v. 2, n. 64, 2022

International Journal of Health Science

CORTICOSTEROID-INDUCED OCULAR HYPERTENSION IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOCYTIC LEUKEMIA AND NON-HODGKIN LYMPHOMA: A SYSTEMATIC REVIEW

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Abstract: **Objective:** Conduct a systematic review to assess the risk of increased intraocular pressure (IOP) associated with corticosteroid use in children and adolescents with acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL). **Methodology:** A search was performed on PubMed, Scopus, Web of Science, Science Direct Cochrane Library, Google Scholar and OpenThesis databases. Relevant studies were read in full and selected according to eligibility criteria (children and adolescents up to 19 years of age with ALL or NHL, regardless of gender, and who were treated with systemic corticosteroids regularly) and those who reported ocular hypertension due to tumor infiltration, and glaucomatous damage and corticosteroid-induced ocular hypertension in initial testing. **Results:** 8 studies were selected: three case reports, a series of 5 cases, two prospective observational studies – one with 55 patients and one with 90 patients – and two retrospective observational studies – one with 54 and one with 12 patients. The results demonstrated eventual control of IOP, and consequences ranging from no ocular impairment to complete loss of vision.**Conclusion:** The possibility of silent ocular hypertension, with risk of irreversible amaurosis, demonstrates the need to evaluate the introduction of an evaluation and treatment protocol in pediatric patients soon after the diagnosis of ALL or NHL. However, given the limited evidence, further studies are warranted evaluating IOP and visual function before treatment initiation, as well as systematic measures during and after treatment.

Keywords: Ocular hypertension; steroids; acute lymphocytic leukemia; non-Hodgkin's lymphoma; children; teenagers.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed cancer in children between zero and 14 years of age and corresponds to 78% of leukemias in this age group. Its peak occurs between the second and fifth years of life (in industrialized countries), with a mean age of 6.5 years, being more frequent in males (1.7:1) and in white individuals[1-3]. Non-Hodgkin's lymphoma (NHL) accounts for approximately 4% of all malignancies during childhood[4]. One of the possible ocular complications is the induction of ocular hypertension and consequent iatrogenic glaucoma by the use of glucocorticoids (GC), a pathology called cortisonic glaucoma[5,6]**.**

Glaucoma is the leading cause of irreversible blindness in the world. It is preventable if diagnosed early and managed with appropriate treatment. The main cause is elevated intraocular pressure (IOP)[7] which can be routinely measured using the applanation tonometry technique after instilling local anesthesia with 0.5% proparacaine and fluorescein dye. GC-induced ocular hypertension (OH) was first described in 1950 with the observation of glaucoma in association with the administration of systemic GC[8]The disorder occurs regardless of the method of medication administration. Previous studies have already shown that the risk of OH is higher in children[9], especially after a few weeks on corticosteroid therapy, which is usually reversible after discontinuation of treatment. However, if ocular hypertension persists for a prolonged period, it can lead to permanent damage to the optic nerve, with consequent impairment of vision[10].

The aim of this study is to conduct a systematic review to assess the risk of elevated eye pressure and its possible repercussions on visual function related to corticosteroid therapy in children and adolescents with ALL and NHL.

METHODOLOGY

The protocol used in this systematic review was previously designed and was registered in the PROSPERO registry base (registration number CRD42018087146).

Data collection was carried out from the beginning until August 2022 through the databases PubMed, Scopus, Web of Science, Science Direct e Cochrane Library. a survey of *grey-literature* was conducted by Google Scholar and OpenThesis. The first 100 Google Scholar results have been recorded. The collection also includes a manual search of common references of original articles and reviews. The structured search strategy used the following terms: *(precursor cell lymphoblastic leukemia-lymphoma OR acute lymphoblastic leukemia OR non-Hodgkin lymphoma) AND (glaucoma OR ocular hypertension)*. Two researchers independently selected search results and identified studies that were potentially relevant based on titles and abstracts. Relevant studies were read in full and selected according to eligibility criteria.

This systematic review included studies that reported the occurrence of corticosteroid-induced ocular hypertension in children and adolescents with ALL and NHL. If the evaluated study included several types of malignancies treated with systemic corticosteroids, individual data for ALL and NHL must be available. Those who reported ocular hypertension due to tumor infiltration, and glaucomatous damage and corticosteroid-induced ocular hypertension as an outcome in initial testing were excluded. Studies were not excluded by criteria of sample size, duration of follow-up, date of publication, or language of publication.

