Delay in diagnosis of retinoblastoma: risk factors and treatment outcome

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Abstract

Background—Delay in diagnosis of retinoblastoma causes considerable parental distress; however, the primary healthcare professional (PHP) may have difficulty detecting the most common presenting symptom—leucocoria. Alternatively, the PHP may not appreciate that retinoblastoma is the pathology underlying more common ocular symptoms in infants and young children.

Method—The parents of 100 recently diagnosed patients with retinoblastoma were interviewed to establish the extent of diagnostic delay, ascertain any associated risk factors, and to determine whether or not delay influenced treatment outcome.

Results—Although nearly 50% of patients were referred to an ophthalmologist within 1 week of first consulting a PHP, one quarter waited more than 8 weeks. There was a significantly increased risk of diagnostic delay in younger patients, those presenting with squint rather than leucocoria, and those first presenting to a health visitor rather than to a general practitioner. The risk of local tumour invasion was significantly increased by diagnostic delay. Treatment with primary enucleation was not increased by diagnostic delay. There were no deaths during the study period.

Conclusion—Primary healthcare professionals require education about the importance of ocular symptoms, especially squint, in paediatric patients.

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ocular symptoms in an uncooperative group of patients.

The 5 year overall survival rate in retinoblastoma is estimated at greater than 90% in developed countries.¹ Treatment is not without significant morbidity which may include visual impairment and severe cosmetic deformity secondary to enucleation and/or irradiation of the orbital region. In genetic retinoblastoma the most serious long term side effect following irradiation is increased risk of second cancers in the radiation field estimated at a cumulative risk of 35% by 30 years of age.² Other irradiation associated side effects include chronic dry eye, cataract, retinopathy, optic neuropathy, and poor orbital bone development. In appropriate cases, primary chemoreduction followed by local therapy is increasingly used to obviate the need for enucleation and external beam radiotherapy.³ Adjuvant chemotherapy is indicated if there is evidence of local invasion on histological examination of an enucleated eye.⁴ Chemotherapy has both short and long term complications. In general, the smaller the tumour at presentation the greater the possibility that methods of treatment such as laser and cryotherapy can be utilised, minimising morbidity.

Information about the interval between symptom onset and diagnosis (symptom interval) in retinoblastoma is relatively scarce. Haik *et al*⁵ examined symptom interval in retinoblastoma but did not attempt to isolate reasons for diagnostic delay. Ervenne and Franco⁶ reported that the risk of extraocular disease was strongly dependent on the age at diagnosis and lateness of referral. DerKinderen *et al*⁷ reported that early diagnosis in bilateral retinoblastoma improved survival and visual outcome in a cohort of patients diagnosed between 1945 and 1970. In developing countries presentation with advanced disease is common and outcome is often dismal.⁸

At a supraregional referral centre seeing 75% of all new cases of retinoblastoma in the UK we were impressed by the frequency with which parents described a prolonged and distressing symptom interval before diagnosis of retinoblastoma in their child. Therefore we designed a study to establish the extent of diagnostic delay in retinoblastoma, to ascertain whether any risk factors were associated with delayed diagnosis, and to examine whether or

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Retinoblastoma is a rare tumour of childhood most often presenting with leucocoria. Patients may present with ocular symptoms that are relatively common in infants and young children: squint, red eye, and orbital cellulitis are examples. Genetic cases make up approximately 40% of the total but three quarters of these are new germ line mutations so that only about 10% of all new cases of retinoblastoma will have a known family history and undergo screening from birth. Diagnosis in the remaining 90%, about 40 cases/year in the UK, will depend on the ability of primary healthcare professionals to recognise the significance of

not delay in diagnosis altered treatment outcome.

Patients and methods

A retrospective study of all patients with retinoblastoma treated at St Bartholomew's Hospital, London, between January 1993 and December 1996 was undertaken. Patients known to have a family history, those with dysmorphic features noted before diagnosis of retinoblastoma, and patients resident outside the UK were excluded. One hundred of 112 patients contacted were available for interview during the study period. Thirty four patients had bilateral disease while 66 had unilateral tumours.

All parents were sent a preliminary letter informing them of the study and its aims. No parent(s) refused an interview. Interviews took place in the outpatient department if possible, or by telephone.

