European Journal of Ophthalmology / Vol. 10 no. 2, 2000 / pp. 149-152

Metachronous tumor development in unilateral retinoblastoma

D. MASTRANGELO, T. HADJISTILIANOU, F. DI PISA, M.C. CAPRETTI, R. FREZZOTTI

Centro per la Ricerca Interdipartimentale per lo Studio delle Affezioni Tumorali dell'Occhio (CRISATO), University of Siena, Siena - Italy

PURPOSE. *A series of 205 retinoblastoma (RB) patients referred to the Department of Ophthalmology at the University of Siena (Italy) was evaluated in order to assess the proportion of unilateral cases later developing tumors in the companion eye ("metachronous" bilateral retinobastoma) (MBRB).*

METHODS. *The total number of unilaterally affected patients developing tumors in the fellow eye was recorded and the risk factors assessed for the development of asynchronous bilateral retinoblastoma, i.e., family history, tumor multifocality and early age at diagnosis.*

RESULTS. *Only two out of 133 (1.5%) unilateral retinoblastoma patients in our series could be considered affected by MBRB.*

CONCLUSIONS. *The incidence of MBRB in our series was negligible (1.5% of all unilateral cases) compared to other reports. None of the reported risk factors for the development of tumors in the fellow eye was relevant in the present series. Although close follow-up of some unilateral cases is still recommended, thorough examination of the fellow eye, to search for lesions in the peripheral retina, is essential in all cases of unilateral RB. MBRB may be a distinctive clinical entity with specific clinical, genetic and prognostic features. However, all these aspects need to be better investigated in larger series. (Eur J Ophthalmol 2000; 10: 149-52)*

KEY WORDS. *Retinoblastoma, Asynchronous retinoblastoma, Metachronous retinoblastoma*

Accepted: January 31, 2000

INTRODUCTION

Patients with unilateral retinoblastoma (RTB) developing tumors in the companion eye within 2-18 months after diagnosis are considered to have asynchronous bilateral retinoblastoma, though the term 'metachronous", rather than "asynchronous" is more commonly used in clinical oncology. Although detailed reports on metachronous bilateral RTB (MBRB) are rare, there seems to be worldwide agreement on its existence. However, the real incidence, clinical, biological, genetic, and prognostic features of MBRB have not been elucidated. It has been suggested that a positive family history, early age at diagnosis (up to 18 months), and tumor multifocality are all risk factors for the development of tumors in the companion eye (1).

The present investigation was designed to verify the incidence of metachronous retinoblastoma in a series of 205 patients, and the role(s) of the reported risk factors.

METHODS

For the present investigation, 205 patients referred to the Ocular Oncology Unit of the Department of Ophthalmology (University of Siena, Italy) were taken into consideration. All relevant data were recorded, retrieved and processed using a clinical database implemented in the department, using a Relational Data Base Management System (RDBMS) Informix V.4.10 running under SCO-UNIX SysV Rel 3.2-V4.2. The hardware was an Intel Pentium computer with attached terminals, console and network connection. A shell interpreter of Structured Query Language (SQL)

 1120-6721/149-04$02.00/0

together with a 4th-generation language (4GL) development tool were used for the creation, manipulation, definition and prototyping of the database (2).

The main criterion for inclusion was a confirmed diagnosis of retinoblastoma. Bilateral cases were only considered from the point of view of their clinical history, focusing on the kinetics of the bilateral involvement, in the search for cases with metachronous tumor development. All unilaterally affected patients were considered for inclusion in a prospective eye examination follow-up study in order to check for tumor development in the fellow eye.

Our current approach to the follow-up of retinoblastoma patients is as follows:

a) unilateral and bilateral cases under treatment: indirect ophthalmoscopy and laser/crio-therapy under general anesthesia (UGA), monthly visits;

b) unilateral and bilateral cases after complete remission: indirect ophthalmoscopy under general anesthesia, visits once every two months, then once every four months and finally once every six months for five years. After five years, once a year;

c) unilateral cases treated with enucleation: if less than 12 months, one visit in three months, if more than 12 months, one in six months.

