Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Volume 29, Issue 2, March 2023, page (107-112) Supplement Issue

Manuscript ID ZUMJ-2011-2011 (R3)
DOI **10.21608/ZUMJ.2021.48055.2011**

ORIGINAL ARTICLE

Ocular Radiological Findings in Children with Acute Lymphoblastic Leukemia: A Cross Sectional Study

Mohamed Ahmed Ahmed Habib[1]*, Laila Metwally Sherief[2], Sherief Abbas Dabour[3], Manar Atef Ghaly[3], Marwa Zakaria[2]

[1] *Pediatric Department, Hehia Central Hospital, Egypt*
[2] *Pediatric Department, Faculty of Medicine - Zagazig University, Zagazig, Egypt*
[3]*Ophthalmology Department, Faculty of Medicine - Zagazig University, Zagazig, Egypt*

***Corresponding author**
Mohamed Ahmed Ahmed Habib

E-mail:
Dr.mohamedhabib@yahoo.com

Submit Date 2020-11-18
Revise Date 2020-12-28
Accept Date 2021-01-18

ABSTRACT

Background: Ophthalmic complications in pediatric acute lymphoblastic leukemia (ALL) have become serious and recognition of ocular manifestations of leukemia is fundamental. In this study, we aimed to detect radiological findings among ALL patients.

Methods: This cross-sectional study was conducted in Pediatric Oncology Unit and Ophthalmology Department; Faculty of Medicine; Zagazig University with a total of 45 patients diagnosed with ALL (18 patients were denovo ALL, 14 patients were receiving treatment of leukemia and 13 patients finished their treatment protocol and were on follow up schedule). Detailed radiological work up was done including MRI of brain and both orbits, fundus photography, fluorescein angiography (FA), optical coherence tomography (OCT) and orbital CT.

Results: Ocular manifestations were detected in 35.6% of ALL patients by ophthalmic examinations. 44.4% of ALL patients had abnormal brain MRI and most commonly, ischemic changes, post-radiation leukomalacia and CNS infiltration were detected. Twenty-two percent of the studied cases reported abnormal orbital MRI and most common abnormalities were sutural metastasis and optic nerve affection. Fundus photographs were done for selected patients. Optic nerve head leukemic infiltration, choroidal, retinal and vitreal infiltration were detected (4.44%). Moreover, CMV retinitis was detected in one patient.

Conclusions: Several ocular abnormalities are present in pediatric ALL and the most common are retinal lesions. Knowledge about ocular problems in children with ALL could be beneficial to reduce morbidity and mortality.

Keywords: Leukemia; ophthalmological; orbital.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy accounting for near 25% of pediatric cancers and 80% of all leukemias in the childhood period. The incidence of ALL occurs predominantly among children 1–4 years of age, accounting for 50% of ALL cases, with a slow decline towards adolescence [1]. Orbital and ocular lesions are the third most frequent extra-medullary location of acute leukemia next to the meninges and testicles and may be the presenting features of the disease [2]. The ophthalmic manifestations of leukemia may result from primary / direct infiltration of ocular tissue or secondary / indirect ocular involvement following systemic changes resulting from the leukemia [2]. Direct leukemic infiltration can have three patterns: the anterior section, vitreal, choroidal and retinal infiltration, optic nerve penetration and orbital infiltration [3]. The indirect eye involvement arises from anemia, thrombocytopenia, hyper-viscosity, or can result from steroidal treatment, chemotherapy, bone marrow transplantation (BMT) or complete body irradiation, or immunosuppression. The ocular involvement may appear as retinal or vitreous hemorrhage, infection, and vascular occlusions [2].Neuroimaging techniques represent a relevant tool in investigating ocular and CNS abnormalities caused by direct leukemic infiltration, vascular complications, hemorrhage, treatment-related infections, and neurotoxicity, as well as secondary

malignant tumors. MRI is the best imaging modality when using a dedicated orbital protocol to evaluate ocular structures and optic nerves. MRI can precisely evaluate the structural involvement and differentiate retro-orbital bleeding from leukemic infiltrations [4]. The aim was to detect the ocular abnormalities in children with ALL using imaging modalities.

