A prospective study of children treated for retinoblastoma: Cognitive and visual outcomes in relation to treatment

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ABSTRACT.
Purpose: **To assess cognitive and visual outcomes in children treated for retinoblastoma.**
Patients and Methods: **A population-based group of 22 children treated for retinoblastoma were followed in a longitudinal, prospective study. Eleven children had unilateral tumours, all of which had been enucleated. The remaining 11 had bilateral tumours. Seven of these had undergone unilateral enucleation and local or external beam radiation to the other eye. Four children had been treated with local or external beam radiation only. Cognitive outcome and visual function was assessed at 4 and 6 years of age.**
Results: **We found no general delay in cognitive or motor development at 4 or 6 years of age. Better cognitive capacities were found in the bilateral/irradiated retinoblastoma patients than in unilateral/non-irradiated patients. However, two of the irradiated children, both of whom had been treated at 1 month of age, performed below group mean. None of the children was totally blind. Three children were visually impaired due to tumours affecting the macular area in the remaining eye; another three had subnormal visual acuity but no macular pathology. A total of 14 children had been enucleated and had normal vision in the remaining eye. Visual fields and dark adaptation were adversely affected in a few cases, but colour vision was normal in all.**
Conclusion: **Bilateral retinoblastoma seems to be associated with superior cognitive capacities. Few children were visually impaired according to WHO criteria. We speculate that children treated during the first months of life may be at risk of adverse cognitive and visual outcomes. The immature brain may be affected by radiation treatment, causing both cognitive and visual deviations.**

Key words: retinoblastoma – treatment – vision – intelligence

Acta Ophthalmol. Scand. 2002: 80: 294–299

Retinoblastoma is the most common malignant intraocular tumour in childhood. It usually presents before 4 years of age (Shields & Shields 1992). The majority of children have sporadic unilateral disease, but about 40% have hereditary retinoblastoma, usually characterized by the presence of tumours in both eyes (Cavanee et al. 1985, 1986). Once invariably fatal, the mortality rate of retinoblastoma has now been reduced to less than 5% in Sweden, as in most countries in the western world (Kock & Naesser 1970; Adami et al. 1992). The expected annual incidence of retinoblastoma in Sweden is only six or seven new cases, necessitating centralization of management. Currently, the National Retinoblastoma Centre is located at St. Erik's Eye Hospital in Stockholm. During 1980–95, 85% of Swedish children with large unilateral tumours were subjected to enucleation, while 50% of those with bilateral disease underwent enucleation of the more affected eye. External beam radiotherapy (EBR), brachytherapy or both have been used for a large proportion of the remaining eyes with tumours (Seregard & Lundell, unpublished data).

Retinoblastoma now rarely results in blindness. In patients with macular retinoblastoma, the visual outcome depends on the size of the tumour and whether the fovea is involved. Holbek & Ehlers (1989) followed the development of visual function in 57 Danish children who had been treated for retinoblastoma with local cobalt application (36 eyes) or EBR (10 eyes). They found poor visual acuity (VA) in eyes where the tumour was at the macula. Refraction was within the normal range. Rod function (i.e. visual fields and dark adaptation) was relatively resistant to the radiation treatment, whereas acquired dyschromatopsia was present in 30% of eyes.

There is no information available about neurobehavioural outcome in children treated with irradiation for retinoblastoma. However, studies have been carried out on the effects of irradiation treatment in infants with brain tumours and leukaemia. Suc et al. (1990) studied 20 children with brain tumours, all treated with irradiation before 3 years of age. A total of 85% of the children had impaired cognitive function, and only two had no late effects. Moreover, a longitudinal study of children with leukaemia who had been treated early in life with irradiation and chemotherapy found that cognitive capacities were impaired (Smedler et al. 1995a; Smedler & Bolme 1995b). In this, the authors stress that irradiation represented the most important risk factor, especially for children treated before 3 years of age. Jannoun (1983) found that children treated at under 3 years of age displayed the greatest reductions in neurobehavioural development. Several investigators have reported that performance IQ was more reduced than verbal IQ. Arithmetic skills were sometimes impaired and visual-motor deficiencies were common. Problems with attention and memory were also noted. The consensus in the literature seems to be that irradiation to the brain is a neuropsychological risk factor, the effects of which are more severe when children are treated early in life. However, the effects of focused irradiation have been less well-explored (Smith 1997). Fletcher & Copeland (1988) discussed the relation between neurobehavioural deficits and age of treatment and cited several studies revealing white-matter alterations in children treated with cranial radiation (CR) before 5 years of age.