General anesthesia is not used over the age of five years.

Descriptive data such as the total number of unilaterally and bilaterally affected patients, the mean age at diagnosis by age group, family history and tumor multifocality (relevant for the assessment of the risk of tumor development in the companion eye) were included in the analysis.

None of the patients in our series has been lost to follow-up.

RESULTS

This series of 205 patients comprises 72 bilateral (35.1%) and 133 (64.9%) unilateral retinoblastomas. In the group of unilateral patients, 61 were diagnosed within the first 18 months of life. The follow-up of the present series ranged from 1-10,991 days (366 months or about 30 years), with a mean of 1390 days (46.3 months or about 3.8 years).

Only two unilaterally affected patients developed tumors in the companion eye. The incidence of MBRB was therefore two out of 133 (1.5%). None of the six cases of unilateral retinoblastoma with a positive family history developed a tumor in the companion eye after a mean follow-up of 15.3 years (range 1.8-40 years). Four unilaterally affected patients had multifocal tumor at diagnosis and two later developed tumors in the companion eye.

One of these two was diagnosed as having unilateral retinoblastoma by the age of six months and developed two tumors in the companion eye, the first one 12 months and the second 19 months after diagnosis. Both were at the ora serrata (seven and four o'clock, respectively), and were treated by cryocoagulation. The patient is relapse-free after a follow-up of more than 24 months. The second patient was diagnosed by the age of one week, within a regional neonatal fundus screening program aimed at the early detection of congenital retinal and optic nerve diseases, and developed a second tiny lesion in the mid-periphery, 12 months after diagnosis. The lesion was treated by argon laser photocoagulation and the patient is still relapse-free after a follow-up of more than 24 months.

DISCUSSION

When considering the incidence of MBRB, there is no agreement among different series of patients. Fontanesi et al (1) reported a global incidence of nine MBRB in 107 (8.4%) unilaterally affected patients while Palazzi et al (3) reported 10 in 288 (3.4%). Our figure is two in 133 (1.5%), the lowest reported so far. One possible explanation for the different incidence rate of MBRB might be the careful inspection of the fellow eye at first diagnosis.

Moreover, some a authors (4, 5) apparently do not make a distinction between "new tumors" appearing in an affected eye and those arising in a previously unaffected eye, since both are "metachronous" and usually bilateral. We do not agree with this since the involvement of the companion eye in a unilaterally, unifocally affected patient always implies a substantial modification of the prognosis. Metachronous bilateral tumors affecting breast (6), lung (7) or kidney (8) are clearly reported to have a worse prognosis than the corresponding metachronous unilateral ones. However, the two MBRB cases in our series showed

very mild behaviour, being relapse-free more than 24 months after conservative treatment of the tumors in the fellow eye. The benign course of these two cases might be due to the expected peripheral location of the new tumor in one case, and the early detection of a small tumor thanks to prospective screening.

Early age at diagnosis (within the first 18 months of life), tumor multifocality and a positive family history have been advocated as risk factors for the development of MBRB. Furthermore, from the point of view of tumor biology and pathogenesis, synchronous and metachronous tumor development cannot be regarded as one and the same process. The two-mutation model proposed by Knudson (9, 10) assumes that in gene carriers the eyes acquire tumors independently, and therefore metachronous rather than synchronous tumor development should be the most frequent pattern, but this is not the case, as shown in worldwide reports (11). It is clear that the early detection plays a significant role in "lowering" the frequency of metachronous tumors. Other factors, however, such as tumor growth rate and host factors (immune response, maturation of retinal tissue, etc.), deserve further investigation in this context.

In this study, none of the six unilaterally affected patients with positive family history later developed tumors in the fellow eye. This suggests there is no specific risk of tumor development in the fellow eye associated with family history.

