RESEARCH ARTICLE

Childhood Core Binding Factor (CBF) acute myeloid leukaemia and its association with French American British (FAB) classification

Naeem Jabbar[1], Neelum Mansoor[2], Sidra Maqsood[3], Zaid Muhammad Aslam[4], Anzal Taufeeq Jangda[5], Syed Ahmer Hamid[6]

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.

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

(JPMA 70: 2408; 2020) **DOI: https://doi.org/10.47391/JPMA.521**

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 leukaemic 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 molecular 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

[1,3,6]Department of Pediatric Hematology Oncology, The Indus Hospital, Karachi, Pakistan; 2 Department of Hematology, The Indus Hospital, Karachi, Pakistan; [4,5]4th Year MBBS Student, Ziauddin Medical University Hospital, Karachi, Pakistan.

Correspondence: Naeem Jabbar. e-mail: naeem.jabbar@tih.org.pk

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.

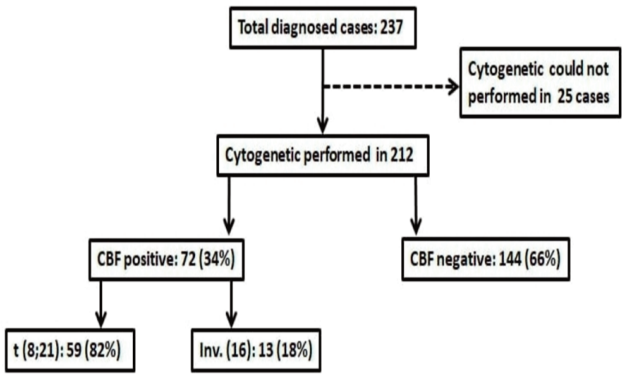


Figure-1: The study flow diagram.

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

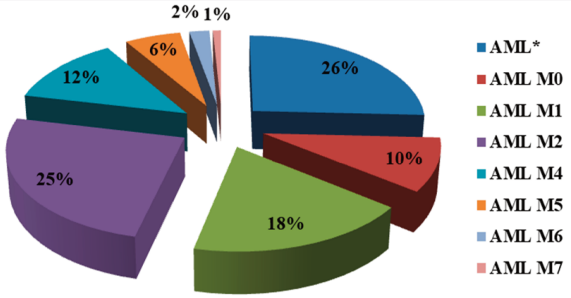
	Patients with CBF (n=72)	Patients without CBF (n=140)	*p*-value
Gender			
Male	45 (63%)	78 (56%)	0.343**€
Female	27 (37%)	62 (44%)	
Mean Age	8.18±3.67	8.38±4.49	0.755**§
Mean WCC	34.74±34.83	89.57±123.06	0.000*§
AML Subtype			
AML M2 & M4	46 (64%)	37 (26%)	
Other	26 (36%)	103 (74%)	0.000*€

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

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

Core Binding Factor	AML n (%)	AML M1 n (%)	AML M2 n (%)	AML M4 n (%)	AML M5	AML M6	AML M7	No. of Cases	*p*-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.



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

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

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.[20,21,22]

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 M413. 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.

Disclaimer: None.

Conflict of interest: None.

Source of Funding: None.

