International Journal of Pediatrics and Genetics
Vol. 3 No. 5 (2025)
ISSN: 2995-5483

Assessing Ocular Involvements in Childhood Leukemia Insights into Pathophysiology and Treatment

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Abstract: Background: Malignancies such as acute leukemia-in its most common form in pediatric age groups-have been associated with eye involvements; these involvements may arise either because of the disease itself, its secondary complications, or side effects of therapy.

Aim of the study: To ascertain the prevalence of ocular involvement in leukemia patients.

Patients and Methods: Patients with leukemia were admitted to Nanakali Hematology and Oncology Hospital in Erbil from February 1 to May 31, 2024. This study included 120 eyes of 60 leukemia patients (58 with acute lymphoblastic leukemia and 2 with chronic myeloid leukemia). Patients' ages, sex, and hematological data were recorded. Their eyes were then examined for any lesions. This included determining visual acuity using a Snellen distance chart, flashlight anterior segment examination, slit-lamp examination, and dilated fundus examination with direct ophthalmoscopy. Ocular changes were correlated with hematological data.

Results: Ocular changes were seen in 23 patients with leukemia (38.3%), of which 22 were acute lymphoblastic leukemics, and 1 was chronic myeloid leukemia.

Conclusion: Ophthalmological manifestations in patients with Acute Leukemia are very common; these involvements can either be secondary to direct infiltration of leukemic cells or due to secondary causes of the disease or even treatment of the disease.

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ISSN: 2995-5483

Key words: Malignancies, Pediatric, Leukemia, Examination, Ophthalmoscopy.

Introduction

Leukemia is the most common childhood malignancy, accounting for 41% of all malignancies in children under 15 years old. It is a group of malignant disorders of hematopoietic tissues characterized by an increased number of primitive white cells in bone marrow. These cells disrupt normal marrow function, leading to marrow failure [1]. Acute leukemias are divided into acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). ALL accounts for approximately 80% of all childhood leukemia cases, with a peak incidence rate of 2-5 years old and decreasing with age before increasing again at around 50 years old. It is slightly more common in males than females and has an increased incidence in people with Down syndrome, Fanconi anemia, Bloom syndrome, Ataxia telangiectasia, X-linked agammaglobulinemia, and Severe combined immunodeficiency. The frequency of leukemia is higher than expected in families of leukemia patients, with siblings having a two to fourfold greater risk of developing the disease than children in the general population. Diagnosis of ALL involves a complete blood cell count, which can reveal the presence of circulatory leukemic blast cells, anemia severity, and various blood cell types [2,3,4,5].

Treatment is the most important prognostic factor since, if untreated, the disease terminates the life of the patient. Therapy depends on the estimated clinical risk of relapse, which is extremely variable according to the subtype of ALL. The most important predictive factors are age at diagnosis, initial leukocyte count, and speed of response to therapy. [6,7]

There are four therapy phases: remission induction and induction, consolidation and delayed intensification, and maintenance. Remission induction erases leukemic cells from the bone marrow, while consolidation and intensification include 14-28 weeks of multiagent therapy followed by delayed intensification and interim maintenance. Maintenance involves daily mercaptopurine and weekly methotrexate with intermittent vincristine and corticosteroid [8,9].

Leukemia has frequent ophthalmological manifestations, and up to 90% of patients may manifest some ocular changes. Ocular involvement with the abrupt alternating frequency of bone marrow relapses and CNS compromise creates the scenario of poor prognosis and low survival rates. Treatment of ocular manifestations is complicated because of poor penetration of chemotherapy drugs into the eye. [10,11,12]

Material and method

The study was conducted within this pediatric department of Nanakaly Hospital for Oncology and Blood Disease in Erbil City, a center for childcare with malignancies and hematological issues in the Erbil governorate. A total of 60 diagnosed leukemia cases, 58 ALL and 2 CML, aged from 4 to 14 years, who attended the hospital in the study period, were included in the study. A questionnaire was designed to gather data such as name, age, sex, weight, stage of disease, date of diagnosis, duration of treatment, eye problems, radiotherapy, and laboratory investigations. All patients were subjected to an ophthalmological examination for any ocular manifestations.

Profiles of patients included WBCs normal according to age, hemoglobin normal according to age, platelets normal, and a statistical test called Fisher's exact test. The data were entered into SPSS, version 19, for analysis, using Fisher's exact test for the exact count of cells and Student's t-test for means comparisons. Graphs and tables were constructed to summarize and display the results.

Results

1. **Distribution of patients according to gender:**

Table 1 shows the distribution of data according to gender: 56.7% of cases were male, and 43.3% of cases were female, P-value 0.64.

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Table 1 Distribution of patients according to gender

Gender		Frequency		P-value
		Total (Percent)	Affected	
	Male	34 (56.7%)	15 (65.3%)	
	Female	26 (43.3%)	8 (34.7%)	0.64
	Total	60 (100%)	23 (100%)	

2-Distribution of patients with eye involvement in each stage of the disease:

Table 2 shows that 26.7% of patients are newly diagnosed, 43.7% of them have eye involvement, and 10% are relapses cases 83.3% have eye involvement.