A different consideration applies to tumor multifocality as related to the development of metachronous retinoblastoma. In the four patients with multifocal tumor seen at diagnosis, not "inferred" from the appearance of the tumor mass, two had metachronous tumor development. Although the relationship between tumor multifocality and heredity of retinoblastoma has been questioned (12), no specific relationship between metachronous tumor development and heredity can be reasonably inferred from our data.

It is worth noting that the patient diagnosed by the age of one week developed a tiny lesion in the companion eye twelve months later, localized in the midretinal periphery. The patient diagnosed by the age of six months developed two tumors in the companion eye, one 12 and the other 19 months later, both in the extreme periphery. Although obviously not statistically significant, this figure seems to be in agreement with recent reports about the topographical distribution of tumors in the retina in relation to the patient's age (13, 14).

Our data suggest that MBRB is an extremely rare condition. The number of cases in our series is far too small to draw conclusions on its clinical behavior. In conclusion, however, MBRB may be a definite, though small, clinical entity, but its real incidence and specific features need further investigation.

Reprint requests to:
Domenico Mastrangelo, MD
Dipartimento di Scienze Oftalmologiche
Policlinico "Le Scotte"
Viale Bracci, 2
53100 Siena, Italy
e-mail: mastrangelo@unisi.it

REFERENCES

1. Fontanesi J, Pratt C, Meyer D, Elvelbig J, Parham D, Kaste S. Asynchronous bilateral retinoblastoma: the St. Jude Children's Research Hospital experience. Ophthalmic Genet 1995; 16, 3:109-12.
2. Di Pisa F, Mastrangelo D, Hadjistilianou T, et al. Design and implementation of a relational database used in the management of patients with retinoblastoma. Comput Biomed Res 1997; 30: 273-89.
3. Palazzi M, Abramson DH, Ellswolth RM. Endophytic vs. exophytic unilateral retinoblastoma: is there any real difference? J Pediatr Ophthalmol Strabismus 1990; 27, 5: 255-8.
4. Abramson DH, Gamell LS, Ellsworth RM, et al. Unilateral retinoblastoma: new intraocular tumours after treatment. Br J Ophthalmol 1994; 78: 698-701.
5. Abramson DH, Niksarli K, Ellsworth RM, Servodidio CA. Changing trends in the management of retinoblastoma. 1951-1965 versus 1966-1980. J Pediatr Ophthalmol Strabismus 1994; 31: 32-7.
6. Singletary SE, Taylor SH, Guinee VF, Withworth PW.

Occurrence and prognosis of contralateral carcinoma of the breast. J Am Coll Surg 1994; 4: 390-6.
7. Adebonjo SA, Moritz DM, Danby CA. The results of modern surgical therapy for multiple plimary lung cancers. Chest 1997; 3: 693-701.
8. Paulino AC, Thakkar B, Henderson WG. Metachronous bilateral Wilms' tumor: the importance of time interval to the development of a second tumor. Cancer 1998; 2: 415-20.
9. Knudson AG. Mutations and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971; 4: 820-3.
10. Hethcote HW, Knudson AG. Model for the incidence of embryonal cancers: application to retinoblastoma. Proc Natl Acad Sci USA 1978; 75: 2453.
11. Matsunaga E. Almost synchronous appearance of bilateral retinoblastomas. (letter). Am J Med Genet 1982; 11: 485-7.
12. Moll AC, Koten JW, Lindenmayer DA, et al. Three histopathological types of retinoblastoma and their relation to heredity and age of enucleation. J Med Genet 1996; 11: 923-7.
13. Blinkert AW, Moll AC, Jager MJ, Den Otter W, Koten JW, Faber JAJ, Tan KEWP. Distribution of tumors in the retina in hereditary retinoblastoma patients. Ophthalmic Genet 1998; 2: 63-7.