References

1. Smith MA, Ries LA, Gurney JG. Leukemia. In: Ries LA, Smith MA, Gurney JG, eds. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Md: National Cancer Institute, SEER Program, 1999; pp 17-34.
2. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, de Bont E, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: Recommendations from an international expert panel. Blood 2012; 120: 3187–205.
3. Bennett JM, Catovsky D, Daniel MT. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med 1985; 103: 620–5.
4. Swerdlow SH, Campo E, Harris NL. Editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008.
5. Betts DR, Ammann RA, Hirt A, Hengartner H, Beck-Popovic M, Kuhne T, et al. The prognostic significance of cytogenetic aberrations in childhood acute myeloid leukaemia. A study of the Swiss Paediatric Oncology Group (SPOG). Eur J Haematol 2007; 78:468–76.
6. Harrison CJ, Hills RK, Moorman AV, Grimwade DJ, Hann I, Webb DK, et al. Cytogenetics of childhood acute myeloid leukemia: United Kingdom Medical Research Council Treatment trials AML 10 and 12. J. Clin. Oncol 2010; 28: 2674–81.
7. Balgobind BV, Hollink IH, Arentsen-Peters ST, Zimmermann M, Harbott J, Beverloo HB, et al. Integrative analysis of type-I and type-II aberrations underscores the genetic heterogeneity of pediatric acute myeloid leukemia. Haematologica 2011; 96:1478–87.
8. Rubnitz JE, Raimondi SC, Halbert AR, Tong X, Srivastava DK, Razzouk BI, et al. Characteristics and outcome of t(8;21)-positive childhood acute myeloid leukemia: A single institution's experience. Leukemia 2002; 16: 2072–7.
9. Pession A, Rondelli R, Basso G, Rizzari C, Testi AM, Fagioli F, et al. AML Strategy & Study Committee of the AssociazioneItaliana di Ematologia e OncologiaPediatrica (AIEOP) Treatment and long-term results in children with acute myeloid leukaemia treated according to the AIEOP AML protocols. Leukemia 2005; 19: 2043–53.
10. Entz-Werle N, Suciu S, van der Werff ten Bosch J, Vilmer E, Bertrand Y, Benoit Y, et al. Results of 58,872 and 58,921 trials in acute myeloblastic leukemia and relative value of chemotherapy vs. allogeneic bone marrow transplantation in first complete remission: The EORTC Children Leukemia Group report. Leukemia 2005; 19: 2072–81.
11. Paschka P. Core binding factor acute myeloid leukemia. Semin Oncol 2008; 35: 410–7.
12. Cheng J, Sakamot KM. Topics in pediatricleukemia--acute myeloid leukemia. MedGenMed 2005; 7: 20.
13. Ghafoor T, Sharif I, Ashraf T, Ahmed S, Ahmed F. Paediatric acute myeloid leukaemia; clinical characteristics and treatment outcome; experience from a developing country. Int J Adv Res 2018; 6: 113-22.
14. Gibson BE, Webb DK, Howman AJ, De Graaf SS, Harrison CJ, Wheatley K. Results of a randomized trial in children with Acute Myeloid Leukaemia: medical research council AML12 trial. Br J Haematol 2011; 155: 366-76.
15. Bashasha S, Kordofani A, Osman I, Musa O, Altayb H. Prevalence of the different FAB sub type of Acute Myeloid Leukemia related to hematological parameters in Sudanese. J Hematol Blood Disord 2017; 3:102.
16. Fadoo Z, Mushtaq N, Alvi S, Ali M. Acute myeloid leukaemia in children: experience at a tertiary care facility of Pakistan. J Pak Med Assoc 2012; 62: 125-8.
17. Gibson BE, Wheatley K, Hann IM, Stevens RF, Webb D, Hills RK, et al. Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. Leukemia 2005; 19:2130-8.
18. Tsukimoto I, Tawa A, Horibe K, Tabuchi K, Kigasawa H, Tsuchida M, et al. Risk-stratified therapy and the intensive use of cytarabine improves the outcome in childhood acute myeloid leukemia: The

AML99 Trial from the Japanese Childhood AML Cooperative Study Group. J Clin Oncol 2009; 27: 4007-13.
19. Jastaniah W, Alsultan A, Al Daama S, Ballourah W, Bayoumy M, Al-Anzi F, et al. Is the outcome of childhood acute myeloid leukemia with t(8;21) inferior in Saudi Arabia? A multicenter SAPHOS leukemia group study. J App Hematol 2017; 8: 41-8.
20. Nucifora G, Dickstein JI, Torbenson V, Roulston D, Rowley JD, Vardiman JW. Correlation between cell morphology and expression of the AML1/ETO chimeric transcript in patients with acute myeloid leukemia without the t(8;21). Leukemia 1994; 8: 1533–8.
21. Ferrara F, Del Vecchio L. Acute myeloid leukemia with t(8;21)/AML1/ETO: a distinct biological and clinical entity. Haematologica 2002; 87: 306–19.
22. Delaunay J, Vey N, Leblanc T, Fenaux P, Rigal-Hugue F, Witz F et al. Prognosis of inv(16)/t(16;16) acute myeloid leukemia (AML): a survey of 110 cases from the French AML Intergroup. Blood 2003; 102: 462-9.
23. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, de Bont E, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood 2012; 120: 3187-205.
24. Jastaniah W, Al Ghemlas I, Al Daama S, Ballourah W, Bayoumy M, Al-Anzi F, et al. Clinical characteristics and outcome of childhood de novo acute myeloid leukemia in Saudi Arabia: A multicenter SAPHOS leukemia group study. Leuk Res 2016; 49:66-72.