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Ocular manifestations in acute lymphoblastic leukemia: A five-year cohort study of pediatric patients

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ABSTRACT

Objective: To characterize ocular manifestations (OM) of pediatric patients treating for acute lymphoblastic leukemia (ALL) and to evaluate whether they are associated with well-described predictive risk factors for relapse, protocol (1999 or 2009), gender and cerebrospinal fluid infiltration.
Methods: A prospective cohort study was conducted in children and adolescents with ALL from January 2013 to December 2017. The patients underwent ophthalmologic evaluations before starting treatment (D0), on the eighth day (D8), at the 28th day (D28), and at six months (D6 months). Ocular hypertension (OH) was considered in results above 21 mmHg. Measures of visual acuity < 20/40 were considered visual loss (VL).
Results: Fifty-five patients were examined and 18 (32.7%) presented OM, been OH (61.1%), retinal hemorrhage (22.2%) and VL (22.2%) the most frequent finds. A strong association was found between patients with OM and those with a high risk of relapse (p = 0.035, Cramer V = 0.31) and who used the 1999 protocol (p = 0.022, Cramer V = 0.32). The risk of OM in patients from the 1999 protocol was 2.917 (CI = 1.099–7.742), while the risk of relapse it was 0.327 (CI 95% 0.107–0.999).
Conclusions: Patients with ALL have a high incidence of OM due to the treatment and the disease itself, and it may even be asymptomatic and evolve with VL. Of these, we can highlight OH as the most prevalent. Patients submitted to the 1999 protocol and at high risk of relapse are more likely to present OM and these variables are strongly associated.

1. Introduction

Ocular manifestations in Acute Lymphoblastic Leukemia (ALL), varying from 43% to 90% depending on the study, are concerning because they are often silent [1,2]. Such manifestations often go unperceived since most patients are asymptomatic. Nevertheless, they can indicate a relapse or early worsening of the condition with a potential risk to the patient's sight.

Generally speaking, the physiopathology of ocular impairment in ALL is attributed to three main mechanisms: I) direct infiltration of the eye and orbit by the neoplastic cells; II) vascular abnormalities affecting the retina or III) neuro-ophthalmic impairment [3]. In the first case, there could be an invasion of the choroid, hyphemia, hypopyon, heterochromia of the iris, secondary glaucoma, proptosis and episcleritis [4,5]; in the second case, retinal hemorrhages, Roth spots, cotton wool exudation, vascular occlusions, retinal detachment, microaneurysms, as well as venal dilatation and tortuosity [4–6]; in the third case, infiltration of the optic nerve can lead to paralysis of cranial nerves and papilledema [2]. One revision observed retinal hemorrhages at 24%, Roth spots at 11% and exudates at 16% [1]. The most frequent appears to be an infiltration of the choroid, ranging from 50% to 82% of the cases [7].

Furthermore, the effects of chemotherapy on the patients' vision cannot be ignored. The use of high doses of glucocorticosteroids (GC) in the treatment entails a significantly higher risk of developing other conditions, such as ocular hypertension (OH), cataracts, cortisone-induced glaucoma, dry eye, diplopia and blindness [8,9], which in some cases can persist even after ceasing treatment with the drug. Among the chemotherapeutic drugs, Vincristine is associated with alterations of ocular motricity, corneal hypoestesia, and optic atrophy [2]. Moreover,

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Methotrexate can induce alterations of motricity, such as internuclear ophthalmoplegia or optic neuropathy, with important repercussions for visual acuity [10]. Cytarabine, in turn, is associated with corneal toxicity [1].

This study characterized the ocular manifestations of pediatric patients during treatment for ALL and assessed whether such manifestations are associated with recurrence risk predictors defined in literature or with other factors, such as chemotherapeutic treatment protocols, gender, and infiltration of CSF. Early identification and treatment of such ocular alterations can prevent permanent visual loss, as well as precocious diagnosing of possible infiltration or incipient recurrence of the disease.