Parents were asked to recall the sequence of events from the time they first noted "something wrong" with their child's eye(s) to the diagnosis of retinoblastoma. Particular note was made of ocular symptom(s), their duration before diagnosis, and the nature of contact with primary healthcare professionals (PHP). Patient records were examined to verify the date of diagnosis of retinoblastoma, tumour laterality, and treatment received. In 90/100 cases it was possible to corroborate the history obtained by parental interview. If discrepancies occurred the version in the medical record was used, especially as interviews took place up to 3 years after diagnosis of retinoblastoma in some cases.

Lag 1 was defined as the time interval between the date the first symptom was noted and the date of first consultation with a PHP and thus represents "parental delay". Lag 2, representing "health professional delay", was the time interval between the date of the first consultation with a PHP and first consultation with a local ophthalmologist. Overall lag was the time from first symptom to referral for therapy in this institution.

STATISTICS

The data were analysed using Minitab software. Data are presented as a median value followed by a range. The Mann-Whitney test was used for two group comparisons while the Kruskal-Wallis test was used for multigroup comparisons. Spearman's rank correlation was used to analyse the relation between age and lag times. The null hypothesis was considered to be rejected at a two tailed alpha rate of 0.05 or less.

Table 1 First symptom and age at first symptom in 100 patients with retinoblastoma

First symptom	Number of patients	Median age in months (range) when symptom first noted by parents
Leucocoria	52	18.5 (0-85)
Squint	29	8.0 (0-42)
Change in eye appearance	10	20.5 (4-95)
Decreased visual acuity	9	3.0 (1-62)
Total	100	12.0 (1-95)

Results

FIRST SYMPTOM NOTED

The first symptoms noted by parents could be divided into four main groups—leucocoria, squint, change in the appearance of the eye, and decreased visual acuity (Table 1) Forty three of the 100 children went on to develop additional ocular symptoms before definitive diagnosis of retinoblastoma.

Leucocoria, denoting a large intraocular lesion, was the initial symptom in 52/100 patients. Parents commonly observe leucocoria only at certain angles in dim light and describe it in a variety of ways—for example, a "flash" in the eye or being able to "see right through the eye".

Squint, due to reduced central vision secondary to tumour or to retinal detachment, was the first symptom noted in 29 patients. If untreated, squint often progresses to leucocoria as the tumour enlarges; this was the case in 16/29 patients.

The parents of 10 patients noted change in the appearance of their child's eye(s). Heterochromia, red, and/or painful eyes are associated with a variety of tumour associated ophthalmic pathologies including the development of glaucoma.

In nine patients the first symptom noted related to decreased visual acuity. Failure to fix and follow or, in bilaterally affected cases, roving eye movements were noted by parents of young babies while in ambulatory children clumsiness, sometimes leading to trauma, was the initial symptom.

AGE OF CHILD WHEN FIRST SYMPTOM NOTED (SEE TABLE 1)

The median age at the time of a parent first noting an ocular symptom was 12.0 (0-95) months. Six patients were over 5 years when the first symptom was noted.

The median age at first symptom of patients with bilateral tumours was 5.0 (0-33) months. Patients with unilateral tumours were significantly older ($p < 0.001$) with a median age of 18.0 (1-95) months at first symptom.

The median age of patients in whom squint was the first symptom was significantly lower than those with leucocoria ($p < 0.05$).

PHP FIRST CONSULTED BY PARENTS

Just over half (54/100) consulted their general practitioner first, 21 consulted their health visitor, and 11 saw an optician. Fourteen patients presented to their local accident and emergency department or consulted a variety of other people including medical members of the family, community medical officers, and midwives.

LAG 1—TIME INTERVAL BETWEEN FIRST

SYMPTOM AND FIRST CONSULTATION WITH A PHP Median lag 1 was 2.5 (1-88) weeks. Lag 1 was not significantly affected by age at symptom onset, first symptom noted by parents, or by first PHP consulted.

NUMBER OF PHPS CONSULTED BEFORE REFERRAL TO A LOCAL OPHTHALMOLOGIST

Forty five parents consulted one and 36 consulted two PHPs before referral to a local ophthalmologist was made. Nineteen parents consulted between three and six PHPs. Twelve parents reported having to insist that referral to an ophthalmologist be made. Eleven parents ignored the advice initially given and sought alternative advice on one or more occasions until referral was made.