In 1991, we began a longitudinal, prospective research project in order to study the long-term effects of retinoblastoma. The project group consisted of the retinoblastoma team at St Erik's Eye Hospital, a paediatric ophthalmologist, a clinical psychologist and a research psychologist. The aims of the study were:

(1) to study the cognitive and visual outcomes in patients after treatment, and

(2) to study the emotional reactions of parents and children after the diagnosis had been made.

This paper aims to address the first question. The second question has been dealt with in a separate paper (Ek 2000).

Methods

Subjects

All children in Sweden diagnosed with retinoblastoma between January 1992 and December 1994 were included in the study and studied prospectively. The total number of children was 22. This represents the total population of patients diagnosed with retinoblastoma during this 3-year period in Sweden. It has been verified with the National Cancer Register of Sweden. Eight of the children were boys; 14 were girls.

Treatment

Five children had familial retinoblastoma. While routine chromosomal screening studies were negative, more detailed studies using single-strand confirmation polymorphism analysis and gene sequencing revealed diverse RB1 gene point mutations and/or small deletions in these children. However, no child had large RB1 gene deletions or clinical evidence of the 13q deletion syndrome.

Eleven children (nos. 1–11) had the unilateral form of the disease and were treated with enucleation of one eye. In addition, one girl (no. 8) was treated with cytotoxic drugs due to a relapse in the orbit. The mean age at the time of diagnosis was 34 months (range 9–89 months). Two children were diagnosed late, at 68 and 89 months.

Eleven children had bilateral retinoblastoma (nos. 12–22). Their mean age at diagnosis was 9 months (range 0.5–36 months. Seven of these children underwent enucleation in one eye. The remaining eye was treated with external beam radiation (five patients) and ruthenium plaques (two patients). In four children (nos. 19–22), no enucleation was performed; three of them underwent external beam radiotherapy bilaterally and the fourth was treated with ruthenium plaques. All data concerning patient characteristics are shown in Table 1.

Between 1980 and 1995, orbital implants were not normally inserted immediately as part of the primary procedure following enucleation. Implants were often inserted as a secondary procedure 6 months or more afterwards. External beam radiotherapy was administered in 23 fractions, delivering 46 Gy over 5 weeks with a lateral, lens-sparing approach. Part of the cerebral frontal lobes is included in the field of radiation when a lateral beam is used in EBR for retinoblastoma. However, the estimated dose received by any part of the brain is quite small (< 5 Gy). The delivery of each fraction required general anaesthesia for about 5–10 min. When only brachytherapy was given, ruthenium 106 radioactive plaques were fixed to the scleral surface for 10–20 hours in order to deliver 45 Gy to the apex of the tumour. Treated and fellow eyes were examined with bilateral indirect ophthalmoscopy at 2–4 weeks after treatment and then at 3-month intervals. Follow-up examinations were usually performed under general anaesthesia (Seregard & Lundell, unpublished data).

Procedure and assessment

At the ages of 4 and 6 years, the development and cognitive levels of 21 children were evaluated by the participating psychologist. (UE) Visual function was assessed by the paediatric ophthalmologist. One girl (no. 11), aged 7.5 years when diagnosed, was excluded from the psychological assessment programme because of her age and one boy diagnosed at 5.5 years was assessed at 6 years only. By October 2000, all children had been evaluated.

