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Epidemiology of Retinoblastoma in Bulgaria

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ABSTRACT: Introduction. Retinoblastoma is the most common intraocular malignancy and one of the most frequent solid tumors in childhood; with an incidence of 1/15,000 – 30,000 live births. It is a tumor of infancy and early childhood, with 95% of cases diagnosed before 5 years of age.
Purpose. The aim of our report was to determine the incidence of retinoblastoma and study epidemiological characteristics of retinoblastoma patients in Bulgaria, Eastern Europe for a five year period.
Patients and Methods. A 5-year (Jan 2013 – Dec 2017) retrospective study of medical records of all patients diagnosed with retinoblastoma at Pediatric Eye Unit, University Hospital "Alexandrovska", Sofia, Bulgaria was conducted.
Results. The present study included 12 children, with retinoblastoma incidence of 1.1/30,000 live births. The mean age at diagnosis was 21.2±12.1 months (range from 2 to 37 months), without any sex differences (6 boys; 6 girls). The most common first sign was leukocoria (75% of children). Nine of patients were with monocular disease, and all three infants with binocular tumor were males. Enucleation was performed in 9 eyes (9 children) and was the most common treatment modality for our study group.
Conclusion. Retinoblastoma is a rare disease for the pediatric population in Bulgaria, showing tendency to be lower than the worldwide average incidence. This partly can be explained with the fact that nevertheless our centre is the biggest and referral, it encompasses most but not all cases in our country.
KEY WORDS. retinoblastoma, epidemiology, incidence

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I INTRODUCTION

Retinoblastoma (RB) is the most common eye malignancy in childhood and the second most frequent intraocular tumor after uveal melanoma (1). Its incidence varies from 1/15,000 to 1/30,000 live births, with 8000 – 9000 new cases diagnosed every year worldwide (2-5). RB is a malignant embryonic tumor with neuroectodermal origin (6), specific for infancy and early childhood; with 95% of cases diagnosed before 5 years of age (7). The tumor results from single genetic mutations in which inactivation of both alleles of tumor suppressor RB1 gene initiates cancer development (8,9). The mutation can involve all cells (germline mutation) or just retinal cells (somatic mutation) which produces two fundamentally different forms of the disease – heritable RB and nonheritable RB (6,8). Although many ocular signs can be first symptom of the diseases, the most common are leukocoria (60%) and strabismus (30%) (6,10), making the differential diagnosis very broad and too complex. Early diagnosis and prompt treatment are vital because nevertheless RB can be curable detected in early stages, it is aggressive and life-threatening if not treated (11,12). Although RB treatment changed significantly in past few decades with implementation of chemoreduction and focal tumour consolidation, enucleation is still the most common treatment modality worldwide (11,13,14). Recurrences of the diseases or involvement of the fellow eye, as well as higher risk for secondary nonocular malignancies in all cases with heritable RB determine the necessity of lifetime follow-up of tumor survivors and their family members (15).

II PURPOSE

The aim of our report was to determine the incidence of retinoblastoma and study epidemiological characteristics of retinoblastoma patients in Bulgaria, Eastern Europe for a five year period.

III PATIENTS AND METHODS

A 5-year (Jan 2013 – Dec 2017) retrospective study of medical records of all patients diagnosed with retinoblastoma at Pediatric Eye Unit, University Hospital "Alexandrovska", Sofia, Bulgaria was conducted.

IV RESULTS

A 5-year (Jan 2013 – Dec 2017) retrospective study of medical records of all patients with newly diagnosed retinoblastoma at Pediatric Eye Unit, Eye Clinic, University Hospital "Alexandrovska", Sofia, Bulgaria was conducted. A total of 12 children with newly diagnosed retinoblastoma were recorded. The average age at diagnosis was 21.2±12.1 months (range from 2 to 37 months), with sex ratio 1:1 (six boys and six girls). Age and sex distribution are presented in details on table 1.

Table 1. Age and sex distribution of retinoblastoma patients.

Age group	Males, n	Females, n	Total, n (%)
under 1 year	3	1	4 (33.3%)
1 – 2 years	1	2	3 (25%)
2 – 3 years	2	2	4 (33.3%)
3 – 4 years	0	1	1 (8.4%)

All children were diagnosed after purposeful eye exam because of parents' awareness. In 9 (75%) children parents had noticed leukocoria (white pupil) or photoleukocoria; in 3 (25%) children first noticed sign had been strabismus with eso/exodeviation ratio 1:2.

