Age At Diagnosis And Bilateralization Of Unilateral Retinoblastoma

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Citation

Abstract

An early age and tumor multifocality at diagnosis, as well as a positive family history, are presently considered major risk factors in the development of metachronous tumors in the fellow eye in unilateral retinoblastoma. In order to verify these assumptions we performed an investigation on a series of 167 unilateral retinoblastoma, and found that metachronous tumors in the fellow eye were observed: 1) in 11 out of 167 patients (6.5%), globally; 2) in 3 out of the 12 patients (7.1%) with a positive family history; 3) in but one of the 23 patients showing multiple foci at diagnosis. Since the three patients with a positive family history who later developed tumors in the fellow eye, in the present series, were all diagnosed at the ages of less than 4 months, we conclude that an early age at diagnosis is the only relevant risk factor for metachronous tumor development in retinoblastoma.

INTRODUCTION

Metachrnonous (or asynchronous) tumor development in the fellow eye of patients initially diagnosed as unilateral retinoblastoma, has been reported by some Authors([1], [2], [7]) and ourselves ([13]). Although rare, accounting for no more than 10 % of all unilateral cases in some series and 6.5 % in the present investigation, "bilateralization", as it can be called, is an event with clinical and prognostic implications in the natural history of retinoblastoma. ([2], [13])

An early age and multiple tumor foci at diagnosis, together with a positive family history of retinoblastoma, all have been claimed to represent the major risk factors of bilateralization of unilateral retinoblastoma. and also the main clinical features pointing at the inherited nature of these cases ([2], [7]).

The evidence reported herein, however, does not support a role for either the family history or the number of tumor foci at diagnosis, while strongly suggesting that the main and only risk factor for "bilateralization" of unilateral retinoblastoma, is represented by an age at first diagnosis of less than 12 months.

PATIENTS AND METHODS

A retrospective analysis of 167 unilateral retinoblastoma, observed during the period 1980 – 2003, was performed at the Ophthalmic Oncology Unit of the Department of Ophthalmology of the University of Siena – Italy.

Relevant clinical data such as age at diagnosis, sex, Reese - Ellsworth group at diagnosis, time lapse between diagnosis and "bilateralization", subsequent treatment modalities, follow-up, and family history, were collected and analyzed.

Chi square analysis, using 2-by-2 contingency tables with Fisher's "exact" test, were used to compare the significance of the chosen risk factors (i.e.: family history, single or multiple tumor foci at diagnosis, and diagnosis of unilateral retinoblastoma before or after the age of 12 months) with respect to the event "bilateralization".

RESULTS

167 unilateral retinoblastoma patients were referred to our institution in the period 1980 – 2003. 64 (38.3%) were diagnosed before the age of 12 months, and the remaining 103 (61.7%), after that age. 11 out of 167 (6.5%), later developed tumors in the fellow eye ("bilateralization").

A positive family history was detected in 12 / 167, (7.2%) and multiple foci at diagnosis in 23/140 (16.5%); 27 patients could not be evaluated for tumor foci because of either hemovitreous, enucleation performed in other institutions.

The analysis of the relationship between the number of tumor foci at diagnosis and the event "bilateralization" (Tab. 1), showed a two-tailed p value of 1.000, i.e. not significant.

Figure 1

Table 1: comparison between tumor focality at diagnosis and "bilateralization" of unilateral retinoblastoma. p = 1.0000 (not significant)

	Metachronous Bilateral (number of pts)	Unchanged (remained unilateral) (number of pts.)	total
Single focus at diagnosis (number of pts.)	6	111	117
Multiple foci at diagnosis (number of pts)	1	18	19
Totals	7	129	136

A positive family history (tab. 2) for retinoblastoma, on the other hand, may have had some significance at this regard (Two-tailed p = 0.0039), but it must be noticed that 9 out of 12 of the familial unilateral retinoblastoma, in this series, did not show bilateralization at all.

Figure 2

Table 2: comparison between family history and "bilateralization" of unilateral retinoblastoma. p = 0.0039 (statistically significant)

	Metachronous Bilateral (number of pts)	Unchanged (remained unilateral) (number of pts)	total
Positive family history (number of pts.)	3	9	12
Negative family history (number of pts)	8	147	155
Totals	11	156	167

Moreover, an age at diagnosis of less than 12 months, seems to be extraordinarily important as a risk factor in our patients, since none of the cases diagnosed after that age (Tab. 3), later developed metachronous tumors in the fellow eye, thus resulting in a p value of 0.0001, i.e.:extremely significant.

