EXTENDED REPORT

Stage of presentation and visual outcome of patients screened for familial retinoblastoma: nationwide registration in the Netherlands

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Background: In the Netherlands a comprehensive programme for screening just after birth for familial retinoblastoma is taking place. In this report the stage of the disease at the time of detection, by way of screening, and the long term visual outcome in these patients was evaluated.

Methods: A nationwide, retrospective study. From January 1992–July 2004, patients at risk for familial retinoblastoma were screened 1–2 weeks after birth, and investigated for laterality, Reese-Ellsworth classification/International Classification of Retinoblastoma, macular involvement, age of primary retinoblastoma , initial therapy, and visual outcome.

Results: 17 patients were diagnosed with familial retinoblastoma. 88.3% developed bilateral, 11.7% unilateral retinoblastoma. Of the 34 eyes, 56% were R-E group I, 16% were group II A-B, 16% were group III A-B, 9% were group IV, 3% were group V. Using the International Classification of Retinoblastoma, 72% were group A, 19% were group B, 6% were group C, 3% were group E. The visual outcome revealed 73.5% of eyes with 20/20–20/40, 26.5% eyes with $\leqslant$20/100–no light perception; 5.9% of eyes were enucleated, all other eyes were treated with local or conservative treatment methods. Of all eyes, 59% had extramacular retinoblastoma, 98% of patients had at least one eye with extramacular retinoblastoma.

Conclusion: Most familial retinoblastoma patients present as a R-E group I or group A when screened within 2 weeks after birth. Nearly 90% of patients had a long term visual acuity of 20/20–20/40. Despite the common occurrence of macula involvement, bilateral macula involvement was infrequent, and since most eyes were salvaged, good vision was obtained in the majority of patients.

Retinoblastoma (RB) is the most common intraocular tumour in children. Retinoblastoma is a rare disease (incidence 1:17 000 live births) and is inherited in an autosomal dominant way.[1 2] Forty per cent of the patients have bilateral (hereditary) retinoblastoma and 60% have unilateral (mostly non-hereditary) retinoblastoma. Patients with hereditary retinoblastoma always carry the germline mutation and therefore they can transmit the disease to their offspring with a risk of 50%. In patients with unilateral retinoblastoma the risk of the hereditary form is plus or minus 10%. Thus, patients with both bilateral and hereditary unilateral disease are at high risk (45%) of having offspring with retinoblastoma. Parents whose children will be at risk of having retinoblastoma often require careful counselling with regard to the likelihood of tumour development and visual sequelae. In this retrospective study we investigated the stage of presentation of all familial retinoblastoma patients that came for screening within 1–2 weeks after birth in the Netherlands. Further we investigated the laterality, the Reese-Ellsworth classification/International Classification of Retinoblastoma, macular involvement, age of primary retinoblastoma, initial therapy, and visual outcome.

MATERIALS AND METHODS

Since 1992 the retinoblastoma centre in the Netherlands has been located at the Vrije Universiteit Medical Center ophthalmology department, Amsterdam. All Dutch retinoblastoma patients are referred to this centre, which counts for plus or minus 10–15 new patients yearly.[1]

Routinely funduscopy is performed by the specialised ophthalmologist within 1–2 weeks after birth and every 2 weeks thereafter without anaesthesia until the age of 3 months. Then funduscopy is performed with all patients under general anaesthesia until the age of 4 years.[3] DNA investigation is performed with every child.

If retinoblastoma is diagnosed by means of funduscopy, ultrasonography, and retinal photography under general anaesthesia, a treatment plan will be made. The following data were documented at diagnosis: laterality, Reese-Ellsworth classification/International Classification of Retinoblastoma, macular involvement, age of diagnosis of primary retinoblastoma and presentation of the second eye, the initial therapy, and the visual acuity at the latest follow-up date. In this study, macular involvement is defined as tumour involvement of the macula and/or tumour location adjacent to the fovea.

RESULTS

From January 1992–July 2004, 135 patients presented to our centre with retinoblastoma. Patients referred form Belgium, the Netherlands Antilles, or Surinam were excluded from this study. In this period, 17 patients were diagnosed with familial retinoblastoma (table 1).