Monocular retinoblastoma was diagnosed in 9 (75%) children. With bilateral disease, diagnosed at the first medical exam were 3 (25%) children and all infants were boys. Two of patients with bilateral tumor were detected before 1 year of age, and one patient was diagnosed at 2.8 years.

A detail ophthalmologic exam, including also RetCam imaging system documentation was performed to all children. When examining red reflex test, a leukocoria or asymmetry in red reflex was diagnosed in 13 eyes – in all 9 cases with monocular tumor; in both eyes in one of the cases with binocular disease and just in one of the eyes in the other two patients with binocular retinoblastoma. Strabismus was documented in 6 (50%) children with eso/exodeviation ratio of 1/5. Two children had increased intraocular pressure with mildly enlarged bulb in one of the children. Staging of the diseases was made according to the International Classification of Intraocular Retinoblastoma (16) and is as follows: stage B – 3 children; stage C – 5 children and stage D – 4 children.

Primary enucleation was treatment modality in 8 children (6 children with monocular disease and 2 children with binocular tumor – the eye with more advanced pathology). One child had secondary enucleation of the monocular tumor after systemic and local chemotherapy. Three children were with local lasertherapy after chemoreduction. The whole information about treatment modalities is summarized on table 2.

Table 2. Treatment modalities in 15 eyes with retinoblastoma.

Treatment modality	Eye (%)
Primary enucleation	8 (53%)
Secondary enucleation	1 (7%)
Local laser therapy	3 (20%)
Local laser therapy after chemoreduction	3 (20%)

V DISCUSSION

Retinoblastoma incidence varies worldwide from 1/15,000 to 1/30,000 live births (17). The incidence in Bulgaria (according to our study) is 1.1/30,000 live births, a rate in but lower than mean world's data (18). This partly can be explained with the fact that our study is hospital-based and nevertheless our centre is the biggest and referral, it encompasses most but most likely not all cases in our country.

RB is a tumor of early childhood with 2/3 of cases diagnosed before 2 years of age (7). The mean age for diagnosis is 18 months – 13 months for binocular cases and 24 months for monocular disease (1). The mean age at diagnosis for our cohort was 1.77 years (21.2 months) with all cases diagnosed before 4 years of age. Our mean patients' age is similar to that reported in Canada (1.44 years) (19) and Singapore (1.6 years) (20), and lower than that reported in Ethiopia (2.29 – 2.8 years) (21) and Tunisie (2.48 years) (22).

Although in historical review there is no sex discrepancy in retinoblastoma incidence (17,18), the results from USA Surveillance, Epidemiology and End Results (SEER) Program showed an excess of retinoblastoma cases in males (23). Similar data for male predisposition were reported also by other authors in recent years (21,22), suggesting the potential effect of sex on cancer origin (23). We found no sex differences for the whole group but male predisposition for bilateral cases.

Monocular retinoblastoma was more common than binocular tumor with ratio 3:1 for our children group. These data are comparable with other authors' results with binocular cases diagnosed earlier than monocular tumors (17,21,22).

The most common first signs reported by the parents of our children group were leukocoria and strabismus. These are the most common first signs reported also by many authors from developed countries (20,22), whereas in low income countries one of the first clinical signs is proptosis because of the delay in diagnosis (21,24).

Nine eyes were removed because of the advanced disease, so making the enucleation the most common treatment modality for our group. It is difficult to explain this fact with just late diagnosis, because our mean diagnostic time is comparable to this in other high income countries. May be the time lost between first signs noticed by parents and first time at which the children are diagnosed in our clinic is the main reason; but also other factors must be discussed. Nevertheless all these, enucleation is still the most common treatment modality worldwide (11,13,14).

The present study has several limitations. First, this is a hospital-based study, not population or based on official pediatric cancer registries in Bulgaria. Second, it is one centre study and nevertheless the fact that our Pediatric Eye Unit is unique for our country and most children are diagnosed for a first time at our department or are referred to us immediately after the child is diagnosed, most but not all cases of retinoblastoma in Bulgaria are presented in this study. The third limitation is the short time (5-year period) of the retrospective study that also can influence the overall incidence of retinoblastoma in our country.

VI CONCLUSION

Retinoblastoma is a rare disease for the pediatric population in Bulgaria, showing tendency to be with lower rate than the worldwide average incidence. This partly can be explained with the fact that nevertheless our centre is the biggest and referral, it encompasses most but not all cases in our country. Most cases are diagnosed in stages requiring enucleation, therefore better knowledge of the problem by pediatricians, general practioners and even parents is mandatory. Early diagnosis and prompt treatment of the tumor by multidisciplinary medical team will give chance not just for child's survival but also for vision sparing.

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