2. Method

A prospective cohort study was conducted with children and adolescents diagnosed with ALL, receiving treatment between January 1st, 2013 through to December 30th, 2017 at the only public service specialized in pediatric oncology in the state of Sergipe, Northeast region of Brazil. The project was approved by the Ethics Commission at the Federal University of Sergipe (CEP-UFS) which deals with research involving human beings, report number 214.759.

The patients were classified at diagnosis into two groups according to their risk of recurrence: patients with a high risk of relapse (HR) were those who met one of the following criteria: age equal to or greater than nine years, white cell count greater than or equal to 50.000 cells/mm^3 at the time of diagnosis, and immunophenotyping compatible with T-cell ALL. The low risk group (LR) encompassed those patients who did not meet any of the above criteria [11].

The ALL treatment protocols, used in this study, were proposed in 1999 and updated in 2009 (ALL-99 and ALL-09) by the "Brazilian Group for Treatment of Acute Lymphoblastic Leukemia during Infancy" of the Brazilian Society of Pediatric Oncology. At the end of the first 28 days of treatment (D28), the ALL-99 protocol called for a total dosage of 1120 mg/m^2 of Prednisone for the LR group and 1680 mg/m^2 of Prednisone for the HR group [12]. The ALL-09 protocol calls for 420 mg/m^2 of Prednisone and 126 mg/m^2 of Dexamethasone for the LR group and 1260 mg/m^2 of Prednisone for the HR group.

The ALL-99 protocol was routinely used with all patients admitted until December 31th, 2014, whereas the ALL-09 was used for patients admitted afterwards.

In this study, patients were included whose diagnosis of ALL was confirmed by immunophenotyping of bone marrow or peripheral blood and who met all of the following criteria: at least one eye examination in the six-month follow-up period beginning at diagnosis, age below 19 years, absence of previous chemotherapeutic treatment, absence of prior ocular pathology, no use of systemic GC in the six months prior to the diagnosis and existence of technical conditions allowing for the performance of eye examinations.

The eye examination was carried out by a single ophthalmologist (C.Q.M.) and consisted of exams before the start of treatment (D0), on the eighth day after admission (D8), at the end of the remission induction phase, which corresponds to the 28th day of treatment (D28), and at the end of the six first months of treatment (D6months). The exams on D0 and D8 were performed on the hospital bed due to the fragile health of these patients at diagnosis and consisted of measurement of IOP, evaluations of the anterior chamber with a portable slit-lamp biomicroscope and of the posterior chamber with direct ophthalmoscopy, without mydriasis. The D28 and D6months examinations were performed at an ophthalmologist's office, analyzing the anterior chamber by slit-lamp biomicroscopy and the posterior chamber by indirect ophthalmoscopy after mydriasis induction with 0.01% Tropicamide, assessment of visual acuity (VA), and measurement of IOP.

In all exams, IOP was measured using a Perkins applanation tonometer, under local anesthesia with 0.5% Proparacaine eyedrops and Fluorescein tracing dye. Intraocular pressure equal or superior to 21 mmHg was considered compatible with OH [13].

Visual acuity was assessed with an optotype auto projector, with and without mydriasis. The Snellen chart was used and VA < 20/40 was considered VL.

Patients diagnosed with any ocular pathology received appropriate ophthalmological treatment.

Data analysis was performed using the SPSS (*Statistical Package for Social Sciences*) software, version 24.0. Categorical variables were described as absolute and relative frequencies and compared using Fischer's exact test with Cramer V-test for strength and the Benjamini-Hochberg False Discovery Rate test for multiple comparison correction. The continuous variables were described in terms of average and standard deviation. The binomial test was also used to compare proportions between non-parametric groups and the Pearson's correlation test was used to analyze the relationship between normally-distributed variables. P-values < 0.05 were considered statistically significant.

3. Results

Out of a total of 78 patients admitted to the service between 2013 and 2017, 67 met the inclusion criteria. However, 12 died before D8. Fifty-five patients had at least one eye examination between D8 and D6months. These patients were divided into two groups: those with normal examination results (n = 37) and patients who presented some ocular manifestation (n = 18). In turn, this last group was further divided into two groups depending on their visual acuity (Fig. 1).