Table 2 Distribution of patients with eye involvement in each stage of the disease

Stage of disease	Total no. (Percent)	No. of patients involved (Percent)
Newly diagnosed	16 (26.7%)	7 (43.7 %)
Induction	3 (5%)	0 (0.0%)
Maintenance	22 (36.7%)	9 (40.9%)
Relapse	6 (10%)	5 (83.3%)
Follow up	13 (21.7%)	2 (15.4%)
Total	60 (100%)	23 (38.3%)

3-Distribution of patients according to initial hematological profile:

Table 3 shows that 38.3% had high WBC counts, 81.7% are anemic, and 70% have low platelet counts**.**

Table 3 Distribution of patients according to initial hematological profile

value	WBCs	Hb	Plts
Low	13 (21.7%)	49 (81.7%)	42 (70%)
Normal	24 (40%)	11 (18.3%)	17 (28.3%)
High	23 (38.3%)	0 (0%)	1 (1.7%)
Total	60 (100%)	60 (100%)	60 (100%)

4- Distribution of patients with eyelid involvement:

Table 4 shows the Distribution of patients with eyelid involvements; most of them (83.3%) have no involvements.

Table 4 Distribution of patients with eyelid involvement

Type of Involvement		Frequency
	Ectropion	2 (3.3%)
	Oedema	6 (10%)
	Ptosis	2 (3.3%)
	No involvement	50 (83.3%)
	Total	60 (100%)

5-Distribution of patients with Conjunctiva involvements:

Table 5 shows those patients with conjunctiva involvement. 76.7% of patients have no conjunctiva involvements, 13.3% of patients have conjunctivitis, and 5% of patients have subconjunctival hemorrhage.

Table 5 Distribution of patients with Conjunctiva involvements

Type of Involvement		Frequency (Percent)
	Chemosis	1 (1.7%)
	Subconjunctival hemorrhage	3 (5%)
	Conjunctivitis	8 (13.3%)
	Subconjunctival hemorrhage conjunctivitis &	2 (3.3%)
	No involvement	46 (76.7%)
	Total	60 (100%)

6-Distribution of patients with corneal involvements:

Table 6 shows 1.7% of patients has corneal ulcers, 3.3% have dry eyes, and 95% have no involvements.

Table 6 Distribution of patients with corneal involvements

Type of Involvement		Frequency (Percent)
	corneal ulcers	1 (1.7%)
	Dry eyes	2 (3.3%)
	No involvements	57 (95%)
	Total	60 (100%)

7-Distribution of patients with iris, angle, and lens involvements:

Table 7 shows that 6.7% have uveitis, which is the most common type of involvement, and the remaining has no iris, angle, or lens involvement.

Table 7 Distribution of patients with iris, angle, and lens involvements

Type of Involvement		Frequency (Percent)
	Glaucoma	1 (1.7%)
	Uveitis	4 (6.7%)
	Pseudohypopyon	1 (1.7%)
	No involvements	54 (90%)
	Total	60 (100%)

8- Relation between mean platelets counts and retinal hemorrhage:

The following Table shows there is a significant association (P-value 0.001) between mean platelet counts and incidence of retinal hemorrhage.

Table 8 Relation between mean platelets counts and retinal hemorrhage

Retinal hemorrhage	No.	Mean platelets count	SD	p
Yes	9	36118.67	59010.57	0.001
No	51	138009.43	150790.62	

9- Distribution of patients with retinal involvements:

Table 9 shows 78.3% of cases have no retinal involvements, 11.8% of cases have a retinal hemorrhage, 3.3% of cases have a vitreous hemorrhage, 3.3% have perivascular infiltrates, 3.3% have peripheral neovascularization and perivascular infiltrates.

Table 9 Distribution of patients with retinal involvements

Type of Involvement		Frequency (Percent)
	Retinal hemorrhage	7 (11.8%)
	Perivascular infiltrates	2 (3.3%)
	Vitreous hemorrhage	2 (3.3%)
	Peripheral neovascularization and perivascular infiltrates	2 (3.3%)
	No involvement	47 (78.3%)
	Total	60 (100%)

10- Relation between mean WBC counts and retinal infiltration:

The following Table shows that there is no significant association (P-value 0.291) between mean WBC counts and the occurrence of retinal infiltration.

Table 10 Relation between mean WBC counts and retinal infiltration

Retinal infiltration	No.	Mean WBC	SD	p
Yes	4	76000.00	77000.58	0.291
No	56	26000.29	42000.54	

11- Mean of the duration of treatment in months and eye involvements.

Fig. 3 shows the mean of duration of treatment of those who have eye involvement is 19.13 months, while the duration of those who have no eye involvement is 15.11 months; newly diagnosed patients and those on follow-up do not receive treatments.

