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Frequency of acute myeloid leukemia in children attended in Belém, Pará from August 2005 to May 2009

Frequência de leucemia mieloide aguda em crianças atendidas em Belém, Pará, no período de agosto de 2005 a maio de 2009

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ABSTRACT

Introduction: Acute myeloid leukemia (AML) has variable incidence in different regions of Brazil. **Objective:** To determine the frequency of AML subtypes in children aged 0-17 years attended at Belém, Pará, from August 2005 to May 2009. **Patients and methods:** A retrospective study was performed with 278 patients diagnosed with acute or chronic leukemia based on clinical and morphological criteria (French-American-British [FAB]/World Health Organization classification [WHO]) and immunophenotyping profile by flow cytometry, to determine the frequency of the subtypes in AML. **Results:** We found 70 (25.18%) cases of AML, 37 of these (52.9%) were children aged 0-17 years (median age of 7 years and 8 months). There was no statistical difference in relation to gender. We observed a higher frequency of AML subtype M2 (18/37 – 48.6%) and M0/M1 (10/37 – 27%), especially in the first decade of life (16/28 [57.1%] AML M2 and 9/28 [32.1%] AML M0/M1). **Conclusion:** In the pediatric population, the types of AML M2, M0/M1 and M3 were respectively the most frequent.

Key words: acute myeloid leukemia; pediatrics; Amazon area.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous group of clonal disease in the hematopoietic tissue, which is characterized by abnormal proliferation of myeloid lineage progenitor, resulting in insufficient production of normal mature blood cells with subsequent replacement of normal tissue[1-6]. The abnormal clonal proliferation, tyrosine kinase-dependent, results in neutropenia, anemia, thrombocytopenia and bone marrow infiltration by myeloid leukemic clones[7-10].

AML is classified into eight subtypes, according to French-American-British classification (FAB) criteria based on clinical, morphological, cytochemical, immunophenotypic and cytogenetic features, morphologic immunophenotypic and cytogenetic patterns (MIC), and the World Health Organization (WHO)[1, 2, 5, 11-14], with each subtype having different biological behaviors and therapies[3, 10, 15].

AML distribution, in turn, is universal, and is more prevalent among adults over the age of 60 years, 80% of the cases[16], representing about 15%-20% of childhood acute leukemia[6, 11, 16-19].

AML incidence in children aged 0-14 years in the United States, in 2005-2009, in turn, was estimated at 7.7 cases per million children. With little variation between racial/ethnic groups in the US, except for a possible increase in the incidence rate in Hawaiian, residents of the Pacific Islands and Hispanic-Latino children, is a fact that in general could suggest shared genetic predisposition among these groups[5, 7, 20].

In Brazil, there are still few existing data on the incidence of AML in pediatric patients[16, 17, 19, 21, 22], when compared with acute

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lymphocytic leukemia (ALL)[10, 14, 22, 23]. According to estimates from the Brazilian National Cancer Institute (Instituto Nacional do Câncer [INCA]) for leukemias in general in 2014 in Brazil, new cases rate from 5.20 in men and 4.24 in women per 100,000 patients. When this analysis was performed in relation to Northern Brazil, INCA estimates for new cases of leukemia in 2014 were 3.57 in men and 2.81 in women per 100,000 patients[30]. This situation is even more precarious when the incidence of pediatric AML is at issue in the Amazonian area, due to underreporting of cases.

Among the unique characteristics of the Northern region of Brazil, possibly associated with the AML incidence, we highlight the exposure to carcinogens derivatives of: (1) mineral mining (gold) and use of mercury; (2) agricultural (soy), indiscriminate use of genotoxic agents and pesticides; (3) heterogeneous characteristics of the local population, due to the strong indigenous influence of different ethnics groups; and (4) high rate of tropical diseases (malaria, hepatitis C virus [HCV], tuberculosis, and human T-lymphotropic virus type I and type II [HTLV I/II]).

Thus, the objective of this study was to determine the frequency of AML subtypes in children aged 0-17 years attended at Belém, Pará, from August 2005 to May 2009.

PATIENTS AND METHODS

Patients

A retrospective study of medical records of patients with AML diagnosis based on clinical and morphological criteria (FAB/OMS), and immunophenotypic profile of blasts by flow cytometry, from August 2005 to May 2009, to determine the frequency of AML subtypes in children aged 0-17 years, treated at Belém, Pará. A Commitment Term for Restricted and Confidential Use of Database was settled and signed by the research coordinator regarding the project which originated this article.

The study included 278 patients diagnosed with AML or chronic myeloid leukemia (CML), of both genders and aged between 10 months and 78 years. AML was confirmed for 70/278 (25.18%) of these, and 37/70 were in pediatric age (0-17 years). Among the epidemiological data were analyzed gender, age, main clinical complaints, and relevant laboratory results on blood cells count and myelogram.