Information was extracted on (1) model and demographic details, including study

type, number of patients, geographic location, malignancy type, sex, age, treatment (chemotherapy, radiation therapy, or systemic corticosteroid use), previous ocular pathology, history of family of glaucoma, diagnosis of corticosteroid-induced ocular hypertension, and methods for measuring eye pressure; (2) details of corticosteroid use and IOP, including data on induction and post-induction therapies (corticosteroid type, duration, and dosage), cycles, baseline IOP, and ocular hypertension values; (3) strategies to control IOP, including antiglaucoma medication use, corticosteroid switching, corticosteroid discontinuation, and complications.

Exposure was considered as the treatment of ALL and NHL with systemic corticosteroids, regardless of corticosteroid type or dose. The result was ocular hypertension occurring after initiation of corticosteroid therapy and defined as an IOP above 21 mmHg in one or both eyes.

RESULTS

In all, 319 reports were selected and, after analyzing the titles and abstracts, 14 full articles were evaluated for eligibility. Of these, 6 were excluded [6,11-15]. The 8 articles [16-23] remaining met the criteria and were included in the systematic review (Figure 1).

The 8 articles reviewed were a case report in abstract form[16], published at the 25th Annual Meeting of the American Society of Pediatric Hematology/Oncology, 2012, New Orleans, Louisiana; and 7 complete studies, two case reports [17,18], a series of 5 cases [19], two prospective observational cohort studies – one with 55 patients20 and one with 90 patients [21] – and two retrospective observational studies – one with 54[22] and one with 12 patients [23]. All included studies were published in English and the presence of ocular hypertension was the assessed outcome. None of the studies were multicenter or randomized.

The first study was presented as a poster at the 25th Annual Meeting of the American Society of Pediatric Hematology/Oncology, 2012, New Orleans, Louisiana, by Pilbeam et al[16]. The authors report the case of a 3-year-old boy diagnosed with ALL, with no prior history of visual problems or a family history of glaucoma. On the 10th day of induction with dexamethasone 3 mg/m2, the patient presented with photophobia, irritability, decreased visual acuity and dilated pupils. The initial diagnostic hypothesis was optic neuropathy, but brain magnetic resonance and magnetic resonance angiography were normal. Eye examination showed visual acuity of 20/200, nonreactive dilated pupils, and elevated IOP (OD 42 mmHg, EO 40 mmHg). The patient, although treated for glaucoma, developed permanent blindness in the right eye and significant loss of vision in the left eye.

In the second study, Tham et al.[17] reported the case of a 9-year-old girl with ALL, in China, who received high doses of systemic corticosteroids (60 mg daily of oral prednisolone) and had an IOP of 52 mmHg in the right eye and 47 mmHg in the left eye on the 10th day of treatment, measured with a Goldmann applanation tonometer. Topical medications were used for the treatment of glaucoma (latanoprost 0.001% once a day and brimonidine 0.2% twice daily) and the pressure dropped to 38 mmHg and 36 mmHg. IOP returned to baseline values after 2 days of discontinuation of corticosteroids and after 6 weeks of follow-up, this level was maintained even without glaucoma medications. Four months later, the patient underwent a new course of treatment with 10 mg of oral dexamethasone daily. The patient developed a similar increase in IOP for both eyes during the course of oral dexamethasone. Oral acetazolamide was prescribed and the patient remained asymptomatic throughout the treatment, except for an episode of decreased

visual acuity in the right eye when the IOP reached 52 mmHg.