METHODS

This cross-sectional study was conducted in Pediatric Oncology Unit and Ophthalmology Department; Faculty of Medicine; Zagazig University during period from March 2019 to March 2020. A total of 45 patients were diagnosed with ALL (18 patients were denovo ALL, 14 patients were receiving treatment of leukemia and 13 patients finished their treatment protocol and were on follow up schedule). They were 23 males and 22 females with age ranging from (2.5-15) years. ALL Subjects who met the following eligibility criteria at enrollment were invited to participate: Both sexes, Age: more than 2 years and ≤ 18 years, newly diagnosed patients with ALL, ALL patients on chemotherapy and ALL survivors. We excluded: Patients diagnosed with other types of leukemia, Syndromic patients, Patients with congenital eye problems, diabetic patients, and hypertensive patients. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. All of the participants were subjected to history taking, physical examinations, laboratory investigations and ocular examinations.Ocular examinations were performed by an experienced ophthalmologist in ophthalmology department, Zagazig University hospitals.

The ophthalmic examination consisted of a Snellen chart for best corrected visual acuity, slit lamp biomicroscope, direct and indirect ophthalmoscopes and slit lamp biomicroscopes with fundus lens. Ocular findings that were not related to leukemia, such as amblyopia, and allergic conjunctivitis, were not reported.

Fundus photographs, fluorescein angiography (FA), optical coherence tomography (OCT) and CT orbits were also performed wherever possible. Orbital and brain MRI were done for all our patients.

STATISTICAL ANALYSIS

The collected data were analyzed by computer using Statistical Package of Social Services (IBM SPSS version 22.0 Armonk, NY: IBM Corp), Data were represented in tables and graphs, Continuous Quantitative variables e.g., age were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage).Suitable statistical tests of significance were used after checked for normality. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$). P-value < 0.001 was considered highly statistically significant (HS), and P-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

Table (1) shows that brain infarctions or ischemic changes and sinusitis are prevalent in MR imaging of the studied pediatric ALL patients.

Table (2) shows that Eleven abnormalities were detected in orbital MR imaging of the studied pediatric ALL patients and the most common finding was sinusitis.

Table (3) shows that on brain MRI examinations, 44.4% of the studied children had abnormal brain MRI and on orbital MRI examinations, 22.2% of the studied cases had abnormal MRI.

Table (4) shows that there was no statistically significant difference between the studied newly diagnosed, on chemotherapy and follow up cases as regards abnormal brain MRI, but on orbital MRI examinations, patients on chemotherapy and follow up cases had more abnormal orbital MRI findings than newly diagnosed cases.

Figure (1) shows colored fundus photography of the left eye of a male child, 12 years old, newly diagnosed with ALL and demonstrating optic nerve head leukemic infiltration (A, B, C). Right eye has normal appearance as shown in D.

Figure (2) shows MRI of both orbits of a male patient, 7 years old, with ALL on chemotherapy demonstrating moderate dilatation of the supra and infra-ventricular system with no obstructive mass lesion with suggesting communicating hydrocephalus. Also, cavum vellum inter-positum and left maxillary sinusitic changes were detected.

Figure (3) shows Non-contrast MRI of orbits of a female patient, 13 years old, an ALL survivor demonstrating left optic nerve sequel of old hemorrhagic lesion.

Table (1): Brain MRI findings of the studied ALL patients:

Brain MRI findings	Total No. of cases (No.= 45)		Newly diagnosed ALL cases (No.= 18)		On chemotherapy ALL cases (No.= 14)		ALL survivors (No.= 13)	
	No.	%	No.	%	No.	%	No.	%
Infarctions or ischemic changes	5	11.1	1	5.6	-	-	4	30.8
Post-radiation leukomalacia	1	2.2	-	-	1	7.1	-	-
CNS infiltration	1	2.2	-	-	1	7.1	-	-
Brain atrophy	1	2.2	-	-	1	7.1	-	-
Neurodegenerative changes	1	2.2	-	-	1	7.1	-	-
Subdural hematomas	1	2.2	-	-	1	7.1	-	-
Subdural hemorrhages	1	2.2	-	-	-	-	1	7.7
Leuko- encephalopathy	1	2.2	-	-	1	7.1	-	-
Hydrocephalic changes	1	2.2	-	-	1	7.1	-	-
Sinusitis	13	28.9	4	22.2	5	35.7	4	30.8
Cavum vellum interpositum	1	2.2	-	-	1	7.1	-	-
Mastoiditis	1	2.2	-	-	-	-	1	7.7