Sixty-seven patients with an average age of 9.10 years (SD = 5.436) were included, presented in Table 1 by protocol, gender, age range, risk, immunophenotyping, deaths, cerebrospinal fluid (CSF) infiltration and ocular manifestations.

The patients that presented ophthalmic alterations (N = 18) were mainly from the ALL-99 protocol (77.8%), male (55.6%), younger than 9 years-old (94.4%), high-risk (82.4%), B-cell Immunophenotype (83.3%), had not died during the 6-month follow-up (61.1%), and 50% of them presented infiltration of CSF in at least one examination. Patients with ophthalmic alterations, when compared to the group with normal examination results, predominantly used the ALL-99 protocol (p = 0.022) and belonged to the HR group (p = 0.035). Both associations were strong, according to the Cramer V-test (0.32 and 0.31, respectively) and Benjamini-Hochberg False Discovery Rate test for multiple comparison correction with a false discovery rate (Q) of 20%. These results can be seen in Table 2.

Intra and/or extra-ocular alterations occurred in 32.7% of the patients examined, with a predominance of OH (61.1%), followed by retinal hemorrhage and VL (22.2%). Some patients accumulated more than one alteration and the distribution of ophthalmic changes per patient is shown in Table 3.

When calculating the relative risk concerning the manifestation of ophthalmic changes using the cited variables, it was observed that the patients from the 1999 protocol have a risk 2.91 times higher for ocular manifestations than those from the 2009 protocol (CI 95% 1.099–7.742) and low risk of relapse acting as a protective factor for presenting ocular manifestations (RR = 0.327, CI 95% 0.107–0.999). These results are shown in Table 4.

The central tendency measurements with regard to IOP are shown using boxplots in Fig. 2. It was observed that higher IOPs were found at D8, including some outliers with values of 24, 26 and 27 mmHg. The highest median was also observed at D8, approximately 17 mmHg. The lowest median, in turn, occurs at D6months, with a value of 14 mmHg. The greatest variation was observed at D28, whereas the smallest variations were observed to be similar at D0 and D6months.

4. Discussion

Childhood lymphoproliferative neoplasms most commonly attack B-

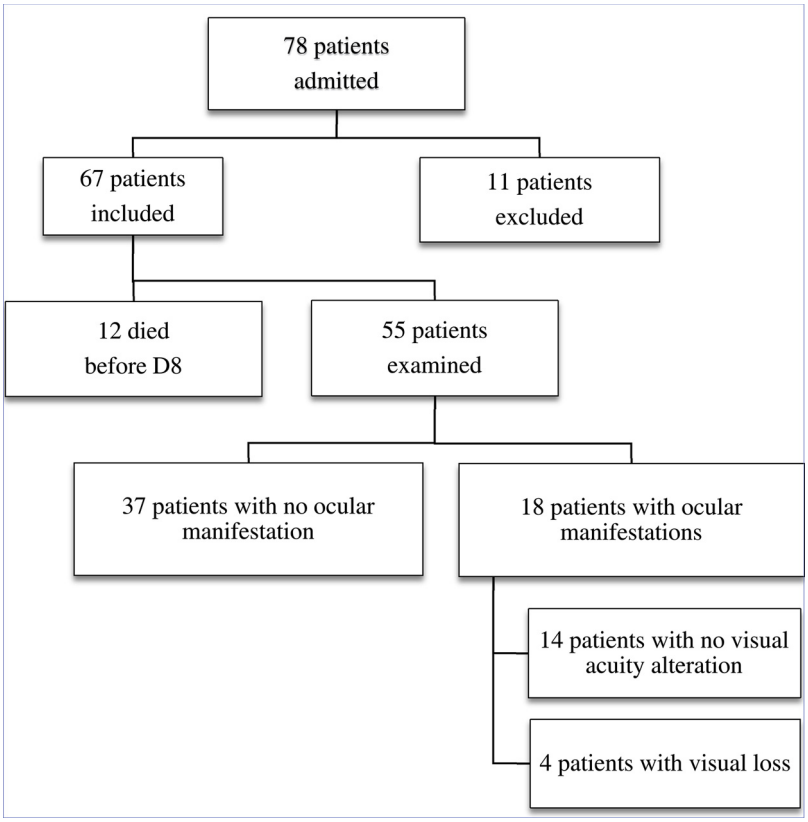

Fig. 1. Flow chart showing the distribution of patients screened for possible ocular alterations in the cohort studied.

