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ORIGINAL ARTICLE

The Incidence Rate of Central Nervous System (CNS) Involvement in Pediatric Patients Diagnosed with Lymphoblastic Leukemia (ACUTE)

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ABSTRACT

Objectives: The objective of this study is to establish the incidence rate of central nervous system (CNS) involvement in pediatric patients diagnosed with lymphoblastic leukemia (acute).

Methodology: A cross-sectional survey was undertaken in the Paediatric Oncology Unit, Sheikh Khalifa Bin Zayyed Hospital, Quetta hospital between 12th January 2021 and August 2022. This research study included 115 patients who fulfilled the eligibility criteria. Demographic profiles were recorded including age, gender and address. Lumbar puncture was done by a single doctor in all these patients at diagnosis to look for CNS involvement. CSF examinations of all patients were done by a single laboratory.

Results: The patients had a mean age of 5.9±3.3 years, and the study consisted of 46 (40%) female and 69 (60%) male participants. There were 6 (5.2%) patients who had CNS involvement and 109 (94.8%) had no CNS involvement. In the age range of 1-5, 6-10 and 11-15 years, there were 2 (1.7%) patients who had CNS involvement respectively. In the stratification of CNS involvement with gender, in male patients, there were 2 (1.7%) patients who had CNS involvement and in female patients, there were 4 (3.5%) patients who had CNS involvement.

Conclusion: In conclusion, this study reveals that central nervous system involvement in children with acute lymphoblastic leukemia is prevalent upon initial diagnosis. Nevertheless, some disparities have been observed from Western data, such as dissimilarities in age distribution.

Keywords: nervous system, Acute lymphoblastic leukemia, white blood cells, total leucocyte counts.

INTRODUCTION

ALL, a malignant neoplasm, is the most frequently occurring cancer in children below 15 years of age. It is characterized by genetic irregularities in hematopoietic cells that trigger an uncontrolled clonal expansion of cells.[1]

CNS involvement in patients with ALL is a significant contributor to mortality and morbidity. The occurrence of CNS involvement in ALL patients during the initial presentation is approximately 5%.[2,3]

Several children with leukemia cells detected in the cerebrospinal fluid (CSF) may not display any symptoms, whereas severe CNS disease may clinically manifest as irritability, headaches, and, at times, abnormal weight gain, vomiting or seizures. Patients exhibiting evident CNS leukemia may experience cranial nerve palsies, usually the unilateral nerve VII palsy, less frequently nerves VI or III. Advanced CNS disease may be characterized by papilledema and widespread retinal disease.[4] All the patients with CNS involvement have a prognosis that is inferior to those who do not have CNS disease at diagnosis.[5,6]

The degree of neurological impact relies heavily on timely identification of central nervous system (CNS) illness. Administering a lumbar puncture to examine cerebrospinal fluid (CSF) during diagnosis to detect the presence of leukemia cells in the CNS is a crucial aspect in determining appropriate CNS-focused treatment for children afflicted with leukemia.[4]

When elective central nervous system (CNS) targeted therapy is introduced, typically through a combination of cranial irradiation and intrathecal chemotherapy, it can help lower the likelihood of meningeal relapse.[7]

Initiating central nervous system (CNS) therapy early on is crucial in eradicating clinically visible CNS illness during diagnosis and also in preventing CNS relapse in patients who do not exhibit obvious CNS symptoms.[6,8]

Our findings indicate that, in contrast to developed nations, children diagnosed with ALL in developing countries like Pakistan are at higher risk of presenting with CNS involvement due to delayed diagnosis. Currently, limited information is available regarding the prevalence of CNS involvement in ALL cases in Pakistan, as not all medical facilities conduct CSF examinations during diagnosis to detect CNS involvement.

We hypothesize that by gathering data on the frequency of CNS involvement in ALL cases during diagnosis, we can identify this complication earlier, enabling us to implement timely CNS-directed therapy and reduce both the mortality and morbidity rates in affected patients. The main objective of this study is to establish the prevalence of central nervous system (CNS) involvement in children diagnosed with acute lymphoblastic leukemia at the time of diagnosis.