Table (2): Orbital MRI findings of the studied ALL patients:

Orbital MRI findings	Total number of patients (No.= 45)		Newly diagnosed ALL patients (No.= 18)		On chemotherapy ALL patients (No.= 14)		ALL survivors (No.= 13)	
	No.	%	No.	%	No.	%	No.	%
Sutural metastasis	1	2.2	-	-	1	7.1	-	-
Optic nerve affection 2ry to old hemorrhagic lesion	1	2.2	-	-	-	-	1	7.7
Mass infiltration in the left orbit and left temporal bone	1	2.2	-	-	-	-	1	7.7
Optic disc lesion with probable leukemic infiltrates	1	2.2	1	5.6	-	-	-	-
Sinusitis	6	13.3	-	-	5	35.7	1	7.7
Probable right nostril foreign body with surrounding opacities	1	2.2	-	-	-	-	1	7.7

Table (3): Radiological findings of the brain and both orbits among the studied cases:

Item	Studied ALL patients (N=45)	
	No.	%
Brain MRI		
▪ Normal	25	55.6
▪ Abnormal	20	44.4
Orbital MRI		
▪ Normal	35	77.8
▪ Abnormal	10	22.2

Table (4): Radiological findings of the brain and both orbits among the studied newly diagnosed, on chemotherapy and follow up cases:

Radiological findings	Newly diagnosed (N=18)		On chemotherapy (N=14)		Follow up cases (N=13)		P- value
	No.	%	No.	%	No.	%	
Brain MRI							
Normal	12	66.7	8	57.1	5	38.5	0.293
Abnormal	6	33.3	6	42.8	8	61.5	(NS)
Orbital MRI							
Normal	17	94.4	8	57.1	10	76.9	0.041*
Abnormal	1	5.6	6	42.8	3	23.1	(S)

P < 0.05 is significant. ***NS: Not significant.***

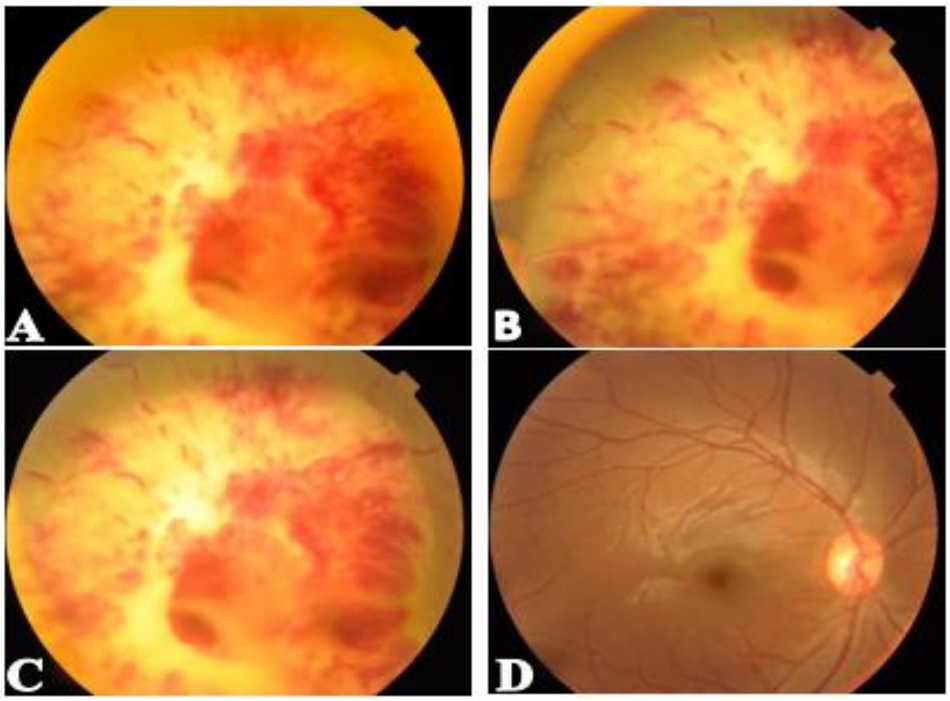

Figure (1): Coloured fundus photography demonstrating optic nerve head leukemic infiltration

.

