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Childhood core binding factor (CBF) acute myeloid leukemia and its association with French American British (FAB) classification

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Abstract

Objective: To find the frequency of core binding factor acute myeloid leukaemia in our population, and to determine its association with morphological subtypes.

Methods: The retrospective study was conducted at The Indus Hospital, Karachi, and comprised data of patients aged 1-17 years who were diagnosed with acute myeloid leukaemia from July 2013 to June 2017. Data was analysed using SPSS 21.

Results: Of the 237 patients, 137(58%) were males and 100(42%) were females. The overall mean age was 8±4.34 years. Cytogenetic testing had been performed in 212(89.45%) cases, and core binding factor was detected in 72(34%) cases. There was significant difference between the mean values of white cell count and the subtypes (p=0.000). Also the difference between core binding factor and the subtypes was significant (p=0.000).

Conclusion: There was found to be a significant association of core binging factor with specific subgroups of acute myeloid leukaemia.

Key Words: Acute myeloid leukaemia, Core binding factor, Cytogenetic abnormalities, Prognosis.

Introduction

Acute myeloid leukaemia (AML), a clonal disorder of bone marrow-derived progenitors, is a heterogonous group of haematological malignancies, representing 15% of all childhood leukaemia. It generally occurs de novo, but the cause is not known.[1] The classification of AML is evolved from the French-American-British (FAB) classification that was mainly based on morphology classification of the World Health Organisation (WHO), which incorporates cytogenetics as the most discriminating feature irrespective of blast percentage. The cytogenetic and molecular characterisation of the leukemic blasts along with response to treatment plays a key role in overall prognosis.[2-4] The most common cytogenetic abnormalities in AML children are t(8;21) and inv.(16), which together are referred to as core binding factor AML (CBF AML) and account for approximately 25% of paediatric de novo AML patients.[5, 6]

According to existing classifications, such as Medical Research Council (MRC) criteria, CBF-AML is considered a favourable cytogenetic subgroup,[7, 8] and long-term survival rate is approaching 70% in the developed countries.[9, 10] CBF AML is known to have strong association with specific subgroups of the FAB classification, such as t(8;21) is mainly seen in AML M1 and AML M2, and inv.(16) in AML M4.[11] At the moleculer level, both cytogenetic abnormalities result in disruption of CBF, which is a transcription factor that functions as an essential regulator of normal haematopoiesis.

The treatment of AML is very expensive and toxic, so children may need hospitalisation during the entire course of induction chemotherapy due to high risk of sepsis.[12] Therefore, due to limited resources and poor outcome,[13] AML treatment has never been the priority in most paediatric oncology centres in Pakistan, and data for this favourable subgroup or its association with

morphological FAB subtypes is very limited. The current study was planned to find the frequency of CBF AML in our population, and to determine its association with morphological subtypes.

Materials and methods

The retrospective, observational, non-therapeutic study dealing with secondary was conducted at The Indus Hospital (TIH), Karachi, and comprised data July 2013 to June 2017. TIH is a tertiary care centre having 50-bed Paediatric Haematology Oncology Department (PHOD). After approval from the institutional ethics review committee, data was reviewed of all children aged 1-17 years who were diagnosed as AML in TIH. The Medical Record (MR) number was used as identification. The diagnosis was established on the basis of bone marrow biopsy and / or flowcytometry. Cytogenetic by inter-phase fluorescence in situ hybridization (I-FISH) was performed on bone marrow aspirate or blood. In some patients, I-FISH results were not available either because sample was not taken or there were low white blood cell (WBC) count for FISH interpretation. Patients having acute promyelocytic leukaemia (APL) were excluded.

Data was collected for age, gender, WBC count at presentation, FAB classification and CBF status.

Data was analysed using SPSS 21. Mean ± standard deviation (SD) values were computed for age and WBC count. Frequency and percentage were computed for gender, cytogenetic status and AML subtypes. Chi-square test/Fisher-exact test was applied as appropriate to assess significant association between diagnosis and cytogenetic status. Independent sample t test was applied on groups of CBF-positive and CBF-negative patients to find the difference between the means of age and WBC count. $P<0.05$ was considered significant.