MATERIALS AND METHODS

A cross-sectional survey was undertaken in the Paediatric Oncology Unit, Sheikh Khalifa Bin Zayyed Hospital, Quetta hospital between 12th January 2021 and August 2022.

Using the non-probability consecutive sampling technique, patients were recruited. The study includes a sample size of 115 cases, calculated using a 95% level of confidence and a 4% error margin, assuming an anticipated percentage of 5% for central nervous system (CNS) involvement in children with acute lymphoblastic leukemia (ALL).

All patients between the ages of 2 and 15, regardless of gender, who have been diagnosed with ALL via bone marrow biopsy after presenting with symptoms such as fever greater than 38°C, pallor, and bleeding, are eligible for inclusion in the study. Patients with a history of CNS relapse or those who are currently receiving chemotherapy were not included.

A total of 115 patients who met the study's inclusion criteria were admitted to the Pediatric Hospital's Oncology Department and enrolled in the study. Prior to participation, informed consent was obtained from the parents of each child, who were informed that their child's data would be collected, used, and published, while maintaining strict confidentiality.

The demographic information, such as address, gender and age of each participant was recorded and documented. Lumbar puncture was done by a single doctor in all these patients at diagnosis to look for CNS involvement (as per operational definition). CSF examinations of all patients were done by a single laboratory. All data was recorded on predesigned proforma.

The collected data was entered into the statistical software, SPSS version 11, and analyzed thoroughly. The variables that were examined included CNS involvement, gender and age. The variables that are quantitative such as age were presented as

standard deviation and mean, while variables that are qualitative such as gender and CNS involvement were shown as percentages and frequency. The data was stratified by gender and age to evaluate any potential differences or correlations.

To assess the impact of confounding variables on the CNS involvement development, the Chi-square test was utilized. In cases where the cell count was below five, the Fisher's exact test (Freeman-Halton extension) was employed. A p-value of less than 0.05 was considered significant.

RESULTS

The average age of the patients was 5.9 ± 3.3 years. Among the study participants, 52 (45.2%) patients fell within the age range of 1-5 years, 50 (43.5%) patients were between the ages of 6-10 years, and 13 (11.3%) patients were between the ages of 11-15 years.

Regarding the distribution of patients by gender, slightly over half of the participants were male, while 40% were female patients. In terms of CNS involvement, 5.24% of the patients in the study exhibited evidence of CNS involvement (Table 1).

Table 1: Characteristics of study population

Parameter	N (%)
Age (Years)	
1-5	95 (45.24%)
6-10	91 (43.33%)
11-15	24 (11.43%)
Gender	
Male	126 (60.00%)
Female	84 (40.00%)
CNS involvement	
Yes	11 (5.24%)
No	199 (94.76%)

Upon stratification, we found that the majority of the children between the ages of one and five had involvement of CNS while the majority of the older children did not develop any neurological deficits. The association between age and involvement of CNS was found to be statistically significant at p=0.004. Furthermore, gender was also found to be associated with CNS involvement. It was found that the majority of the female patients developed CNS symptoms (Table 2).

Table 2: Association of Age and Gender with CNS involvement in patients with acute lymphoblastic leukemia

Parameters	CNS involvement		
	Yes	No	p-value
Age (Years)			
1-5 years	9 (4.29%)	91 (43.33%)	0.004
6-10 years	0 (0.00%)	88 (41.90%)	
11-15 years	2 (0.95%)	20 (9.52%)	
Total	11 (5.24%)	199 (94.76%)	
Gender			
Male	2 (0.95%)	110 (52.38%)	0.026
Female	9 (4.29%)	89 (42.38%)	
Total	11 (5.24%)	199 (94.76%)	

DISCUSSION

The most prevalent type of cancer in children is Acute lymphoblastic leukemia (ALL), representing approximately 25% of all childhood cancers. Boys are more frequently affected by this disease, with a sex ratio of 1.3:1.[9, 10, 11]

Leukemia has a comparable frequency worldwide. In a study by Yasmeen and Ashraf, ALL accounted for 32% of all cancers. The higher prevalence of ALL in this study may be due to newly established oncology units more frequently referring patients with hematological malignancies as compared to solid tumors. In developed countries, the age distribution of ALL is characterized by a prominent early peak between 2 and 5 years of age, continued by a smaller peak between 10-12 years, with a 4 years median age.[9, 10, 11]