Laterality

One to 2 weeks after birth 29.4% (five) of all the 17 patients presented with unilateral retinoblastoma, of whom four eventually developed retinoblastoma in the second eye; 41.2% (seven) of the patients presented with bilateral retinoblastoma 1–2 weeks after birth, and 29.4% (five) of the patients developed their first retinoblastoma at the age of 2–7 months, four bilateral and one unilateral. In all,

Abbreviations: CRED, chemoreduction; EBRT, external beam radiotherapy; FC, finger counting; LP, light perception; NP, no perception; RB, retinoblastoma; RE, Reese-Ellsworth; TCT, thermochemotherapy; TT, thermotherapy (diode laser)

Table 1 Results of presentation of familial retinoblastoma detected by regular screening from 1–2 weeks after birth

Patient	RB	R-E classification	International classification	Macula involved	Age of first tumour	Therapy	Visual acuity
1	RE	IIa	B	Y	1–2 weeks	CRED/plaque/TCT	FC
	LE	Ia	A	N	5 months	TT	20/20
2	RE	Ib	A	N	1–2 weeks	EBRT	20/20
	LE	Ib	A	N	1–2 weeks		20/20
3	RE	Ib	A	N	1–2 weeks	Plaque/TCT	20/30
	LE	Ib	A	Y	1–2 weeks	TCT	20/30
4	RE	IIb	B	Y	1–2 weeks	EBRT	20/30
	LE	Ib	A	N	1–2 weeks		20/30
5	RE	Ia	A	Y	1–2 weeks	EBRT	20/40
	LE	No RB					20/20
6	RE	IIIa	A	N	2 months	Plaque/TCT	20/30
	LE	Ia	A	N	5 months	TT	20/20
7	RE	IIIb	B	Y	2 months	E	No LP
	LE	IIa	B	N	2 months	Plaque	20/30
8	RE	IIIa	A	N	5 months	Cryo	20/20
	LE	Ia	A	Y	1–2 weeks	TCT	20/100
9	RE	Ia	A	Y	2 months	TCT	20/40
	LE	Ia	A	N	6 months	TT	20/20
10	RE	Ia	A	Y	1–2 weeks	EBRT	20/20
	LE	Ia	A	N	1–2 weeks		20/20
11	RE	Ib	A	N	7 months	TCT	20/20
	LE	Ib	A	N	4 months	TT	20/20
12*	RE	V	E	Y	1–2 weeks	E	NP
	LE	Iva	C	Y	1–2 weeks	EBRT+hemo	FC
13	RE	Ib	A	N	1–2 weeks	TCT	20/40
	LE	IIa	B	Y	1–2 weeks	TT	FC
14	RE	IIIa	A	N	4 months	TT	20/20
	LE	No RB			19 months		20/20
15	RE	Ib	A	Y	1–2 weeks	EBRT	FC
	LE†	IIb	B	N	1–2 weeks		20/200
16	RE	IVa	C	Y	1–2 weeks	CRED+plaques+cryo+TT	LP
	LE	IIIa	A	N	4 months	TT	20/20
17	RE	IVb	A	N	3 months	TT	20/20
	LE	Ia	A	Y	1–2 weeks	TCT	20/40

RE, Reese-Ellsworth; CRED, chemoreduction; Chemo, adjuvant chemotherapy; E, enucleation; EBRT, external beam radiotherapy; TCT, thermochemotherapy; TT, thermotherapy (diode laser); plaque = ruthenium plaque; FC = finger counting; LP = light perception; NP, no perception.
*Cells in cerebrospinal fluid, †visual acuity deteriorated by radiation retinopathy.

88.3% (15) of the patients developed bilateral retinoblastoma. 11.7% (two) developed retinoblastoma in one eye, of whom one was treated with EBRT before developing tumours in the contralateral eye. Total of affected eyes was 32.

Reese-Ellsworth classification

In all 17 patients (32 eyes) were affected, of whom 56% (18) presented with group I A-B, 16% (five) with group II A-B, 16% (five) with group III A-B, 9% (three) group IV, 3% (one) group V. Two eyes did not develop retinoblastoma.

International classification of retinoblastoma

In all 17 patients (32 eyes) were affected, 72% (23) presented with group A, 19% (six) with group B, 6% (two) with group C, and 3% (one) with group E.

Macular involvement (table 2)

Of all 34 eyes, 41% (14) had macular involvement and 59% (20) did not. Two eyes did not develop retinoblastoma. Only one patient (both eyes) had advanced retinoblastoma (V/IIIB, E/C) and both macular areas were involved. All other patients had at least one eye without involvement of the macula. Immediate patching of the uninvolved eye was started with the majority of patients.