Results

Of the 237 patients, 137(58%) were males and 100(42%) were females. The overall mean age was 8±4.34 years. Cytogenetic testing had been performed in 212(89.45%) cases, and, among them, CBF was detected in 72 (34%) cases, of which t(8;21) was seen in 59(82%) and inv.(16) in 13(18%) cases (Figure 1). Within the group, the frequency of t(8;21) and Inv. (16) was 59 (28%) and 13 (6%) respectively. Central nervous system (CNS) status was available for CBF-positive cases only; and 15(21%) of them were positive for CNS involvement.

Clinical characteristics of both CBF and non-CBF patients were compared and the significant differences were found in terms of WBC counts and AML subtypes (Table 1). The frequency of AML subtypes was done according to FAB classification (Figure 2). There were 26(11%) cases categorised as AML, but FAB sub-classification could not be done as bone marrow aspirate morphology was not available.

The association of CBF-positive cases was seen with respect to FAB classification (Table 2).

Discussion

The retrospective study investigated childhood AML for the presence of CBF and its association with FAB subtypes. CBF AML is known to have better prognosis and overall survival is >70% cases in the developed countries.[14] However, due to limited resources and poor outcome, AML treatment is not the priority in low and middle income countries (LMICs) like Pakistan. Due to this general approach, low-risk cases are missed that have high treatment potential.

The present study analysed 237 AML cases and FAB classification was applicable in 176, while in the rest of the cases bone marrow aspirate morphology was not available for sub-classification. Among these 176 cases, majority (33%) were AML M2, followed by AML M1 (24%) and M4 (17%). Similar results for AML M2 in local and internationally published studies have

been reported.[13, 15] However, there is difference in the reported prevalence of M1 and M4 subtypes.[15-17] In the current study, CBF was detected in 34% cases, which is higher than 18-20% reported by major treatment groups in western countries, but in line with a the study from Japan.[2, 17, 18] Out of these 34% CBF cases, majority (28%) had t(8;21) and only 6% showed Inv.(16). The presence of t(8;21) was found to be higher in the study compared to most published studies.[17, 19]

Association of CBF with AML subtypes was also explored and majority (85%) of t(8;21) cases were seen in AML M2 and AML M1. This cytogenetic lesion was not seen in any case of AML M0, M6 or M7. Similarly, Inv.(16) had significant association (62%) with AML M4. This association of CBF with specific FAB subtype is comparable with literature [20-22]

There was no statistically significant difference for age and gender in both CBF and non-CBF groups. The results for both the variables were also comparable with local and international studies. [8,16,17,19]

The mean WBC count for CBF group was significantly lower than non-CBF patients, while one study did not find any such difference. [8] In our cohort, CNS status was mainly documented for CBF group, and it showed positivity in 21% cases. This finding is higher than 3-17% reported earlier.[17, 23, 24] CNS leukaemia is reported to be more prevalent in some specific subgroups of AML, such as AML M4[13]. The higher incidence in our cohort may partially be explained due to testing of CNS status in CBF cases only which included significant numbers of AML M4.

The study findings can be helpful in making a cost-effective strategy for cytogenetic studies in relevant subtypes of AML.

Conclusion

There was high frequency of CBF AML. There was strong association of t(8;21) with AML M2 and of inv.(16) with AML M4 morphology.

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Table 1: Clinical characterstics of CBF and Non-CBF AML.

	Patients with CBF (n = 72)	**Patients without CBF (n = 140)**	***P* - value**
Gender			
Male	45 (63%)	78 (56%)	0.343**[€]
Female	27 (37%)	62 (44%)	
Age			
Mean ± SD	8.18 ± 3.67	8.38 ± 4.49	0.755**[§]
WCC			
Mean ± SD	34.74 ± 34.83	89.57 ± 123.06	0.000*[§]
AML Subtype			
AML M2 & M4	46 (64%)	37 (26%)	
Other	26 (36%)	103 (74%)	0.000*[€]

CBF: Core binding factor; AML: Acute myeloid leukemia; WCC: White cell count; SD: Standard deviation. *=Significant value, **=Non- Significant value, [§]=Independent Sample t Test, [€]= Chi square test

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Table 2: Distribution of CBF AML and its association with FAB Classification

Core	**AML**	**AML**	**AML**	**AML**	**AML**	**AML**	**AML**	**No. of**	***P* -**

Binding Factor		M1	M2	M4	M5	M6	M7	Cases	value
t(8;21)	6 (10%)	16 (27%)	34 (58%)	3 (5%)	-	-	-	59	0.000*€
Inv. (16)	1 (8%)	3 (23%)	1 (8%)	8 (61%)	-	-	-	13	
Total Cases	7 (10%)	19 (26%)	35 (49%)	11 (15%)	-	-	-	72	

*Significant value, €= Chi square test

CBF: Core binding factor; AML: Acute myeloid leukaemia; FAB: French-American-British classification.

