ORIGINAL ARTICLE J. Med. Sci. (Peshawar, Print) April 2013, Vol. 21, No. 2: 81-83

FREQUENCY OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN ACUTE LYMPHOBLASTIC LEUKEMIA AT PRESENTATION

Inamullah[1], Shah Taj Khan[2], Hameeda Qureshi[2], Fazli Raziq[2]

[1]Department of Pathology, Khyber Teaching Hospital, Peshawar - Pakistan

[2]Department of Pathology Hayatabad Medical Complex, Peshawar - Pakistan

ABSTRACT

Objective: To assess the frequency of central nervous system (CNS) involvement in childhood acute lymphoblastic leukemia (ALL) at presentation.

Material and Method: This descriptive study was conducted on children below 17 years of age, over a period one year from January 2008 to January 2009. A total of 50 newly diagnosed ALL patients from all over Khyber Pukhtunkhwa were included in the study. Complete Blood Count and Bone Marrow findings of these patients were recorded and lumbar puncture was performed to assess the cerebrospinal fluid for central Nervous System involvement. Data was collected and statistically analyzed using soft ware SPSS 13.

Results: Out of these 50 newly diagnosed ALL patients, 33 were males and 17 were female with a M:F ratio of 1.9:1. Two patients were found with nervous system involvement. L1 and L2 morphology was seen in 92% and 8% of patients respectively. The prognostically favorable age group (1-10 years) had 6.5% L2 morphology compared with 10.5% in the prognostically unfavorable age group (above 10 years) indicating poor prognosis with increasing age. The frequency of CNS involvement in ALL was found in 4 % of these children.

Conclusion: For better prognosis, cerebrospinal fluid (CSF) examination must be done in every ALL child to find CNS involvement and initiate specific CNS directed therapy.

Key Words: Acute Lymphoblastic Leukemia, Bone Marrow, Central Nervous System, Cerebrospinal Fluid.

INTRODUCTION

Being a malignant hematologic disorder, Acute Lymphoblastic Leukemia (ALL) originates in a single B or T lymphocyte progenitor. Exramedullary accumulation of lymphoblasts may occur in various sites, especially the meningese, gonads, thymus, the spleen, liver or lymph nodes[1,2]. The Central Nervous System (CNS) is a well recognized site of extramed ullary leukemia that is involved with greater frequency in ALL than in myeloid leukemias[3].

ALL, the most common childhood acute leukemia, represents about 80% of child hood acute leukemias[4]. It has a bimodal distribution; an early peak at approximately 4 and 5 years with an incidence as high as 4-5 per 1,00,000 persons, followed by a second gradual increase to a peak at about age 50 years. Here the incidence is up to 2 per 1,00,000 persons[5]. CNS involvement is seen in 5% of children and in less than 10% of adults with ALL. However, many patients will eventually develop CNS disease if not adequately treated[6,7]. Acute Lymphoblastic Leukemia commonly involves the meningese and may be present at diagnosis or at any time in the course of the disease[8].

Address for Correspondence:
Dr. Inam Ullah
Assistant Professor
Pathology Department, Khyber Medical College,
Peshawar - Pakistan
Cell: 0333-9108339
E-mail: drinamkmc@yahoo.com

The international definition of overt CNS leukemia is the presence of a White Blood Cell (WBC) count of 5/µl or more in the cerebrospinal fluid (CSF) with documented blasts and/or the presence of a cerebral mass or cranial nerve palsy[9,10]. Accurate detection of CNS involvement in children with newly diagnosed acute lymphoblastic leukemia (ALL) could have profound prognostic and therapeutic implications[11].

CNS leukemia usually presents with symptoms of increased intracranial pressure in 90% of cases, resulting in headache, nausea and vomiting, lethargy, irritability and disturbance of vision. Some patients may present with signs of meningismus, cranial nerves palsy, mostly III,1V,VI and VIII[5]. or "Numb chin syndrome"[5,12].

Cerebrospinal Fluid Examination examination is an established procedure for the evaluation and

staging of hematopoietic malignancies[13]. Early attempts at intrathecal (IT) chemotherapy provided some relief from hydrocephalus, but it did not eradicate CNS leukemia. Pinkel was the first to effectively control meningeal leukemia by combining cranial irradiation with combination chemotherapy. This approach resulted in 5-year relapse-free survival in approximately 50% of children with ALL. Investigations eventually showed that cranial irradiation in conjunction with intrathecal methotrexate (IT MTX) reduced the incidence of CNS relapse from over 65% to less than 10%[9]. The purpose of this study was to find frequency of CNS involvement in childhood acute lymphoblastic leukemia at presentation in KPK and create awareness in physicians about the presence of CNS leukemia and help the patient through timely diagnosis and proper management of ALL patients with prompt CNS directed therapy.