Assessment of visual function

Visual function was assessed at 4 years of age in all but two children, both of whom were diagnosed after the age of 4 years. Monocular single and linear optotype acuities were evaluated. Visual fields were assessed with confrontation techniques and only the outer limits were measured. Children with binocular disease were retested at 6 years. At that age, colour vision and dark adaptation were assessed. The PV-16 Quantitative Colour Vision Test (a version of Farnsworth-Munsell D-15, adapted for children) and a dark adaptation test for children were used (Thornton 1977). Both tests were designed by Lea Hyvärinen and produced by Precision Vision, Villa Park, Illinois, USA. Refraction was measured with retinoscopy under cycloplegia.

The term 'subnormal visual acuity' is used in this text when linear optotype acuity is less than 0.8.

Visual impairment was categorized according to WHO criteria (i.e. VA <0.3). The term 'total blindness' refers to a condition of no light perception.

Developmental assessment

The developmental assessment included an evaluation of the intellectual level and the cognitive profile. The Swedish adaptation of the Griffiths', Developmental Scales was used at the 4-year assessment (Alin-Åkerman & Nordberg 1980; Griffiths 1990). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R 1999) was used when the children were 6 years old. In a few cases, subtests from the neuropsychological test battery NEPSY (NEuroPSYchological assessment for children) were added (Korkman 1988). The mean period between initial treatment and the final psychological assessment was 4 years for children with unilateral retinoblastoma and 5 years for those with bilateral retinoblastoma. Parents were interviewed about the child's behaviour. No comparison group was used; test results were compared to the standardized test norms. The study group was treated mainly as a multiple case study and the results of the visual and cognitive assessments were discussed in relation to treatment with members of the research team.

Results

Visual function

All children with unilateral disease had normal VA in their only eyes at the age of 4 years. Three children with bilateral retinoblastoma were visually impaired with VA less than 0.2 (nos. 13, 14, 16), as a consequence of tumours located at the macula. Two children with bilateral disease (nos. 15, 20), both of whom had been treated with EBR very early in life, each had subnormal VA in the better eye. None of them had tumours affecting the macular region. One boy (no. 19), treated at 12 months, had subnormal linear acuity but displayed normal VA when assessed with single optotypes, thereby indicating a crowding problem (Flom et al. 1963). His macular regions were normal in appearance. See Table 1.

Children with bilateral disease were assessed again at 6 years of age (Table 2).

Table 1. Visual outcome at 4 years and cognitive outcome at 4 and 6 years.

Patient no.	Sex	Sporadic/ familial	Uni/Bi lateral	Age at diagnosis (months)	Treatment L/R	Visual acuity optotype L/R 4 years	DQ 4 years	IQ 6 years
1	F	S	U	24	–/E	0.8/0	127	128
2	M	S	U	68	E/–	7 yrs 0/1.0	*	100
3	M	S	U	29	E/–	0/0.8	93	92
4	M	S	U	29	E/–	0/1.0	101	110
5	F	S	U	9	E/–	0/0.8	118	129
6	M	S	U	32	E/–	0/0.8	104	107
7	M	S	U	24	–/E	1.0/0	106	115
8	F	S	U	28	–/E	0.8/0	106	115
9	F	S	U	19	E/–	0/0.8	117	115
10	F	S	U	29	–/E	0.8/0	110	126
11	F	S	U	89	–/E	9 yrs 1.0/0	†	†
12	M	S	B	33	E/RU	0/1.0	116	131
13	F	S	B	1	EBR/E	0.03/0	104	100
14	F	S	B	12	EBR/E	0.15/0	135	149
15	F	S	B	1	E/EBR	0/0.5	90	85
16	F	S	B	5	E/EBR	0/0.08	127	125
17	F	F	B	36	E/RU	0/1.0	117	109
18	M	S	B	3	E/EBR	0/0.8	119	127
19	M	F	B	0.5	RU/RU‡	0.15/0.4	107	111
20	F	F	B	3.5	EBR/EBR	0.03/0.5	130	122
21	F	F	B	4	EBR/EBR	0.8/1.0	133	156
22	F	F	B	3	RU/RU	1.0/1.0	129	140

M = male; F = female; U = unilateral; B = bilateral; L = left; R = right
E = enucleated; EBR = external beam radiation; RU = ruthenium plaques
DQ = Developmental Quotient
IQ = Intelligence Quotient
* Subject 2 assessed at six years of age
† Subject 11 was excluded from the developmental assessment
‡ Treated with EBR at 12 months

Visual acuity had improved in the three children with subnormal acuities and normal macular appearances, indicating a delay in visual development. Each of these three children had problems with attention. Dark adaptation was abnormal in three children. Two of these had extensive scarring of the posterior pole after treatment (nos. 13, 16). Colour vision, however, was normal in all children. Four children had visual field defects.

