CLINICAL CHARACTERISTICS AND DIFFERENTIAL DIAGNOSIS OF RETINOBLASTOMA

The purpose of our work was to analyze the clinical presentation of patients with retinoblastoma who were admitted to ocular oncology department on different stages of the neoplastic process. There were hospitalized 369 children with diagnosis of retinoblastoma to ocular oncology department of National Oncology Center of Uzbekistan between 2001 and 2011, on age from 1 month to 11 years. We have analyzed the case reports and outpatient clinical records of these patients. Taking into account the variability of clinical presentation the early case finding, examination and adequate treatment of patients with retinoblastoma is a pressing challenge. That is why it has to be performed in big centers with available modern equipment and qualified specialists, who can adequately interpret the examination results and timely perform the necessary treatment.

Keywords: Malignant tumor of eye, retinoblastoma, leukocoria, frequency

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Introduction

Retinoblastoma is a rare malignant tumor. If in 60s of the previous century the incidence of it was 1 per 40000 newborns, according to data of the most of authors nowadays it is increased several times - 1 per 10000-15000 newborns (Brovkina, 2005; Panteleyeva, 1997; Saakyan, 2005; Shields and Shields, 2004). In this connection Kivela (2009) proposes to call it not rare, but frequent pediatric tumor. Retinoblastoma develops from immature retinal cells of eye, and is found in children from 0 to 5 years old, after 5 years it is a rare case (Brovkina, 2005; Wallach, Balmer et al., 2006; Seregard, Lundell et al., 2004). But, as mentioned by Brovkina (2005), lately retinoblastoma tends to become older, which means it is more frequently found in the age after 5. According to some authors the course of retinoblastoma in older children is different (Saakyan, 2005). Retinoblastoma is extremely rare case in adults; there are only few cases described in literature (Biswa, Mani et al., 2000).

The main symptom, according to the most of sources, is the white glow of pupil - leukocoria (Brovkina, 2005; Panteleyeva, 1997; Saakyan, 2005). In other way this symptom is called “cat’s eye”. It should be mentioned, that retinoblastoma has also other symptoms, which are unknown to the most of ophthalmologists. Some authors call them rare symptoms, because they do not appear when the tumor is found at early stage and adequately treated (Saakyan, 2005). In case of incorrect diagnostics and late referral these symptoms slowly start to appear. The tumor growing in the eye on its different stages simulate, or, in other words, mask under many diseases of eye in children (Català-Mora, Parareda-Salles et al., 2009).

The purpose of our work was to analyze the clinical presentation of patients with retinoblastoma admitted to ocular oncology department on different stages of the neoplastic process.

Materials and methods

There were hospitalized 369 children with diagnosis of retinoblastoma to ocular oncology department of National Oncology Center of Uzbekistan between 2001 and 2011. The age
of patients varied from 1 month to 11 years. We have analyzed the case reports and outpatient clinical records of these patients.

All patients admitted to the hospital are examined according to the diagnostic standards adopted in our clinic. All patients were examination using the following methods: external examination of the eye, ophthalmoscopy (OS-250), biomicroscopy (XCEL-300 SL), visual acuity test (if the patient is older than 3 years), ultrasound examination, CT. Currently there is performed also ultrasound Doppler sonography (VOLUSON-730pro).

Results

In the result of complex examination of 369 patients, in 55(14%) out of them the retinoblastoma diagnosis was not confirmed, although all of them were hospitalized with symptoms similar to retinoblastoma. There are made the following diagnoses and the patients are forwarded to pediatric ophthalmologists: Coats retinitis - 7(2%), retrolental fibroplasia - 5 (1.3%), fibrosis of vitreous body - 9 (2.4%), uveitis - 6 (1.6%), endophthalmitis - 3 (0.8%), retinal detachment - 3 (0.8%), coloboma of choroid - 3 (0.8%), congenital glaucoma - 6 (1.6%), secondary glaucoma - 7 (2%), residual artery hyaloidea - 2 (0.5%), haemophthalma - 3 (0.8%), phthisis bulbi - 1 (0.3%).

Out of 314 patients with confirmed retinoblastoma there were 169 (53.8%) boys and 145 (46.2%) girls. At the moment of referral to us and making the diagnosis there were 63 children under 1 year old (18.6%), 75 patients from 2 to 3 years old (23.5%), 58 patients (18.6%) from 3 to 4 years old, 42 patients from 4 to 6 years (13.7%), and 18 patients (6%) at the age between 6 and 11 years old.

