Research Article

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RETINOBLASTOMA - Clinical Therapeutic Considerations in Retinoblastoma

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ABSTRACT

Retinoblastoma (RB) is the most common primary malignant intraocular tumor in children of 1-3 years old, with staged evolution, which has a favorable response if the diagnosis is made early. The major clinical signs are: leukocoria (white reflex in the pupil amaurotic cat's eye), strabismus, painful, red eye, associated with orbital inflammation, exophthalmos, lymph node or brain metastases, intracranial hypertension. RB requires for diagnostic confirmation, CT scan, MRI highlighting calcifications, optic nerve invasion, CNS extension, presence of pineoblastoma, B-scan ultrasound.

RB can be complicated by: cataract, secondary glaucoma, retinal detachment, vitreous hemorrhage. The prognosis of the disease is relatively good, with 70-85% survival rate, if enucleation was done before the extraocular extension of the tumor.

Treatment in RB depends on the size and location of the tumor:
- stage 1 tumors, without invasion of the optic nerve, require cryotherapy, radiotherapy; the consumptive treatment of RB is controversial
- RB is a radiosensitive tumor; external radiotherapy must be individualized according to the size and location of the tumor, bilateralization, metastasis, and can be external radiotherapy and brachytherapy in the form of radioactive plates placed on the site where the tumor is.
- enucleation is indicated in large tumors; extensive RD, in optic nerve invasion, secondary glaucoma

In RB with intracranial orbital extension or distant metastases, palliative treatment is required: chemotherapy, exenteration, external radiotherapy. Chemotherapy with carboplatin, etoposide, vincristine, cyclosporine, is strengthened by laser photocoagulation, cryotherapy, brachytherapy.

Keywords

Retinoblastoma, RB genetics, Leukocoria, Amaurotic cat's eye, Intraocular tumor, Laser photocoagulation, Cryotherapy, Enucleation, Chemotherapy.

Introduction

- Retinoblastoma - RB - is the most common primary malignant intraocular tumor in children of 1-3 years old, with a favorable response to treatment, if the diagnosis is made in time [1,2]:
- Incidence 1/20000 births without sex predisposition.
- RB is bilateral in 20-30% of cases, unilateral in 2/3 of cases, trilateral very rarely, with the third tumor in the brain having a reserved prognosis
- RB is congenital, but is not recognized at birth, it becomes clinically evident at the age of 1-2.

- Genetic RB has a known family history, but can also be produced by genetic mutation [3-5].
- Patients with the hereditary form are at risk of developing other forms of tumor
- The RB gene is located on the long arm of chromosome

13, involved in the development of other forms of cancer: osteosarcoma, lung, breast, bladder cancer
- The hereditary form of RB is AD with a 50% risk of transmission of the genetic mutation, of which 50% of the offspring may develop RB.
- Non-hereditary sporadic forms are present in 60% of cases, in which 85% are forms of unilateral RB, and the tumor is non-transmissible.

Early Diagnosis of RB is Essential for Eye Preservation and Survival.

Clinical Aspects in RB

The positive diagnosis of RB is based on the presence of the following clinical signs [3,4,6]:

• Major clinical signs:
- Leukocoria – white reflex in the pupil (most common)
- Amaurotic cat's eye
- Strabismus – 20% of cases
- Red, painful eye when glaucoma develops

• Associated clinical signs:
- Infectious orbital inflammation
- Exophthalmos in neglected cases
- Ganglion or brain metastases
- Intracranial hypertension in cases of trilateral RB – associated pineoblastoma

Clinical onset of RB is in the first two years

• Eye fundus examination with dilated pupil highlights:
- The presence of tumors of different sizes (small or large, single or multiple), located in different areas of the retina, some prominent in the vitreous with polycyclic, yellowish-white edges, accompanied or not by hemorrhages.
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Clinically, RB evolves in 4 stages [2,4]:

- **Stage 1**

➢ Small-sized tumors, with a cotton swab appearance, polycyclic outline, prominent, white/yellowish, with endophytic development (toward the inside of the eyeball), in the form of a whitish formation with a "cheesy" appearance, with vessels on the surface, or exophytic, white formation, multilobar, located under the detached retina with the external layer of the retina as the starting point.
➢ Hereditary tumors are frequently multifocal tumors, possibly bilateral.

