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Comparison of Clinical, Biological and Evolutionary Characteristics between Childhood Acute Lymphoblastic and Myeloid Leukemia in Western Algeria, from 2016 to 2018

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ABSTRACT

Background and Objectives: Haematological malignancies account for approximately 40% of all cancers by the age of 15 years. Acute leukaemia (AL) account for one-third of childhood cancer cases; consisting of Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukaemia (AML). The aim of this work is to describe the epidemiological, clinical, biological and evolutionary characteristics of children with acute leukaemia in the western and south-western region of Algeria.

Patients and Methods: A three-year retrospective study was undergone from January 2016 to December 2018 on children with acute leukaemia. The study was conducted at the paediatric oncology department of the anti-cancer -Emir AEK- of Missreghine in Oran.

Results: During this period, we identified 135 cases of diagnosed AL. The sex ratio M/F was 1.1. The "two to five-year" age group was the most affected. The prevalence of ALL, AML, and biphenotypic acute leukaemia (BAL) was 60.45%, 23.88%, and 15.57%, respectively. The clinical signs were mainly presented by the tumour syndrome dominated by the presence of lymphadenopathy (63%) and splenomegaly (56.3%). The most frequent abnormal blood abnormalities were anaemia (66.66% in ALL and 28.14% in AML), thrombocytopenia (75.9% in ALL and 24.4% in AML) and leukocytosis (76.3% ALL and 23.7% AML).

Conclusion: Paediatric acute leukaemia is a real public health problem that requires special care and attention. This management must involve all epidemiological, clinical and biological aspects for this highly sensitive age group.

Keywords: Acute Leukaemia, Children, Epidemiology, Acute Lymphoblastic Leukaemia, Acute Myeloid Leukaemia.

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INTRODUCTION

Haematological malignancies account for about 40% of all cancers by the age of 15. Acute leukaemia remains the most common malignant tumour in children and represents one-third of paediatric cancers.[1, 2] In Europe and the US, AL accounts for 80% of leukaemia and about 35% of childhood cancers.[3] Acute leukaemia are a group of hematologic disorders characterized by malignant proliferation and accumulation of a large number of clonal modularly precursors (blasts) of blood lines, blocked at a specific stage of differentiation that are found in the marrow, blood and sometimes other tissues. Depending on the line concerned, they are subdivided into acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL).[4] In children, 80% of acute leukaemia is called lymphoid or lymphoblastic (ALL). Of these cases, 80% are LALs of line B (affecting the development of B lymphocytes), called common.[5] AML is relatively rare in childhood, accounting for 15% to 20% of AL, but the most prevalent among adults.[6] Epidemiological studies of acute childhood leukaemia have examined risk

factors, including genetic, infectious and environmental factors. The majority is idiopathic: no identified cause.[7, 8] The clinical presentation of acute leukaemia results from infiltration of bone marrow or extramedullary sites by explosions. As a result, the first symptoms may be due to the presence of anaemia, neutropenia or thrombocytopenia. All tissues and organs can be affected, including ganglia, spleen and liver.[9]

Since these first descriptions, the diagnosis of ALL and AML is made on cytological and immunological criteria of bone marrow blasts. The contributions of immunophenotyping, cytogenetics and finally molecular biology have made it possible to describe more and more AL entities from one patient to another.[10, 11]

The therapy differs considerably depending on the type of leukaemia developed in the child. It is risk-based optimizes the healing potential while minimizing risks and side effects. All acute leukaemias are treated with chemotherapy, but the treatment can be adapted, more intensive, for the most serious forms with sometimes a bone marrow transplant.[5] The aim of this work is to describe the epidemiological, clinical, biological and evolutionary characteristics of children with acute leukaemia in the western and south-western region of Algeria, in the service of paediatric oncology of the anti-cancer centre -Emir AEK- Misserghine in Oran, north western Algeria.

METHODS

Objectives of the study

The objective of this study is to describe the clinical, biological and evolutionary characteristics of children with acute leukaemia in the West and South-West of Algeria.

Type of study

The study that we conducted is a retrospective descriptive and cross-sectional study, involving 135 files of patients who were treated for acute leukaemia in the Paediatric Oncology Department of the anti-cancer centre -Emir AEK- Misseghine in Oran, during the period from January 2016 to December 2018. The processing of the files covered duration of 3 months, from February 2019 to May 2019.

