ARTICLE

The Development of Young Children With Retinoblastoma

Gail Ross, PhD; Evelyn G. Lipper, MD; David Abramson, MD; Lawrence Preiser, MA

Objectives: To assess the health and development of children with retinoblastoma (RB), or cancer of the retina, and to determine if they are at greater risk for developmental delays than normal children. Specific aims were to determine if type of RB (unilateral vs bilateral), family history, and number of treatment types affected mental and motor development.

Design: Descriptive study based on medical record review and pediatric, psychological, and visual evaluations.

Setting: Major referral center for patients with RB and early intervention program in a voluntary urban hospital.

Subjects and Methods: Fifty-four children younger than 41 months with RB who attend an ophthalmology oncology clinic were recruited for study. Measures included demographic variables such as social class and race/ethnicity, and medical factors such as age at diagnosis (<18 months vs >18 months), type of RB (unilateral or bilateral), family history of RB, and number and types of treatments. All children received a pediatric examination that assessed physical growth and health; a behavioral test of visual acuity using Teller acuity cards; and the Bayley Scales of Infant Development II, a standardized test of mental and motor development. Children found to have delays were referred to intervention services to treat their specific areas of weakness.

Results: Three quarters of the children had had 1 eye enucleated; 51 of 54 had normal vision in at least 1 eye, and the other 3 had partial vision in 1 eye. Except for the RB, 46 children were largely normal in growth and health, and 8 had medical diagnoses that were unrelated to RB or its treatment. The average mental and motor development scores were in the normal range (91.4±16.3, and 91.1±13.4) and not significantly lower than the normal population. Twenty-six children were referred for early intervention services, and 21 of 26 were referred for services to improve their visuomotor coordination. Demographic variables were not associated with medical variables or outcome. Children with bilateral RB, in which both eyes are affected, performed significantly less well in motor development, received many more types of treatments, and were more likely to be referred for visuomotor therapy than children with unilateral RB.

Conclusions: Children with RB generally function normally in terms of physical health and mental and motor development. However, they are more likely to show delays in visuomotor integration. Early developmental evaluations may improve the visuomotor development of children with visual impairment due to RB.

Arch Pediatr Adolesc Med. 2001;155:80-83

From the Departments of Pediatrics (Drs Ross and Lipper and Mr Preiser) and Ophthalmology (Dr Abramson), New York Presbyterian Hospital, New York, NY.

RETINOBLASTOMA (RB), a cancer of the retina, affects 1 in every 15000 to 30000 infants born in the United States.[1] Unilateral tumors are diagnosed in 75% of children with RB, and the remaining 25% have bilateral tumors.[2] At present, 95% of children in the United States survive RB; the survival rate is highest in children diagnosed prior to 2 years of age.[2]

Retinoblastoma can be successfully treated with several modalities. The most common treatment is surgical removal of the eye(s), or enucleation.[3] External beam irradiation is effective and well tolerated by the eyes.[4] With cryotherapy, the tumors are destroyed by freezing the tumor foci.[3] Lasers have been used to burn the tumors themselves, with or without destroying the retinal blood supply.[5] Focal radiation (brachytherapy) can irradiate small tumors without exposing the brain or sinuses to radiation.[6] Systemic chemotherapy has been used to shrink tumors (chemoreduction)[7] so that they can be treated with lasers, cryotherapy, or plaques. Recently, periocular injections of chemotherapy have been effective in treating intraocular tumors without systemic toxicity.

One reason for studying children with RB is to assess the effects of visual impairment on development in a group of children who are otherwise normal. Most studies on the relationship between visual impairment and development are of children who are blind. In general, blind children are delayed in acquisition of social, cognitive, and motor skills.[8-10] However, as the causes of most childhood blindness are also associated with neurologic impairment,[8,11] it is often difficult to determine to what ex-

SUBJECTS AND METHODS

STUDY GROUP

The sample consisted of 54 of 62 consecutive children between 6 and 40 months old who attended the Ophthalmology Oncology Center at New York Presbyterian Hospital in 1998 and 1999. The Ophthalmology Oncology Center is a major treatment center for children with RB. Eight of the 62 children did not participate because of constraints of medical treatment or travel. **Table 1** presents the demographic background characteristics of the children. The race/ethnicity and social class (A. B. Hollingshead, unpublished data, 1975) of the participants were representative of the total population treated at the Ophthalmology Oncology Center.

