Retinoblastoma management: a systematic review

Manejo do retinoblastoma: uma revisão sistemática

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ABSTRACT
Retinoblastoma is a rare cancer that occurs in children under 5 years of age from which leukocoria and strabismus are the characteristic signs of this disease. For every 16,000 to 18,000 newborns worldwide, one will get retinoblastoma, while at the Latin American context there are no reported data due to scant research. Therefore, the reason for this research is to describe the management of retinoblastoma. Trauma, human papillomavirus (HPV), and genetic alterations in the RB1 gene are possible causative factors for retinoblastoma. The diagnosis is based on the clinic, genetic tests, imaging tests and in cases of metastasis, a cerebrospinal fluid (CSF) aspiration is performed through lumbar puncture. There is another method such as non-invasive prenatal diagnosis (NIPD), here the main diagnosis is indirect ophthalmoscopy. The treatment is directly related to the evolution of the disease using different methods such as enucleation, cryotherapy, chemotherapy and radiotherapy that can be used individually or in combination to improve the quality of life of the patient; however, enucleation followed by chemotherapy remain as the main method of treatment.

Keywords: diagnosis, epidemiology, etiology, retinoblastoma, treatment.

RESUMO
O retinoblastoma é um câncer raro que ocorre em crianças menores de 5 anos, sendo a leucocoria e o estrabismo os sinais característicos dessa doença. Para cada 16.000 a 18.000 recém-nascidos no mundo, um terá retinoblastoma, enquanto no contexto latino-americano não há dados relatados devido à escassez de pesquisas. Portanto, o motivo desta pesquisa é descrever o manejo do retinoblastoma. Trauma, papilomavírus humano (HPV) e alterações

genéticas no gene RB1 são possíveis fatores causadores do retinoblastoma. O diagnóstico é baseado na clínica, exames genéticos, exames de imagem e em casos de metástases é realizada aspiração do líquido cefalorraquidiano (LCR) por meio de punção lombar. Existe outro método como o diagnóstico pré-natal não invasivo (NIPD), aqui o diagnóstico principal é a oftalmoscopia indireta. O tratamento está diretamente relacionado com a evolução da doença utilizando diversos métodos como enucleação, crioterapia, quimioterapia e radioterapia que podem ser utilizados individualmente ou em associação para melhorar a qualidade de vida do paciente; no entanto, a enucleação seguida de quimioterapia permanece como o principal método de tratamento.

Palavras-chave: diagnóstico, epidemiologia, etiologia, retinoblastoma, tratamento.

1 NTRODUCTION

In 1597, Pawis described retinoblastoma as fungal hematodes and presented enucleation as the main treatment, taking into account that an early diagnosis helps to propose an effective treatment when recovering the eye and its vision (1). On the other hand, even if the treatment is adequate, advanced tumors limit good recovery of the eyeball, increasing the risk of mortality (2).

Retinoblastoma is a type of cancer that affects the cones of the retina of newborns, the disease appears before the age of 5; leukocoria occurs in 60% of children, which is why it is considered the most common symptom; however, this symptom is characteristic of the advanced stages. Other symptoms such as strabismus, decreased visual acuity, anisocoria, ocular inflammation, glaucoma, among others, may occur. A late or erroneous diagnosis after 6 months of undergoing the symptoms can lead to metastasis (3–7).

From a genetic perspective , retinoblastoma occurs in an autosomal dominant way or in a sporadic way or in a non-hereditary manner. The formation of retinoblastoma begins from a photoreceptor cell of the retina that is related to the mutation of the RB1 gene on chromosome 13q14; all people receive a copy of this gene from the mother and father (8,9).

This pathology is considered rare, since for every 16,000 to 18,000 newborns worldwide, one will get retinoblastoma, with a prevalence of 15% of pediatric cancers (10,11); on the other hand, it is estimated that more than half of retinoblastoma cases come from Asia-Pacific and almost a quarter from Africa (12,13). In Korea they report an incidence of 11.2 cases per 100,000 inhabitants, in the United States and Europe they have similar records (14). In India the incidence is 1.9 to 12.3 per million cases in boys and 1.3 to 6.7 per million cases in girls and in China per year there are between 1,100 to 1,500 cases of which 50% of the children do not survive (15). In Latin American countries, there is no incidence rate due to the lack of

retinoblastoma records; however, in Mexico the mortality rate is between 9.1-16%, in Argentina 7%, and in Ecuador there are no data on this disease (16,17). The mortality of these patients increases when the patient abandons the treatment due to the little collaboration of the pediatric patient, the parents not being aware of the risks of the disease and above all the socioeconomic factor. It has been shown that in countries with higher incomes, malignant neoplasms are considered the highest mortality, while in countries with medium and low incomes, the highest mortality is due to extraocular retinoblastoma or metastasis, since it is legally easier to abandon treatment in comparison with the rest of the countries (18,19). In developed countries there is an incidence of 2.2-6.2 cases per million inhabitants with a survival rate of 95%, and in less developed countries this incidence increases to 24.5 per million inhabitants with the 10-30% survival rate (17,20).