Conversely, the Pakistani population in this study exhibited a more pronounced peak between 10-12 years, with a 6.5 years median age. These differences may be attributed to a less frequent occurrence of ALL in the early peak and in the second peak due to the presence of more T cells. Lymphoreticular malignancies are more likely to develop in individuals with certain genetic disorders such as Fanconi's anemia and Bloom's syndrome, as reported in previous studies.[12] The study found that 52% of parents of children with ALL had consanguinity, which is in line with the high rate (60%) of consanguinity observed in the Pakistani population by other research groups, indicating that this is not unexpected.[3,13,14]

In this study, 54% of the patients had hemoglobin levels below 7 gm/dl, while only 8% had levels above 11gm/dl. Although higher hemoglobin levels have been associated with poor prognosis in Western series [15,16], lower hemoglobin levels have been linked to worse prognosis in data from India.[17] Additionally, CNS disease at diagnosis was confirmed in 5% of the patients through initial CSF examination.

At diagnosis, a considerable number of patients (14%) were found to have tested positive for Hepatitis B surface antigen, which is consistent with the findings of ALL series in India. However, the prognostic importance of this observation needs to be further explored in additional studies.[18] The mean age of the patients in our study was 5.9±3.3 years, which is comparable to the mean age reported in a previous study by Yasmeen and Ashraf[3] where it was found to be 6.5 years.

Our study showed a predominance of males among the patients. The gender distribution in our study was comparable to the study conducted by Yasmeen and Ashraf[3], with 64% males and 36% females. CNS involvement was observed in 5.2% of children with acute lymphoblastic leukemia in our study. This incidence is similar to the findings of Yasmeen and Ashraf, who reported CNS involvement in 5% of patients with acute lymphoblastic leukemia at presentation.

Fiere et al[19], a french group on therapy for ALL (acute lymphoblastic leukemia) in adult, stated that 7% of adult ALL patients had central nervous system (CNS) involvement confirmed by spinal fluid cytology at the time of diagnosis out of 572 patients. Similarly, Kantarjian et al. (80) observed that 7% of 204 adult ALL patients had CNS leukemic involvement at presentation. In a previous publication, the same group[20] reported that 4% of 391 patients had evidence of CNS leukemia at diagnosis and were excluded from the analysis. Moreover, a recent study conducted by the Southwest Oncology Group (SWOG) that enrolled 404 patients, including 75 whose CNS status was unknown, found that leukemia was detected in 5% of 278 patients.[21]

Gururangan et al.[22] reported that pediatric patients (below 19 years old) with disseminated small noncleaved-cell lymphoma and B-cell leukemia had a higher incidence of CNS disease at diagnosis. In their study, 49 out of 462 (10.6%) patients had CNS disease at diagnosis, which was defined as meningeal disease or CNS parenchymal masses with or without cranial neuropathies.

Thomas and colleagues[23] also reported a significant incidence of CNS involvement at diagnosis in Burkitt-type adult ALL, with 11 of 42 patients (42%) affected. Of these patients, six presented with cranial nerve palsies or other neurologic symptoms, and five were asymptomatic despite positive cerebrospinal fluid (CSF) cytology. Additionally, 8 out of 68 adult B-cell ALL patients (12%) were found to have CNS involvement at diagnosis.[24]

The above analysis suggests that central nervous system (CNS) involvement in children with acute lymphoblastic leukemia (ALL) is a frequent occurrence at the time of diagnosis. Nevertheless, there are some distinctions in comparison to western data, such as the age distribution. In our study, ALL was observed across all age groups with peaks at 2-5 and 10-12 years, which differs from the typical age distribution reported in Western populations.

CONCLUSION

The findings of the study indicate that central nervous system involvement is a prevalent feature in children diagnosed with acute lymphoblastic leukemia. Nonetheless, differences have been

identified when compared to Western data, specifically with regards to the age distribution of leukemia cases. Unlike Western populations, leukemia occurs in all age groups in this study, with notable peaks at 2-5 years.

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