Table 1
Profile of the patients included in the cohort.

Variables	N (%)
Protocol	67
ALL-99	35 (52.2)
ALL-09	32 (47.8)
Gender	67
Feminine	30 (44.8)
Masculine	37 (55.2)
Age Range	67
≥9 Years	57 (85.1)
< 9 Years	10 (14.9)
Risk	65
Low	25 (38.5)
High	40 (61.5)
Immunophenotyping	67
B-Cell	57 (85.1)
T-Cell	10 (14.9)
Deaths	67
Yes	27 (40.3)
No	40 (59.7)
CSF Infiltration	22
Infiltrated	15 (68.2)
Negative	7 (31.8)
Ocular Manifestations	55
Present	18 (32.7)
Absent	37 (67.3)

Table 2
Comparison of patient groups with normal and altered ophthalmic examination for different variables.

Variables	Group with Ophthalmic Alterations N (%)	Group with Normal Exam Results N (%)	P Value*	Corrected P-value**
Protocol	18	37	0.022	0.029
ALL-99	14 (77.8)	16 (43.2)		
ALL-09	4 (22.2)	21 (56.8)		
Gender	18	37	1.000	0.200
Feminine	8 (44.4)	15 (40.5)		
Masculine	10 (55.6)	22 (59.5)		
Age Range	18	37	0.651	0.143
≥9 years	1 (6.6)	5 (13.5)		
< 9 years	17 (94.4)	32 (86.5)		
Risk	17	36	0.035	0.057
Low	3 (17.6)	18 (50.0)		
High	14 (82.4)	18 (50.0)		
Immunophenotyping	18	37	0.671	0.171
B-Cell	15 (83.3)	33 (89.2)		
T-Cell	3 (16.7)	4 (10.8)		
Deaths	18	37	0.208	0.086
Yes	7 (38.8)	8 (21.6)		
No	11 (61.1)	29 (78.4)		
CSF Infiltration	4	16	0.587	0.114
Altered	2 (50.0)	11 (68.8)		
Negative	2 (50.0)	5 (31.3)		

* Fisher exact-test.
** Benjamini-Hochberg False Discovery Rate.

cells and can affect the ocular appendix, including orbits, conjunctiva, eyelids and lacrimal glands [3]. Eye manifestations associated with the treatment of ALL are common, especially after the considerable increase in survival rate that followed the use of standardized multicentric protocols and better risk stratification, including the immunophenotyping of blasts. Furthermore, ocular impairment may be the first manifestation or sign of recurrence of the disease [13].

During the treatment, 327% of patients were confirmed as having ocular impairment, contrasting with previous studies that obtained 17%, 15%, 20% [3,14,16], but approaching others which found 29%, 39%, 38% [15,17,18]. This data divergence is recurrent in the literature and reflects the application of different methods. Furthermore, in the

Table 3
Distribution of eye manifestations per patient.

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Alteration of retinal pigment epithelium																x		
Amaurosis															x			
Chorioretinal Atrophy															x			
Visual Loss		x													x	x	x	
Orbital Cellulitis			x															
Papilla Edema															x			
Retinal Hemorrhage				x	x										x	x		
Ocular Hypertension							x	x	x	x	x	x	x	x		x	x	x
Leukemic Infiltration																		x
Optic Nerve Pallor	x	x													x			
3rd Nerve Palsy															x			
Retinochoroiditis						x												
Uveitis from Herpes Zoster																	x	

Table 4
Relative risk of ocular manifestations.

	RR	CI 95%[a]
Deaths	1.697	0.811–3.553
Immunophenotype	0.729	0.281–1.891
CSF Infiltration	0.538	0.095–3.041
Protocol	2.917	1.099–7.742
Gender	1.113	0.521–2.379
Age Range	2.082	0.334–12.976
Risk of relapse	0.327	0.107–0.999

[a] 95% confidence interval (CI).