The third study, also a case report, by Lai et al.[18], nine-year-old girl with acute lymphoblastic leukemia who was referred by a pediatric hematologist with a 3-day history of bilateral blurred vision and mild intermittent headache during maintenance-phase chemotherapy. She was treated according to the Taiwan Pediatric Oncology Group protocol: prednisolone 40 mg/m^2/day for 4 weeks during induction therapy and dexamethasone 12 mg/m^2/day for 5 days every four weeks in the maintenance phase. The patient had very high intraocular pressure, 33.4 mmHg in the right eye and 29.4 mmHg in the left eye (measured by a non-contact tonometer), during maintenance treatment when taking oral dexamethasone (6 mg/m^2/day). Her IOP rose on day 5 after taking dexamethasone, peaked on day 7, and returned to baseline on day 13 before taking antiglaucoma medications. After daily IOP monitoring with an electrical applanation tonometer (Tono-Pen) throughout chemotherapy, intraocular pressure was observed to increase only when oral dexamethasone was administered. Thus, IOP-lowering agents were prescribed for 10 consecutive days, starting on the day oral dexamethasone was to be administered, and it was reported that not only did peak values decrease, but IOP levels returned to baseline more quickly. The child did not develop visual field defects 31 weeks after the initial manifestation. In the fourth article, Yamashita et al.[19] reported a case series including children up to 6 years of age diagnosed with ALL (2 boys and 3 girls, mean 4.2 ± 1.6 years). Each of the 15 treatment cycles consisted of induction therapy (prednisolone 60 mg/m2/day for 4 weeks) followed by delayed intensification therapy (dexamethasone 6 mg/m2/day for 2 weeks) and a maintenance regimen (dexamethasone 6 mg/m2/day for 2 weeks), 6 mg/m2/day for 2 weeks, then 1 week of taper and a 5 week break). Patients with ocular symptoms were referred to an ophthalmologist and monitored throughout the treatment. Children were examined for visual acuity and IOP was measured by non-contact tonometry (CT-80, Topcon, Japan) on day 7 of induction therapy and day 7 of maintenance regimen. All patients had IOP above 21 mmHg, with a mean of 39.6 ± 7.2 mmHg (range 28 to 47). Antiglaucoma medication was given to all who had an IOP above 25 mmHg. Of the 5 patients included in this study, one received only antiglaucomatous medication; 3 were treated with antiglaucoma medication and the steroid switched from dexamethasone to prednisolone; and one had IOP well controlled with antiglaucomatous medication and discontinuation of corticosteroid therapy, although he developed severe glaucomatous optic atrophy and thinning of the retinal nerve fiber layer. In all cases, regardless of the method of IOP control, the pressure was normalized.

In the study by Mendonca et al.20, proposed in 1999 and updated in 2009 (LLA-99 and LLA-09) by the "Brazilian Group of the fifth of this review, 55 children and adolescents with ALL were examined from January 2013 to December 2017, in the only public service specialized in pediatric oncology in the state of Sergipe, Northeast region of Brazil. The treatment protocols for ALL of the evaluated patients were "Treatment of Acute Lymphoblastic Leukemia in Childhood" of the Brazilian Society of Pediatric Oncology, at the end of the first 28 days of treatment, the total dose of prednisone administered in the 1999 protocol is 1120mg/m2 for patients with low risk of recurrence (BR) and 1680 mg/m2 for those at high risk (RA), and in 2009 420 mg/m2 of prednisone and 126 mg/m2 of dexamethasone for the BR group and 1260 mg/m2 of prednisone for the AR group.

The children and adolescents underwent ophthalmological evaluations by a single ophthalmologist (C.Q.M.) and consisted of examinations before the start of treatment (D0) and on the eighth day (D8) in the hospital bed, and on the 28th day (D28) and after six months. (D6 months) in the eye clinic. In all exams, IOP was measured using a Perkins applanation tonometer, under local anesthesia with 0.5% proparacaine eye drops and fluorescein tracking dye. During the study, 18 patients developed ocular manifestations, and of these, 61.1% had IOP values greater than 21 mmHg. The highest IOPs were measured on D8, with values of 24, 26 and 27 mmHg. It was also observed that patients in the 1999 protocol were at 2.91 times greater risk for ocular manifestations than those in the 2009 protocol (95% CI 1.099–7.742). Among the 55 patients evaluated, 4 developed permanent visual impairment, however none of them had ocular hypertension as an isolated ocular manifestation. Those diagnosed with any eye pathology received ophthalmologic treatment with adequate IOP control.

