Budny Agnieszka, Grochowski Cezary. Retinoblastoma. Journal of Education, Health and Sport. 2018;8(7):204-213. eISNN 2391-8306. DOI
http://dx.doi.org/10.5281/zenodo.1299573
http://ojs.ukw.edu.pl/index.php/johs/article/view/5611

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.05.2018. Revised: 18.05.2018. Accepted: 28.06.2018.

Retinoblastoma

Agnieszka Budny[1], Cezary Grochowski[2]

[1]Radiotherapy Department, St. John's Cancer Center, Lublin, Poland

[2]Neurosurgery and Pediatric Neurosurgery Department, Medical University of Lublin, Poland

Introduction

Retinoblastoma is a tumor originating from the nuclear layer of the primary retinal photoreceptor cells, genetically determined. It develops due to a mutation in chromosome 13 in the q14 band. It is the most common, originally malignant intraocular change in childhood and accounts for 10-15% of cancer cases occurring in the first year of life [1]. Usually this cancer manifests itself as a leukocoria in a child under two years of age. In a congenital form, it can be multifocal, on both sides, and the risk of secondary cancers should also be taken into account. Diagnosis of retinoblastoma requires indirect ophthalmoscopy and research using imaging diagnostics techniques: ultrasonography (USG), magnetic resonance imaging (MRI) or computed tomography (CT). If left untreated, it leads to metastasis and death of the child. With the advancement of medicine, survival with modern treatment methods is> 95%. More and more often it is possible to save the mutant eye enucleation surgery. Immediate referral to an ophthalmologist's oncologist and proper management by an interdisciplinary team are necessary to optimize the visual effect and survival [2].

Epidemiology

Retinoblastoma is a rare disease among children, constituting in them no more than 1% of all cancers. The incidence decreases with age, and most cases are diagnosed before 4 years of age. The incidence of the disease is estimated at 1:15 000 - 20,000 live births [3]. The Polish clinical record from 2004 specifies the incidence rate at 3.7: 1,000,000 children before 14 years of age [4]. This epidemiological data was consistent with the incidence of this type of cancer among the American population in the years 1990 - 1995, where among children under 15 years of age. there were 4 cases per million per year [5]. In older children, retinoblastoma occurs sporadically, and in adolescents and adults it is practically not manifested. Boys suffer slightly more often than girls (1.5: 1). Diagnosis is most often established at the time of birth, 80% of cases are detected up to 3-4 years of age. The median age at the time of diagnosis is 2 years. About 1/3 of cases are conditionally hereditary, and the tumor manifests itself by binaries in about 60% of them. A binocular form, usually detected in infancy, is diagnosed earlier than one-year, and changes in one eye may precede their appearance in the second eye for a few months. When diagnosing retinoblastoma, especially its congenital form, one should take into account the possibility of congenital malformations, especially on the part of the vascular and cardiac systems, bone, facial changes, or mental retardation. Due to the high cure rate currently in place, a tendency is assumed to increase in the offspring of ill people in the past.

Etiology and pathogenesis

Retinoblastoma was the first cancer for which the influence of genetic factors on the development of the disease has been proven. The pathogenesis of this disease has become a model example of the role of suppressor genes in carcinogenesis and has demonstrated the key role of the RB1 gene as a regulatory factor in the cell cycle that is also involved in the formation of other cancers. Retinoblastomas can occur both in the family as well as sporadic tumors. Taking into account the sporadic and familial occurrence of the disease, Alfred Knudson in 1971 proposed the famous hypothesis "two hits" [6]. Retinoblastoma is a cancer associated with a mutation in the RB1 anti-tumor encoding the retinoblastoma protein found on chromosome 13 (13q14). For the disease to appear, it is necessary to have mutations of both alleles ("two strokes"). Both normal alleles located in the RB locus must be inactivated. About 40% of tumors are the result of mutations in the RB1 gene in germline cells, which is why they are hereditary. In family cases, children inherit one damaged copy of the RB gene in the germline, the second copy is correct. Retinoblastoma arises when the second, normal RB gene is lost in retinoblasts as a result of the somatic mutation. In these cases, a single somatic mutation, most often a deletion at the 13q14 locus, is enough to develop the disease, which is why family transmission is an autosomal dominant inheritance. Family cases are