- **Stage 2**

➢ Intraocular hypertension due to tumor invasion of the eyeball and secondary glaucoma with red, painful eye.
➢ A yellowish mass, prominent in the vitreous, can be seen in the pupil.
➢ Is the stage in which the diagnosis of RB is made most frequently.

Retinoblastoma	
Clinical	**Treatment**
– Primitive intraocular malignant tumor, most common in children, gene 13q14 with average onset at 24 months old, unilateral 70%, bilateral with hereditary forms, with risk of transmission and non-hereditary (somatic) forms; - **Detected by:** leukocoria (amaurotic cat's eye appearance), strabismus, exophthalmos, nystagmus, secondary glaucoma, uveitis, and late - by signs related to distant metastases with intracranial hypertension, ganglion, cerebral metastases; – they can be: the **exophytic** tumor is a multilobar whitish formation under the detached retina, the **endophytic tumor** with vitreous invasion is a prominent, round formation with vessels on the surface, **multifocal tumors** (rarely bilateral), **infiltrative tumor** with anterior and posterior extension; – **CT** detects tumor calcifications, optic nerve invasion, CNS extension, presence of pineoblastoma, bilateral retinoblastoma (RB), brain tumor; – **MRI, ultrasound**, general clinical examination are necessary **clinically,** the tumor can be intraocular, exoendophytic with complications, extraocular extension and metastasis through optic nerve to the brain, through vessels to the liver, lymphatic;	***Long section enucleation of optic nerve (more than 5 mm)** – external radiotherapy – brachytherapy - chemotherapy **Locally:** - cryotherapy – xenon photocoagulation – Iodine-125 brachytherapy – thermochemotherapy (carboplatin followed by diode laser) ***Treatment depending on tumor size** – small tumors – cryotherapy – medium tumors – brachi-, cryotherapy – large and extensive tumors, enucleation ***Chemotherapy** in metastatic tumors ***Treatment for optic nerve invasion** - radiotherapy - chemotherapy ***Palliative treatment** - chemotherapy – exenteration
– **Differential diagnosis:** persistence of primitive vitreous, Coats disease, retinopathy of prematurity, eye infection with toxocariasis, astrocytoma, retinal dysplasia; – **Reserved prognostic factors:** large tumor, with reduced cellular differentiation, optic nerve invasion in the optic nerve sectioning area, choroidal invasion through vortex veins, extrascleral extension, diagnosis + late, possible recurrences; □ reserved vital prognosis for the forms with extrascleral extension; – the **Reese-Ellsworth classification** divides RB into 5 stages, depending on the clinical appearance, the size and location of the tumor and allows establishing the therapeutic attitude and the ocular and vital prognosis; **- periodic check-up of the child;** **– genetic advice**	

- **Stage 3**

➢ Extension of the tumor with scleral perforation (rarely corneal) with invasion of the orbit, optic nerve and skull.

- **Stage 4**

➢ Metastases in the brain, meninges, cervical nodes, mediastinum, liver, bone system

Mandatory complementary examinations to establish the positive diagnosis of RB, the clinical stage and appropriate therapeutic indication [3,5,6].

- CT scan – detects calcifications, optic nerve invasion, CNS extension and the presence of pineoblastoma.
- Ultrasound - B scan - to measure the size of the tumor and highlight calcifications.
- MRI – to assess optic nerve invasion, intracranial extension and presence of pineoblastoma.
- Lumbar puncture with bone marrow aspiration.

Intraocular RB with 85% survival, the hereditary one has a possible second malignancy in 30-50% of cases.

Clinicotherapeutic aspects in RB [2,3,5,6]

Complications

- Cataract
- Secondary glaucoma
- RD (retinal detachment)
- Vitreous hemorrhage

The differential diagnosis of leukocoria

- Cataract
- Retinopathy of prematurity
- Persistence of hyperplastic primitive vitreous
- Coats disease
- Toxocariasis

Differential diagnosis

➢ Endophytic RB

- Neurofibromatosis and tuberous sclerosis
- Astrocytoma
- Exudative choroiditis

➢ Exophytic RB must be differentiated from other causes of RD

The positive diagnosis of RB is confirmed:

- After bilateral ocular clinical examination, under general anesthesia, with the pupil in maximum mydriasis, measurement of IOP and corneal diameter.
- Highlighting the calcifications present in 75% of cases by radiography.
- Identification of the level of lactic dehydrogenase in aqueous humor.
- Examination of CT scan and ultrasonography to highlight the extension of optic nerve, orbit, CNS.