In the most recent article included in this work, Barzilai-Birenboim et al.[21] performed a prospective observational study comprising 90 children (40 girls and 50 boys) with a mean age of 6.83 years who were being treated for newly diagnosed ALL at a tertiary pediatric hematology/oncology center in Israel between June 2018 and January 2018. 2021. The author reports that at the time of diagnosis of the malignancy, 36 patients had elevated IOP values and that 26 had a positive family history of glaucoma. None of the children received previous treatment with steroids that could influence the baseline IOP value or had significant ocular pathology. All children were treated with high-dose steroids during the first month of induction: all received oral prednisone (60 mg/m^2/d) for 30 days with the exception of children with T-cell ALL and a good response to prednisone who, on day 8, were switched to oral dexamethasone (10 mg/m^2/d) for 21 days. Patients were evaluated by a qualified ophthalmologist using a calibrated tonometer (Tono Pen Avia) at three time points: before treatment (D0), after 15 days of induction therapy (D15) and at the end of the induction course (D33) and ocular hypertension, such as > 21 mmHg, was considered. 64 patients had IOP > 21 mmHg throughout the study (D0-D33) – patients who already had altered values had an increase in IOP compared to baseline – of these, 52 patients were diagnosed with OH during the treatment induction period. The study also reports IOP > 25 mmHg in 34 patients and IOP > 28 mmHg in 14 children. The highest IOP value recorded on D0 was 29 mmHg; on D15, 64 mmHg; and on D33, 40 mmHg. In total, 13 children were treated with topical medication, at the discretion of a glaucoma specialist, for IOP reduction, and three children with extreme ocular hypertension required treatment with various medications for adequate IOP control. In none of the patients was steroid replacement or suspension performed or surgery required. Additional eye exams were performed as needed and no complications were reported.

The seventh article selected was a retrospective observational study by Chang et al.[22] which evaluated 54 children diagnosed with non-Hodgkin's lymphoma - 16 with mature B-cell lymphoma (MBL) and 38 with lymphoblastic lymphoma (LBL) -, aged between 1 and 15 years, 14 female patients and 40 male patients, without previous eye pathologies. The MBL group received oral dexamethasone at a dosage of 10 mg/m2/day for 5 days in cycles A and B, and 20 mg/m^2/day for 5 days in cycle C, totaling 6 monthly cycles. In the protocol for patients with LBL, oral prednisolone was administered at a dose of 60 mg/m^2/ day for 28 days 2 months apart,

then a 3 week cycle of oral dexamethasone at 10 mg /m^2/ day and finally oral dexamethasone at a dose of 6 mg/m2/day for 5 days repeated every 2 months for a duration of 1.5 years. All children had their intraocular pressure measured initially by Icare rebound tonometry every 2 to 3 days and, in cases of high values, confirmed by Goldmann applanation tonometry. Ocular hypertension was defined as 2 consecutive IOPs with values greater than 21 mmHg. In total, 31 patients (57.4%) developed OH during or after corticosteroid therapy, 24 patients in the LBL group – 87.5% in the first 4 weeks of treatment – and 7 patients in the MBL group – 85.7% in the first 3 weeks. chemotherapy cycles. Seven patients had symptoms, which were pain in 2 patients, pruritus in 2, eye redness in 3 and tearing in 3. Symptomatic patients had a higher mean peak IOP than asymptomatic patients (36.8 mmHg and 30.2 mmHg, respectively). All children with elevated intraocular pressure were treated with topical antiglaucoma drugs (single or combined eye drops), so the entire MBL group and 16 patients in the LBL group had adequate control. In the 8 remaining LBL patients, for pressure control, corticosteroids were switched (from dexamethasone to prednisolone) and/or the dose was reduced. No patient required systemic medication, evolved with glaucomatous damage, or required surgical treatment for glaucoma.

Finally, Sugiyama et al.[23] also performed a retrospective study analyzing 15 patients in total, but for this review 12 patients were considered – 3 with NHL and 9 with ALL – because the other children were being treated for other hematological malignancies. Of the patients analyzed, there were 7 boys and 5 girls with a mean age of 8.3 years, and all received treatment at an institution in Japan from January 2016 to December 2018. IOP was measured by a ophthalmologist within seven days of starting the standard corticosteroid dose, which was defined as 60 mg/m2/day for prednisolone and 10 mg/m^2/ day for dexamethasone. Mean peak IOP during each cycle of dexamethasone-containing chemotherapy (30 mmHg) was significantly higher compared to values during cycles of prednisolone-containing chemotherapy (15.5 mmHg). In only one patient, being treated for ALL, of the 12 examined, IOP > 21 mmHg was not found. Those diagnosed with intraocular hypertension were treated with antiglaucoma medications and reassessed for 2 to 5 days repeatedly until the IOP dropped below 22 mmHg. A 10-year-old male patient with Ph1-positive ALL required surgical intervention because, although funduscopic findings were normal, IOP did not decrease after stopping dexamethasone therapy. Tables 1 and 2 summarize the results of this review.

