Clinical and Pathological Predictor Factors of Fellow Eye Affliction in Patients with an Initial Unilateral Retinoblastoma

Mohamed A. Ibrahim and Mansour Al-Mohaimeed*

Department of Ophthalmology, Faculty of Medicine, Qassim University, Saudi Arabia

Abstract

Objective: To identify the clinical and pathological predictor factors for the fellow eye affliction (asynchronous bilateralization) in patients who were initially diagnosed with unilateral retinoblastoma.

Methods: The present study was conducted in the Department of Ophthalmology of the Faculty of Medicine at Zagazig University in Zagazig, Egypt. All patients initially diagnosed with unilateral retinoblastoma from January 2005 to December 2007 were followed up meticulously for at least 32 months for the development of metastatic disease and/or fellow eye affliction. At pathological examination, all specimens were stained with hematoxylin (HX) and eosin (E). The specimens also underwent special immunohistochemical staining for neuron-specific enolase (NSE). Care was given to detect optic nerve invasion by the tumor, tumor focality, and tumor differentiation during pathological examination.

Results: Only 3 (16.7%) of the 18 patients initially diagnosed with unilateral retinoblastoma developed a fellow eye affliction, asynchronous bilateralization of retinoblastoma, during the follow-up period. The time lapse to fellow eye affliction ranged from 3 to 14 months. All 3 patients (100%) were diagnosed at less than 12 months of age (mean, 6.3 months; \( P < 0.001 \)). Only 1 (33.3%) of the 3 patients had a multifocal tumor \( (P > 0.05) \). Of the 3 patients, 2 (66.7%) had a positive family history of retinoblastoma \( (P < 0.05) \). Optic nerve invasion and poor tumor differentiation were found in 2 (66.7%) and 1 (33.3%), respectively, of the 3 patients with asynchronous bilateralization. A statistically significant correlation was found between negative NSE staining and asynchronous bilateralization of retinoblastoma \( (P < 0.05) \).

Conclusions: This study suggests that earlier age at diagnosis (less than 1 year), positive family history, and negative immunohistochemical staining with NSE are possible predictor factors for the development of fellow eye affliction in patients initially diagnosed with unilateral retinoblastoma.

Keywords: Retinoblastoma; Asynchronous bilateralization; Hematoxylin; Eosin

Although retinoblastoma is a rare tumor, occurring in only about 1 in 15,000 live births, it is the most common primary malignant intraocular tumor of childhood [1-3]. Unilateral retinoblastoma with later affliction of the fellow eye, known as asynchronous bilateralization, is a rather uncommon event, occurring in only about 10% of all unilateral cases [3-5].

Asynchronous bilateralization of retinoblastoma has relevant implications for both management and prognosis of such cases [4-5]. Identification of the predictor or risk factors for this type of affliction of the fellow eye will allow for its earlier detection, which may be of great value in planning treatment strategies for such patients, possibly leading to the preservation of useful vision and even the saving of lives [5-7].

The aim of this study is to identify the clinical and pathological predictor factors for the affliction of the fellow eye (metachronous or asynchronous bilateralization) in patients with initial unilateral retinoblastoma in our locality.

Patients and Methods

A series of 18 patients were initially diagnosed with unilateral retinoblastoma in Department of Ophthalmology at the Faculty of Medicine, Zagazig University in Zagazig, Egypt, from January 2005 to December 2007 with follow up period meticulously for at least 32 months. The following demographic and clinical characteristics of patients were obtained: age at diagnosis, sex of the patient, direct family history, focality of the lesion, time lapse to fellow eye affliction, and the development of metastatic disease of retinoblastoma. The diagnosis of retinoblastoma was based on indirect ophthalmoscopy with scleral indentation following full mydrias under general anesthesia. If necessary, ancillary tests—such as ultrasonography, particularly with the B-scan and computed tomography (CT) scanning (for the detection of intraocular calcification)-were performed (Figure 1). Metastatic disease work-up included repeated CT scans of the brain (for the detection of central nervous system metastasis or trilateral retinoblastoma) and of the orbit, cerebrospinal fluid examination, radionucleotide bone scan, and, if necessary, a chest x-ray.

In this study, all patients were followed up meticulously for at least 32 months for the detection of recurrence, metastatic disease, or fellow eye affliction. If any of these conditions were detected, metastatic work-up and repeated careful examinations of both eyes were performed (sometimes under general anesthesia).

All specimens were taken from enucleated eyes with significantly large tumor occupying most of the globe with no hope of any useful vision “stage V”. All specimens were fixed in 10% formalin, embedded in paraffin wax, and stained with hematoxylin (HX) and eosin (E)
(Figure 2, 3). The specimens also underwent immunohistochemical staining for neuron-specific enolase (NSE) (Figure 4). Pathological examinations were conducted in the Pathology Department of the Faculty of Medicine at Zagazig University. Care was taken to detect optic nerve invasion by the tumor and tumor differentiation during pathological examination.