Age at diagnosis first and second eye

Of the 17 patients, 70% (12 patients) presented with retinoblastoma in the first or second week after birth, of whom 66.6% (eight) had retinoblastoma in both eyes and 33.3% (four) developed tumours in their second eye at 3, 4, 5, and 5 months, respectively; 18% (three patients) presented with their first tumours in one eye at 2 months after birth (and their second eye at 2, 5, and 6 months respectively) and 12% (two patients) at 4 months (second eye at 7 months and 19 months). Patients with more advanced stages of retinoblastoma (Reese-Ellsworth III-V, groups B-C-D) all presented within 1 week after birth, except one patient who presented at the age of 2 months with IIIB-IIA/group B/C).

Table 2 Outcome of visual acuity in relation with macular involvement in all eyes and in the best eyes

	Visual acuity						
Macular involvement	20/20	20/30	20/40	20/100–20/200	FC, LP	NP	Total
No	14	4	1	1	–	–	20
Yes	1	2	3	1	5	2*	14
Total	15	6	4	2	5	2*	34
Visual acuity better eye	11	3	1	1	1		17

*Enucleated eyes.

Therapy

Patients diagnosed with familial bilateral retinoblastoma in the first years of this survey (1992–5) were then mostly treated with external beam radiotherapy; 14.7% (five) of the patients were treated with EBRT alone. Two patients presented with advanced retinoblastoma: one patient had advanced retinoblastoma in both eyes at the age of 1 week and was treated with EBRT left eye (LE), and with chemotherapy because of retinoblastoma cells in the cerebrospinal fluid. The right eye (RE) had a secondary enucleation. The other patient presenting with retinoblastoma at 2 months had RE enucleated, and LE was treated with a Ruthenium-106 plaque. Of all eyes (34), 5.9% (two) were lost to enucleation, 29.4% (10) were treated with EBRT, 23.5% (eight) were only treated with thermotherapy (diode laser), 11.8% (four) were treated with thermochemotherapy and ruthenium plaque, 17.6% (six) of the eyes were treated with thermochemotherapy, 5.9% (two) of eyes were treated with cryotherapy and/or ruthenium plaque, 5.9% (two) of eyes did not develop retinoblastoma.

Visual acuity (table 2)

The visual outcome revealed 73.5% (20) of eyes with 20/20–20/40, 26.5% eyes with $\leqslant$20/100–no light perception. Of the 17 patients, 88.2% (15) had a visual acuity in one or both eyes of $\geqslant$20/20–20/40 and 11.7% (two) had a visual acuity of finger counting-20/200 in their better eye; one because of tumour involvement in both maculas and the other as a result of radiation retinopathy in her better eye. Of the 41% (14) of eyes with macular involvement, two were enucleated, six had large tumours treated with conservative (plaque, EBRT, TCT) therapy (visual acuity $<$20/100). Six eyes with macular retinoblastoma developed a visual acuity of $>$20/40. These eyes were all treated with occlusion therapy from diagnosis. Occlusion therapy was started with 1 hour a day extending to 6 hours a day at the age of 4–6 years. All six eyes remained amblyopic compared to the other eye without macular retinoblastoma.

DISCUSSION

Most patients treated for retinoblastoma in developed countries will become long term survivors. That is why they want to be informed about the risk of having a child with retinoblastoma and sometimes even more about the severity of the disease of their offspring. Information on patient survival, visual acuity, stage of the disease at diagnosis, and treatment options are important to parents when considering their family planning. This study was performed to be able to inform patients in an optimal way about the ophthalmological consequences of familial retinoblastoma.

In the Netherlands, most parents are aware of the potential risks of heredity of retinoblastoma and the benefits of an early diagnosis. Thus, the majority of children of affected parents present for routine clinical examination as soon as possible after birth. Prompt treatment will be started if any tumours are discovered and a lifelong follow up in our clinic is recommended.

Laterality

In retinoblastoma it is well known that the disease develops in an asymmetrical pattern. Mostly one eye is more severely affected than the other eye at diagnosis.[4] Eyes with Reese-Ellsworth group I are the most common and new subsequent tumours develop in a centrifugal pattern.[4 5] These early diagnosed tumours are generally more susceptible to conservative treatment. In the study of Abramson *et al* it was found that 85% of patients who initially were seen with tumours in one eye eventually developed bilateral disease.[4] In our study 47% (8/17) of patients developed asynchronously bilateral retinoblastoma. The majority (94%) of eyes were affected after a follow up of at least 19 months. Since all tumours that subsequently appeared in the second eye were detected within 7 months after birth, frequent examinations (every 2–4 weeks) are warranted with these children during this period.