Figure 3

Table 3: comparison between age at diagnosis (age threshold = 12 months) and "bilateralization" of unilateral retinoblastoma. p < 0.0001 (extremely statistically significant)

	Metachronous Bilateral (number of pts)	Unchanged (remained unilateral) (number of pts)	total
Age at diagnosis < 12 months (number of pts.)	11	53	64
Age at diagnosis > 12 months Number of pts)	0	103	103
Totals	11	156	167

It has to be outlined that the only three patients who had a positive family history in the group of the 12 metachrnous

retinoblastomas in this series (patients G.R, D' A.E. and B.M)., had been diagnosed with unilateral Rb at the ages of 1, 4, and 4 months, i.e. within the age range most significantly at risk for this event. They also developed tumors in the fellow eye after 6, 12, and 12 months respectively, with a mean time lapse between the first and second diagnosis of 10 months, considerably higher if compared with the mean of the non familial group, which was 3.1 months (Tab. 4).

Figure 4

Table 4: Metachronous bilateral retinoblastoma and family history. Only 3 out of the 11 patients undergoing tumor development in the fellow eye (bilateralization), had a positive family history for the disease. On column 4 the time lapse between first diagnosis and tumor development in the fellow eye is reported

Pt.	Age at diagnosis (unilateral Rb)	Family history	1st eye	Time lapse to bilateral Rb diagnosis
1. G. R.	1 month	yes	OD: Cons. treatment	6 months
2. D'A. E.	4 months	yes	OD: Cons. treatment	12 months
3. F. E.	2 months	no	OD: En	1 month
4. D.M.C.	11 months	no	OD: En	1 month
5. V.L.	2 months	no	OS: En	2 months
6. V.E.	1 month	no	OD: En	1 month
7. C. R.	6 months	no	OS: En	5 months
8. D'A. .M.	0 months	no	ct	12 months
9. B. M.	4 months	yes	En-ct	12 months
10. F.L.	2 months	no	En-ct	4 months
11. S. E.	0 months	no	En-ct	2 months

Figure 5

Table 5: mean time to tumor development in the fellow eye after the diagnosis of unilateral retinoblastoma in patients with positive and negative family history.

Family history	No. of patients	Mean time to bilateralization
yes	3	10 months
no	9	3.1 months

DISCUSSION

Unilateral retinoblastoma with late "bilateralization" is a rather rare event in retinoblastoma, ranging from 10 ([7]) to 6.5 % of all unilateral cases (present sieries, and [9]).

Although rare, this event has a number of relevant implications for both prognosis and treatment, and therefore, the identification of "risk factors" allowing its early detection, may be of great value in planning therapeutic strategies.

Previous reports ([1, 2, 3, 4, 5, 6, 7, 8, 12, 13]), based on the assumption that the great majority of bilateral retinoblastoma are either new germline or directly transmitted mutations ([10, 11, 14, 15]), have tried to identify these risk factors with those

clinical aspects more closely related to the inheritance of the affected Rb1 gene, such as a positive family history for the disease together with multiple foci and an early age at diagnosis. It has been concluded that multiple foci and an early age at diagnosis, as well as a positive family history for retinoblastoma, all carry an increased risk of late "bilateralization" in unilateral retinoblastoma ([1, 2, 3, 4, 5, 6, 7])

However, looking at our data, while it can be confirmed that an age at diagnosis of less than 12 months carries a substantial and highly statistically significant risk of late "bilateralization", not the same can be said about tumor multifocality at diagnosis and family history.

In particular, it has been shown that the finding of multiple foci when unilateral retinoblastoma is initially diagnosed does not imply and increased risk of late "bilateralization"

On the other hand, while there seems to be a statistically significant correlation between a positive family history and metachrnous tumor development in the fellow eye in three of our twelve familial cases in this series, clinical evidence says that:

- nine out of twelve (3 / 4) familial unilateral retinoblastoma, did not transform into bilateral Rb, i.e.: only a minority of familial unilateral retinoblastoma carry the risk of late bilateralization;

- the three familial unilateral RB who later developed tumors in the fellow eye, had their diagnosis made by the ages of 1, 4, and 4 months, i.e. within the age range at risk for late bilateralization in this series, thus indicating that they became bilateral because of their early age rather than their family history;

- looking at the mean age at bilateralization in non familial cases (9 out of 12 patients), it must be observed that it is shorter (3.1 months) than that of the familial ones (3 out of 12 cases) which is 10 months, and although this observation needs to be confirmed by studies on larger series, it represents a rather singular feature in the light of the current knowledge concerning the inheritance in retinoblastoma.

As a consequence, the simple clinical reasoning applied to these data, seems to indicate that:

- the only consistent and reliable risk factor for late "bilateralization" of unilateral retinoblastoma is represented by an age at diagnosis of less than 12 months;

- inheritance does not play any role in metachronous tumor development in the fellow eye in unilateral retinoblatoma

To conclude, our data do not support any role for multiple tumor foci and a positive family history at diagnosis, but rather emphasizes the relevance of a diagnosis made before the age of 12 months as the only significant and reliable risk factor of subsequent bilateralization of unilateral retinoblastoma.

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