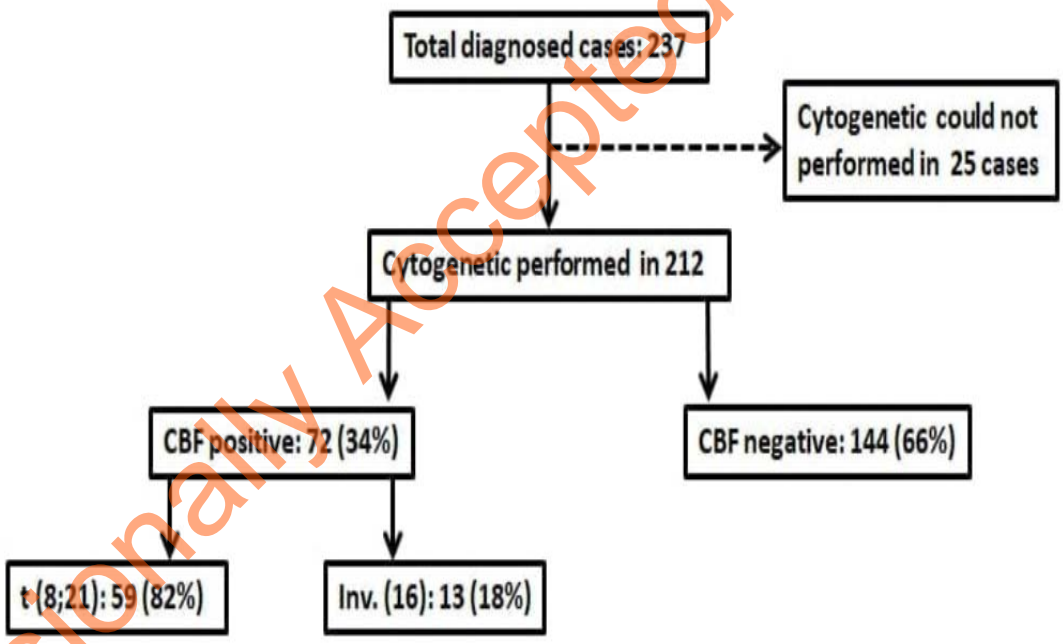

Figure 1: The study flow diagram.

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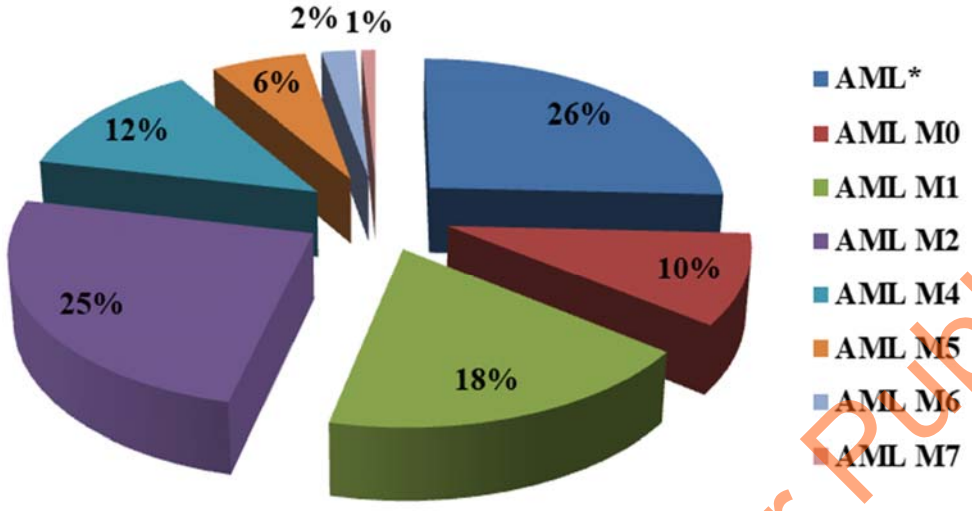
265 **Figure 2: Distribution of** acute myeloid leukaemia (**AML) subtypes.**



266
267 *AML = Not classified according to French-American-British (FAB)
268 classification, as bone marrow aspirate morphology was not available
269