Prognosis

• Untreated RB is accompanied by death, extremely rarely regression

- Relatively good prognosis 70-85% survival rate if enucleation was done before extraocular extension of the tumor
- Very reserved prognosis if the ON has been invaded, the tumor has undifferentiated cells and there is massive choroidal invasion.

• Unfavorable prognostic factors

- Large tumor
- Minimal cell differentiation
- Optic nerve invasion beyond the area of surgical section
- Invasion of the choroid or vortex veins
- Extrascleral extension

Treatment

The Treatment of RB Must Be Early and Appropriate, Because RB is an Extremely Serious Disease, And the Parents Must Know the Real Situation of the Child's Disease [3,5-8].

- Interdisciplinary collaboration for diagnosis, treatment, extended clinical follow-up ophthalmologist/pediatrician/ oncologist/radiologist.
- Family genetic counselling.
- Early positive diagnosis and immediate appropriate treatment.
- Late diagnosis, incorrect treatment of RB leads to metastasis and death.
- Prolonged clinical follow-up.
- The treatment of RB depends on the stage of the tumor: intraocular, extraocular.

Treatment Depends On the Size and Location of the Tumor

• **Tumor destruction is indicated when [6,7]:**

- The diagnosis of RB is in stage 1, without optic nerve invasion

➢ local therapy:

o Cryotherapy for small tumors < 4-5 mm in diameter and < 2.5 mm in thickness, located anterior to the equator.

o External radiotherapy for tumors < 1-2 mm in diameter and < 8 mm in thickness.

o Laser photocoagulation in small tumors < 3 mm located posterior to the equator, to the fovea.

o Laser diode thermotherapy for small tumors located posterior to the equator, far from the macula.

• **Conservative treatment of RB is controversial, but with appropriate indication could have favorable therapeutic effects [4,9,10]**

➢ ***Small tumors up to 4 mm located in the posterior pole***

- **Laser photocoagulation treatment with laser impact applied to the tumor** until the local temperature rises, which produces a whitening of the impacted tissue [9,11,12]

➢ sessions repeated 2-3 times successively

➢ beneficial effects in 2-3 weeks, obtaining a flat tumor scar

➢ This treatment modality can only be indicated in small tumors located posterior to the equator

➢ complications

o ineffective treatment

o edema, localized and transient retinal hemorrhages

o Therapeutic failure with local tumor recurrences and regional (even systemic) invasion.

- **Transpupillary thermotherapy in RB** in which the laser wave is applied to the tumor and peritumoral, transpupillary, focusing the vessels
➢ **The the**rapeutic method is effective ONLY in small tumors.
➢ PTT uses infrared laser applications directly on the tumor with 810 nm diode laser by which the laser energy could destroy cancer cells or small size tumors or laser photocoagulation destroys the blood supply of the tumor.
➢ PTT can be used to reduce tumor size, followed by other tumor ablation techniques.

- **Thermochemotherapy** is PTT associated with chemotherapy treatment, used in the conservative treatment of RB in order to avoid:
➢ Excessive irradiation and is indicated in large tumors
➢ Laser beam directed at the tumor for a few minutes under a transpupillary operating microscope
➢ General anesthesia
➢ Intravenous carboplatin
➢ The temperature of the tumor increases and reinforces the effectiveness of chemotherapy
➢ In 4 sessions cure can even be accomplished

- **Thermoradiotherapy in which PTT is associated with radiotherapy**

- Laser plasma accelerator where the plasma is created by a very intense and short laser pulse directed at the target with the ultrafast manipulation of plasma electrons with laser pulses

- **Laser Treatment Assisted By Plasmonic Nanoparticles as an Alternative**

- **To Chemotherapy Treatment.**
➢ It achieves the significant increase in temperature at the site of impact, which kills cancer cells
➢ Uses nanosecond pulsed laser and 100 nm gold nanoparticles.
➢ Tumors located earlier with a diameter of up to 7 mm – cryotherapy
➢ ***Large tumors:*** **chemotherapy, radiotherapy, surgical treatment (enucleation) or a combination of them.**
➢ ***Metastatic tumors*** **– high doses of chemotherapy.**