MEASURES

A study coordinator attended the Ophthalmology Oncology Center to recruit children for developmental examinations given through the Early Intervention Program at New York Presbyterian Hospital. All parents signed consent forms for their children to participate. Data were collected on the children's demographic and medical background, including the age of diagnosis, extent of RB (unilateral or bilateral), type(s) of treatment (enucleation, cryotherapy, laser, chemotherapy, radiation therapy, or plaque), family history of RB, and other medical factors. Each child received a pediatric examination, a test of visual acuity,[16] and a psychological evaluation. Level of development was assessed with the Bayley Scales of Infant Development II,[17] a standardized test of mental and motor development for children between birth and 40 months of age. The Mental Scale is composed of test items covering language, problem solving, imitation, and visuomotor ability. The Motor Scale measures gross and fine motor abilities. Although the Mental Scale yields only an overall score, the test items have been factor-analyzed into 5 domains: eye-hand coordination, manipulation, object relations, imitation/comprehension, and vocalization.[18]

The Early Intervention Program team referred children with developmental delays to early intervention services such as visual training, visuomotor therapy, cognitive stimulation, speech therapy, and behavior modification. Because funding is provided solely for children with documented problems, only those children who had documented delays were referred for interventions, and the recommendations were specific to the domain(s) in which the delays were found.

DATA ANALYSIS

Analyses of variance, correlations, and χ^2 tests were conducted to determine if demographic variables such as social class, race, or gender were related to developmental outcome on the Bayley Scales and to determine the relationships among medical variables. A multivariate analysis of variance was performed with type of RB (bilateral vs unilateral), family history of RB, age of diagnosis ($\leq$18 months vs $>$18 months), and treatment (enucleation only vs 2, 3, 4, or 5 combinations of treatments) as the independent variables. The average mental ability (Bayley MDI), average motor ability (Bayley PDI), and visuomotor development (as indexed by referral for visuomotor therapy) tests were the dependent variables. The F statistic from the multivariate analysis of variance is based on the Roy test.[19] We calculated the percentage of test items requiring visuomotor skills that each child failed on the Bayley Mental Scales. A *t* test was performed to compare the percentage of visuomotor items failed by children referred for visuomotor intervention with those who were not.

tent visual impairment, independent of other disabling conditions, accounts for developmental delays. A comparison of a heterogeneous group of children in which some were blind, some had partial vision, and some had normal sight found that whereas blind children are delayed in motor development, those with partial sight move normally but tend to have problems with balance and visuomotor skills.[11]

Most research specifically on children with RB deals with the medical aspects of their illness,[12] but a few studies have examined the children's development. One study on children who were blind from RB suggested that they were more intelligent than either children who were blind from other causes or children with sight.[13] Two other studies had more equivocal results. One found that although children blind from bilateral RB had higher IQ scores than their sighted siblings, unilaterally affected children did not differ from their siblings, and children with bilateral RB who had normal vision performed less well than their siblings.[14] The other indicated that blind children with RB performed significantly better on a tactile analog of a block design task than children with sight or those blind from other causes, but that they were not superior to the other 2 groups in verbal abilities.[15] Those studies are confounded by small numbers of subjects and the use of different IQ measures for blind and sighted children. Most important, they were published 30 years ago, when diagnosis and treatment for RB were considerably different from today. In contrast, our study is of a larger number of children with RB who have benefited from recently developed medical treatments. The children in our study are also younger and less likely to be blind in both eyes.

The aim of this study was to assess the mental and motor development of a current group of young children with RB to determine if they are at greater risk of developmental delays than the normal population. Other objectives were to determine whether the children's medical characteristics, such as type of RB (unilateral vs bilateral), family history of RB, age of diagnosis, and type and number of treatments, were related to developmental outcome.