characterized by the presence of numerous tumors located bilaterally, although monofocal and unilateral tumors are quite common, and develop at an earlier age than non-hereditary cases [7]. The hereditary form, through autosomal dominant inheritance, shows 90% penetration (15% of monocular and 25% binomial). The mutation in the RB1 gene may also be associated with other types of cancer, including breast cancer, small cell lung cancer and bladder cancer [8,9]. Among the carriers of germinal mutations, the total risk of developing a second primary tumor to 40 r. is around 40%. Patients with familial retinoblastoma have a higher risk of developing osteosarcoma (osteosarcoma) and some types of soft tissue sarcoma. Osteosarcoma is found in about 13% of patients with retinoblastoma, including 70% in the irradiation field [10]. The incidence of secondary cancers in the case of the use of teleradiotherapy before the first year of life may increase up to approximately 10% to 10 years and 30% to 30 years [11]. Often, there is a development of a three-sided retinoblastoma in which tumors occur in both eyeballs as well as in the pineal gland or periairculatory area. Szyżyniak is a neuroectodermal tumor resembling a low-differentiated retinoblastoma tumor. Such a trilateral form is usually diagnosed up to 5 years of age or most frequently within 22 months of diagnosing the tumor in the eye [12]. Most tumors are sporadic in nature and are the result of mutations in the RB1 gene within somatic cells. All sporadic, non-hereditary tumors are monofocal and occur unilaterally. They appear much later than a hereditary cancer. The probability of developing retinoblastoma in the offspring of a cured patient, with a positive family history, or treated for sporadic binocular, when the mutations concern reproductive cells, is as much as 50%. In the case of the unilateral one-year mutation, the reproductive cell mutation reaches 10-20% of cases, hence the risk of disease in the offspring is 7-10%, and the risk of sibling another 3% siblings and decreases gradually with the birth of the next healthy child. One should remember about the need for meticulous ophthalmological examination in each of these children and about the genetic counseling of the families of patients.

Clinical picture

The diagnosis of cancer most often occurs in 2nd year, although it can be detected already at the moment of the child's birth - in the majority of cases the first symptoms of the disease occur in the first year of life. Sometimes retinoblastoma is long asymptomatic. In the non-hereditary form, neoplastic changes may occur up to the age of 5. The most common clinical symptoms that allow suspicion of retinoblastoma are a white reflex from the fundus (otherwise known as leukocoria) and squinting. Leukokoria, or white pupillary reflex (so-called "cat's" eyesight), arises as a result of retinal masses of the retinoblastoma through the pupil. Initially, when the tumor is small, the leukocoria is visible only at a certain angle of view, and when the tumor grows can be a permanent symptom. The presence of strabismus along with visual disturbances indicates that the neoplastic lesions occupy the

macula and the child lost the central vision ability. As a result of macular changes in both eyes, nystagmus may appear. Quite often, they also accompany such symptoms as: redness, tenderness and pain of the eyeball caused by secondary superinfection, choroidal inflammation of the eye or bleeding into the eye chamber. Other ailments are rare and are characteristic of advanced retinoblastomas (glaucoma, differences in the color of the iris of both eyes, the occurrence of white tumor cells in the anterior chamber of the eye, unilateral dilation of the pupil). Different color of the iris is caused by the development of vessels in the iris (the so-called neovascularization) as a result of secretion of angiogenesis factors by the retinoblastoma. The superficial development of these pathological vessels on the iris can be manifested by nodules that, when bleeding, cause the hematoma of the anterior chamber of the eyeball. In some low-developed countries, where the diagnosis of disease is usually made late, exophthalmos is a secondary symptom suggesting the involvement of orbital tissue [13]. A disseminated form, including tripartic retinoblastoma with symptoms of skull metastases (such as headache, nausea, vomiting), and metastases to the lungs, bones, bone marrow, or meninges, can only be diagnosed at the time of diagnosis.