• **Enucleation [3,7,11]**
- large tumor, 20 mm, at base 10 mm high with RD extending more than half of the retina
- the optic nerve invasion
- secondary glaucoma
- postoperative
➢ radiotherapy 5000 r
- chemotherapy: vincristine, carboplatin, etoposide which can be combined with cyclosporine

• **Palliative treatment**
- RB with orbital, intracranial extension or distant metastases
- Treatment includes: **Chemotherapy, exenteration, external radiotherapy.**

• **RB is A Radiosensitive Tumor and Requires** individualized external radiotherapy according to: tumor size and location, risk of metastasis, bilaterality, systemic status using [2]:
- External radiotherapy
- Brachytherapy – radioactive plates placed on the site where the tumor is.

• **Chemotherapy:** periocular and subconjunctival treatment with carboplatin, intravitreal treatment with Thiotepa, Melphalan, intraarterially with Melphalan in the ophthalmic artery (experimental)
- The following are used: cyclophosphamide, vincristine, doxorubicin, etoposide, carboplatin.
- Chemotherapy indications [7,13,14]:
- Eyes with good visual prognosis, but with large tumors that do NOT allow focal treatments
- Children younger than 1 year to avoid the adverse effects of external radiotherapy
- Any advanced unilateral or bilateral RB.
- Chemotherapy treatment is done with: alkylating agents: carboplatin, cisplatin
- DNA inhibitors: etoposide, teniposide
- Vinca alkaloids - vincristine
- Cyclosporine

Most Commonly Used: Vincristine, Etoposide, Carbaplatin.
Tumor control by chemotherapy is strengthened by laser photocoagulation: cryotherapy, brachytherapy if necessary.

Adverse effects: fatigue, nausea, vomiting, diarrhea, fever, leukopenia (anemia), thrombocytopenia, ototoxicity (carbaplatin), myeloid leukemia. Metastatic RB in the CNS (reserved prognosis with almost 100% mortality) or distantly in lymph nodes, distant organs, bone marrow – palliative treatment.
International treatment recommendations in RB [2,7,8].

• **Unilateral RB**
- Group A – cryotherapy or laser photocoagulation
- Groups B, C – chemotherapy or brachytherapy
- Group D – carboplatin chemotherapy, enucleation
- Group E – enucleation

• **Bilateral RB**
- Groups A, B, C, D similarly as unilateral BR
- Group E – enucleation unless RB is bilaterally advanced when chemotherapy and radiotherapy can be tried

Conclusions

Retinoblastoma is the most common primary intraocular malignancy in childhood, with staged evolution, with a hereditary form, AD with a 50% risk of transmission, of which 50% of the offspring may

develop RB and non-hereditary sporadic forms in 60% of cases of which 85% are unilateral RB with non-transmissible tumor. The evolution of RB is stadial, initially with small, prominent, white/yellow tumors, with endophytic or exophytic development under the detached retina with multifocal hereditary tumors, sometimes bilateral. In evolution, there is tumor invasion of the eyeball, ± secondary glaucoma and the presence in the pupil of a yellowish mass prominent in the vitreous. Tumor expansion with scleral perforation, orbital invasion of the optic nerve and skull is possible, sometimes metastases in the brain, liver, bone system. The positive diagnosis is confirmed after clinical examination under general anesthesia. Highlighting of calcifications 75% by CT MRI examination. The prognosis of RB treated early is favorable with survival up to 80%. The unfavorable prognosis is related to the large tumor size, minimal cellular differentiation, optic nerve invasion, extrascleral extension. Treatment in RB must be early and appropriate: in small tumors, conservative treatment can be tried (judiciously) which is controversial. The important treatment is timely high section enucleation of the optic nerve. Palliative treatment is indicated in the extended forms, with cerebral optic nerve invasion, metastases with: chemotherapy treatment (carboplatin, etoposide, vincristine), consolidated with laser photocoagulation, cryotherapy, brachytherapy, exenteration if necessary. RB is a serious disease occurring in children of 1-3 years old, in whom diagnosis must be made early, and then the treatment appropriate to the stage of evolution should be applied.

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