There were 243 patients (77.4%) with unilateral retinoblastoma, total number of eyes affected - 385. There were 109 (37.8%) patients with affected right eye and 114 (39.5%) - left eye.

Out of 314 patients 300 were inhabitants of different regions of the Republic. Urban residents have comprised 25.2%, rural area residents made 74.7% of patients. In total there were 14 patients (4.8%) from neighboring republics. They were residents of: Kazakhstan - 9, Turkmenistan - 3, Tajikistan - 2, Kyrgyzstan - 2. Amongst the 300 patients there were also representatives of other nationalities living in our republic: Tajiks - 6, Kazakhs - 5, Russians - 3, Turks - 2, Koreans - 2, Armenians - 1.

The frequency of retinoblastoma varied very much by years from 19 (2002) to 39 (2009) with trend to increase, in average there were 30 cases per year.

As the result of the examination of 314 patients (385 eyes) in 62 eyes (17.5%) there were revealed retinoblastoma at the stage T1N0M0. In 182 eyes (51%) there was diagnosed the stage T2N0M0. In 72 eyes (20.4%) there was stage T3N0M0 and in 32 eyes (9%) - stage T4N0M0. It should be mentioned, that in 3 cases (0.8 %) patients with stage T3 at admission had enlarged parotid lymphatic nodes, and in 25 cases (6.9%) with stage T4 there were metastases in parotid lymphatic nodes and brain. Tumors at stage T1 were mainly revealed in paired eyes in patients with bilateral retinoblastoma (60 eyes), only in 2 patients the stage T1 was diagnosed primarily in unilateral process.

There was found during history taking, that appealaability of patients to ocular oncologist after appearance of first symptoms varied widely. The time period passed after parents noticed first signs of retinoblastoma to the beginning of examination and adequate treatment varied from 1 week to 5 years. In 4 patients (1.4%) the signs of retinoblastoma - whitish reflex from pupil - were noticed immediately after birth, but they referred to ocular oncologist after 2, 6, 9 and 10 months correspondingly. Only in three cases (1%) the patients were brought to ocular oncologist in one week after appearance of the disease symptoms. In 138 patients (48%) there have passed from 1 up to 6 months from the date of revealing the symptoms to admission to hospital. In 108 patients (37%) it took from 6 months up to 1 year to be hospitalized. In 30 patients (10.4%) from 1 to 3 years passed
from the date of disease onset to hospitalization. In three patients (1%) 3 years passed before referral to ocular oncologist, in one patient (0.3%) 5 years passed from emergence of first symptoms to getting adequate treatment. In one patient (Sh-v, 7 years old), according to his parents, there were no any complaints and disease symptoms, while during examination there was revealed 1st stage bilateral retinoblastoma. He was twin brother of the patient with bilateral retinoblastoma who has been treated in our clinic.

It was also clarified from parents, that in overwhelming majority of cases - 235 (81.6%) - the first sign in the child that attracted their attention was whitish luminescence of pupil - leukocoria. In 29 cases (10.1%) parents first noticed the squint, and sometime later - whitish luminescence. In 19 cases (6.6%) only squint was noticed.

While examining patients in the hospital the external examination has been performed without putting to sleep, distracting the child’s attention in different ways. Examination of deep ocular media has been performed in line with standard practice under general anesthesia at maximal mydriasis medicamentosus.

As the result of examination in 133 patients (37.6%) there was found eye reddening with signs of uveitis, in 110 (31%) - varying degrees of eyeball enlargement with signs of secondary glaucoma, however in 7 patients (2%) the eye was shrunk and hypotonic. The cornea was enlarged in 89 patients (25%), edematous in 8 (2.2%), turbid in 6 patients (1.7%). There was hyphema in the aqueous humor of an anterior chamber in 18 patients (5.2%), pseudohypopyon was found in 16 (4.5%) patients, and in 6 cases (1.7%) anterior chamber was not visible due to non-transparency of cornea. The anterior chamber in 99 cases (28%) was shallow, in 12 cases (3.4%) - deep, in 24 cases (6.8%) was not within view. The iris in 34 cases (9.6%) had dilated neogenic vessels - rubeosis, in 17 cases (4.8%) it was dichromatic, in 16 cases (4.5%) - atrophic. The pupil in 131 cases (37.1%) was dilated and did not react to light - mydriasis. The cavity of eyeball in 112 cases (31.7%) was completely filled with the tumor, in 114 cases (32.3%) for half; in 16 cases (4.5%) filled with blood - haemophthalmia. In 221 cases (62.6%) eye fundus was not visible, in 24 cases (6.8%) - only partially visible, and only in 43 cases (12.1%) the ophthalmoscopy of eye fundus was possible. In 169 cases (47.8%) the intraocular pressure (IOP) at palpation was high, in 119 cases (33.7%) IOP was normal.