DISCUSSION

This systematic review included 124 children diagnosed with steroid-induced ocular hypertension, 90 on treatment for ALL and 34 for NHL. Unfortunately, although we used an explicit method to identify and select relevant studies, a limited number were found for inclusion. Only two studies, among the 8 that met the eligibility criteria, were prospective, by Mendonca et al.[20] and by Barzilai-Birenboim et al.[21], and estimated the incidence of steroid-induced glaucoma in samples of 55 and 90 children, respectively.

The increased risk of cortisonic glaucoma remains controversial. In 2010, Whelan et al.[11] in a multi-institutional collaborative study of individuals who survived at least 5 years after cancer diagnosis during childhood or adolescence found no increased risk of ocular hypertension among survivors treated with glucocorticoid therapy. However, the authors suggest that the true incidence of ocular hypertension may be underestimated, as patients may remain asymptomatic, and

that regular eye examinations and additional follow-up could reveal an increased risk of glaucoma in corticosteroid-treated childhood cancer survivors. It is also important that IOP is measured at the beginning of corticosteroid therapy, making it possible to assess the actual increase in blood pressure levels and the ideal reading to indicate its control. Of the 8 studies included in this review, only 3[17,20,21] 21 reported the measurement of ocular pressure at the beginning of corticosteroid therapy.

The absence of symptoms does not exclude the possibility of glaucoma in younger patients. In the study published by Mendonca et al.20, all patients with ocular hypertension were asymptomatic. In, Barzilai-Birenboim et al.[21], with the exception of a child with IOP extreme (64 mm Hg), who complained of headache, all diagnosed children were asymptomatic. E, Chang et al.[22] reported that only 7 of the 31 patients with OH developed symptoms during the evaluations. Thus, it is inferred that pediatric patients with ALL or NHL receiving corticosteroids may remain asymptomatic despite severe ocular hypertension.

The use of different methods to measure IOP may also explain differences in the incidence of ocular hypertension in children receiving corticosteroids. In the study carried out by Yamashita et al.[19], IOP was measured by air puff, non-contact tonometry (Topcon CT-80),without confirmation by other methods, which does not have the reliability of contact tonometry, resulting in possible overestimation of values in children. Thus, controlled studies with IOP assessment by applanation tonometry become necessary to ensure more accurate diagnoses and treatment decisions, as shown by Mendonca et al.20, Barzilai-Birenboim et al.[21] and Chang et al [22].

The treatment protocols for hematological neoplasms evaluated in this study[16-23] are based on high doses of corticosteroid therapy: prednisolone and/or dexamethasone. In studies by Barzilai-Birenboim et al.[21], Chang et al.[22], Sugiyama et al.[23] and Lai et al.[18], dexamethasone therapy was the most significant of the potential risk factors for ocular hypertension evaluated. Dexamethasone increases the protein load secreting extracellular matrix proteins in the endoplasmic reticulum (ER) of trabecular meshwork cells, thereby inducing chronic ER stress[24] and promoting IOP increase through transforming growth factor signaling β2[25]. As all children with ALL receive high-dose dexamethasone therapy at some point in treatment, these findings raise serious concerns about the potential development of cortisonic glaucoma in this group.

In addition to high doses of dexamethasone, other risk factors have been reported: NHL of the lymphoblastic subtype and a positive family history. Only two authors in this review, Chang et al.[22] and Sugiyama et al.[23], studied children diagnosed with NHL, but only Chang et al.22, when evaluating 31 patients, could observe that the lymphoblastic subtype had a higher percentage of patients with IOP elevation and within these, higher peak values and more difficult to control. E, Barzilai-Birenboim et al.[21] was the only one in the review that described the presence or absence of a family history of glaucoma and correlated it with the results of measuring intraocular pressure – 50% of patients with ocular hypertension had a positive family history – in agreement with other studies that describe an increased risk of hypertension corticosteroid-induced ocular if the patient has a first-degree relative with a history of glaucoma[26,27].

73 patients diagnosed with steroid-induced ocular hypertension included in this study were treated with ocular hypotensives, with adequate IOP control in most cases. However, some serious complications were observed in the studies by Pilbeam et al.[16], Tham et

al.[17], and Yamashita et al.[19], including severe glaucomatous optic atrophy and permanent blindness. In Mendonca et al.[20], 4 children developed definite visual impairment, even though none of them presented OH as an isolated ocular manifestation, it is known that the risk of glaucomatous nerve damage is directly related to the level and duration of IOP[28]. And, a patient in the study by Sugiyama et al.[23] required surgical intervention to control blood pressure, but there were no reports of glaucomatous nerve damage.