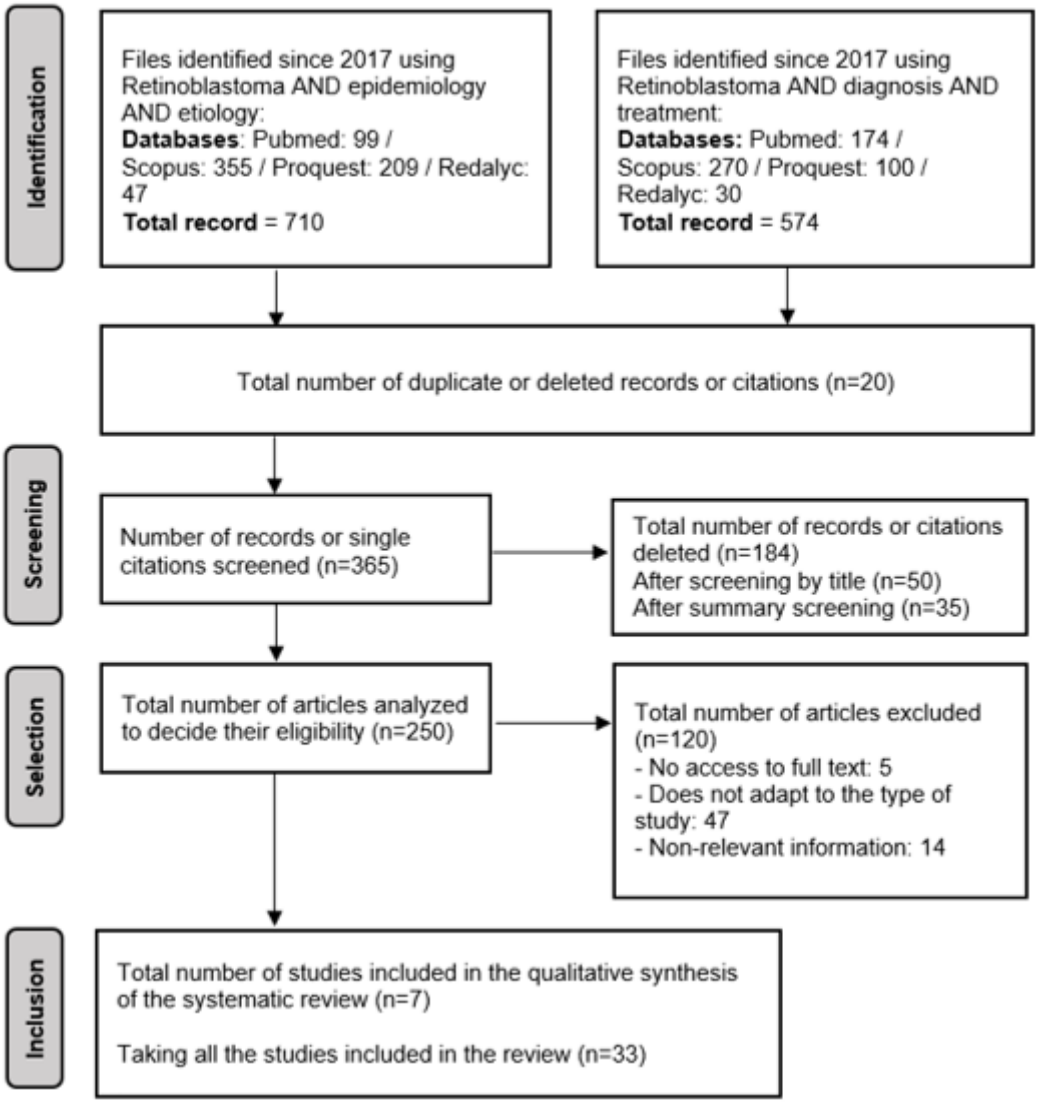
The clinical diagnosis is based on the most common symptoms such as leukocoria and strabismus, while the genetic diagnosis finds the RB1 gene mutation. To complement the diagnosis, imaging tests are useful where the extension of the intraocular tumor is observed using ultrasound, computed tomography and magnetic resonance imaging to detect the possibility of invasion of the optic nerve and pineoblastoma. In addition, cerebrospinal fluid (CSF) aspiration through lumbar puncture helps determine possible metastasis (21,22). Non-invasive prenatal diagnosis (NIPD) has begun to be implemented, which can be performed from the eighth week of gestation (23). The main treatment for retinoblastoma is enucleation of the eye; however, other therapies such as chemotherapy, radiotherapy, ophthalmic artery (24,25)chemosurgery, among others, are also useful .

