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Retinoblastoma: Evolving Concepts and Future Challenges

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Abstract

Retinoblastoma is the most common ocular malignancy in children. It results from mutations in the RB1 gene or from MYCN oncogene amplification. We distinguish between the more common unilateral form and the rarer bilateral form. It is important to note that bilateral retinoblastoma is always hereditary. The most common and characteristic symptom is the white pupillary reflex. In addition, the child may develop strabismus or heterochromia. Treatment methods vary, ranging from those aimed at salvaging the eye to those involving total enucleation. Prognosis depends on the location and stage of the tumor. This review aims to explore the literature on new therapeutic methods and recent discoveries in the field of retinoblastoma.

Keywords: retinoblastoma, heterochromia

Introduction

Retinoblastoma is the most common malignant intraocular tumor in children. It is caused by a mutation in the RB1 gene. [1] [2]. This tumor occurs with a frequency of 1 in 17,000 live births. It is hereditary in about 1/3 of cases, while the remaining 2/3 are spontaneous tumors. Retinoblastoma arises due to the damage of both alleles of the Rb tumor suppressor gene. It should also be noted that the RB1 gene consists of 27 exons, containing 183 kilobases of genomic DNA, encoding a phosphoprotein that acts as a cell cycle regulator, with activity dependent on the level of phosphorylation. The hypophosphorylated form of pRb binds transcription factors, causing the cell cycle to be arrested at the G1 checkpoint. In the case of retinoblastoma, we deal with the deactivation of the pRb protein due to deletions or mutations. The damaged protein prevents apoptosis and exit from the cell cycle, ultimately resulting in uncontrolled cell division and the formation of a tumor [3].

Epidemiology

In all populations, the incidence of retinoblastoma is virtually the same, approximately 1 in 17,000 live births. No significant difference in the incidence of retinoblastoma has been detected in any ethnic, geographic, or gender group. The majority of cases occur in Asia and Africa due to higher birth rates on these continents. Alarmingly high mortality rates are observed in low- and middle-income countries, ranging from 25-40% in South America and Asia (excluding Japan) to 70% in Africa. In contrast, mortality rates in Europe, Japan, and North America are at 4-5%. There are many reasons for these differences, including less accessible healthcare, poor nutrition during pregnancy, and high treatment costs. Additionally, the average age of diagnosis of retinoblastoma in Asia and Africa is much higher (unilateral: 26 months, bilateral: 20-22 months) compared to developed countries (unilateral: 24-27 months, bilateral: 13-15 months)[4]

Pathogenesis

RB1 is a large gene consisting of 27 exons. It encodes a 4.7 kb mRNA, which is then translated into a 928 amino acid protein, pRB. Many modifications, such as promoter methylation, point mutations, and small and large deletions, impair the function of pRB. Additionally, chromothripsis, also known as genomic region shattering, has been identified as the cause of some mutations. Most mutations that have the greatest impact on the gene's function are located in the A/B pocket region.[5]

pRB binds to E2F transcription factors to repress genes associated with cell proliferation. Hyperphosphorylation of pRB by cyclin-dependent kinases (CDKs) in response to mitogenic signals normally relieves this repression and promotes the transition from the G1 to S phase. When pRB is lost, the repression is relieved in the absence of mitogenic signals, allowing the cell to enter the cycle. It is tempting to hypothesize that pRB is primarily needed to suppress E2F transcription factors, and that the loss of this function may be the leading cause of retinoblastoma formation. [6]

Looking at the epigenome, we can conclude that DNA methylation, histone modification, RNA modification, and chromosome conformation are potential factors that lead to the development of retinoblastoma. pRB undergoes many post-translational modifications, such as phosphorylation, ubiquitination, acetylation, and methylation. These changes significantly affect the subcellular localization and molecular function of the protein. Depending on the sites involved in the phosphorylation process, different effects can occur, which in turn influence the interactions between E2F and pRB. This leads to pro-apoptotic changes, ultimately impacting cancer resistance. Ubiquitination, on the other hand, affects the proliferation of cancer cells by accelerating the degradation or proteasomal turnover of pRB. Acetylation and methylation play important roles in regulating the effect of pRB on the cell cycle and cell differentiation. [7]

Clinical Features

The first symptoms of retinoblastoma are typically leukocoria (a white reflex visible through the pupil) and strabismus (misalignment of the eyes). The most important factor in early detection of this cancer is raising awareness among as many people as possible about the initial signs of the disease.[6]. Unfortunately, in countries where awareness is low and access

to healthcare is more difficult, this cancer is often diagnosed too late. The most common late symptom is proptosis. Retinoblastoma can affect one or both eyes. [8]

Retinoblastoma is one of the few cancers that can be detected by people with no medical background because it is a visible tumor with distinct features. Parents of affected children now have access to increasingly innovative sources of information designed to educate them about early signs of the disease. For example, a smartphone application has been created that helps detect eye conditions, including retinoblastoma, at an early stage.