One girl (no. 15), who had been treated with EBR at the age of 1 month, did not show any scarring within the macula in her only eye. Nevertheless, she had subnormal VA (0.6) and apparent problems in seeing at night. She also exhibited nystagmus and, in addition, had attention problems.

Cognitive outcome

At the 4-year assessment, the raw scores for each child were converted into developmental quotients (DQ) (mean = 100, SD = 15). Stanine scores (standard 9, mean = 5, SD = 2) were calculated for each of the six subscales of Griffiths Developmental scales and individual profiles were drawn for each child. We found no typical profile and no evidence of lower scores on the performance scales than on the verbal scales. Surprisingly, the mean scores of the irradiated/bilateral group were higher than those of the non-irradiated/unilateral group on three out of six subscales. Two of these (speech and practical reasoning) are mainly verbal scales measuring language development, short-term memory and understanding of concepts. The third, performance, contains visual-motor and non-verbal reasoning items. Mean DQ, for all six subscales, was 108 for the unilateral group and 119 for the bilateral group.

At the 6-year assessment, the raw scores on six verbal and five performance tests of WPPSI-R were converted into scaled scores (mean = 10, SD = 3) and a profile was drawn for each child. Verbal IQ, performance IQ and full scale IQ were calculated for each child. As in the 4-year assessment, we found no typical profile and no differences between verbal and performance scores. Mean IQ was 114 for the unilateral/non-irradiated subjects and 123 for the bilateral/irradiated subjects. However, two children (nos. 13, 15) in the irradiated group differed markedly from the rest at both the 4-year and the 6-year assessments. Both their overall scores and their profiles were depressed. They had been treated with EBR during

Table 2. Visual function at 6 years in children with bilateral retinoblastoma.

Patient	Sex	Age at radiation (months)	Treatment L/R	Visual acuity optotype 4 years L/R	Visual acuity optotype 6 years L/R	Refraction L/R	Visual field	Colour vision†	Dark adaptation
12	M	39	E/RU	0/1.0	0/1.0	–/0	defect	normal	normal
13	F	1.5	EBR/E	0.03/0	0.05/0	+ 3.5/–	defect	normal	subnormal
		24	RU/						
14	F	13	EBR/E	0.15/0	0.15/0	+ 1.5 = – 1c0°//-	nc	normal	normal
15*	F	1.5	E/EBR	0/0.5	0/0.6	–/ + 2.75	normal	normal	subnormal
16	F	6.5	E/EBR	0/0.08	0/0.1	–/ + 1 = – 2.5c15°	defect	normal	subnormal
17	F	36	E/RU	0/1.0	0/1.0	–/ + 1	np	normal	np
18	M	7	E/EBR	0/0.8	0/1.0	–/ + 2	np	normal	normal
19	M	0.5	RU/	0.15/0.4	0.8/0.6	+ 1.5 = – 1c135°//0	normal	normal	np
		3	/RU						
		12	EBR/EBR						
20	F	3.5	EBR/EBR	0.03/0.5	0.03/0.6	+ 2/ + 0.75	defect	normal	np
21	F	4.5	EBR/EBR	0.8/1.0	0.8/0.8	+ 2.5/ + 2.5	nc	normal	normal
22	F	3	RU/RU	1.0/1.0	1.0/1.0	+ 1.0/ + 1.5	normal	normal	normal
		42	RU/RU						

M = male; F = female; U = unilateral; B = bilateral; L = left; R = right
E = enucleated; EBR = external beam radiation; RU = ruthenium plaques
nc = no co-operation; np = not performed
* Crowding, nystagmus, tvh
† Colour vision was tested monocularly in subjects 19, 21, 22 and binocularly in subject 20

their first month of life. When comparing the results of these children to the results of those treated at the age of 3 months or more, they were 2 SD below on both occasions (Fig. 1.).