Characterization of the population

Our work is carried out on a population included all the patients aged 1 month to 16 years, of both sexes suffering from acute leukaemia, and coming from several regions of West and Southwest Algeria (Oran, Sidi-Bel-Abbes, Chlef, Bechar, Adrar, Ain Timouchent, El Bayadh, Mascara, Mostaganem, Naama, Retizane, Saida, Tiaret, Tlemcen and Tissemsilt).

Criteria for diagnosis

Only patients whose definitive diagnosis was made in the paediatric oncology department by a symptomatic clinical examination of more or less complete insufficiency (Anaemic syndrome and/or infectious syndrome and/or syndrome hemorrhagic) with or without tumour syndrome (splenomegaly, hepatomegaly, lymphadenopathy, gingival hypertrophy, bone pain) and paraclinical examination with specimens in the laboratory haematology based on biological and/or histological examinations: the blood count, morphological examination of blood smears, and a study of the medullogram (a medullar blast cell count ≥ 20%). However, patients benefit from cytometric confirmation by flow cytometry (CMF).

Data collection

For the collection of data, we used the medical file of the patient, to fill out a record of exploitation which aims to specify the epidemiological, clinical, biological and evolutionary aspects of each patient admitted for AL. The parameters on which our study focused are:

1. Age, sex, usual residence and anthropometric parameters (height, weight, BMI).
2. Clinical information that pertains to antecedents (family, inbreeding between parents and personal history), reason for consultation, consultation time and symptoms.
3. Radiological data: Chest X-ray and abdominal ultrasound.
4. Biological data they concern:

a. The hemogram

b. Peripheral blood smear (blood film)

c. Biochemical assessment

d. Assessment of haemostasis

e. Medullogram

f. Lumbar puncture (LP)

g. Flow cytometry

5. Therapeutic aspects:

a. Start date of treatment induction

b. Evaluation date with the result of the medullogram exam

6. Evolutionary aspects: Remission, Relapse, Death, Lost of sight.

Statistical analyzes

The statistical analysis is based on the use of the SPSS 22 software (Statistical Package for the Social Sciences, IBM Corporation, Chicago, IL, August 2013). Quantitative variables by groups were compared by Student's "*t*" test. Only significant differences at the 5% level were retained. Whereas, the Chi-square test was used for studying qualitative variables.

RESULTS

During the study period, 135 cases of diagnosed LA were identified (96 ALL and 39 AML), the sex ratio M/F in all participants was 1.1. The two to five-year age group was the most affected in both males and females (table 1). However, no significant differences were revealed between the two genders regarding all the studied parameters (age, anthropometric parameters, family history and consanguinity).

The comparison of clinical parameters between ALL and AML are summarized in table 2. As sign of spinal cord impairment, the infectious syndrome was significantly higher in ALL ($p<0.001$) comparing to AML patients. Furthermore, regarding the tumor syndrome, the splenomegaly ($p=0.002$) and the inguinal lymphadenopathy ($p=0.044$) were significantly frequent in ALL comparing to AML. No case of monocytic anemia has been recorded in AML group. However, higher significant positive ($p=0.045$) cytochemical staining was recorded in AML patients.

Table 3 highlight the comparison of biochemical parameters between the groups. Higher significant rates of lymphocytes and platelets were observed in ALL patients (p=0.031 and p=0.026, respectively) comparing to higher levels of neutrophils (p=0.002) and MCH (p=0.013) in AML patients. As a very important parameter, the blast rate was significantly higher in ALL comparing to AML patients (p<0.001).

We also evaluated progressive aspect of the disease (presence of blasts, risk, clinical remission, loss of sight and death) in our study patients (table 4). Low rates of blats were observed in the two groups. The risk was higher in both ALL and AML with no significant difference. The loss of follow-up frequency was low in the two patients' groups. However, the general rate of death was about 11% in the both ALL and AML patients.