Discussion

The analysis made shows, that in our republic the retinoblastoma is more frequent in boys (53.8%), than in girls (46.2%), the most of patients were revealed in the age between 2-3 years - 23.5%, this is confirmed by the average age of patients 2 years and 3 months. More than half of patients - 61.8% - are revealed at the age under 3 years old, the most of patients - 94.1% - were revealed at the age under 6. The number of patients is dramatically reduced between 6 and 11 years - 6%.

Comparing multiple symptoms and various clinical presentation of retinoblastoma with the data obtained after performing complex examinations (biomicroscopy, ophthalmoscopy, CT, ultrasound examination and dopplerography) on the size of intraocular mass, its` density, mobility, availability of blood vessels in its mass, relation to other structures, extent, it is possible to make diagnosis and specify the stage of the disease. By means of complex examination it is necessary to make differential diagnosis of retinoblastoma with the diseases, which can look like it, and the diseases under which the retinoblastoma can disguise.

The sequence of appearance of retinoblastoma symptoms also can indicate the stage of the disease. The white luminescence of pupil like “cats’ eye” is not inconstant, so is not always noticed by people around. When the tumor develops from periphery it is not always visible. When the tumor develops in the central zone of retina the squint can appear, which makes difficult to notice the luminescence. These symptoms can
correspond to the stage of tumor T1N0M0. The growing tumor occupies the major portion of retina and vitreous body. In this case the luminescence becomes constant, but not white, because the tumor is already rich of own vessels and there might be hemorrhagic foci on its surface, so its color is yellowish-pinkish. It corresponds to the 2nd stage of the tumor growth. The phenomenon of uveitis, endophthalmitis, and haemophthalmia can correspond to both T2N0M0 and T3N0M0 stages of neoplastic process. As far as the disintegrated tumor tissues can cause toxic uveitis and the tumor masses floating in vitreous body can simulate the feature of panophthalmitis. In line with disintegration of the tumor there can occur hemorrhage to ocular cavity, which can be partial, like hyphema or total haemophthalmia. The signs of secondary glaucoma, initially with enlargement of cornea, then - of the eye ball too, up to buphthalmia correspond to the stage T3N0M0 of retinoblastoma. The feature of orbital cellulitis appears at the stage T4N0M0, when the tumor, tearing the sclera, bursts out to orbit.

While analyzing our data and comparing it with those of other researchers one can notice, that in Asian countries and countries with high birthrate the retinoblastoma is more frequently found in boys (Bhurgri, Muzaffar, Ahmed et al., 2004, Harini, Ata-ur-Rasheed et al., 2001; Zhao, Li et al., 2011). Although the majority of authors from developed countries, where the birthrate is not so high, report that incidence of retinoblastoma is equal in both sexes (Saakyan, 2005, Broaddus, Topham, and Singh, 2009). The significant dispersion of rates in different ages can be explained by the fact that the majority of patients (about 50%) refer to ophthalmologist long after the disease started (from 6 months to 5 years later). Final diagnosis is made to them in later years. The causes of such late referral to ocular oncologist are multiple; in the first place it is inadvertence of parents and lack of any knowledge about oncologic diseases of eye. That is why even those parents, who have noticed pupil whitish luminescence in child, disregarded it. Sometimes it is the fault of despotic grandparents, who do not allow referring to doctors, and, instead, using for a long time services of traditional healers. But very often the responsibility for advanced cases lies with doctors who do not have enough knowledge about diverse clinical picture of retinoblastoma and have no oncologic alarm. As a result they treat the patients from other diseases for months, or perform absolutely unnecessary surgeries, like anti-glaucomatous, paraequesis with extracting blood or “hypopyon”, extraction of “cataract”, eye evisceration in “endophthalmitis”.

Such a diverse picture of retinoblastoma creates difficulties in diagnostics for out-patient facility doctors in provinces, where there is a lack of equipment and specialized scientific literature. Besides the examination and making right diagnosis with adequate treatment in young children requires availability of other specialists: anesthesiologists, radiologists, chemotherapists and radiotherapists.

**Resume**

Taking into account the variability of clinical presentation the early case finding, examination and adequate treatment of patients with retinoblastoma is a pressing challenge. That is why it has to be performed in big centers with available modern equipment and qualified specialists, who can adequately interpret the examination results and timely perform the necessary treatment.

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