RESULTS

MEDICAL CHARACTERISTICS

As presented in **Table 2**, the most common type of treatment for RB was enucleation, which had been performed on three quarters of the children. Approximately half of the children had undergone at least 3 different types of treatments (eg, enucleation, cryotherapy, laser therapy).

Table 1. Demographic Background of 54 Children With Retinoblastoma

Characteristic	No. (%)
Sex	
Male	23 (43)
Female	31 (57)
Race/ethnicity	
White	21 (39)
African American	17 (31)
Hispanic	13 (24)
Asian	3 (6)
Social class	
Major business and professional	7 (13)
Medium business, minor professional, technical	9 (17)
Skilled crafts workers, clerical, sales workers	12 (22)
Machine operators, semiskilled workers	17 (31)
Unskilled laborers, menial service workers	9 (17)

Table 2. Medical Characteristics of Children With Retinoblastoma*

	Unilateral	Bilateral	Total
Type of retinoblastoma	21	33	**54**
Family history	0	15	**15**
Type of treatment			
Enucleation	20	21	**41**
Cryotherapy	1	29	**30**
Laser therapy	1	19	**20**
Radiation therapy	0	7	**7**
Plaque	1	13	**14**
Chemotherapy	3	22	**25**
No. of treatment types			
1	16	1	**17**
2	3	6	**9**
3	2	11	**13**
≥4	0	15	**15**
Age of diagnosis, mo			
Mean ± SD	17.6 ± 7.5	7.6 ± 7.1	. . .
≤18	11	30	**41**
>18	10	3	**13**

**Data are given as number of patients unless otherwise indicated.*

Significant differences occurred in the backgrounds of children with unilateral and bilateral RB. Children with bilateral RB were much more likely to have a family member with RB than were children with unilateral RB (χ^2_1=13.3, P<.001). Regarding treatment, 16 of 21 children with unilateral RB had only enucleation of the eye, whereas 32 of 33 children with bilateral RB had more and different types of treatments than those with unilateral RB. Only 1 child with bilateral RB had just enucleation (χ^2_1=31.84, P<.001).

OVERALL OUTCOME

As seen in **Table 3**, 46 children (85%) were physically healthy other than having RB. Only 5 of 54 children were below the fifth percentile in height and weight. All but 3 children had normal visual acuity in at least 1 eye, and the other 3 had partial visual acuity in 1 eye. Although most of the children with RB had normal mental and motor development, 26 (48%) were referred for intervention services. Of these children, 21 were referred for visuomotor skills, some of whom were also referred for visual training, language, behavior, and cognitive development. Children referred for visuomotor intervention were much more likely to fail test items requiring eye-hand coordination on the Bayley Mental Scale (eg, putting pegs into a pegboard) than children who were not referred for visuomotor intervention (t_{52}=5.87, P < .001; means=50.6% ± 13.5%, and 27.4% ± 14.4%, respectively).

Table 3. Developmental Outcome of 54 Children With Retinoblastoma*

	Unilateral (n = 21)	Bilateral (n = 33)	Total (N = 54)
Bayley MDI score			
Mean ± SD	96.3 ± 15.6	88.3 ± 16.1	91.4 ± 16.3
>90	16	15	**31**
80-89	2	11	**13**
70-79	2	4	**6**
<70	1	3	**4**
Bayley PDI score			
Mean ± SD	99.9 ± 10.9	85.4 ± 11.8	91.1 ± 13.4
>90	16	14	**30**
80-89	5	11	**16**
70-79	0	5	**5**
<70	0	3	**3**
No. of subjects with no other medical problems	18	28	**46**
Growth			
<5th percentile, height	2	3	**5**
<5th percentile, weight	2	3	**5**
Referred for intervention			
Any intervention	9	17	**26**
Visual training	2	2	**4**
Visuomotor	7	14	**21**
Language	2	4	**6**
Cognitive	2	2	**4**
Behavior	1	1	**2**

**Data are given as number of subjects unless otherwise indicated. Bayley MDI indicates average mental ability test; Bayley PDI, average motor ability test.*

The mean Bayley MDI score was 91.4±16.3; the mean Bayley PDI score was 91.1±13.4. Those scores are both within the average range and are not significantly different from the standardized normal score of 100±15. None of the demographic variables of sex, race/ethnicity, or social class were related to MDI or PDI scores or to referral for visuomotor therapy.