Table 1: Basic characteristics of participants

	All patients (n=135)	**Males** (n=72)	**Females** (n=63)	*p* value *
Age (years), mean±SD	6.20±3.99	6.24±4.19	6.16±3.78	0.912
Weight (kg), mean±SD	20.10±10.67	20.59±11.48	19.52±9.71	0.563
High (cm), mean±SD	103.63±23.23	104.32±24.86	102.83±21.39	0.711
Age group (years), n (%)				
≤ 2	20 (14.8)	11 (8.1)	9 (6.7)	0.274
>2 and ≤ 5	51 (37.8)	28 (20.7)	23 (17.0)	
> 5 and ≤ 12	49 (36.3)	22 (16.3)	27 (20.0)	
> 12	15 (11.1)	11 (8.1)	4 (3.0)	
Type of leukaemia, n (%)				
ALL	96 (71.1)	48 (35.6)	48 (35.6)	0.223
AML	39 (28.9)	24 (17.8)	15 (11.1)	
Family history, n (%)				
Yes	15 (11.9)	9 (6.7)	6 (4.4)	0.583
No	120 (88.9)	63 (46.7)	57 (42.2)	
Consanguinity, n (%)				
Yes	27 (20.0)	13 (9.6)	14 (10.4)	0.546
No	108 (80.0)	59 (43.7)	49 (36.3)	

(*) Comparison between males and females; mean values were compared using Student's *t*-test. Percentages were compared with Chi-square test, a p<0.05 was considered as significant; ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloid Leukaemia.

Table 2: Comparison of clinical parameters between ALL and AML

		ALL (n=96)	**AML** (n=39)	*p* value *
Signs of spinal cord impairment, n (%)				
Anemic syndrome	No	6 (4.4)	1 (0.7)	0.381
	Yes	90 (66.7)	38 (28.1)	
Infectious syndrome	No	29 (21.5)	25 (18.5)	**<0.001**
	Yes	67 (49.6)	14 (10.4)	
Hemorrhagic syndrome	No	45 (33.3)	12 (8.9)	0.086
	Yes	51 (37.8)	27 (20.0)	
Fever	No	56 (41.5)	22 (16.3)	0.838
	Yes	40 (29.6)	17 (12.6)	
Arthralgia	No	61 (45.2)	25 (18.5)	0.951
	Yes	35 (25.9)	14 (10.4)	
Asthenia	No	40 (29.6)	13 (9.6)	0.369
	Yes	56 (41.5)	26 (19.3)	
Paleness	No	16 (11.9)	7 (5.2)	0.857
	Yes	80 (59.3)	32 (23.7)	
Tumor syndrome, n (%)				
Splenomegaly	No	34 (25.2)	25 (18.5)	**0.002**
	Yes	62 (45.9)	14 (10.4)	
Hepatomegaly	No	51 (37.8)	26 (19.3)	0.150
	Yes	45 (33.3)	13 (9.6)	
Axillary lymphadenopathy	No	59 (43.7)	30 (22.2)	0.086
	Yes	37 (27.4)	9 (6.7)	
Inguinal lymphadenopathy	No	59 (43.7)	31 (23.0)	**0.044**
	Yes	37 (27.4)	8 (5.9)	
Cervical lymphadenopathy	No	45 (33.3)	17 (12.6)	0.728
	Yes	51 (37.8)	22 (16.3)	
Gingival lymphadenopathy	No	89 (65.9)	36 (26.7)	0.936
	Yes	7 (5.2)	3 (2.2)	
Testicular lymphadenopathy	No	96 (71.1)	38 (28.1)	0.115
	Yes	0 (0.0)	1 (0.7)	
Cytopenia, n (%)				
Pancytopenia	No	73 (54.5)	30 (22.4)	0.992
	Yes	22 (16.4)	9 (6.7)	
Bicytopenia	No	32 (23.9)	10 (7.5)	0.362
	Yes	63 (47.0)	29 (21.6)	
Leucocytosis	No	36 (47.0)	29 (21.6)	0.362
	Yes	32 (23.9)	10 (7.5)	
Anaemia type, n (%)				
Macrocytic anaemia		10 (7.5)	0 (0.0)	**0.035**
Hypochromic microcytic anaemia		85 (63.4)	40 (29.62)	
Cytochemical staining, n (%)				
Negative		96 (71.1)	13 (9.6)	**0.045**
positive		0 (0.0)	26 (19.3)	

(*) Comparison between ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloid Leukaemia using Chi-square test, a $p<0.05$ was considered as significant.

