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

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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 mydriasis 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, radionuclide 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).

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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).

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
Table 1: Correlation between Age at Diagnosis, Tumor Focality, Family History, and Asynchronous Bilateralization of Retinoblastoma.

| Patient no. | Age at diagnosis, months | Tumor focality | Family history | Time lapse to fellow eye affection, months |
|-------------|--------------------------|----------------|----------------|------------------------------------------|
| 1           | 4                        | Multifocal     | Positive       | 14                                       |
| 2           | 5                        | Unifocal       | Positive       | 11                                       |
| 3           | 10                       | Unifocal       | Positive       | 3                                        |

Table 2: Age at Diagnosis, Tumor Focality, Family History, and Time Lapse to Fellow Eye Affliction in Patients with Asynchronous Bilateralization of Retinoblastoma.

gene mutations has prompted many researchers [3,5,8,9] to investigate the relationship between the metachronous bilateralization of retinoblastoma and family history. In the present study, 2 (66.7%) of the 3 patients who developed asynchronous bilateralization of retinoblastoma had a positive history of retinoblastoma (P < 0.05) — a feature that may augment the role of positive family history as a predictor of later affliction of the fellow eye. However, positive family history was also reported in 1 (6.6%) of 15 patients without a fellow eye affliction.

Because the cells of origin of retinoblastoma (primitive retinal cells) usually disappear within the first few years of life, this type of tumor is seldom seen after 3 to 4 years of age [2,8,10]. In the present study, the age at diagnosis of less than 12 months was reported in all 3 patients (100%) with metachronous bilateralization of retinoblastoma (P < 0.001), a finding that supports early age at diagnosis (within the first years of life) as a substantial predictor or risk factor of such an event. This finding is in accordance with those reported by several researchers [3,5,9] who emphasized the importance of age less than 1 year at presentation as a predictor factor for later affliction of the fellow eye. The age at diagnosis for the 1 patient with asynchronous bilateralization and a negative family history of retinoblastoma was 10 months, which further supports the importance of early presentation of retinoblastoma at less than 12 months of age as a predictor of the metachronous bilateralization of the disease.

When we investigated the possible relationship between tumor focality at diagnosis and the asynchronous bilateralization of retinoblastoma, we detected multifocal lesions in 1 (33.3%) of the 3 patients with asynchronous bilateralization of retinoblastoma (P > 0.05). However, we also found multifocal lesions in 4 (26.7%) of the 15 patients without affliction of the fellow eye. Therefore, tumor focality 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 focality 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 negative NSE staining and asynchronous bilateralization of retinoblastoma (P < 0.05). This finding might support the relationship between tumor histogenesis and such 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

Table 3: Correlation between Tumor Characteristics (Optic Nerve Invasion, Tumor Differentiation, and Tumor Histogenesis) and Asynchronous Bilateralization of Retinoblastoma or Metastatic Disease.

| Optic nerve invasion | Patients without fellow eye affliction (n = 15) | Patients with asynchronous bilateralization (n = 3) | Total (n = 18) | Metastatic disease |
|----------------------|-----------------------------------------------|-----------------------------------------------|----------------|-------------------|
| No. %                | No. %                                         | No. %                                         | No. %          | No. %             |
| Not invaded          | 7 46.7 1 33.3 8 44.5 1 12.5                   |
| Invaded              |                                              |                                               |                |
| Not reach resection margin | 5 33.3 1 33.3 6 33.3 2 33.3 |                      |
| Reach resection margin | 3 20 1 33.4* 4 22.2 3 75** |
| Total                | 15 100 3 100 18 100 6 33.3 |

| Tumor differentiation | Well differentiated | Poorly differentiated | Total |
|-----------------------|---------------------|-----------------------|-------|
| Patients without fellow eye affliction (n = 15) | 11 73.3 2 66.7 13 72.2 2 15.4 |
| Patients with asynchronous bilateralization (n = 3) | 4 26.7 1 33.3* 5 27.8 4 80 |
| Total (n = 18) | 15 100 3 100 18 100 6 33.3 |

| Tumor histogenesis | Positive (NSE) | Negative (NSE) | Total |
|--------------------|---------------|---------------|-------|
| Patients without fellow eye afflicted patients (n = 15) | 8 53.3 1 33.3 9 50 2 20.2 |
| Patients with asynchronous bilateralization (n = 3) | 7 46.7 2 66.7*** 9 50 4 40.4 |
| Total (n = 18) | 15 100 3 100 18 100 6 33.3 |

* A nonsignificant statistical correlation was found between optic nerve invasion/tumor differentiation and asynchronous bilateralization of retinoblastoma (P > 0.05)

** A statistically significant correlation was found between optic nerve invasion reaching the resection margin/poor tumor differentiation and metastatic disease of retinoblastoma (P < 0.05)

*** A statistically significant correlation was found between negative neuron-specific enolase (NSE) staining and asynchronous bilateralization of retinoblastoma (P < 0.05)
resection margin; \( P < 0.05 \) and poor tumor differentiation with no detectable rosettes or fleurettes [4 (80\%) of 5 patients with poor tumor differentiation; \( P < 0.05 \)], findings that are in agreement with those of several studies [5,11,12,15].

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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