British Journal of Ophthalmology 1993; 77: 354–357

Lens opacities in neurofibromatosis 2: further significant correlations

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Abstract

This prospective study of 96 individuals from 29 families with neurofibromatosis 2, 49 of whom were affected, confirms in an extended series the previously reported association between posterior subcapsular/capsular cataract and neurofibromatosis 2. Posterior subcapsular/capsular cataracts were found in 36 (80%) of the 45 affected individuals (four individuals were excluded from statistical analyses). In addition, the association of peripheral cortical lens opacities with neurofibromatosis 2 was found to be statistically significant. Seventeen of the patients with neurofibromatosis 2 (37·8%) had peripheral cortical cataracts in comparison with none of the unaffected family members ($p<0·0001$). In three patients peripheral cortical opacities were present despite the absence of posterior subcapsular/capsular cataracts. These findings support the inclusion of cortical cataracts of early onset, in addition to posterior subcapsular/capsular cataracts, in the diagnostic criteria of neurofibromatosis 2.

(*Br J Ophthalmol* 1993; 77: 354–357)

Neurofibromatosis 1 (NF1), formerly called von Recklinghausen or peripheral neurofibromatosis, and neurofibromatosis 2 (NF2), formerly called central neurofibromatosis or bilateral acoustic neurofibromatosis, are distinct autosomal dominant disorders with well defined clinical findings. As established by the NIH consensus development conference[1] the diagnostic criteria for NF1 are met in an individual with at least two of the following (1) six or more café au lait macules, (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) freckling in the axillary or inguinal regions, (4) optic glioma, (5) two or more Lisch nodules, (6) a distinctive osseous lesion, (7) a first degree relative with NF1. The diagnostic criteria for NF2 include: (1) bilateral eighth nerve masses or (2) a first degree relative with NF2 and either a unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, posterior subcapsular lens opacity.

NF2 is less common than NF1. The most recent estimation of its prevalence is about 1:250 000. The gene has been assigned to the long arm of chromosome 22.[2] About 50% of the cases have no family history and appear to result from a new germline mutation.

The association of lens opacities in patients with NF2 was first noted in 1986.[3] As a result of this observation, a prospective study of 47 individuals from 11 families was undertaken and the association with posterior subcapsular/capsular (PSC) opacities (the terminology used reflects the fact that these opacities were either immediately anterior to or physically continuous with the posterior lens capsule) was found to be present in 17 (85%) of the 20 affected individuals with NF2.[4]

Other ophthalmic findings in NF2 are rare. The association with combined pigment epithelial and retinal hamartomas,[5–9] Lisch nodules,[10 11] and optic disc gliomas[12] has been reported. Compressive neuropathy, corneal hypoaesthesia, papilloedema, and decrease in lacrimal secretion can occur secondary to the presence of intracranial tumours or to complications from neurosurgical interventions.[13 14]

This study reports the findings of the lens examination in 45 patients with NF2 and 46 unaffected family members.

Materials and methods

A complete medical and ophthalmic examination and magnetic resonance imaging (MRI) of the brain with gadolinium were performed on 96 members of 29 families with NF2. Forty seven individuals (21 affected) were included in a previous report.[4]

All patients were examined following the appropriate consent and approval of the study by the institute review board.

A detailed medical history was taken to determine any factors that might result in cataractogenesis (associated ocular diseases, radiotherapy, corticotherapy), that would lead to exclusion from analysis.

The presence of lens opacities, their location, and other characteristics were noted by two independent observers (EAB, MIK-K) and documented photographically by direct illumination and retroillumination. Examiners were masked to the diagnosis of NF2; masking could not be controlled for patients with marked hearing impairment.

Follow up data (1 to 4 years, mean 2·6 years) were available for 24 affected individuals and used to determine changes in the appearance of the lens over time. The status of the lens on the most recent examination was used for the statistical analysis.

The data were analysed to evaluate the association of NF2 with two types of lens opacities: (1) PSC opacities of variable size located centrally either close to or abutting against the posterior capsule, from which they were indistinguishable as seen by slit-lamp biomicroscopy and Scheimpflug photography[4]; (2) peripheral cortical opacities often wedge shaped, usually of uniform density and well circumscribed borders, which involved the anterior and/or posterior peripheral cortex; the opacities in some cases

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Accepted for publication 12 January 1993

Table 1 Patient characteristics

	NF 2+	*NF 2−*
Number	45	46
Age (years) <50	37 (82·2%)	36 (78·3%)
Range	12–70	9–71
Mean	35·4	36·3
Median	34	35
Women	18 (40·0%)	24 (52·2%)
PSCC	36 (80·0%)	2 (4·3%)
CC	17 (37·8%)	0
PSCC/CC	39 (86·7%)	2 (4·3%)

NF 2+ = affected by neurofibromatosis 2; NF 2− = unaffected family members; PSCC = posterior subcapsular/capsular cataract; CC = cortical cataract; PSCC/CC = posterior subcapsular/capsular and/or cortical cataract.

extended axially. Increase in the density of the posterior capsule or small cortical changes such as flecks, dots, and vacuoles were not considered positive findings.