Retinoblastoma is diagnosed based on the clinical features of the tumor visible in the eyeball after pupil dilation. The diagnostic approach in this cancer differs from others, as no histopathological sample is taken, since it could lead to tumor seeding. [9]

In retinoblastoma, calcifications are often observed. These can be seen with the naked eye or detected by ultrasound. The calcifications in this cancer are dystrophic, meaning they occur in response to necrosis or tissue damage. They are more commonly observed in older patients or in more advanced tumors.

Growing retinoblastomas produce seeds that detach and adhere below the retina or float into the vitreous body. This is associated with a worse prognosis. Large tumors can detach and lift the retina, which may cause necrosis and significant inflammation.

Retinoblastoma can spread beyond the eye by crossing the retinal boundaries and entering the choroidal layer, reaching the blood supply. The tumor can also spread through the optic nerve, potentially reaching the brain.[10]

Diagnosis

The most important aspect of diagnostics is the early detection of cancer, which can help preserve the patient's vision. Retinoblastoma is often hereditary and caused by downregulation of the RB gene.[11] [12] Silencing of the RB gene results in a lack of cell cycle regulation, leading to uncontrolled cell proliferation and tumor formation. A higher incidence rate of retinoblastoma is observed in developing countries. In severe cases, ocular

inflammation may occur due to the external growth of the tumor. Retinoblastoma can metastasize to the brain, lungs, or spinal cord. Blood vessels in the choroid may also be infiltrated by cancerous cells.

The diagnosis of this cancer is most often made by an ophthalmologist. A whitish tumor causing damage to the retina and vitreous body is typically visible during fundoscopy. In young children, ultrasonography is used for diagnosis, as computed tomography (CT) is not recommended. Another diagnostic tool employed is magnetic resonance imaging (MRI) of the orbit and brain. Traditional optical examinations are not effective for diagnosing this type of cancer.

With advancements in medicine, new diagnostic methods have been developed to detect retinoblastoma at an early stage. Nanotechnology offers molecular contrast agents and nanomaterials that enable earlier and more precise detection of retinoblastoma. Currently, numerous studies are underway to explore their use in diagnosing this cancer. [13].

We cannot forget that parental vigilance is also crucial. The primary symptom of retinoblastoma, leukocoria, can actually be detected using a mobile phone. It’s worth noting that there is now an app called "White Eye Detector," designed specifically to detect leukocoria. Using the cover test, a doctor can detect strabismus, which also often coexists with this cancer. Regular screening examinations are necessary for children with a positive family history of retinoblastoma. Offspring and siblings of patients with retinoblastoma require regular check-ups unless genetic testing has ruled out an RB gene mutation.

Currently, many techniques are available to precisely diagnose this cancer. PCR testing identifies exon deletions in chromosome 13 in patients whose parents carry the RB1 gene mutation. Fluorescein angiography is a technique in which a small amount of fluorescein material is injected into the patient’s bloodstream. This material reaches the ophthalmic artery, and then a specialized camera takes images of the eye. Importantly, for many years, attempts were made to diagnose retinoblastoma using PET scans. However, it was ultimately concluded that this method does not offer an advantage over other available techniques and is associated with significantly greater complications. For this reason, PET is no longer used. Currently, MRI is the gold standard for diagnostic imaging. [14]

Staging

In the era when radiotherapy was the main treatment for retinoblastoma, the staging of the disease was based on the predicted response to this treatment. When chemotherapy emerged, the International Intraocular Retinoblastoma Classification (IIRC) was developed. This system is based on the natural progression of the disease, both for small tumors located away from the macula and for larger, central tumors. Like other cancers, retinoblastoma can also be staged using the TNM system. In this system, each eye is considered separately, and the stage of the disease is determined based on the eye in which the tumor is more advanced. The latest TNM classification for retinoblastoma also includes a new parameter, "H," which corresponds to a hereditary trait that can lead to multifocal tumors that may localize in both eyes and the brain. [15].

Currently, retinoblastoma is classified according to the International Intraocular Retinoblastoma Classification. According to this classification, retinoblastoma can be divided into 5 groups:

Group A: A small tumor confined to the retina, with the largest dimension not exceeding 3 mm. Located more than 3 mm from the fovea and 1.5 mm from the optic disc.

Group B: A tumor larger than 3 mm, located 3 mm or less from the fovea and less than 1.5 mm from the optic disc. This group also includes tumors with subretinal fluid less than 3 mm from the tumor margin.

Group C: A tumor with seeding, which can be subretinal within 3 mm of the main tumor mass, vitreous seeding located < 3 mm from the main tumor, or both vitreous and subretinal seeding.

Group D: Extensive seeding, which may be subretinal > 3 mm from the tumor, vitreous seeding > 3 mm from the tumor, or both at once.