A *t*-test for equality of means was performed. The two groups differed significantly at 4 years ($p = 0.003$) and 6 years ($p = 0.022$) of age in favour of the bilateral group. The two children irradiated at 1 month of age were excluded. No correction for multiple scales was used as only IQ and DQ were used in the analyses. We also found a high correlation ($r = 0.89$) between the results at 4 and 6 years of age.

By the end of the study, all children had started school. They were all in mainstream education; the visually impaired children had access to assistant teachers.

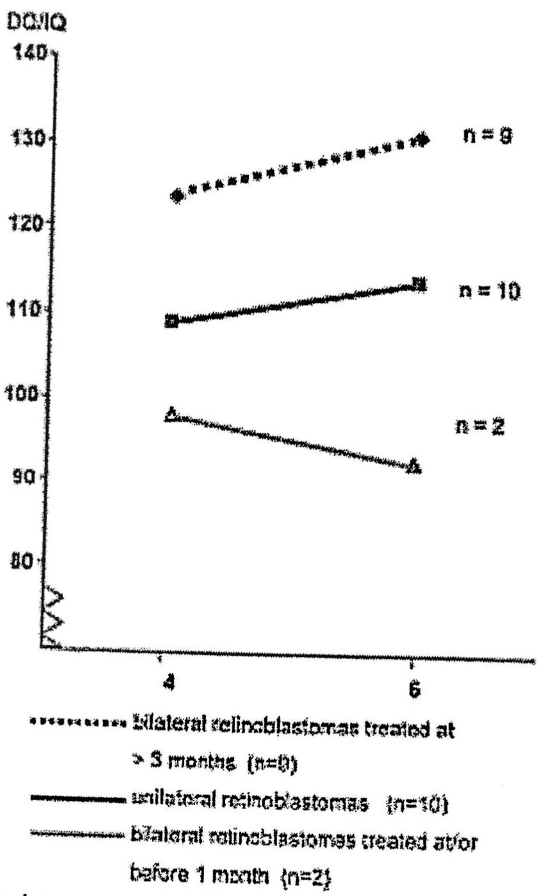

Fig. 1. Mean development quotient (DQ) and mean intelligence quotient (IQ) at 4 and 6 years of age.

Discussion

Our study group comprised all children diagnosed with retinoblastoma in Sweden between 1992 and 1994. The group was population-based and can be considered representative.

The outcome for the children in the study group was surprisingly good. All children survived. No child was totally blind. Three children of 22 were visually impaired according to WHO criteria.

However, 18 children had only one eye, with a consequent loss of the binocular visual field. Several authors have evaluated VA outcome in children treated for retinoblastoma (Migdal 1983; Lam et al. 1990; Lueder & Goyal 1996). Tumours affecting the macula result in poor VA. Holbek & Ehlers (1989) assessed not only acuity but also visual fields and colour vision in patients previously treated for retinoblastoma. They found visual field defects and acquired colour vision defects in some subjects.

In the present study, macular involvement resulted in low visual acuity. Colour vision, however, was found to be normal, including in those children with macular scarring. Three children, two with extensive scarring of the posterior pole and one who was treated very early in life, all had a history of severe visual problems at night. We found that they had poor dark adaptation. These findings suggest the rods are less resistant to external beam radiation than the cones, at least in the immature retina.

Retinoblastoma and intelligence were intriguing fields of research in the 1960s and 1970s. Thurrell & Josephson (1966) assessed a clinical impression held by many teachers in schools for the blind that children who become blind from retinoblastoma are very intelligent. The authors speculated about possible factors that might account for this finding and a genetic link was discussed. Other authors confirmed the cognitive superiority discussed by Thurrell & Josephson, comparing sighted and blind retinoblastoma patients to their normal siblings (Williams 1968; Eldridge et al. 1972). Levitt et al. (1972). The blind group scored, on average, 10 IQ points more than their controls, but unilaterally affected patients did not score differently to controls. The authors concluded that retinoblastoma associated with blindness may result in selective cognitive superiority, and that retinoblastoma per se was not associated with intellectual superiority or inferiority. They argued that the superior results of the blind subjects were mainly due to their having developed good compensatory techniques involving attention, memory and concentration.