LAG 2—TIME INTERVAL BETWEEN FIRST CONSULTATION WITH A PHP AND FIRST CONSULTATION WITH A LOCAL OPHTHALMOLOGIST

Median lag 2 was 2.0 (1–80) weeks. In 49 patients lag 2 was 1 week or less. In 23 patients it was more than 8 weeks, in 14/23 more than 16 weeks, and in 2/23 patients lag 2 was more than 1 year.

Lag 2 was inversely related to age of the patient at the time of first presentation to a PHP ($p < 0.01$). Patients presenting with squint had a significantly longer lag 2 ($p < 0.05$) compared with the other three symptom groups. Patients whose first PHP contact was with a health visitor had a highly significantly longer lag 2 ($p < 0.001$) compared with patients

Table 2 Time interval between first consultation with a primary healthcare professional (PHP) and first consultation with an ophthalmologist by first symptom noted in 100 patients with retinoblastoma

First symptom	Median lag 2 time* in weeks (range)
Leucocoria	1 (1–48)
Squint	7 (1–80)
Change in eye appearance	1 (1–8)
Decreased visual acuity	2 (1–22)
Overall	2 (1–80)

*Lag 2, time interval between first consultation with a PHP and first consultation with a local ophthalmologist.

Table 3 Time interval between first consultation with a primary healthcare professional (PHP) and first consultation with an ophthalmologist by first PHP consulted in 100 patients with retinoblastoma

First PHP consulted	Median lag 2 time* in weeks (range)
General practitioner	1 (1–56)
Health visitor	13 (1–46)
Optician	1 (1–10)
Miscellaneous	1 (1–15)
Overall	2 (1–56)

*Lag 2, time interval between first consultation with a PHP and first consultation with a local ophthalmologist.

Table 4 General practitioners (GPs) compared with health visitors (HV) for rapidity of referral of 62 patients with retinoblastoma presenting with leucocoria and squint

First symptom	First PHP consulted		
	GP	HV	Total
Leucocoria	n=27 patients median lag 2=1 week range 1–48	n=10 patients median lag 2=14 weeks range 1–46	n=37 patients median lag 2=2 weeks range 1–48
Squint	n=15 patients median lag 2=3 weeks range 1–80	n=10 patients median lag 2=10.5 weeks range 2–26	n=25 patients median lag 2=7 weeks range 1–80
Total	n=42 patients median lag 2=1 week range 1–80	n=20 patients median lag 2=13 weeks range 1–46	n=62 patients

*Lag 2, time interval between first consultation with a primary healthcare professional (PHP) and first consultation with a local ophthalmologist.

presenting to general practitioners, opticians, or the miscellaneous group of other PHPs (see Tables 2 and 3).

Table 4 compares lag 2 for general practitioners and health visitors with respect to squint and leucocoria. There was no significant difference in lag 2 between general practitioners and health visitors for patients presenting with squint but lag 2 for patients first consulting a general practitioner with leucocoria was significantly less ($p < 0.01$) than patients consulting a health visitor with that symptom.

OVERALL LAG TIME

Median overall lag time was 8.0 (1–96) weeks. Delay after referral to a local ophthalmologist occurred in five cases. There was no significant difference in overall lag time between unilateral and bilateral cases.

AGE AT DIAGNOSIS

For all cases median age at diagnosis was 19.0 (2–102) months. For bilateral cases it was 9.0 (2–37) months whereas for unilateral cases it was 24.0 (2–102) months ($p < 0.001$).

INITIAL TREATMENT VERSUS OVERALL LAG TIME

Twenty seven of 68 eyes in the 34 bilateral cases (one bilateral enucleation) and 54/66 unilateral cases were treated with primary enucleation. There was no significant difference in overall lag time for enucleated compared with non-enucleated eyes.

Of the 80 patients treated by primary enucleation, 12 required adjuvant chemotherapy for local tumour invasion (major choroidal invasion and/or post-laminal optic nerve extension). Overall lag time for patients requiring adjuvant therapy (27 weeks, range 2–61) was significantly longer than those patients with no evidence of local tumour invasion (8 weeks, range 1–94).

