Delay in diagnosis of retinoblastoma: risk factors and treatment outcome

Andrea G Goddard, Judith E Kingston, John L Hungerford

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.

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 10% of all new cases of retinoblastoma but did not attempt to isolate reasons for diagnostic delay. Erwenne and Franco reported that the risk of extraocular disease was strongly dependent on the age at diagnosis and latency of referral. DerKinderen et al 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.

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
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 Kruskall–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

<table>
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<tr>
<th>First symptom</th>
<th>Number of patients</th>
<th>Median age in months (range)</th>
</tr>
</thead>
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<tr>
<td>Leucocoria</td>
<td>52</td>
<td>18.5 (0–85)</td>
</tr>
<tr>
<td>Squint</td>
<td>29</td>
<td>8.0 (0–42)</td>
</tr>
<tr>
<td>Change in eye appearance</td>
<td>10</td>
<td>20.5 (4–95)</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>9</td>
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<td>Total</td>
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Results

Table 1

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

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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 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-laminar 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 signif-
ically more likely to suffer delay. Diagnostic
tic 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 symp-
toms in this study were in accordance with
clinical experience of retinoblastoma in devel-
oped countries.7 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 al5 where median lags 1
and 2 were 5 and 9 weeks respectively. Median
overall lag in Erwenne’s study was 5 (0–45)
months.8 This most probably reflects differ-
ences 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.9

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 out-
come, 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
comfortable examining a toddler than 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 examina-
tion 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 deform-
ity 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 domes-
tic 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
elevated levels of psychological distress and
may impair the family’s coping mechanisms. Occasionally,
diagnostic delay is a factor provoking parents
to pursuing negligence claims.

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

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Poster presentation at the 1997 International Symposium on
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