Natural course

Retinoblastoma develops very rapidly, therefore the main criterion for improving prognosis is early diagnosis and initiation of treatment. Usually, within a few weeks, the retina is completely destroyed and the tumor spreads rapidly within the eye. The local spread can be done by detaching the cells from the main mass of the tumor and growing independently around it. Further tumor growth, beyond the retina, can occur in two basic directions: exophytic towards the subretinal space or endophytic towards the vitreous. Such proliferation within the vitreous body is associated with the danger of misdiagnosis of the inflammatory process, and some of the cells may enter the anterior chamber to form pseudoarthrosis or iris nodules. The exophytic tumor causes secondary retinal detachment, and in very advanced cases behind the lens there are visible islands of high retinal retina and white translucent tumor masses. Occupation of the uveitis with the uterus accelerates its intraocular spread and increases the risk of distant metastases. The propagation of the tumor inside the sclera occurs through the continuity of the choroid or along the vessels passing through it. In the case of optic infiltration, there is a risk of spreading beyond the eyeball into the subarachnoid space. The most well-known are metastases to the central nervous system, skull, bone marrow, peripheral bones and lymph nodes, primarily from the pre-buckling, submandibular and cervical groups. A single tumor is characteristic of sporadic retinoblastoma, and multifocal changes are typically in the form of an inherited retinoblastoma. Multifocal disease can affect only one eye or tumors can arise binocularly. Their appearance can be synchronous, that is, simultaneous or metachronic, when in subsequent

studies we find new focuses of retinoblastoma. Sometimes spontaneous tumor regression occurs and in those patients in the presence of a tumor in the family, this means that there is no increased risk of osteosarcoma or other soft tissue cancers.

Diagnostic methods

The basic diagnostic test, performed immediately after the appearance of any suspected retinoblastoma in a child, is ophthalmoscopy. Ophthalmologic examination is performed under general anesthesia after pupil dilation, which allows you to accurately visualize and examine the retina. The intraocular pressure is measured, the protective device of the eye and the anterior segment of the eyeball assessed in the operating microscope. Pathognomic for retinoblastoma is the finding of pale pink masses with vessels forming on their surface. The whitish avascular mass is also found. Cancer has a tendency to create regular nodules, often with satellite limbs. During the test, the number and size of tumors, their position relative to the macula and optic disc should be determined, whether fluid has accumulated under the retina and whether it has spread to the vitreous or under the retina. It should be emphasized that performing diagnostic biopsies in the case of suspected retinoblastoma is contraindicated, and the final diagnosis can be made after removal of the eyeball and histopathological verification. In microscopic examination, these tumors are composed of undifferentiated, fine, round cells, with large hyperchromatic nuclei and a small amount of cytoplasm, corresponding to undifferentiated retinoblasts. A characteristic feature of the retinal histopathology is the Flexner-Wintersteiner rosette, although it can also be seen in cervix and medulloblastoma. The examination supplementing the diagnostics is the ultrasound (USG) of the eyeball assessing the size or location of the tumor, internal features of the tumor (including the presence of calcifications) and possible extra-ocular propagation. In cases of doubt, imaging tests such as computed tomography (CT) or magnetic resonance imaging (MRI) are recommended, which reveal the extent of lesions by detecting neoplastic infiltrations outside the eyeball and metastases [14]. Both ultrasound and computed tomography reveal tumor-specific calcifications characteristic of retinoblastoma. Magnetic resonance, although it does not show calcification within the tumor, is necessary to confirm the presence of a trilobular retinoblastoma. MRI enables detection of precise changes in the optic nerve, subarachnoid metastases and inside the skull. In cases of justified suspicion of metastasis, bone marrow puncture, cerebrospinal fluid (pleocytosis, cytological assessment) and bone scintigraphy are performed [7]. In order to diagnose the form of the disease, a genetic test for the presence of mutations in the RB1 suppressor gene should be performed and the examination of siblings and parents [15].