Figure (2): MRI of both orbits demonstrating moderate dilatation of the supra and infraventricular system with no obstructive mass lesion with suggesting communicating hydrocephalus. Also, cavum vellum inter-ositum and left maxillary sinusitic changes were detected.

Figure (3): Non-contrast MRI of orbits demonstrating left optic nerve sequel of old hemorrhagic lesion.

DISCUSSION

Ocular manifestations in acute lymphoblastic leukemia are alarming as they sometimes stay silent. These incidents often go unnoticed because most patients are asymptomatic [5].

Nonetheless, these manifestations may indicate a relapse or early deterioration of the condition with a possible risk to the sight of our patients [5].

Due to the scarcity of data on this topic, we conducted this study to determine the pattern of ocular involvement in pediatric patients with acute leukemia. Forty-five children with ALL who were treated in our pediatric oncology department were enrolled in this study. Ocular involvement in leukemia is very common and 9% to 90% prevalence has been reported in various studies [6] [7].In this study, ocular manifestations were noticed in 35.6% of our patients by ocular examinations. In addition, in our study, neuroimaging modalities revealed that 44.4% had abnormal brain MRI and 22.2% had abnormal orbital MRI. CNS affection with ophthalmic manifestations among our patients was in 10 (22.2%) patients (7 optic nerve, 1 cranial nerve involvement and 2 orbital affection).

Similarly, Orhan; et al. found in their study 7 (17%) patients with CNS involvement and ocular manifestations (3 optic disc, 2 orbital, and 2 cranial nerve involvement) at the time of diagnosis. Only 1 patient who had CNS relapse also had orbital relapse [7].Also, Kincaid and Richard Green reported that 37 out of 384 patients had infiltration of optic nerve and meninges which was more common in acute leukemia [6].Also, Ridgway et al. found a high correlationbetween CNS leukemia and ocular invasion, where among acute leukemia patients with ocular invasion, 27 of 29 had concurrent CNS involvement [8]. In brain MR imaging, brain infarctions or ischemic changes and sinusitis were prevalent. By orbital MRI, leukemic infiltrates in the ocular system were detected. On orbital MRI examinations, patients on chemotherapy and follow up cases had more abnormal orbital MRI findings than newly diagnosed cases (P-value= 0.041). Also, Fundus photographs were obtained from selected patients as needed and we detected optic nerve head leukemic infiltration, choroidal, retinal and vitreal infiltration. Fluorescein angiography was introduced by early pioneers in medical retina research investigating retinal vasculature in both health and disease as it was possible to assess blood vessel layout, blood flow, and leakage from impaired or diseased retinal vessels using a simple technique [9].Also, OCT continues to quickly arise, offering more detailed qualitative and quantitative knowledge to health care providers about both the superficial and deep eye structures [10].

Herein, CMV retinitis (CMVR) in one of our patients was detected by both fluorescein angiography (FA) and optical coherence tomography (OCT). Similarly, Celiker et al. reported a case of bilateral CMVR in an ALL-child maintenance phase of therapy who was not treated with autologous or allogenic HSCT before [11].

CMVR in ALL was previously reported in six patients during maintenance chemotherapy [12-17].

CT orbits were also performed for suspected cases of orbital affection, and we detected some abnormalities (anterior chamber calcification, lacrimal gland processes and extraconal mass with bone erosion).

Conflict of interest: No conflict of interest.

Financial disclosures: No financial disclosures.

REFERENCES

[1] Snodgrass R, Nguyen LT, Guo M, Vaska M, Naugler C, Rashid-Kolvear F, Incidence of acute lymphocytic leukemia in Calgary, Alberta, Canada: a retrospective cohort study. BMC Res. Notes, 2018; 11(1): 1-4.