MATERIAL AND METHOD

This was a prospective study with a duration of one year. The subjects for study included ALL patients below 17 years from all areas of KPK who visited Khyber Teaching Hospital (KTH), Post Graduate Medical Institute, (PGMI) Hayatabad Medical Complex, Peshawar and Institute of Radiotherapy and Nuclear Medicine (IRNUM). Patients with other malignancies, those already receiving chemotherapy and those with infectious meningitis were excluded from the study.

Data was collected on preformed performa, recording blood counts (Hb, TLC, DLC & Platelets count) and bone marrow findings (including the %age of blasts in the marrow nucleated cells and the type of ALL ie L1, L2 or L3) of known newly diagnosed ALL patients and the CSF findings obtained through laboratory examination of the patient's CSF, using the cytocentrifuge for proper cell morphology of the CSF. CSF samples used to be collected in three sterile tubes through lumbar puncture (LP) allowing 1 to 2 cc of CSF to flow into each of the three sterile tubes. Sent the first tube for glucose and protein, the second for Gram stain, and the third for cell count and differential. When needed, the second tube would first be used for culture /sensitivity (C/S) and then for Gram staining.

Tests performed on the CSF samples included Total Cell Count (using New Improved Neubar counting Chamber or Sysmex KX 21 hematology analyser) and Differential Count using the cytocentrifuged deposit of the CSF stained with Giemsa Stain for differential count and morphology of abnormal cells. The CSF proteins were estimated using Selectra XL Chemistry Auto analyzer. Data was analyzed using computer soft ware SPSS 13. Continuous variables were analyzed as such or changed into medically meaningful categories.

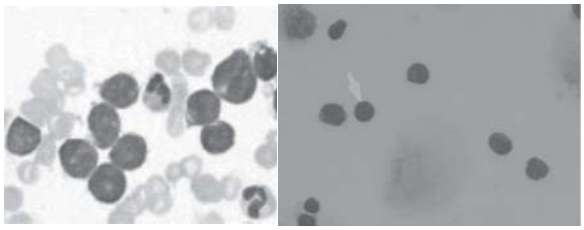

Figure 1: Acute Lymphoblastic Leukemia ALL-L1. Picture on left is peripheral blood film and on the right is CSF showing L1 blasts.

RESULTS

In this study a total number of 50 newly diagnosed ALL patients were included. Out of these 50 cases 33 were male and 17 were female with an overall male to female ratio of 2:1. Figure 1 shows diagramitic representation of L1 blast cells in blood and CSF. The male female ratio in the favorable age group (up to 10 years age) was 1.58:1 and in unfavorable age group (above 10 years) was 2.8:1. Nervous system involvement was noted in two patients out of the 50 studied patients representing 4% of the total cases. Both of the cases were male and both presented with L1 morphology. In the first case the age was 02 years and the 2nd patient was 12 years old. One patient was leukopenic with a TLC of 2,100/cm^3 while the 2nd patient had a high TLC of 1,40,000/cm^3. 46 patients in the study had ALL L1 and 04 having ALL L2 morphology.

DISCUSSION

Central nervous system is one of the various sites involved in the extramedullary accumulation of lymphoblasts. Children are most commonly affected by the disease[1,2]. CNS is a well recognized extramedullary site of leukemic involvement affected with greater frequency in ALL than AML[3]. The CNS involvement may be present at the onset of leukemia or can occur at any time during the course of treatment. It is diagnosed by CSF examination which is an established procedure for the evaluation and staging of hematopoietic neoplasms[14]. Accurate detection of central nervous system (CNS) involvement in children with newly diagnosed acute lymphoblastic leukemia (ALL) could have profound prognostic and therapeutic implications[11]. Pfiefer et al[3] studied 107 patients of Ph chromosome positive ALL or blast crisis of CML. Thirteen patients developed CNS leukemia during Imatinib (Glevic) therapy. Interestingly, none of them had received prophylactic cranial or craniospinal radiation. Conversely, none of the 29 patients previously treated with prophylactic cranial irradiation developed CNS leukemia during Imatinib therapy. The protective effect of prophylactic CNS directed therapy was statistically significant ($p=0.018$). Seibel[15] has described the probability of occurrence of CNS leukemia from 50%-70% in patients who do

not receive proper CNS directed prophylactic therapy. The timely diagnosis of CNS leukemia is critical for the proper management of ALL.

This study showed the frequency of CNS involvement in ALL at 4%. Cortes & Kantarjian[5], Esperza et al[6] and Berg et al[7], have stated the incidence as 5% in US. Seibel[15] found the incidence in US at 3%. In Pakistan, Yasmin and Ashraf[16] have also found the incidence at 5%. These studies show nearly the same trend. For unknown reasons, Pusponegoro et al[17] have described a higher incidence (8%) in Indonesia. Compared to the classification of CNS ALL into four categories, the CNS involvement in this study was noted in CNS3 stage (indicating a late stage)[11]. Apart from other unknown causes, this could be due to late examination of the patient by the physician and delay in CNS prophylaxis.