Differential diagnosis

Many disease entities may imitate the intraocular retina. The most common confirmation of retinopathy requires the exclusion of: Coats, parasitic toxocarosis, retinopathy of premature babies (ROP), persistent hyperplastic primary vitreous (PHPV), familial exudative vitreoretinopathy, congenital cataract, retina dysplasia (associated with Norris disease, Patau syndrome, Edwards, Walker, Warburg), hamartoma, choroidal fissure, astrocytoma, juvenile delamination of the retina, medulloepitheliomy, or congenital glaucoma. PHPV is characterized by the coexistence of cataracts, microvessels and the presence of fibrous vascular tissue in the eye stromal region. These changes cause the appearance of the white pupil symptom - leukocoria. In Coats' disease, abnormal, telangiectically dilated vessels with increased wall permeability are observed, resulting in intra and subretinal lipid exudates. It is more common in boys, generally before 10 years of age. Coats disease in advanced cases can cause retinal detachment and leukocorrosis. The cause of toxocarosis are Nematodes Toksocara canis parasitizing in the gastrointestinal tract of dogs. Nematodes cause the formation of granulomas in the posterior pole of the retina and inflammation of the inside of the eyeball. The average age of patients with this zoonotic disease is about 7-8 years. The clinical picture of granulomas may resemble retinoblastoma, and the inflammation of the inside of the eyeball is a type of tumor growth. ROP is more likely to develop in high-risk premature babies - born before 28 weeks of gestation and with birth weight less than 1500g. Premature delivery leads to inhibition of normal vessel development and fibrotic proliferation. The disease is multistep, the initial stages may be self-regressive, or it may occur after laser therapy. In advanced stages, retinal detachment occurs, which is the cause of the white pupil symptom. Before the final diagnosis of the retinoblastoma, the doctor has to take into account numerous other diseases that cause similar symptoms.

Classification

Every case of retinoblastoma should first be carefully assessed before choosing the right treatment. The most common are two classifications of retinoblastoma: historically according to Reese-Ellsworth and the newer International Classification of Intraocular Retinoblastoma. The Reese-Elsworth classification, valid for many years, was developed in 1963 for the purpose of evaluating the ocular prevalence after using external beam irradiation. It takes into account the size, location, number of intraocular tumors and the dissemination of tumor cells in the vitreous. The Reese-Ellsworth classification is shown in Table 1. After the introduction of chemotherapy for treatment of retinoblastoma, it was replaced by the International Classification of Retinoblastoma, which emphasizes the dissemination of tumor cells into the vitreous and under the retina. It also takes into account the size and location of tumors and, most importantly, indicates the prognosis for the patient

using chemotherapy and laser phototherapy. Table 2 presents this classification. It is recommended to use this classification for a locally restricted tumor. If metastases occur, the current TNM classification should be followed to ensure optimal therapy (Table 3).