Lens opacities were coded as present when found in either one or both eyes. To test the association of the presence of PSC and/or cortical cataracts with NF2, a summary marker was created (PSCC/CC). This marker was coded as present if there was PSC or cortical cataract or both, in at least one eye of the subject. To estimate the association of each of these types of lens opacities separately and the summary marker with NF2, two sided significance tests were performed and the odds ratios (relative odds) were computed with the 95% confidence interval.[15] The odds ratios adjusted for age group (<50 years, ≥50 years) as a possible confounding factor were computed using the Mantel-Haenszel method.[15] This age division was based on the prevalence of non age-related cataracts in the general population in an attempt to eliminate the possibility of dealing with age-related cataract. Odds ratios adjusted for age as a continuous variable were estimated using a logistic regression model.[15]

Results

Forty nine of the 96 examined individuals had confirmation of NF2 based on the presence of bilateral eighth nerve masses in 48 cases and positive family history plus neurofibromas and meningiomas in one case.[1] Thirty four patients were from families with two or more affected individuals and 15 were sporadic. Forty five patients with NF2 were retained for the statistical analyses; the reason for exclusion of four cases was bilateral aphakia in one case, corneal opacities obscuring the visibility of the lens in two cases, and refusal of dilated examination in one case.

Of the 47 unaffected family members, 46 were retained for the statistical analyses; one was excluded because of history of pars planitis treated with topical steroids.

Table 1 presents the characteristics of the sample of 91 individuals with complete records, retained for the statistical analysis. Two types of cataracts were found to be important: PSC and cortical. They were present in both men and women and both familial and sporadic cases, with similar frequency.

Thirty six of 45 patients with NF2 (80%) had PSC cataracts (Fig 1) compared with two of 46 unaffected family members. Table 2 shows a highly significant ($p<0·0001$) association between NF2 and PSC cataract. The lower limit of the 95% confidence interval for the odds ratio of PSC cataract and NF2 was 15·9. The odds ratio of PSC cataract and NF2 adjusted for age group was very similar (Table 2), as was the odds ratio adjusted for age as a continuous variable (not shown).

The peripheral cortical cataracts (Figs 1, 2) were unilateral or bilateral and in some patients more than one cortical opacity was found in each lens. Peripheral cortical opacities were present in 17 of the 45 patients with NF2 (37·8%) but in none of the 46 non-affected individuals. There is a highly significant ($p<0·0001$) association between NF2 and cortical opacities. It was not possible to estimate the odds ratio of cortical opacities and NF2 because none of the non-affected individuals had cortical opacities.

Three of the subjects who had NF2 and no PSC cataract had peripheral cortical lens opacities resulting in an 86·7% frequency of PSC cataract and/or cortical cataract in NF2. Therefore the data were analysed for the association of the summary marker (PSCC/CC) with NF2. Table 3 demonstrates a highly significant ($p<0·0001$) association between NF2 and this marker. The lower limit of the 95% confidence interval for the odds ratio of PSCC/CC and NF2 was 23·7. The odds ratio adjusted for age group (Table 3) and the odds ratio adjusted for age as a continuous variable (not shown) were similar.

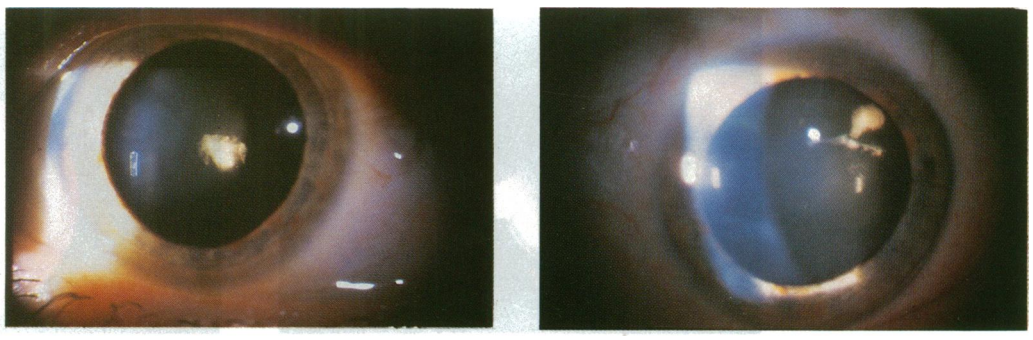

Fig 1A *Fig 1B*

Figure 1 Slit-lamp photographs of posterior subcapsular/capsular (A) and peripheral cortical (B) lens opacities, present in the right and left eye respectively of a 43-year-old man with neurofibromatosis 2.