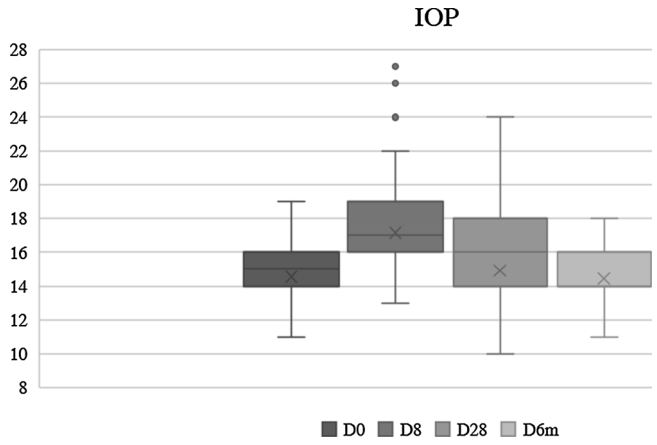

Fig. 2. Boxplots showing the distribution of Intraocular Pressure in patients during the six-month follow-up period.

present study, the highest proportion of ocular changes is due to the inclusion of the OH cases, which were actively traced in this cohort, even in the absence of symptoms, as was previously reported [9].

Risk of relapse acted as a protective factor, with a relative risk of 0.33, meaning that it is 67% less likely that one with low risk of relapse develop some ocular manifestation that one from the high-risk group, compatible with results in the literature [14]. This is also valid for those treated with the ALL-99 protocol, who had 2.91 times greater risk of presenting ocular manifestations than the ALL-09 patients, which could be explained by the lower total doses of GC in this group.

Direct ocular involvement occurred in one patient (2%) as leukemic infiltration of the optic nerve, an alteration observed in 7.3% of the cases in a previous study [15]. Among secondary ophthalmic alterations, the retina was the most affected tissue, with hemorrhage occurring in 7.3% of the cases, with similar proportions consistently described previously: 8% and 8.8% [3,16].

Other secondary alterations were the development of orbital cellulitis (2%) and uveitis due to Herpes zoster (2%). Patients with ALL can contract opportunistic germ infections and reactivate viral infections during the neutropenia phase, resulting in an elevated risk of death [19].

It was observed that during the remission induction phase, when high doses of GC are used, there was significant elevation of IOP in ten patients (20%), whose values were compatible with OH (IOP > 21 mmHg). The result was greater than that presented in another study which reported 16.6% [9]. As in previous studies [3,9,13–15,19], no patient had developed isolated OH symptoms, making a diagnosis difficult when there is no systematic tracking of all patients.

Four patients suffered definitive visual impairment (7.3%) and none of those patients had developed isolated OH. These patients had other alterations secondary to the disease, such as retinal hemorrhage, optic nerve pallor, leukemic infiltration and uveitis, and suffered from reduced visual acuity.

There are remarkable differences observed between low and middle-income countries compared to that of developed countries in relation to indexes of mortality during induction, mortality at six months after diagnosis (the beginning of the maintenance phase), CSF infiltration and the proportion of patients with high risk of relapse [20]. These differences are more directly related to access to adequate infrastructure for treatment of complications than to the biological aspects of the disease. The data related to avoidable ocular complications, when promptly identified, can probably be generalized to apply to countries of all levels of income.

Thus, there exists the possibility of ocular involvement and silent OH, with the consequent risk of irreversible visual loss, in patients without any ocular alterations before the diagnosis. Thus, there is a need for systematic and universal ophthalmological evaluation of children and adolescents with neoplasia in the lymphoid lineage from the very beginning of treatment.

5. Conclusion

Patients with ALL have elevated incidences of ocular manifestations due to the treatment and the disease itself. Among those, OH is the most prevalent. Patients treated with a protocol using higher doses of GC (ALL-99) and with high risk of recurrence had a higher risk of presenting ocular alterations, with strong association between those variables. Therefore, a protocol is proposed that contemplates systematic ophthalmological examination with the measurement of IOP immediately after diagnosis of ALL, before the introduction of GC (D0) and subsequently at D8, D28 and D6months.

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Disclosure of potential conflicts of interest

None.

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