Treatment

Retinoblastoma therapy must be adapted to the individual patient. The main goal is to save the patient's life, and only then to save the busy eye, save sight or prevent the development of secondary cancers. Until a few decades ago, the only effective method of treating retinoblastoma was the removal of the eyeball - enucleation. Introduction of new methods, such as radiotherapy or chemotherapy, radically changed the treatment of retinoblastoma and prognosis for the patient. Modern medicine not only allows the eyeball to be preserved, but often also good vision. Currently, two methods of retinoblastoma treatment are used: general and local. Speaking of general treatment, we mean chemotherapy, i.e. intravenous anticancer drugs. Local methods include: cryotherapy, laser photocoagulation, brachytherapy, teleradiotherapy, local chemotherapy and, unfortunately, often necessary, enucleation. Enucleation is currently used in the case of a large advancement of the retinoblastoma with infiltration into the orbital structures. It is important to provide an eye prosthesis after the procedure - not only for mental comfort, but also for the even development of the eye socket in the growing child, in order to ensure symmetry of the entire facial skeleton [16]. Topical treatment can be used as primary or associated with prior chemistry-reduction. Primary treatment without chemotherapy is reserved for small group A tumors and involves photocoagulation or cryotherapy. In most cases, treatment starts with chemotherapy aimed at reducing tumor mass under the influence of strong chemotherapeutics (so-called chemotherapy of cancer). Induction chemotherapy is the main treatment for B, C and D tumors. The therapy consists of 6-10 cycles of vincristine, carboplatin and etoposide (VEC regimen) every 3 weeks. In order to prevent the development of drug resistance, the patient may be additionally given cyclosporin A. Then, various local treatments are considered to completely destroy the remaining cancer cells after induction chemotherapy and to obtain a permanent regression of the retinoblastoma. In the case of advanced tumors (found on the basis of imaging tests) and in cases of disseminated disease, chemotherapy is absolutely recommended. Unfortunately, systemic treatment is often associated with serious side effects, such as neutropenic fever, weakened internal immunity and susceptibility to infection, ototoxicity and neurotoxicity [17,18,19]. In order to prevent these undesirable consequences, attempts are being made to administer chemotherapeutic agents locally, e.g. by injecting carboplatin or subconjunctival topotecan, into the Tenon's capsule, intravitreal injections or administration of melphalan with topotecan and carboplatin directly into the ophthalmic artery [20]. After using retinal mass chemotherapy you can use the local

treatment method preferred by the center. Retinoblastoma cells are susceptible to ionizing radiation, however, teleradiotherapy, i.e. radiation from external fields, has now been practically displaced from retinoblastoma treatment schemes due to numerous complications. However, its effectiveness is estimated at around 85%. Local side effects include: dry eye syndrome, keratinization of the cornea, corneal ulcers, cataracts, glaucoma, vitreous hemorrhage, retinal detachment or also hypoplasia of the eye socket [3]. In the hereditary form of retinoblastoma, the use of teleradiotherapy significantly increased the risk of secondary tumors [21]. Currently, an alternative method of irradiation is more readily used, e.g. brachytherapy or proton radiotherapy. Brachytherapy, or contact radiotherapy, is more commonly used because of the lower risk of side effects. It consists in patching the applicators with a radioactive element, mainly 131I, 125I or 106Ru. The dose for the tumor top recommended for retinoblastoma is 45Gy [22]. The distribution of proton radiation is more beneficial than in the case of photons. Most of the dose accumulates in the depths of the tumor tissue, while saving the surrounding orbital tissue, and therefore is associated with fewer side effects of the therapy [23]. Another method of local treatment is laser therapy. The oldest method classified in this group is laser photocoagulation, currently replaced by transcriptional laser therapy (TTT) [24]. Photocoagulation involves the use of laser light to warm the tumor tissue to temperatures above 65 ° C. For this purpose, argon laser length 532 nm or diode 810 nm is used. Intra-thermotherapy involves direct destruction of tumor masses by heating its tissues with a diode laser light of 810 nm. Indications for cryotherapy, due to the technique of implementation, are tumors located in the peripheral front part of the retina. Cryotherapy works by mechanically damaging cell membranes through crystals of forming ice - during the procedure the tumor is exposed to a temperature of -60 to -80 ° C, which causes cell krionekrozę. The choice of the local treatment method depends on the severity of the disease, the experience of the given treatment facility and preferences of the patient himself.

Summary

Retinoblastoma is currently a curable disease in about 95% of children. It is extremely important to quickly diagnose and implement treatment in order to prevent distant metastases that dramatically worsen the survival. Covering the patient and his family with genetic counseling is part of the algorithm for dealing with this type of cancer. Further regular check-ups with the oncologist are necessary due to the increased risk of secondary cancers.