Results showed that type of RB was significantly associated with development ($F_{3,44}$=5.0, P < .006). The children with bilateral RB scored significantly less well on motor ability than children with unilateral RB ($F_{1,54}$=6.88, P < .001). Children with bilateral RB were more likely to be referred for visuomotor therapy because of developmental assessment than children with unilateral RB ($F_{1,54}$=3.70, P < .06). However, there was no significant difference between children with unilateral and bilateral RB on mental ability scores. Children with unilateral and bilateral RB also did not differ with regard to other medical illnesses or deficits in height or weight.

The number of treatment types that children received was also related to overall outcome ($F_{3,44}$=4.48, P<.005). In particular, children who had various treat-

ments were much more likely to be referred for visuomotor problems than children who received only enucleation ($F_{1,54}$=3.28, $P < .02$). Three (18%) of 17 children given only enucleation were referred for visuomotor therapy in contrast to 18 (49%) of 37 children who received several treatments. Thus, the children with bilateral RB were more likely to have multiple types of treatments for their disease and to require referrals for delays in visuomotor coordination.

Age of diagnosis, family history of RB, and number of treatments were not significantly related to mental and motor scores on the Bayley Scales, and age of diagnosis and family history were not associated with referrals for visuomotor difficulties.

COMMENT

Most of the children we studied had normal vision in at least 1 eye. Other than having RB, most of them exhibit good health, good physical development, and normal mental and motor ability scores. Nonetheless, 39% were referred for intervention to improve their visuomotor development. Most children with RB (both unilateral and bilateral) had good vision in 1 eye. The fact that many evidenced difficulty in visuomotor tasks confirms previous studies indicating that children with partial vision exhibit problems with visuomotor integration and with movement in space.[11] Tasks of visuomotor development require eye-hand coordination and depth perception, such as placing pegs into holes or putting puzzle pieces into form boards. Binocular vision is also important for moving in space; therefore, it is expected that children with limited depth perception and limited field of vision may have delays in achieving motor milestones. The Mental Scales of the Bayley examination measure eye-hand coordination, and the Motor Scales include measures of gross motor development, such as crawling or walking up stairs, and fine motor development, such as picking up small objects or tracing lines. The presence of those items on the Bayley Scales may explain why the average scores for children with RB, although within the normal range, are somewhat below expectations for the average child without RB. Furthermore, observations during testing indicated that poor visuomotor integration and coordination was not always reflected in children's developmental scores. Frequently, children with RB were able to pass test items that required visuomotor coordination, although they accomplished the tasks at a slower pace or with poorer quality of movement than normal children.

The finding that children with bilateral RB have significantly lower motor scores than children with unilateral RB may be because they undergo a greater number of treatments, including chemotherapy and plaque, laser, and radiation therapy. These therapies, particularly in combination, may have more debilitating effects on motor development than a single incidence of enucleation, the most common treatment for children with unilateral disease. Age at diagnosis was not related to either developmental scores or referrals for visuomotor problems. However, if early diagnosis had led to early developmental interventions, there might have been a positive association between age at which RB was first diagnosed and good developmental outcome.

In summary, despite retinal cancer, nearly all of the children studied had normal vision in 1 eye. In addition, most of them displayed normal physical health and growth, with the exception of the RB. On average, the children's mental and motor ability scores were in the normal range and were not significantly different from norms for children in the United States. Nonetheless, more than a third were referred for intervention services because of delays in visuomotor coordination. Children with bilateral RB (but with vision in 1 eye) were more likely to receive multiple types of treatment, to be delayed in motor development, and to require referrals for visuomotor coordination than children with unilateral RB. Results indicate that the prognosis for children with RB is good, but that they should receive developmental evaluations and both visual and visuomotor training as soon as possible after diagnosis to enhance their overall development.