Statistical analysis

Data were grouped according to age and gender information of patients diagnosed with AML in children attended during this period. They were stored and analyzed using software BIOESTAT 5.0 (Aires *et al*., 2007), applying the chi-square test, with $p < 0.05$.

RESULTS

In the chosen period from the 278 cases studied, 70 (25.2%) patients had clinical, morphological and immunophenotypic AML diagnosis confirmed; the remaining patients were diagnosed as follows: 146 (52.5%) with ALL, and 62 (22.3%) with chronic lymphoproliferative syndromes.

Regarding the age distribution of all AML (70/278) cases, we observed that the pediatric age group aged 0-10 years (28/70 cases) showed the highest number (40%) of individuals (**Table 1**), with a median age of 7 years and 8 months.

Concerning gender, regardless the age, there was no statistical difference ($p = 0.633$) between female 37/70 (53%) and male 33/70 (47%).

In a general review of AML subtypes (Table 1), without taking age into account, according to the WHO classification, we observed distribution of 20 (28,57%) cases of AML classified as M0/M1, 27 (38.57%) of AML M2, seven (10%) of AML M3, ten (14.28%) of AML M4, one (1.43%) of AML M5, one (1.43%) of AML M6, and four (5.71%) of secondary AML or AML not otherwise specified.

Regarding the study of the pediatric population, in accordance with the Brazillian Ministry of Health (Ministério da Saúde), which considers the age between 0 and 17 years, 37/70 (52.9%) individuals with AML. Thus three cases of patients aged 11-20 years were excluded (3/15) (Table 1), because they have reached the age of 19 years.

The male (19/37) and female (18/37) distribution analysis in the pediatric population of this study showed no statistical difference ($p = 0.752$).

We could observed that the highest frequency of AML in the first decade of life ($n = 28$) were M2 (16/28 – 57,1%) and M0/M1 (9/28 – 32,1%) types (Table 2). It is noteworthy, however, the low frequency (≈10%) of AML M3 on either the general population 07/70 (Table 1) or the pediatric population 04/37 (**Table 2**) of this study.

Among the most common clinical and laboratory data observed in the AML diagnosis in pediatric patients were studied: (1) hepatosplenomegaly and bone pain; (2) fever, diarrhea and pallor; and (3) occasional presence of petechiae and ecchymoses; furthermore (4) leukocytosis, anemia, thrombocytopenia, and blasts in the blood count; (5) high lactate dehydrogenase (LDH); and (6) hypo- or hypercellular myelogram, greater than 20% blasts.

TABLE 1 – AML subtypes according to age group

Subtype	Age group in years								
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total
MO/M1	9	3	1	1	3	1	2	-	20
M2	16	4	1	-	1	2	2	1	27
M3	1	4	-	-	1	-	1	-	7
M4	-	3	3	1	1	1	-	1	10
M5	-	1	-	-	-	-	-	-	1
M6	1	-	-	-	-	-	-	-	1
NOS	1	-	1	2	-	-	-	-	4
Total	28	15	6	4	6	4	5	2	70

Source: Hospital Ophir Loyola and Fundação HEMOPA, period 1 August 2005 to 31 May 2009.
AML: acute myeloid leukemia; NOS: not otherwise specified; HEMOPA: Centro de Hemoterapia e Hematologia do Pará.

TABLE 2 – AML subtypes in children aged 0 to 17 years

Subtype	Age group in years		Total
	0-10	11-17	
MO/M1	9	1	10
M2	16	2	18
M3	1	3	4
M4	-	2	2
M5	-	1	1
M6	1	-	1
NOS	1	-	1
Total	28	9	37

Source: Hospital Ophir Loyola and Fundação HEMOPA, period 1 August 2005 to 31 May 2009.
AML: acute myeloid leukemia; NOS: not otherwise specified; HEMOPA: Centro de Hemoterapia e Hematologia do Pará.

DISCUSSION

The laboratory advances in the diagnosis of AML, based primarily on the development of monoclonal antibodies on cytogenetic, molecular biology, and flow cytometry techniques, have increased not only the accuracy in the definition of myeloid lineage as well as in the classification of AML subtypes[14, 15, 21, 22]. However, today, in many Brazilian states of the northern region, AML diagnosis and epidemiology are still quite precarious, due to the distances to be covered between the places of origin of the patients and the diagnostic centers, and due to financial difficulties for this displacement or even the low reporting of positive cases who die even before the definitive diagnosis and treatment.

Given these facts, this study sought to identify the frequency of AML, its subtypes and most relevant clinical, morphological and immunophenotypic findings, observed among patients who were able to overcome the initial difficulties and get to the main diagnostic and treatment centers for this type of pathology between 2005 and 2009.