According to Tham et al.[17], the most effective way to normalize IOP appears to be discontinuation of corticosteroid therapy, but this approach is impossible in most cases due to the nature of the underlying medical condition. In studies carried out by Yamashita et al.[19] and Chang et al.[22] different methods were used to control IOP, but all of them included the use of antiglaucoma drugs when necessary. The use of ocular hypotensives seems, therefore, to be an adequate choice for the control of ocular hypertension in patients with hematologic malignancies, especially those who receive corticosteroids more frequently, regardless of whether the type of corticosteroid is changed or not, and for those with high IOP untreatable, trabeculotomy may be an alternative option. However, further studies are needed to verify the best combination therapy in the treatment of steroid-induced ocular hypertension in pediatric patients with ALL and NHL.

Furthermore, studies carried out by Mendonca et al.[20] and by Barzilai-Birenboim et al.[21] were the only ones that showed IOP measurement at the beginning of steroid induction, as well as systematic measurements throughout treatment. Both authors [20,21] observed a significant increase in IOP from baseline when high doses of glucocorticosteroids were used. In Mendonca et al.[20], during the treatment induction phase, values compatible with ocular hypertension (IOP > 21 mmHg) were measured in ten patients. E, Barzilai-Birenboim et al.[21] observed values above 21 mmHg in 64 patients (71.1%), 52 of them also during the induction period. Even though 36 of the 90 children examined already had elevated baseline IOP at diagnosis, they evolved with increased baseline levels after exposure to corticosteroids. In both studies[20,21], with the early diagnosis of OH, it was possible to maintain an ophthalmological evaluation and treat the condition, when necessary, and thus, all children achieved adequate control of intraocular pressure values.

CONCLUSIONS

Patients with ALL have a high incidence of ocular manifestations due to treatment and the disease itself. Among these, ocular hypertension is the most prevalent. The possibility of silent elevation of intraocular pressure, with consequent risk of irreversible visual loss in patients without ocular alterations before treatment, associated with increased survival of pediatric oncology patients under corticosteroid therapy, indicate the need to evaluate the introduction of a protocol to verify risk factors and intraocular pressure in young patients immediately after the diagnosis of ALL or NHL that allows an early approach and a better quality of life for these children. However, as to date, there have been no randomized controlled trials to adequately quantify the role of corticosteroid dose and duration in the development of intraocular hypertension, further studies on IOP assessment and visual function prior to initiation of treatment are needed, as well as systematic measurements during and after chemotherapy.

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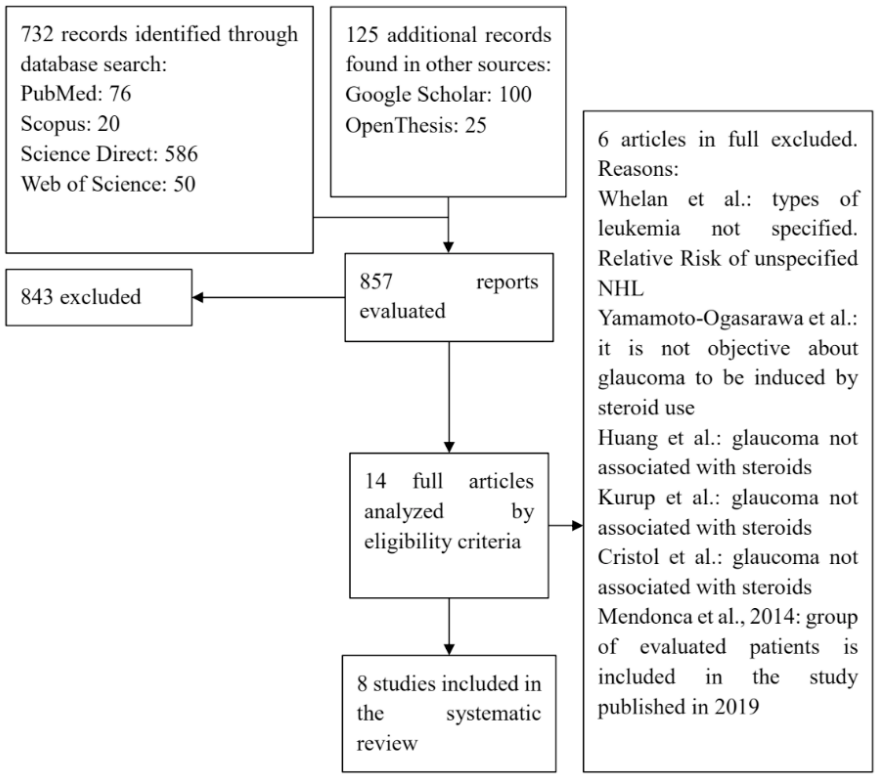