Table 3: Comparison of biological parameters and blast rate between ALL and AML

	ALL (n=96)	**AML** (n=39)	*p* value *
White blood cells, $10^3/mm^3$	34.75±5.47	27.54±3.25	0.443
Lymphocytes, $10^3/mm^3$	19.29±2.72	9.44±1.08	**0.031**
Neutrophils, $10^3/mm^3$	6.04±1.27	16.64±2.56	**0.002**
Red cells, $10^6/mm^3$	2.76±0.73	2.68±0.50	0.491
Haemoglobin, g/dl	8.02±1.97	8.28±1.46	0.449
Mean corpuscular volume, FL	85.67±6.49	86.27±12.15	0.708
MCHC, g/dl	33.75±2.72	34.24±2.65	0.350
MCH, gp	29.05±2.81	30.47±3.30	**0.013**
Platelet, $10^3/mm^3$	67.93±7.94	38.56±2.53	**0.026**
Blast rate per myelogram, %	83.92±1.68	60.10±2.40	**<0.001**

(*) Comparison between ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloid Leukaemia using Student *t* test, a $p<0.05$ was considered as significant; MCHC: mean corpuscular hemoglobin concentration; MCH: mean corpuscular hemoglobin.

Table 4: Evolutionary characteristics for all participants between 2016 and 2018

	ALL (n=96)	**AML** (n=39) (%)	*p* value *
Lumbar puncture, n (%)			
Normal	95 (70.4)	38 (28.1)	0.507
Presence of blasts	1 (0.7)	1 (0.7)	
Risk, n (%)			
Very high	32 (25.8)	17 (13.7)	0.100
Moderate	59 (47.6)	16 (12.9)	
Clinical remission, n (%)			
No	68 (50.4)	30 (22.2)	0.472
Yes	28 (20.7)	9 (6.7)	
Lost of follow-up, n (%)			
No	95 (70.4)	36 (26.7)	**0.039**
Yes	1 (0.7)	3 (2.2)	
Death, n (%)			
No	80 (59.3)	24 (17.8)	**0.006**
Yes	16 (11.9)	15 (11.1)	

(*) Comparison between ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloid Leukaemia using Chi-square test, a $p<0.05$ was considered as significant.

DISCUSSION

Data from the medical literature report that child's AL, although rare in itself, is the leading cause of pediatric cancer (30%) and occurs mostly before the age of 9 years. In Europe and the United States, ALLs account for 75 to 80% of leukaemia and about 20% of cancers in children under 15 years of age.[12] There are two main types of AL; ALL and AML.

In our series, 135 cases of children with AL were recorded during the period from January 2016 to December 2018. The distribution of ALL and AML and biphynotypic AL reveals a predominance of ALL with 60.45% of cases, followed by AML (23.88%). The prevalence of biphynotypic leukaemia is in the order of 15.67%. These results are in agreement with the statistics of the Ibn-Sina University Hospital Centre.[10]

We recorded a sex ratio M/F of 1.1 vis-à-vis acute leukaemia (both types combined). This male dominance has also been observed in several other studies including the investigation of "frequency of childhood leukaemia in Qazvin province" and its correlation with sex, age and blood groups between 2006-2016 where sex ratio M/F was 1.24.[13] Similarly, in 2016, Doumbia et al. noted the same observations with a sex ratio M/F of 1.08 (10). In contrariwise, Cumin et al. (1995) reported a sex ratio of 0.79 in favour of females.[14]

The age is an important prognostic factor; it is associated with poor progression when it is less than 1 year or older than 10 years.[15] In the UK, the incidence is 30 per million children a year. This incidence is greatest between the age of 2 and 5 years.[16] In France, the annual incidence is 137 per million children under 15 years of age.[17] The highest rates are found in male children and children aged 1-4 years.[18]

In our study, the highest prevalence of AL was recorded for the 2- to 5-year and 5 to 12-year age groups with a predominance of ALL. Dargahi et al. (2016) reported the same results.[13]

The present study revealed that the duration between onset of symptom and diagnostic confirmation was about 50 days for ALL is almost 40 days for AML. This situation was described by Roganovic in 2013; "*The symptoms can vary from a few days to a few months and often accumulate in a few days or weeks and result in an event that brings the child to medical attention.*"[19]

In our case, most children had symptoms for 3-4 weeks. The symptoms and signs presented correlate with leukaemia cell load and the degree of bone marrow replacement, leading to cytopenia. The initial presentation includes the manifestations of the main clinical signs of bone marrow failure that have been reported by several studies.