References:

1. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2012 (Accessed on March 30, 2016).
2. Dimaras H, Kimani K, Dimba EAO, Gronsdahl P, White A. et al: Retinoblastoma. Lancet 2012; 379: 1436–1446.
3. Ray A, Gombos DS, Vats TS: Retinoblastoma: An overview. Indian J Pediatr. 2012; 79: 916–921.
4. Perek D. Nowotwory lite. W: Pediatria. Kawalec W, Grenda R, Ziółkowska H, PZWL 2014 s.646
5. Young J.L., Smith M.A., Roffers S.D. i in. *Retinoblastoma*. W: *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program, 1975-1995*, Ries L.A., Smith M.A., Gurney J.G. i in., National Cancer Institute, Bethesda, Maryland 1999. s. 73.
6. Knudson A. *Mutation and cancer: statistical study of retinoblastoma*. „Proc Natl Acad Sci U S A". 68. 4, s. 820-823, 1971. PMID: 5279523.
7. Kaliki S, Shields CL, Rojanaporn D, et al.: High-risk retinoblastoma based on international classification of retinoblastoma: analysis of 519 enucleated eyes. Ophthalmology 120 (5): 997-1003, 2013.]
8. Fletcher O, Easton D, Anderson K, et al.: Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 96 (5): 357-63, 2004. [PUBMED Abstract]
9. Marees T, van Leeuwen FE, de Boer MR, et al.: Cancer mortality in long-term survivors of retinoblastoma. Eur J Cancer 45 (18): 3245-53, 2009.
10. Kleinerman RA, Tucker MA, Abramson DH, et al.: Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 99 (1): 24-31, 2007.
11. Shinohara ET, DeWees T, Perkins SM: Subsequent malignancies and their effect on survival in patients with retinoblastoma. Pediatr Blood Cancer 61 (1): 116-9, 2014
12. de Jong MC, Kors WA, de Graaf P, et al.: Trilateral retinoblastoma: a systematic review and meta-analysis. Lancet Oncol 15 (10): 1157-67, 2014.
13. Truong B, Green AL, Friedrich P, et al.: Ethnic, Racial, and Socioeconomic Disparities in Retinoblastoma. JAMA Pediatr 169 (12): 1096-104, 2015.]
14. Khurana A, Eisenhut CA, Wan W, et al.: Comparison of the diagnostic value of MR imaging and ophthalmoscopy for the staging of retinoblastoma. Eur Radiol 23 (5): 1271-80, 2013.]

15. Richter S, Vandezande K, Chen N, et al.: Sensitive and efficient detection of RB1 gene mutations enhances care for families with retinoblastoma. Am J Hum Genet 72 (2): 253-69, 2003.
16. Chojniak MM, Chojniak R, Testa ML, et al.: Abnormal orbital growth in children submitted to enucleation for retinoblastoma treatment. J Pediatr Hematol Oncol 34 (3): e102-5, 2012.
17. Lambert MP, Shields C, Meadows AT: A retrospective review of hearing in children with retinoblastoma treated with carboplatin-based chemotherapy. Pediatr Blood Cancer 50 (2): 223-6, 2008.
18. Batra A, Thakar A, Bakhshi S: Ototoxicity in retinoblastoma survivors treated with carboplatin based chemotherapy: A cross-sectional study of 116 patients. Pediatr Blood Cancer 62 (11): 2060, 2015.
19. Qaddoumi I, Bass JK, Wu J, et al.: Carboplatin-associated ototoxicity in children with retinoblastoma. J Clin Oncol 30 (10): 1034-41, 2012.
20. Jabbour P, Chalouhi N, Tjoumakaris S, Gonzalez LF, Dumont AS. et al: Pearls and pitfalls of intraarterial chemotherapy for retinoblastoma. J Neurosurg Pediatrics 2012; 10: 175–181.
21. Sethi RV, Shih HA, Yeap BY, et al.: Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer 120 (1): 126-33, 2014.
22. Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B: Plaque radiotherapy for retinoblastoma—Long-term tumor control and treatment complications in 208
23. Krengli M. Hug EB, Adams JA et al. Proton radiation therapy for retinoblastoma: comparison of various intraocular tumor locations and beam arrangements. Int J Radiat Oncol Biol Phys 2005; 61: 583-593
24. Shields CL, Santos C, Diniz W, Gündüz K, Mercado G. et al: Thermotherapy for retinoblastoma. Arch Ophthalmol. 1999; 117: 885–893.