows. The time that pain occurred was predominantly during the daytime (50% of the cases). Cutaneous involvement (purpura) and hepatosplenomegaly occurred in 28 (46%) and seven (28%) patients respectively.
Table 1 - Musculoskeletal signs and symptoms at presentation of leukemia (n = 61)

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb pain and/or joint pain</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>daytime</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>nighttime</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>continuous</td>
<td>15</td>
<td>39.4</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>24</td>
<td>39.3</td>
</tr>
<tr>
<td>Arthritis (anamnesis)</td>
<td>14</td>
<td>22.9</td>
</tr>
<tr>
<td>Arthritis at physical examination</td>
<td>8</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Table 2 lists the laboratory test results. We should point out that three patients presented completely normal hemogram and six of them only anemia (< 11g%), ranging from 7.1 to 10.9 g%. ESR (erythrocyte sedimentation rate) was greater than 50mm for all patients tested (7/61).

A lactate dehydrogenase (LDH) test was performed for 45 patients, with abnormal values found in 42 (93.3%) cases, with very high values being reached (up to 6000 IU), and in 55% of the patients these values were twice as high as the normal levels.

Discussion

It is very well documented that musculoskeletal symptoms can be the initial manifestation of leukemia in children.

The time elapsed between the initial rheumatic complaint and the diagnosis of leukemia varied from five days to seven months, with an average of two months. Rheumatic diseases, in particular rheumatic fever and juvenile rheumatoid arthritis are important differential diagnoses for leukemia and five of the 61 patients described were misdiagnosed , delaying the introduction of the appropriate therapy.

The incidence of rheumatic symptoms or findings as presentation of neoplasms is highly variable and its importance as a “marker” for cancer has not yet been sufficiently evaluated. There are a number of works which observed the frequency and characteristics of this type of initial manifestation of lymphoproliferative diseases. In our study, 62% of the cases were similar to those found in the studied literature. It is known that cases of leukemia which have a more insidious clinical presentation tend to exhibit these complaints with greater frequency.

Pain was more frequent during the daytime, which differs from the pattern described in literature, and the characteristic pain that wakes the child up during the night was observed in just 10.5% of cases in this study. Severe joint pain, disproportionate to inflammatory symptoms, as happens with rheumatic fever, is also a characteristic of leukemia, often leaving the patient bedridden or in a wheelchair. In our study, 39.3% of the patients exhibited difficulties walking. Tuten et al. studied 77 children with leukemia and observed that claudication was the initial complaint for 11.6%.

As described in literature, arthritis predominantly involved the lower limbs and was pauciarticular (75%). In acute leukemia, the knee joints are most affected, as occurred in our study, nevertheless, ankle, wrist, elbow and hip joints have also been described.

The hemogram may be normal during the initial phases as occurred with three of the 61 patients or it may present simply mild to moderate anemia, with no alterations to the white cell or platelet count.

The hemogram should be repeated in order to detect early alterations which are suggestive of leukemia. Leukocytosis or leukopenia, as observed in around 42 and 23% of our patients respectively, alerts us to leukemia, principally when accompanied by lymphocytosis. The number of patients with blasts in the peripheral circulation at the onset of the disease, 13%, was less than that described in the literature, 33%. This, perhaps, is owing to the fact that these initial hemograms were performed routinely in laboratories and not by a hematologist with the intention of locating these cells.

Thrombocytopenia is another detail that is relevant to the diagnosis of leukosis, because systemic JRA, which is an important differential diagnosis between rheumatic diseases, exhibits normal platelet counts or platelet counts with thrombocytosis. Platelet counts lower than 150,000/mm³ were found in 75% of cases, which are greater than those shown in the literature.

The erythrocyte sedimentation rate is abnormal in 100% of the cases and, as it is a nonspecific test, it does not help with differential diagnosis.
Of the 45 patients in our patient population from where the LDH value was taken, 93.3% presented higher than normal levels (> 400), with 55% of them being more than twice the normal value. Wallendal et al. 19 studied 12 children with a diagnosis of malignant neoplasia and arthralgia or arthritis in the diagnostic presentation, and compared them with 24 patients diagnosed as having JRA.

The authors found that in the neoplasm group, LDH levels were 2.2 times normal whereas in the children with JRA, just 0.8 times. Therefore, children with symptoms consistent with JRA exhibiting high LDH levels should undergo investigation for neoplasia.

The use of corticosteroids in children with arthritis and with a suspicion of collagenosis, even without a definitive diagnosis, can delay the identification of leukemia, because it relieves the symptoms and can change the cytology and histology of the bone marrow.

Conclusions
Musculoskeletal complaints are frequently the initial manifestations of acute leukemia in childhood and should be considered in the differential diagnosis of limb pain and of chronic and acute arthritis.

Initially laboratory test results can be absolutely normal or show discrete changes which do not point to diagnosis of neoplasia. It is necessary to bear this differential in mind so that we may follow these children closely and request serial tests, until there is a clearly defined diagnosis. LDH testing can be a useful aid to differential diagnosis.

References

Corresponding author:
Dr. Cássia Maria P.L. Barbosa
Rua Itagyba Santiago, 360/63
CEP 04635-051 – São Paulo, SP, Brazil
Tel.: +55 11 5666.0801 – Fax: +55 11 5666.1195
E-mail: cassia@vicnet.com.br