The interest in the AML stratification in children, in turn, appeared due to the demand on identification of frequency of this disease in pediatric groups in Belém, especially because AML, in pediatric oncology, an entity, together with neuroblastoma and central nervous system tumors, is one of the three most frustrating conditions in relation to patients survival[5, 17].

Borato *et al*.[16] and Zanichelli *et al*.[15] point out in their study that the greatest challenges in the treatment of AML in children is to reduce the mortality rate in the initial phase of treatment (remission induction), with consequent reduction of infectious and hemorrhagic complications and ensuring adequate hospital support, compromised by the high treatment costs.

In our study, about 85% to 90% of attended patients belonged to the Brazilian Unified Health System (Sistema Único de Saúde [SUS]), without major financial resources to stay away from home, and usually tin a more advanced stage of the disease, showing therefore, the importance of knowing the frequency of this disease among patients seeking expert healthcare. This process allows the exchange of successful experiences with other Brazilian diagnostic and treatment centers, besides State financial planning and prospects for implementing a hematopoietic stem cell transplant (HSCT) center, to attend the region.

The results of this study with children aged 0-17 years showed similarities with the studies of Zanichelli *et al*.[15], Viana *et al*.[19], Emerenciano *et al*.[6], who also observed higher frequencies of AML M2 and AML M0/M1 subtypes in children.

The lower overall frequency in adults and children with AML M3 observed in our study, although different from the Brazilian literature

in general[3, 22], corroborates other studies with specific population in the States of Piauí (7,8%)[18] and Amazonas (13%)[23], possibly due to population characteristics and similar ethnic composition.

Supporting this aims, general studies have tried to show the association between HLA risk variants for some types of leukemia and miscegenation of the Brazilian population[1], such as the associations observed by Barion *et al*.[16] of the relationship between HLA B53 and HLA-B56 with ALL; HLA-B7 with AML; and HLA-A24, HLA-B45, HLA-DRB1*04 and DRB1*08 with CML, although further studies on the subject in Brazil are still necessary.

Extrinsic etiological factors have also been associated with AML, such as exposure to ionizing or non-ionozantes radiation, organophosphates, benzene, ethylene oxide, antineoplastic agents, chlorinated pesticides (chlordane and heptachlor), among other myelotoxic and carcinogenic agents[25-29]. Among these, in the Amazon region, the extrinsic etiologic factors most likely to be associated with increased incidence of pediatric are the organophosphates (insecticides and herbicides), methylmercury and chlorinated pesticides associated with food contamination[28, 29], since this is a region of great agricultural expansion and gold exploration, where the use of these products are quite common. These organophosphate and chlorinated pesticides, however, beyond what has already been mentioned, are also present in the construction and maintenance of roads, the treatment of wood for construction, storage of grains and seeds, the production of flowers, to combat endemics and epidemics, and domestic use (detergents, waxes, disinfectants, insecticides, soap powders, among others)[28].

As regards the clinical and laboratory data observations most commonly noticed at the time of AML diagnosis, our data were concordant with those described in the literature[2, 4, 8, 12, 25].

We also did not observe in this study, significant differences in the distribution of AML subtypes in children when the analysis period was from 2009 to October 2013 (data not shown).

CONCLUSION

AML was diagnosed in 25.2% of the studied cases regardless of age. Regarding the pediatric population, the highest frequencies were types AML M2 (57.1%), AML M0/M1 (32.1%), and AML M3 (10.8%).

RESUMO

Introdução: *A leucemia mieloide aguda (LMA) tem incidência variável nas diferentes regiões do Brasil.* ***Objetivo:*** *Determinar a frequência dos subtipos de LMA em crianças entre 0-17 anos, atendidas em Belém, Pará, no período de agosto de 2005 a maio de 2009.* ***Casuística e métodos:*** *Estudo retrospectivo com 278 pacientes com diagnóstico de leucemias agudas ou crônicas com base nos critérios clínicos, morfológicos (classificação franco-americana-britânica [FAB]/Organização Mundial da Saúde [OMS]) e de perfil imunofenotípico por citometria de fluxo para determinação da frequência de subtipos de LMA.* ***Resultados:*** *Foram encontrados 70 (25,18%) casos de LMA; destes, 37 (52,9%) eram crianças entre 0-17 anos (idade mediana de 7 anos e 8 meses). Não houve diferença estatística em relação ao gênero. Observou-se maior frequência de LMA dos subtipos M2 (18/37 – 48,6%) e M0/M1 (10/37 – 27%), principalmente na primeira década de vida (16/28 [57,1%] LMA M2 e 9/28 [32,1%] LMA M0/M1).* ***Conclusão:*** *Na população pediátrica, os tipos de LMA M2, M0/M1 e M3 foram, respectivamente, as mais frequentes.*

Unitermos: *leucemia mieloide aguda; pediatria; Amazônia.*

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