Figure 1. Flowchart

Study	Type of study	N	Country	neoplasm	Sex	Age	Treatment		Previous eye change	glaucoma HF	GC-induced HO	IOP measurement
							QT	CO				
Pilbeam et al.[16]	case report	1	USA	LLA	M	3 years	YES	YES	NOT	NOT	YES	ND
Tham et al.[17]	case report	1	China	LLA	F	9 years	ND	YES	NOT	NOT	YES	Goldmann applanation tonometer
Lai et al.[18]	case report	1	Taiwan	LLA	F	9 years	YES	YES	ND	ND	YES	Non-contact tonometry and Tono-Pen XL applanation tonometer
Yamashita et al.[19]	case series	5	Japan	LLA	3F: 2M	4.2 years (average)	YES	YES	ND	ND	5 patients	Non-contact tonometry (CT-80, Topcon)
Mendonça et al.[20]	prospective observational	55	Brazil	LLA	23F:32M	9.1 years (average)	YES	YES	NOT	NOT	10 patients	Perkins applanation tonometer
Barzilai-Birenboim et al.[21]	prospective observational	90	Israel	LLA	4F: 5M	6.8 years (average)	YES	YES	36 pacientes com PIO elevada no diagnóstico	45 pacientes	64 patients	TONO-PEN AVIA applanation tonometer
Chang et al.[22]	retrospective observational	54	China	LNH	7F: 20M	8.1 years (average)	YES	YES	NOT	ND	31 patients	Icare rebound tonometry and confirmed with Goldmann applanation tonometer
Sugiyama et al.[23]	retrospective observational	12	Japan	3 LLA: 1LNH	5F: 7M	8.3 years (average)	YESYES	YES	ND	ND	11 patients	ND

QT: chemotherapy; CO: oral corticosteroid; HF: family history; OH: ocular hypertension; GC: glucocorticoid;

IOP: intraocular pressure; ALL: acute lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; ND: not described.

TABLE 1. Demographic characteristics and details of studies included in the systematic review

Study	patients	%	METHOD:			Intraocular Pressure	Complications
			antiglaucoma medication	exchange of GC	Suspension of GC		
Pilbeam et al.[16]	1 patient	100%	YES	NOT	NOT	inadequate control	Permanent blindness in the right eye and significant visual loss in the left eye
Tham et al.[17]	1 patient	100%	YES	NOT	NOT	Inadequate control	An episode of decreased visual acuity
Lai et al.[18]	1 patient	100%	YES	NOT	NOT	Adequate control	No complications
Yamashita et al.[19]	5 patients	60%	YES	YES	NOT	Adequate control	No complications
		20%	YES	NOT	NOT	Adequate control	Hassle free
		20%	YES	NOT	YES	Adequate control	Severe glaucomatous optic atrophy and thinning of the retinal nerve fiber layer
Mendonça et al.[20]	10 patients	40%	YES	NOT	NOT	Adequate control	permanent visual impairment
		60%	YES	NOT	NOT	Adequate control	hassle free
Barzilai-Birenboim et al.[21]	64 patients	20,3%	YES	NOT	NOT	Adequate control	hassle free
		79,7%	NOT	NOT	NOT	Adequate control	hassle free
Chang et al.[22]	31 patients	93,5%	YES	NOT	NOT	Adequate control	hassle free
		6,5%	YES	YES	NOT	Adequate control	hassle free
Sugiyama et al.[23]	12 patients	91,7%	YES	NOT	NOT	Adequate control	hassle free
		8,3%	YES	NOT	NOT	Inadequate control	hassle free

GC: glucocorticoid.

TABLE 2. IOP control and complications in patients with steroid-induced ocular hypertension.