According to Esparza & Sakamoto (2005),[20] common constitutional symptoms include fever (60%), fatigue (50%) and pallor (25%). In our children, clinical signs were recorded in 90.4% of patients (94 cases) with fever in 61% of cases and hemorrhagic syndrome in 50% of cases. Anaemia at the time of diagnosis was present in most of our patients (85%), which corroborates the findings of Pérez et al. (2018).[21]

However, the most common manifestations in our study were fever (55.8%) and pallor (53.7%). Hemorrhagic complications are common in patients with acute leukaemia (approximately 20%).

Tumour syndrome is the result of the infiltration of different hematopoietic organs or even other organs by blast cells. It is more common in ALL than in AML resulting in hepatomegaly, splenomegaly, lymphadenopathy, bone pain, skin infiltrates and swollen gums. This syndrome was mainly present in our series in the form of adenopathies (63% of cases), splenomegaly was found in 56.30% of cases and hepatomegaly in 43% of cases. Bone involvement, which can manifest as spontaneous bone pain, was found in 36.30% of cases.

This situation is frequently encountered in other studies: in the study by Sall et al. (2015), splenomegaly was present in more than 75% of cases, associated with symmetrical lymphadenopathy rarely bulky while hepatomegaly was present in half of the cases.[22] In their works, Acharya et al. (2018),[23] hepatomegaly was the most common presentation (95%), followed by splenomegaly (77%), lymphadenopathy (58%) and arthralgia (17.5%).

Osteo-articular manifestations are an infrequent form of revelation of AL of the child, representing about 14% of cases, sometimes before the appearance of haematological signs.[24]

The hemogram which directs towards the diagnosis of the AL, shows most often the attack of three lineages; white, red and platelet. It was performed in all patients in this study. Many studies show physiological variations in the blood count data. A high number of white blood cells (WBCs) (> 10,000/mm^3) occurs in about half of the children, with 20% showing that the initial WBC level is greater than 50,000/mm^3. Normochromic and normocytic anemia (hemoglobin <10 g/dL) occurs in approximately 80% of children. Thrombocytopenia (platelet count <100,000 / mm^3) occurs in 75% of children at diagnosis. Spontaneous bleeding occurs in patients with less than 20,000-30,000 platelets/mm^3.[19]

In our series, 29 patients had a WBC rate greater than 50 000/mm^3, of which 20 cases (76.3%) of ALL and 9 cases (23.7%) of AML. Those with profound leukocytosis with neutropenia account for 82.9% of ALL and 17.1% of AML. The presence of anaemic syndrome with a haemoglobin level between 7 and 10 g/d was recorded in 69% of ALL patients and 30.7% of AMLs.

The myelogram allows the diagnosis of AL when the marrow is invaded by at least 20% of abnormal blasts, in practice often more than 80% of AL. In our series, we found a highly significant difference (p <0.001) between the two types of leukaemia with respect to blast content: in ALL (83.92 ± 16.89%) was significantly elevated compared to blast levels in AML (60.10 ± 24.05%). These results are similar to those of Doumbia et al. (2016).[10]

Immunophenotyping has become an essential step in the diagnosis of acute leukaemia, it makes it possible to confirm the cell line involved in the leukemic process, and to specify the blocking stage of blasts in their differentiation.[25]

Lumbar puncture examination was normal in the vast majority of cases for ALL (70%) or AML (28.15%) with a clear appearance. These findings were also reported by Mwirigi et al., 2017, who found leukemic infiltration of the central nervous system in less than 10% of patients with ALL.[26]

The treatment of childhood leukaemia has changed dramatically over the past 50 years. The overall cure rate is 80% with variations depending on the different AL subtypes. Several studies show results about the evolution of AL. During the course of our study, we recorded a complete remission in the vast majority of cases (51 cases), followed by relapses (28 cases) and death (16 cases) and we recorded a single case of lost sight. In parallel, 15 cases of death were recorded for AML leukaemia, 11 cases of complete remission and 9 cases of relapse. Several authors have noted nearly similar results.[10, 27]

CONCLUSIONS

Our results reveal that LA in children in the west and southwest region of Algeria is increasing alarmingly. The characteristics of our population are similar to the data in the literature on clinical, biological and evolutionary levels without a specific unusual feature for our region. The management of this disease must bring together all stakeholders in public health professionals and must integrate the local and regional networks of pediatric cancer care. Indeed, the specificity of the care of children with cancer must build a national and an international strategy.

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Conflict of Interest: No

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