2 METHODOLOGY

A systematic review has been performed to determine the management of retinoblastoma. The information sources used are scientific search engines available on the web, with the purpose of describing the bibliography associated with the management of retinoblastoma with the help of search engines such as PubMed, Scopus , Proquest and Redalyc. With the use of the search engines previously described, the scientific search will continue, which used Descriptors in Health Sciences (DeCs) that in Spanish were: “Retinoblastoma”, “Epidemiología”, “Etiología”, “Diagnóstico”, “Tratamiento” and in English: “Retinoblastoma”, “ Epidemiology ”, “ Etiology ”, “Diagnosis” and “ Treatment”, likewise a combination of these will be carried out through the Boolean operator “AND” without language restriction. The search strategy was: retinoblastoma AND epidemiology AND etiology AND diagnosis AND treatment. In addition, the time period was limited from 2017 to 2022, however,

a citation from 2014 was used due to its relevant information. To carry out the work, the Preferred Reporting Ítems for Systematic reviews and Meta-Analyses (PRISMA) has been used, which details the process for selecting the articles (Figure 1). The inclusion criteria for the selection of articles in this review were: articles published between 2017 and 2022, complete articles reporting on the management of retinoblastoma , cohort articles, bibliographic reviews, and systematic reviews. The exclusion criteria were: letters to the editor, degree thesis, meta-analysis, expert opinions and articles with incomplete text. By having this bibliographic search from various sources, a screening was carried out by title and abstract, having 33 articles for this systematic review.

Figure 1. Flowchart of the search process followwing the PRISMA methodology



3 RESULTS

TABLE 1. Retinoblastoma Treatment.

AUTHOR	YEAR	TYPE	RESULTS	CONCLUSIONS
Pandey (1)A.N.	2014	Bibliographic review	Several therapies are used that are administered depending on the size of the tumor in which cryotherapy, photocoagulation, thermotherapy are used that help the tumor not to grow, while chemotherapy is used in large tumors, there is a new treatment such as plaque brachytherapy, which has a shorter treatment time; and finally, enucleation, which continues to be the choice for intraocular retinoblastoma .	Chemotherapy remains useful in saving the prudently advanced neonatal eye, while enucleation remains the main treatment for unilaterally advanced retinoblastoma .
Ancona Lezama D, et al .(9)	2017	Retrospective	Intravenous chemotherapy is used as an adjuvant to and is referred to as chemoreduction, cryotherapy is used in combination with chemotherapy, while thermotherapy has gradually replaced photocoagulation. It is frequently used and can be combined with intravenous and intra-arterial chemotherapy. Enucleation is used in cases of chemosis, conjunctival cysts, blepharoptosis, infection, among others.	In order to treat retinoblastoma , they must be personalized for each patient, depending on the economy, culture and, most importantly, the degree of the disease. That is why the help of several specialists is necessary to improve the quality of life of the newborn.
Machin E, Bermudez V, et al.(26)	2017	Bibliographic review	Cryotherapy is used in combination with chemotherapy, photocoagulation is used in cases where the tumor is in the back. In small tumors thermotherapy is used and in large tumors chemotherapy is recommended to shrink the tumor and try to avoid enucleation of the eye.	It is taken into account that chemotherapy together with other therapies and an opportune diagnosis help to increase survival and decrease the incidence of retinoblastoma .
Vargas Cedeño JD, et al.(19)	2021	Bibliographic review	There are extrafoveal tumors that can be unilateral or bilateral using cryotherapy, laser photocoagulation or radiotherapy with plaque in these cases, in addition laser photocoagulation can be used in conjunction with chemotherapy. Systemic chemotherapy or simultaneous chemotherapy of the ophthalmic artery and neurosurgical resection followed by chemotherapy and radiotherapy is used as primary therapy. In cases of unilateral tumors, ophthalmic artery chemosurgery or intravenous chemotherapy is recommended. Radioactive plaque therapy is used in cases where the tumor is small and when this tumor has reached advanced stages, enucleation is recommended.	Retinoblastoma is the most common primary intraocular malignancy of childhood. Its diagnosis can be made based on indirect ophthalmoscopic examination and imaging studies with particular findings without the need to confirm the diagnosis histologically. Immediate referral to a pediatric ophthalmologist and appropriate management by a multidisciplinary team are necessary to optimize visual outcome and patient survival.
Tacle Humanante SS, et al. (27).	2022	cohorts	In cases where the tumor is anterior, cryotherapy is used followed by photocoagulation, in small tumors thermotherapy, and in large tumors chemotherapy and enucleation depending on the size. Radiotherapy is used less frequently due to complications such as cataracts, retinopathy, among others.	The treatment depends on the degree of severity of the tumor, which with the help of a timely diagnosis and together with a group of professionals helps to make the therapies favorable to reduce the risk of the appearance of a new tumor and avoid enucleation.
Moreira Da Silva RV, Cardozo Barreira AC , et al. (28).	2022	Bibliographic review	Chemotherapy is used in cases where the tumor is bilateral, in which it can be administered intravitreal as ocular globe rescue therapy and not as primary therapy due to its limited effectiveness in primary tumors and intra-arterially in cases of patients older than 3 months. and the intravenous; chemoreduction in turn reduce the volume of the tumor and	The treatments will be based on chemotherapies (IVC, IAC and IvitC), consolidation therapies and those based on radiation and enucleation. It is essential to help health professionals in the correct conduct for early diagnosis and