Results

This study included 18 patients (10 males, 8 females) who were initially diagnosed with unilateral retinoblastoma. Only 3 (16.7%) of the 18 patients developed a fellow eye affliction, known as asynchronous bilateralization, during the follow-up period, with the time lapse to fellow eye affliction ranging from 3 to 14 months.

All 3 (100%) patients with asynchronous bilateralization of retinoblastoma were initially diagnosed with a unilateral retinoblastoma before the age of 12 months, whereas 3 (20%) of the 15 patients without a fellow eye affliction were initially diagnosed with a unilateral retinoblastoma before the age of 12 months. Of the 3 patients with asynchronous bilateralization of retinoblastoma, 1 patient (33.3%; P > 0.05) had a multifocal tumor at diagnosis, whereas 4 (26.7%) of the 15 patients without a fellow eye affliction had a multifocal tumor at diagnosis. Of the 3 patients with asynchronous bilateralization of retinoblastoma, 2 patients (66.7%; P < 0.05) had a positive family history of retinoblastoma, whereas 1 (6.7%) of the 15 patients without a fellow eye affliction had a family history of retinoblastoma (Table 1). Table 2 shows the age at diagnosis, tumor focality, family history, and time lapse to fellow eye affliction in patients with asynchronous bilateralization of retinoblastoma.

We detected optic nerve invasion in 2 (66.7%) of the 3 patients with asynchronous bilateralization of retinoblastoma and in 8 (53.3%) of the 15 patients without a fellow eye affliction. Poor tumor differentiation was found in 1 (33.3%) of the 3 patients with asynchronous bilateralization of retinoblastoma compared with 4 (26.7%) of the 15 patients without a fellow eye affliction. Metastatic disease of retinoblastoma was reported in 3 (75%) of the 4 patients with optic nerve invasion reaching the resection margin and in 4 (80%) of the 5 patients with poorly differentiated tumors. A statistically significant correlation was found between negative NSE staining and asynchronous bilateralization of retinoblastoma, P < 0.05 (Table 3).

Discussion

Retinoblastoma is worldwide in its distribution and can affect all races [1,2,6,7]. Heritable and nonheritable forms may occur [8], and unilateral or bilateral presentation is a well known and common finding [1,4]. However, unilateral retinoblastoma with later affliction of the fellow eye, known as asynchronous bilateralization, is not common. It has a reported incidence of about 10% to 15% in several studies [3,5,9], which is similar to the finding in this study (16.7%). Understanding asynchronous bilateralization of retinoblastoma is important for developing management strategies and determining prognosis. Thus, the identification of the predictor risk factors of such an event, either clinically or pathologically, will allow for its earlier detection, possibly resulting in the preservation of useful vision and even the saving of lives [3,5,9].

Retinoblastoma results from malignant transformation of primitive retinal cells before their final differentiation [2,10]. The gene that predisposes to retinoblastoma is located at region 14 on the long arm (q) of chromosome 13 (13q14) [8]. The assumption that the great majority of bilateral retinoblastoma cases is caused by transmitted
When we investigated the possible relationship between tumor foci as a predictor factor for later affliction of the fellow eye. However, we also found multifocal lesions in 4 (26.7%) of the 15 patients without the fellow eye affliction. Therefore, tumor foci as a predictor for asynchronous bilateralization of retinoblastoma seems controversial. Several studies have provided some support for this role, whereas others have not [3,5,9]. Thus, long-term multicenter studies of larger patient groups in different localities need to be conducted to determine whether tumor foci has a predictor role for asynchronous bilateralization of retinoblastoma [3,5].

Although optic nerve invasion and poor tumor differentiation were found in 2 (66.7%) and 1 (33.3%), respectively, of the 3 patients with asynchronous bilateralization, they were also reported in 8 (53.3%) and 4 (26.7%), respectively, of the 15 patients without a fellow eye affliction. It seems that optic nerve invasion and poor tumor differentiation are more closely correlated with metastatic disease than to the metachronous bilateralization of the disease [10-12]. Furthermore, a statistically significant correlation was found between positive family history and asynchronous bilateralization of retinoblastoma [13,14]. Future immunohistochemical studies are strongly recommended in this field.

Of the 18 patients included in this study, 6 (33.3%) developed metastatic disease of retinoblastoma during the follow-up period of at least 32 months. The main prognostic markers for metastatic disease in this study were optic nerve invasion reaching the resection margin [3 (75%) of 4 patients in whom optic nerve invasion reached the
Our findings suggest that earlier age at diagnosis (less than 1 year), positive family history, and negative immunohistochemical staining with NSE are possible predictor factors of fellow eye affliction in patients who are initially diagnosed with unilateral retinoblastoma. However, our findings also indicate that optic nerve invasion and poor tumor differentiation are more closely correlated with metastatic disease of retinoblastoma than with asynchronous bilateralization of the disease. Conducting large multicenter studies with the same study protocol and a long follow-up period is necessary to confirm these findings. Protein arrays investigation for the fellow eye affliction patients and their possible family members may be included in the future studies. Identifying which factors predict the development of asynchronous bilateralization of retinoblastoma may allow for earlier detection, which in turn may result in the preservation of useful vision and the saving of lives of those unfortunate to be afflicted with this disease.

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References