Accepted for publication September 3, 2000.

This study was funded by the New York Community Trust and by the Rudin Foundation, New York, NY.

Presented as a poster at the 1999 Annual Meeting of the Pediatric Academic Society, San Francisco, Calif, May 1999.

We wish to thank Barbara Ladenheim, PhD, for her work in assessing the visual acuity of the children and Stacey Weinberg, MA, for her review of the medical records.

Corresponding author and reprints: Gail Ross, PhD, Department of Pediatrics, N506, Weill-Cornell Medical College, New York Presbyterian Hospital, 525 E 68th St, New York, NY 10021.

REFERENCES

1. Pendergass TW. Incidence of retinoblastoma in the United States. *Arch Ophthalmol.* 1980;98:1204-1210.
2. Abramson DH. The diagnosis of retinoblastoma. *Bull N Y Acad Med.* 1988;64:283-317.
3. Alberti WE, Sagerman RH. Diagnosis and management of retinoblastoma. In: Alberti WE, Sagerman RH, eds. *Radiotherapy of Intraocular and Orbital Tumors.* Berlin, Germany: Springer Verlag; 1993.
4. Abramson DH, Kevork N, Ellsworth RM, et al. Changing trends in the management of retinoblastoma. *J Pediatr Ophthalmol Strabismus.* 1994;31:32-37.
5. Abramson DH. The focal treatment of retinoblastoma with emphasis on xenon arc photocoagulation. *Acta Ophthalmologica.* 1989;67:1-63.
6. Abramson DH, Javitt J, Ellsworth RM, et al. Treatment of bilateral groups I through II retinoblastoma with bilateral radiation. *Arch Ophthalmol.* 1995;99:1761-1762.
7. Abramson DH. Retinoblastoma. *CA Cancer J Clin.* 1982;32:130-142.
8. Fraiberg S. *Insights From the Blind.* New York, NY: Basic Books; 1977.
9. Ferrell K, Trief E, Deitz S, Bonner MA, Cruz D, Stratton JM. The visually impaired infants research consortium. *J Vis Impairment Blindness.* 1990;84:404-410.
10. Griffin HC. Motor development in congenitally blind children. *Educ Vis Handicapped.* 1981;12:106-111.
11. Jan JE, Sykanda A, Groenveld M. Habilitation and rehabilitation of visually impaired and blind children. *Pediatrician.* 1990;17:202-207.
12. Augsburger JJ, Oehlschlager U, Manzitti JE. Multinational clinical and pathologic registry of retinoblastoma. *Graefes Arch Clin Exp Ophthalmol.* 1995;233:469-475.
13. Williams M. Superior intelligence of children blinded from retinoblastoma. *Arch Dis Child.* 1968;43:204-210.
14. Witkin HA, Oltman PK, Chase JB, Friedman F. Cognitive patterning in the blind. In: Hellmuth J, ed. *Cognitive Studies.* New York, NY: Brunner/Mazel; 1971;16-46.
15. Levitt EA, Rosenbaum AL, Willerman L, Levitt M. Intelligence of retinoblastoma patients and their siblings. *Child Dev.* 1972;43:939-948.
16. Teller DY, McDonald M, Preston K, Sebris SL, Dobson V. Assessment of visual acuity in infants and children. *Dev Med Child Neurol.* 1986;28:779-789.
17. Bayley N. *Bayley Scales of Infant Development.* 2nd ed. San Antonio, Tex: Psychological Corp; 1993.
18. Kohen-Raz R. Scalogram analysis of some developmental sequences of infant behavior as measured by the Bayley Infant Scale of Mental Development [monograph]. *Genet Psychol Monogr.* 1967;76:3-21.
19. Roy J, Bargmann RE. Tests of multiple independence and the associated confidence bounds. *Ann Math Stat.* 1958;29:491-503.