			perform local thalmological treatment, instead of enucleation and external radiotherapy.	adequate treatment of retinoblastoma .
Schaiquevich P, Francis JH, et al. (13).	2022	Bibliographic review	Ophthalmic artery chemosurgery is implemented as a rescue for retinoblastoma , which reduces the time from the beginning to the end of therapy and avoids second tumors; In addition, there are injections such as intravitreal, periocular, which evades the blood -retinal barrier, helping to avoid puncture of the eyeball, and intrathecal. intracameral chemotherapy occurs in cases where the previous tumor is found and gene therapy and oncolytic viruses are still under Phase I study. Chemotherapy has high antitumor activity along with other therapies.	Intravitreal chemotherapy injection and ophthalmic artery chemosurgery have resulted in globe salvage not previously achievable with systemic chemotherapy or external beam irradiation. New drugs, oncolytic viruses, and immunotherapy are useful tools in the treatment of intraocular retinoblastoma . In addition, it must be taken into account that the local administration of drugs helps to have new treatments for metastatic disease in the future.

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The main objective of the treatment is to save the child's eye and his life, in the same way to protect his vision, all this can be done as long as there is an early diagnosis; however, not all cases can reach a favorable prognosis, since, when not diagnosed or treated quickly, the tumor grows to the point of invading the adjacent lymph nodes, bone marrow or reaching the central nervous system (CNS), the latter being the condition with the worst prognosis because the hematoencephalic barrier precludes systemic chemotherapy therapy. So, in order to arrive at an opportune treatment, it is necessary to take into account the age of the patient, where the tumor is located, which adjacent tissues are affected and the economic factor, among the most important. On the other hand, people who have access to timely treatment receive education about the pathology, as well as the risks of contracting new malignant neoplasms. Developing countries do not usually have the resources available for the treatment of retinoblastoma, compared to developed countries (29–32).

Enucleation is the main treatment for retinoblastoma and consists of the removal of the tumor together with the structures of the eyeball and a part of the optic nerve, it is used in advanced tumors when chemotherapy or radiotherapy have not had a favorable result, this procedure has a 90% to 95% cure rate; however, by having good results, it does not rule out the idea of possible complications, not only physical such as intraoperative bleeding or infections, but also psychological. Rehabilitation with an ocular prosthesis in these patients can be performed after 6 weeks when there is no bleeding or infection, this procedure improves the patient's quality of life (26,27,33–35).

Cryotherapy is useful in small tumors (<4 mm in diameter) is used at intervals of 4 to 6 weeks, but has complications such as transient retinal detachment or retinal tear. This technique

is used through indirect ophthalmoscopy, placing the cryotherapy probe in the conjunctiva or in the sclera and performing a triple freezing-thawing process causing damage to the vascular endothelium with secondary thrombosis and infarction. Using cryotherapy 2 to 3 hours before chemotherapy allows the release of chemotherapeutics helping the synergistic effect through the blood -retinal barrier . Other alternatives for small tumors are photocoagulation and thermotherapy, where the first one uses an argon or xenon laser and is used for later tumors with monthly intervals of 2 to 3 sessions, helping to prevent blood flow; however, care must be taken in tumors near the macula as it can cause amblyopia; and the second is used in tumors smaller than 3 mm using heat directly on the tumor with a temperature of 45ºC-60ºC (1).