Both the cases in our study were male children. However, this is due to the limited nature of the study and does not reflect the overall status. One patient with CNS involvement belonged to the favorable prognostic age group (1-10 years) where as the other patient was in the unfavorable prognostic age group (12 years). The younger patient had TLC of 2,100/cmm, whereas the other patient had a high leukemic cell burden (1,43,000/cm^3). Higher TLC count at diagnosis indicate an increased risk of treatment failure in precursor B-cell ALL and so a poor prognosis[18].

CONCLUSION

CSF examination is needed in every child with ALL to look for CNS involvement. CNS directed therapy is essential for proper management of ALL, resulting in good prognosis.

REFERENCES

1. Pui CH. Acute lymphoblastic leukemia. In Williams Hematology: Bentler E. Litchman MA, Coller BS, Kipps TJ, Seligsohn, U. Eds. 6th Ed. Mc Graw Hill: New York, US, 2001; 1141-55.
2. Piatkowska M, Styczynski J. Pediatric acute lymphoblastic leukemia: state of the art and new trends. JPS 2010; 2(3): 22-27.
3. Pfeifer H, Wassmsnn B, Hoffman WK. et al. Risk and Prognosis of Central Nervous System Leukemia in Patients with Philadelphia Chromosome Positive Acute Leukemias Treated with Imatinib Mesylate. Clin Cancer Res. 2003; 9(13): 4674-81.
4. Jabbour EJ, Faderl S, Kantarjian HM. Adult acute lymphoblastic leukemia. Symposium on oncology practice: hematologic malignancies. Mayo Clin Proc. 2005; 80(11): 1517- 27.
5. Cortes JE, Kantarjian.HM. Acute Lymphocytic Leukemia: a comprehensive review. Cancer. 1995; 76(12): 2393-417.
6. Esperza SD, Sakamoto KM. Topics in Pediatric leukemia-Acute Lymphoblastic Leukemia. Med Gen Med. 2005; 7(1): 23.
7. Berg SL, Steuber CP, Poplack DG. Clinical manifestations of ALL. In Hematology - Basic Principles and Practice; Hoffman R. Eds.; 4th Ed.; Churchill Livingstone: Philadelphia, U S, 2005; 1155- 60.
8. Athens JW, Ward JH. Complications of Hematopoietic Neoplasms. In Wintrobe's Clinical Hematology; Richard Lee, G, Bithel TC, Foerster J, Athens JW, Lukens JN. Eds.; 9th Ed.; W B Saunders: Philadelphia, US, 1993; Vol. 2, 1792- 42.
9. Laningham FH, Kun LE, Reddick WE, Ogg RJ, Morris EB, Pui CH. Childhood central nervous leukemia: Historical perspective, current therapy and acute neurological sequelae. Neuroradiology 2007; 49(11): 873-88.
10. Tamaddoni A, Nesheli HA, Bali KB. Central nervous system relapse prophylaxis in acute lymphocytic leukemia: intrathecal chemotherapy with and without cranial irradiation. Casp J Intern Med 2010; 1(1): 27-30.
11. Pine SR, Yin C, Matloob YH.; Sabaawy HE, Sandoval C, Tugal OL, et al. Detection of Central Nervous System Leukemia in Children with Acute Lymphoblastic Leukemia by Real-Time Polymerase Chain Reaction. J Mol Diagn 2005; 7(1): 127-32.
12. Kurzbaun A, Yaganeh S, Qarawany M, Riefler J. Numb chin syndrome as an initial presentation of acute lymphoblastic leukemia. ISRJEM 2005; 5(3): 19-33.
13. Evans DIK, Rourke CO, Jones PM. The cerebrospinal fluid in acute leukaemia of childhood: studies with the Cytocentrifuge. J Clin Pathol 1974; (3): 226-30.
14. Renshaw AA, Hughes JH, Wang E, CTJH, Wilber D, Henry MR, et al. Leukemia/Lymphoma in CSF: Distinguishing between cases that performed well and poorly in the college of American Pathologists Interlaboratory Comparason Program in Nongynaecologic cytology. Arch Pathol Lab Med 2006; 130(12): 1762- 65.
15. Seible N L. Treatment of Acute Lymphoblastic Leukemia in Children and Adolescents: Peaks and Pitfalls. ASH Educ Program 2008; 374-80.
16. Yasmin N, Ashraf S. Childhood Acute Lymphoblastic Leukemia: Epidemiology and clinicopathological features. J Pak Med Assoc 2009; 59 (3):150-53.
17. Pusponegoro HD, MZ M, Kaban RK, Suradi R, Windiastuti E. Clinical features and survival pattern of central nervous system leukemia in children with acute lymphoblastic leukemia. Paediatrica Indonesiana 2001; 41: 247-52.
18. Armstrong J, Pomeroy M, Fennelly JJ, Cahalane S. Prognostic factors in childhood acute lymphoblastic leukemia. IJ MS. 1990; 159(2): 40-43.