Stage of retinoblastoma

The generally adopted Reese-Ellsworth classification developed for staging of intraocular retinoblastoma was designed specifically for use of radiotherapy. Another system that has since evolved may offer greater precision in stratifying risk for newer therapies such as local radiotherapy and thermochemotherapy. The novel international classification system for intraocular retinoblastoma is based on the extent and location of intraocular retinoblastoma. In our population, the majority of patients presented with Reese-Ellsworth group I (57%) and International Classification A (72%). Nevertheless, 5.9% (2/34) of eyes presented with Reese Ellsworth IIIB and V, International Classification B and E and were lost to enucleation. We found that children with familial retinoblastoma screened from birth are generally diagnosed in a stage with minimal intraocular disease. However, the risk of advanced stage retinoblastoma is still possible.

Macular involvement

It is well known from the study of Abramson *et al* that retinoblastoma tumours begin to grow in the posterior pole at the earliest age, and then extend anteriorly with time.[4 5] Macular tumours are of special interest. Abramson *et al* noted that macular tumours were diagnosed at an average age of 4 months and none was first diagnosed before 7 months of age. They even concluded that second eyes never developed a macular tumour; thus, second eyes have better visual potential than first eyes. These findings are supported by our study. Only one patient diagnosed with advanced retinoblastoma had two macular areas involved. All other patients had either one macula involved in the first eye or no macula involved in the second eye or both eyes.

Age of primary and secondary retinoblastoma

The majority (70%) of familial retinoblastoma patients seen at our ophthalmic oncology centre within 1–2 weeks after birth were diagnosed with tumour(s) in at least one eye. In four of those patients the second eye developed retinoblastoma after 3–5 months. 29.4% of patients developed tumours in the first eye as early as at 2 months and in the second eye not after at 7 months of age. Abramson *et al* studied the timing of new tumours in familial retinoblastoma and found that when the first eye was affected at birth the second eye was not involved within the first 2.5 months of life and not later than after 44 months of age.[4 8] These findings emphasise the importance of early follow up and frequent examinations with dilated pupils in children with a positive familial history with or without informative DNA results.

Therapy

During the first years of this study EBRT or enucleation were the standard treatments for retinoblastoma. As for our study, one eye had declining visual acuity as a result of radiation retinopathy. No other late effects of EBRT were noted in this group. Since 1995 local treatment methods, such as thermo(chemo)therapy and radioactive plaques, have been introduced in our centre.[6 7] As a result of early diagnosis only two eyes were lost to enucleation, all other eyes were treated with local or conservative treatment methods. Clinicians should keep in mind that all patients with familial retinoblastoma carry the germline mutation and are therefore

at risk of second primary tumours.[9] This risk may be enhanced by radiotherapy and possibly by chemotherapy.

Visual outcome

Many studies have explored the results of retinoblastoma management, but few have focused on visual outcomes. However, the most important issue brought up by parents with familial retinoblastoma is the visual outcome of their children when they are affected with retinoblastoma. Therefore, we conducted this study to be able to clear up uncertainties and to answer their questions. From our study, it can be concluded that the majority (88.2%) of patients achieved a visual acuity of 20/20–20/40. Hall *et al* concluded from their study that the visual outcome was not easily predicted on the basis of initial presentation and did not correlate with the classification of Reese-Ellsworth.[10] It has to be noted that in their study patients were either treated with enucleation and/or external beam radiotherapy (EBRT). EBRT can also affect the visual acuity by causing cataract or retinopathy.

Amblyopia superimposed on the organic disease poses an important problem in retinoblastoma.[10 11] We find it important to prescribe occlusion therapy because it may help to develop useful vision even in eyes with macular involvement. This study did not investigate the results of amblyopia treatment.

From this study it can be concluded that early diagnosis of familial retinoblastoma results in a good prognosis for visual acuity because of minor macular involvement, favourable tumour classification and, nowadays, less aggressive local treatments, such as thermo(chemo)therapy and radioactive plaque therapy. Finally, education of parents, ophthalmologists, and general doctors as to the risk of familial retinoblastoma is important to be able to avoid preventable late diagnosis.

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