External beam radiation therapy is indicated when the retinoblastoma is bilateral and chemotherapy has not been helpful. The treatment consists of using high-power energy such as X-rays and protons with a dose of 35 to 46 Gray allowing cancer cells to be destroyed, it should be used with caution as it can cause dry skin, eyelids, inflammation or even hair loss. tabs(19,27,28)

Chemotherapy can be administered by different routes such as intravenous, intraarterial, intravitreal or periocular, it is used in large tumors, allowing its size to be reduced in order to use another therapy indicated in small tumors (9,26–28). Finally, ophthalmic artery chemosurgery helps significantly when the disease is advanced. It consists of inserting a microcatheter (similar to a Foley catheter, but smaller) into the femoral artery and reaching above the ophthalmic artery and The chemotherapy drug, melphalan, is administered, with a high success rate (9,13,28). Table 1 shows these procedures and mentions chemotherapy along with other methods, in addition to therapies with radioactive plaque, gene therapy, and oncolytic viruses.

4 DISCUSSION

Pandey AN (1)mentions different treatment methods, one of them is individual methods such as photocoagulation and thermotherapy; The joint method such as cryotherapy with chemotherapy have good results in reducing the size of the tumor, as well as avoiding invasive processes such as eye enucleation that is applied in advanced stages. Similarly, Ancona D, et al. (9) mentions the same treatments, but has alluded that thermotherapy has begun to replace photocoagulation; however, it does not reduce complications such as focal cataract, iris atrophy, anterior or posterior synechiae, and serious complications such as vitreous hemorrhage, retinal neovascularization, retinal detachment, among others. Machin E, Bermudez V. et al. (26)mentions some treatments previously described; however, this author takes into account

that photocoagulation is contraindicated in patients with choroidal invasion, vitreous seeding, and foveal compromise, among others. Although these therapeutic methods mention that they have great benefits, Tacle Humanante SS et al mention that radiotherapy is also useful, but it is used less frequently than other treatments due to complications such as cataracts, retinopathy, among others. On the other hand, Vargas Cedeño JD, et al. (27) began to use advanced procedures such as cryotherapy, laser photocoagulation or radiotherapy with plaque (focal techniques), laser photocoagulation and different methods for chemotherapy such as intravenous, single agent system, systemic, in addition to new techniques such as chemosurgery of the ophthalmic artery useful as primary therapy that allows saving both eyes, neurosurgery followed by chemotherapy and cranial radiotherapy , ophthalmic artery chemosurgery agents such as melphalan , carboplatin and topotecan , radioactive plaque therapy that helps control the tumor until in 80% it is performed in small tumors. Moreira Da Silva, Cardozo Barreira AC, et al. (28)indicate that chemoreduction makes it possible to reduce the volume of the tumor and start ophthalmological treatment avoiding resorting to enucleation or radiotherapy; it will also be carried out as adjuvant therapy in patients with metastasis associated with an orbital tumor or retolarsocavus tissue invasion. Chemotherapy remains essential as treatment for retinoblastoma, having CAI or intravitreal chemotherapy. Schaiquevich P, Francis JH, et al. (13)mentions that the primary therapy for retinoblastoma is ophthalmic artery chemosurgery , also includes a therapy to attack the vitreous disease by means of a vitreous injection that is administered according to the response and toxicity that occurs, likewise to avoid the blood-retinal barrier periocular injection is used; however, the transscleral diffusion of the drug has some difficulty, and the author also includes new methods such as gene therapy and oncolytic viruses that are based on the administration of intravitreal chemotherapy followed by ganciclovir therapy; however, chemotherapy continues to have high antitumor activity along with other therapies such as cell lines and xenografts.

5 CONCLUSIONS AND RECOMMENDATIONS

There are several treatments for this tumor depending on the size, such as the case that they are small tumors in which cryotherapy can be combined with other therapies and have a good result, however, it usually has complications such as retinal tears or detachment, among other. Other therapies are photocoagulation that is used for small tumors, but in the same way that cryotherapy has complications such as vascular occlusion, retinal hole, among others. Chemotherapy is used to reduce the size of the tumor, allowing the other therapies already mentioned to have a better effect and thus being able to avoid enucleation of the eye, which

continues to be the best therapy for newborns in advanced stages. For chemotherapy it has different routes such as intravitreal, intrathecal, intracameral, periocular. Ophthalmic artery chemosurgery is currently used to help avoid increased risk of orbital disease or secondary cancers. before some alteration at the level of the eye of the newborn, it should alert the parents to have a prompt and adequate diagnosis and observe the family background.

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