TREATMENT OF SECOND EYE IN BILATERAL CASES

In bilateral retinoblastoma, the extent of involvement of the “second” or less affected eye often determines outcome with respect to visual impairment. Of the 34 patients with bilateral disease, two had spontaneous regression in the second eye. Of the remaining 32 patients, the second eye was treatable with local or focal modalities in eight cases, while in 23 cases treatment with chemotherapy and/or external beam radiotherapy was required. There was no significant difference in overall lag between the two treatment groups.

MORTALITY

No patients died during the study period where follow up ranged from 9 to 60 months.

Discussion

We found that almost half of a group of 100 of paediatric patients presenting with ocular symptoms were referred to a local ophthalmologist within 1 week of presenting to a PHP but a quarter of patients experienced a delay in referral of more than 8 weeks. Older patients were referred more rapidly. Patients in whom squint was the first symptom and those whose

parents first consulted a health visitor were significantly more likely to suffer delay. Diagnostic delay was distressing for the parents and increased the risk of local tumour invasion. The need for enucleation was not influenced by diagnostic delay.

Age at presentation and presenting symptoms in this study were in accordance with clinical experience of retinoblastoma in developed countries.⁹ In our study parental delay (lag 1), PHP delay (lag 2), and overall delay were of shorter duration than those reported in the study of Haik *et al*⁵ where median lags 1 and 2 were 5 and 9 weeks respectively. Median overall lag in Erwenne's study was 5 (0–45) months.⁶ This most probably reflects differences in the structure of different health systems. Haik *et al* did not report treatment outcome. In Erwenne's study nearly 50% of patients had gross diagnostic delay (overall lag >6 months) and almost 50% had extraocular disease at presentation. A similar pattern is seen in developing countries.⁸

Parental interview was used as a means of obtaining information about onset and nature of symptoms and nature of contact with primary health professionals. Validation of this potentially biased information was possible from the case notes in 90% of cases. Lag times were not compared with visual outcome as it was not possible to assess visual acuity in all cases. Follow up ranged from 9 to 60 months and therefore information regarding diagnostic delay versus subsequent treatment and outcome, including death, in this group of patients was not examined.

Examination of eyes in infants and young children is difficult and it is commendable that about half of PHPs responded promptly to their young patients. The inverse relation between age and lag 2 may have occurred as a result of several factors. Many observers are more comfortable examining a toddler than a delicate infant although wriggling toddlers are often difficult to examine. PHPs may be more responsive to squint in a toddler as there seems to be a widely held, quite incorrect, view that squint is normal before 6 months of age. In a large study of development of normal ocular alignment, Sondhi *et al* found an incidence of constant ocular deviation of about 50% in normal infants between birth and 1 month.¹⁰ By 3 months this had decreased to only about 20% and by 6 months less than 10% of infants had any deviation. The most appropriate management of young children with squint is a difficult issue: referral of all children would overburden current ophthalmological services for relatively little gain. Secondary screening by a community based orthoptist may be a cost effective solution. Diagnostic and treatment failure in children presenting with squint is an emerging cause of malpractice claims.¹¹ Education of primary healthcare professionals about squint in paediatric patients needs revision in accord-

ance with the guidelines set out in the report of the Third Joint Working Party on Child Health.¹² General practitioners and health visitors should be encouraged to refer immediately a child whose parents have noted leucocoria or a similarly ominous ocular symptom, even when the examining PHP is unable to detect the abnormality. Full mydriasis and examination under anaesthesia are often required to detect abnormalities in the posterior pole of the eye. Opticians were significantly better than other PHPs at recognising and responding to the significance of ocular symptoms in these patients.

Parents of children with retinoblastoma experience considerable stress associated with learning that their child has cancer. In addition, in about three quarters of cases, the child undergoes enucleation. The family may have to deal with significant cosmetic deformity and visual impairment for the rest of the child's life. In addition to its side effects chemotherapy requires repeated inpatient stays with consequent disruption to normal domestic and working life. In previously undiagnosed family cases another child may have been born before retinoblastoma was detected in an older sibling. Delay in diagnosis adds to already high levels of psychological distress and may impair the family's coping mechanisms. Occasionally, diagnostic delay is a factor provoking parents into pursuing negligence claims.

Further studies are required to establish the extent to which diagnostic delay influences visual, cosmetic, and overall outcome in retinoblastoma.

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