Group E: An extensive tumor occupying more than 50% of the eye socket. It may be accompanied by neovascular glaucoma, opacification caused by hemorrhage from the vitreous,

anterior chamber, or subretinal space. This group also includes tumors with invasion of the optic nerve, orbit, sclera, or choroid.[3]

Treatment

Retinoblastoma, in its natural course, is a fatal disease. If left untreated, it leads to death within a maximum of 2 years; however, with appropriate and effective treatment, the survival rate increases to 95%. [16] Treating a child with retinoblastoma requires finding a balance between saving the child's life and preserving the eye. Enucleation, along with segmental removal of the optic nerve, is an effective treatment method for approximately 85% of children with the non-hereditary form of retinoblastoma limited to one eye and without extraocular disease. As for conservative methods, intravenous chemotherapy, transpupillary thermotherapy, laser therapy, cryotherapy, brachytherapy, external beam radiotherapy, and local chemotherapy (administered subconjunctivally with carboplatin, intravitreally with melphalan, or intra-arterially) are available. Intravenous chemotherapy is used for bilateral retinoblastoma, extraocular disease, and also for intraocular disease to avoid enucleation. In this case, intravenous chemotherapy is combined with aggressive local therapies. [17] The drugs used in the treatment of retinoblastoma include carboplatin, etoposide, cyclophosphamide, doxorubicin, vincristine, and ifosfamide. The most commonly used combination is carboplatin, vincristine, and etoposide. Carboplatin is the main drug due to its ability to achieve high concentrations in the vitreous humor and cerebrospinal fluid. High-risk retinoblastoma causes metastasis in about 25% of patients if treated without systemic chemotherapy, compared to only 4% of those who receive it.

New Treatment

Among the new treatment methods for retinoblastoma, the use of melphalan in monotherapy has proven effective. Synthetically modified melphalan derivatives exhibit increased cytotoxicity. In the thermotherapy model, some derivatives show a greater increase in cytotoxicity with rising temperature. The effectiveness of retinoblastoma treatment may be

enhanced by modifying melphalan with perfluorinated chains of varying lengths, linked by an ester bond. This modification results in fewer side effects. [18]

Conclusion

Retinoblastoma, though rare, is the most prevalent intraocular malignancy in children and represents a model disease for understanding tumor genetics, early diagnosis, and evolving treatment strategies. Its development is strongly linked to mutations in the *RB1* gene or amplification of the *MYCN* oncogene, with bilateral cases always indicating a hereditary pattern. The disease's hallmark clinical feature, leukocoria, allows for potential early detection, even by non-specialists, highlighting the critical role of public awareness and parental vigilance in timely diagnosis. Despite similar incidence rates worldwide, significant disparities in survival persist, largely due to differences in healthcare access, awareness, and diagnostic infrastructure.

Advancements in imaging, including MRI and ultrasonography, along with genetic testing and emerging nanotechnologies, have enabled earlier and more precise diagnoses. Treatment has evolved significantly from primarily enucleation and radiotherapy to include eye-sparing methods such as systemic and local chemotherapy, thermotherapy, cryotherapy, and brachytherapy. In particular, the development of intra-arterial and intravitreal chemotherapy has revolutionized the management of advanced intraocular disease, offering improved ocular outcomes and reduced systemic toxicity.[19]

New therapeutic avenues, such as modified melphalan derivatives and nanomedicine-based drug delivery systems, promise enhanced efficacy and reduced side effects. [20] Ongoing research is focused on improving drug targeting, minimizing invasiveness, and preserving vision without compromising survival. To further improve outcomes, especially in low- and middle-income countries, global efforts must prioritize early detection programs, education, and equitable access to advanced diagnostics and treatment. Retinoblastoma serves not only as a clinical challenge but also as a powerful reminder of how early genetic insight and multidisciplinary care can transform a once-lethal disease into one with high cure rates and preserved quality of life.

DISCLOSURE

Author's contribution

Conceptualization: Mateusz Wiekiera, Adrianna Jasiuk, Natalia Madeja, Emilia Kowalczyk Martyna Niemczuk, Sylwia Koziej; methodology: Mateusz Wiekiera, Adrianna Jasiuk Natalia Madeja, Emilia Kowalczyk, Martyna Niemczuk, Sylwia Koziej; software: Mateusz Wiekiera, Adrianna Jasiuk, Natalia Madeja, Emilia Kowalczyk; formal analysis: Martyna Niemczuk, Natalia Madeja, Sylwia Koziej; investigation: Mateusz Wiekiera, Adrianna Jasiuk, Natalia Madeja, Emilia Kowlaczyk, Martyna Niemczuk Sylwia Koziej; resources: Mateusz Wiekiera, Adrianna Jasiuk; data curation: Sylwia Koziej, Martyna Niemczuk; writing - rough preparation: Natalia Madeja, Emilia Kowalczyk; writing - review and editing: Mateusz Wiekiera, Adrianna Jasiuk, Martyna Niemczuk, Natalia Madeja, Sylwia Koziej, Emilia Kowalczyk; visualization: Mateusz Wiekiera; supervision: Mateusz Wiekiera, Adrianna Jasiuk; project administration: Mateusz Wiekiera.

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