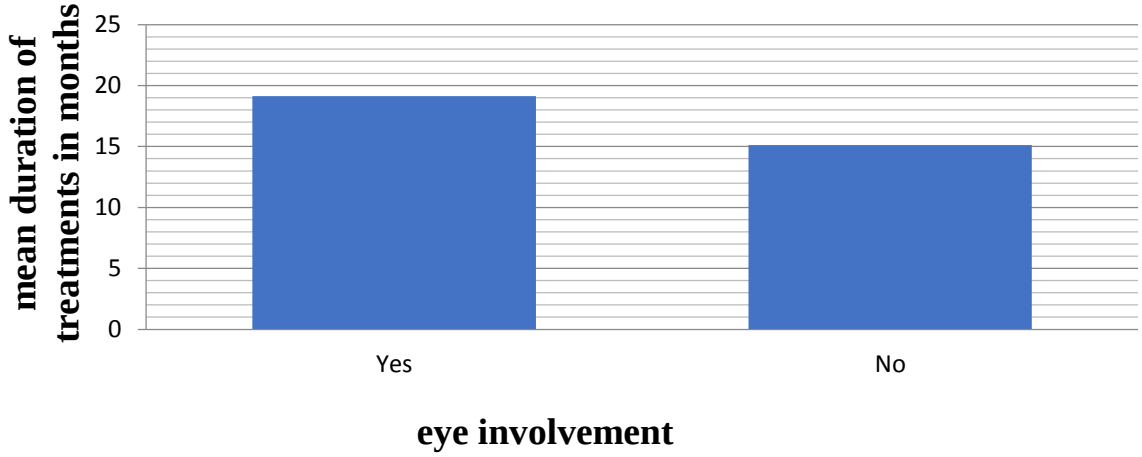

Fig. 3 Mean of the duration of treatment in months and eye involvement

Discussion

In our study, we considered sixty diagnosed leukemic patients in different stages of disease for ocular involvement. At the time of examination, 38.3% of patients had ocular involvements; the rest of, 61.7 % were normal. We compare the results of our study with the results of for ocular manifestations on

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ISSN: 2995-5483

sixty leukemic patients and which found that 41% of patients with leukemia had the ocular manifestations. A prospective study of ocular manifestations in childhood acute leukemia that showed ocular involvements occur in 32% of children with acute leukemia.

Ocular involvements were more common in males with the male: female ratio of 1.8:1; the affected males accounted for 65.3% while the females accounted for 34.7; this may be related to the disease being commoner in males, size of the sample of randomly selected subjects (34/60 were males), stage of disease (most of the males being newly diagnosed or in relapse), or type and duration of treatments received by those males. Study who found that ocular manifestations were more common in males also found that males being more commonly affected than females.

The authors stated that the most common ophthalmic manifestations that are present at leukemia relapse include thrombocytopenia and retinal hemorrhages (low platelets 70% and retinal hemorrhages 87.5%); both constitute the clinical picture of leukemia. Newly diagnosed patients commonly present with thrombocytopenia; 43.7% of these patients had retinal hemorrhages. [13,14] The association between low platelet counts and retinal hemorrhage was significant (P-value 0.001).

The study also found no relation between high WBC counts and the incidence of retinal infiltration (P-value 0.291). Only two patients had retinal infiltration with leukemic cells, which means contradicting Robb's statement of an increase in white cell level predisposing to leukemic retinal infiltration being associated with an increased risk of ocular infection. [15]

8 out of 23 patients had conjunctivitis, and 6 out of 23 had eyelid infections and edema, which may be due to low immunity from either the disease process or therapeutics involved in treatment. Eye involvement occurred in two CML patients. One presented with increased intraocular pressure (glaucoma) caused by Imatinib mesylate (Gleevec), which has side effects including an increase in intraocular pressure.

Two patients suffered diplopia, maybe because of vincristine use, which is toxic to the CNS and can affect the motor nerves of the eye. Steroids can cause cataracts, but in this study, no cases were found as steroids were only used for the short term [16].

There has been much discussion about the treatment durations and the ocular manifestations: The longer the treatment duration, the higher the mean of treatment duration and prevalence of eye findings. Thirteen patients on regular follow-ups were fully cured of the disease and had a low prevalence of ocular findings. Eye symptoms were found in only 2 out of 23 involved patients (3.3%), while others had none. Ocular lesions were diagnosed on routine ophthalmic examination by the ophthalmologist, aligning with the observations of previous researchers.

The findings reported most commonly were retinal hemorrhages seen in 11.6% of the patients; all cases were new diagnoses and showed low platelet counts. Overall, this study draws our attention to ocular involvement in leukemia and the remedial aspect.

Conclusion

A considerable number of patients suffering from acute leukemia show ophthalmic manifestations. Such involvements can be due to direct infiltration by leukemic cells or secondary to the complications of the disease or the drugs used in the treatment of the disease. Involvements can affect all eye structures, but the retina was the most commonly affected structure.

In newly diagnosed cases, the commonest involvements seen were retinal hemorrhages related to low platelet counts, which are part of the clinical presentation of leukemia, whereas ocular involvements were the commonest in relapse cases.

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