[2] Koshy J, John MJ, Thomas S, Kaur G, Batra N, Xavier WJ, Ophthalmic manifestations of acute and chronic leukemias presenting to a tertiary care center in India. Indian J Ophthalmol, 2015; 63 (8): 659-64.
[3] Vishnevskia-Dai V, Sella King S, Lekach R, Fabian ID, Zloto O, Ocular Manifestations of Leukemia and Results of Treatment with Intravitreal Methotrexate. Sci. Rep., 2020; 10 (1): 1994.
[4] Blumenthal DT, Glenn MJ, Neurologic Manifestations of Hematologic Disorders. Neurol Clin, 2002; 20 (1): 265-81.
[5] de Queiroz Mendonca C, Freire MV, Viana SS, Silva Tavares MKG, Almeida Silva WM, Cipolotti R, Ocular manifestations in acute lymphoblastic leukemia: A five-year cohort study of pediatric patients. Leuk. Res., 2019; 76: 24-8.
[6] Kincaid MC, Green WR, Ocular and orbital involvement in leukemia. Surv. Ophthalmol, 1983; 27 (4): 211–32.
[7] Orhan B, Malbora B, Akca Bayar S, Avci Z, Alioglu B, Ozbek N, Ophthalmologic Findings in Children with Leukemia: A Single-Center Study. Turk J Ophthalmol, 2016; 46 (2): 62-7.
[8] Ridgway EW, Jaffe N, Walton DS, Leukemic Ophthalmopathy in Children. Cancer, 1976; 38 (4): 1744–9.
[9] Spaide RF, Klancnik JM, Cooney MJ, Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol, 2015; 133 (1): 45-50.
[10] Mwanza JC, Budenz DL, New developments in optical coherence tomography imaging for glaucoma. Curr Opin Ophthalmol, 2018; 29 (2): 121-9.
[11] Celiker H, Karaaslan A, Kepenekli Kadayifci E, Atici S, Soysal A, Kazokoglu H; et al., Cytomegalovirus Retinitis in an ALL Child during Maintenance Therapy Treated Successfully with Intravenous Ganciclovir. Case Rep Ophthalmol Med, 2014; 2014: 1-3.
[12] Taha R, Al Hijji I, El Omri H, Al-Laftah F, Negm R, Yassin M; et al., Two Ocular Infections during Conventional Chemotherapy in a Patient with Acute Lymphoblastic Leukemia: A Case Report. Case Rep Oncol, 2010; 3 (2): 234-9.
[13] Kobayashi R, Takanashi K, Suzuki D, Nasu T, Uetake K, Matsumoto Y., Retinitis from cytomegalovirus during maintenance treatment for acute lymphoblastic leukemia. Pediatr. Int, 2012; 54 (2), 288- 90.
[14] Singh R, Singh R, Trehan A, Jain R, Bhalekar S., Cytomegalovirus retinitis in an ALL child on exclusive chemotherapy treated successfully with intravitreal ganciclovir alone. J Pediatr Hematol Oncol, 2013; 35 (3).
[15] Wakai K, Sano H, Shimada A, Shiozawa Y, Park MJ, Sotomatsu M; et al., Cytomegalovirus retinitis during maintenance therapy for T-cell acute lymphoblastic leukemia. J Pediatr Hematol Oncol, 2013; 35 (2), 162–3.
[16] Moritake H, Kamimura S, Kojima H, Shimonodan H, Harada M, Sugimoto T; et al., Cytomegalovirus retinitis as an adverse immunological effect of pulses of vincristine and dexamethasone in maintenance therapy for childhood acute lymphoblastic leukemia. Pediatr. Blood Cancer, 2013; 60 (2), 329-31.
[17] Samia L, Hamam R, Dbaibo G, Saab R, El-Solh H, Abboud M; et al., Cytomegalovirus retinitis in children and young adults with acute lymphoblastic leukemia in Lebanon. J. Leuk. Lymphoma, 2014; 55 (8), 1918- 21.

To Cite:
Habib, M, Sherief, L., Dabour, SH., Ghaly,M., Zakaria,M. Ocular Radiological Findings in Children with Acute Lymphoblastic Leukemia: A Cross Sectional Study. *Zagazig University Medical Journal*, 2023; (107-112): -.doi: 10.21608/ZUMJ.2021.48055.2011.