To a certain extent, our findings agree with the studies carried out in the 1960s and 1970s. The children in our study with bilateral retinoblastoma obtained higher IQ scores as a group, and those treated at 3 months of life and later performed almost 2 SD above standard norms. The children with unilateral retinoblastoma performed slightly above the mean in the developmental tests on both occasions. Thus, in the present study, we found better cognitive capacities in bilateral retinoblastoma subjects on both occasions. The children who had been treated at the age of 3 months or more performed extremely well in the tests, including those with visual impairment (nos. 14, 16) whose results were 3 and 1.5 SD above the mean, respectively, at 6 years of age. Several bilateral subjects scored extremely well on the tests and three were more than 2.5 SD above standard test norms at the age of 6 years (nos. 14, 21, 22). As mentioned earlier, some data have suggested that children blind from bilateral retinoblastoma have a high cognitive level. This has been mainly ascribed to selective development of verbal and cognitive functions to compensate for blindness. None of the children in our study were blind, and we therefore have to seek an explanation elsewhere. Children with bilateral retinoblastoma carry the genetic defect in every cell. Subjects with unilateral disease carry their defect in individual cells in the retina. In these children, we found a lower, but still normal, developmental level. The literature of the 1960s and 1970s has already suggested the possibility of a genetic link accounting for the high intelligence found in bilateral retinoblastoma subjects. Our results appear to support these speculations and the finding ought to be further explored.

Two children were treated with EBR during their first months of life for bilateral retinoblastoma. Their test results were substantially lower, depressing mean results for the bilateral group. If their results were treated separately and compared to the results of the nine bilateral retinoblastoma subjects who were treated later, the difference is 2 SD at 4 years and 2.5 SD at 6 years (Fig. 1). The relatively low results for these two children lead us to speculate that very early treatment might cause adverse effects. The frontal lobe cannot be completely spared from radiation by the method used. It is well-known that the frontal area subserves executive functions; it is also known that the immature brain is more vulnerable to radiation. This could account for the cognitive deviations exhibited by these cases compared to those treated later in life.

Many studies indicate that diffuse irradiation impairs cognitive development, especially in young children. In the literature, 'young' usually means from 3 years. No studies are available on the effects of irradiation in children during the first year of life. In our study, 11 children with bilateral disease were irradiated at less than 1 month to 3 years of age. Our test results and interviews with the parents indicated no general delay in the children as a group, in cognitive and motor development, when assessed at 4 and 6 years of age.

It should also be noted that EBR may induce second tumours within the field of radiation in children treated before 12 months of age (Abramson & Frank 1998), further indicating that, whenever possible, EBR should be avoided in the treatment of retinoblastoma in young children.

The finding of subnormal, but gradually increasing, VA in the three children who were treated with external beam radiation leads us to question whether EBR not only affects cognitive functions but also affects the immature cerebral visual system. None of these three children had tumours affecting the macular region, and all of them displayed problems with attention. Another plausible explanation for subnormal VA in early irradiated eyes where the tumour has spared the macula may be that radiation treatment interferes with maturation of the immature retina. Animal experiments have shown the fovea to mature relatively late, and it may not reach maturity before 4 months of age (Hendrickson & Youdelis 1984).

However, this population-based group of children with retinoblastoma is small, and only a few children were treated very early with EBR. Interactions with other factors such as social and economical background and family history of cognitive superiority have not been taken into account. Likewise, we do not know what the specific effects of very early hospitalization and treatment might be, regardless of treatment method used. Future studies on cognitive development and visual function after treatment for retinoblastoma, carried out with the aid of electroretinography and functional brain imaging, may increase our understanding of the benefits and risks of early radiation for visual and cognitive development.

Acknowledgements

This study was financed by the Children's Cancer Foundation.

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Received on September 7th, 2001.
Accepted on February 26th, 2002.

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