Table 2 Relation of NF 2 to PSCC, by age

Ages	NF 2+	NF 2−
All*		
PSCC+	36	2
PSCC−	9	44
<50 years†		
PSCC+	31	2
PSCC−	6	34
≥50 years†		
PSCC+	5	0
PSCC−	3	10

NF 2+ = affected by neurofibromatosis 2; NF 2− = unaffected family members; PSCC = posterior subcapsular/capsular cataract in at least one eye; PSCC− = no posterior subcapsular/capsular cataract in either eye.
*Test for association: χ^2 (1 df) = 49·9, p<0·0001, the lower limit of the 95% confidence interval for the odds ratio of PSCC and NF 2 is 15·9.
†Age-adjusted χ^2 (1 df) = 49·6, p<0·0001, the lower limit of the 95% confidence interval for the odds ratio adjusted for age group is 16·8.

Table 3 Relation of NF 2 to PSCC/CC, by age

Ages	NF 2+	NF 2−
All*		
PSCC/CC+	39	2
PSCC/CC−	6	44
<50 years†		
PSCC/CC+	33	2
PSCC/CC−	4*	34
≥50 years†		
PSCC/CC+	6	0
PSCC/CC−	2	10

NF 2+ = affected by neurofibromatosis 2; NF 2− = unaffected family members; PSCC/CC+ = posterior subcapsular/capsular cataract and/or cortical cataract in at least one eye; PSCC/CC− = no posterior subcapsular/capsular cataract and no cortical cataract in either eye.
*Test for association: χ^2 (1 df) = 58·3, p<0·0001, the lower limit of the 95% confidence interval for the odds ratio of PSCC/CC and NF 2 is 23·7.
†Age-adjusted χ^2 (1 df) = 57·8, p<0·0001, the lower limit of the 95% confidence interval for the odds ratio adjusted for age group is 24·8.

The age of the patients with NF2, at the time the diagnosis of cataract was made in this study, ranged from 12 to 70 years (mean age 35·2 years) for PSC cataracts and from 12 to 66 years (mean age 36·8 years) for cortical cataracts; the distribution by age group is shown in Figure 3. Three of these patients, however, had a history of lens opacities (cortical in two cases and PSC in one case) present from early childhood. The two at risk unaffected individuals with PSC cataract were 22 and 46 years old.

Among the 24 patients with NF2 for whom follow up data were available, progression of the lens opacities was noticed in four (two PSC, two cortical) (Fig 4). In addition, three affected individuals developed PSC cataracts during the follow up period at ages 23, 38, and 45 years.

Discussion

The diagnostic value of lens opacities centrally located immediately anterior or juxtaposed to the posterior capsule (as documented by Scheimpflug photography) in NF2 has been reported in a prospective study in which 85% of 20 patients with NF2 had PSC lens opacities.[4] The study was expanded to include more than twice the number of patients and the association was reaffirmed. The terminology recommended by the editor in the previous article[4] for these opacities (based on the morphological appearance and the Scheimpflug imaging) was posterior capsular cataracts. However, currently available clinical tests do not allow precise localisation of the opacities of the posterior subcapsular/capsular area. On the other hand both terms posterior subcapsular and posterior capsular cataracts may evoke specific aetiologies while the pathogenesis of cataracts in NF2 is unclear. Therefore, we elected to use the term posterior subcapsular/capsular lens opacities to describe the lens opacities which are located centrally and adjacent to or continuous with the posterior capsule in patients with NF2.

Although 'other cataracts' were noticed in two affected members of one of the families previously reported,[4] the smaller number of patients in that series did not provide sufficient power to allow a statistically significant association of any other type of cataract with NF2. In this extended series, the highly significant association of NF2 with a second, different type of lens opacities, located in the peripheral cortex, has been demonstrated for the first time. Peripheral cortical cataracts were found in 37·8% of the affected individuals and none of the unaffected ones.

PSC cataracts have been included in the diagnostic criteria for NF2.[1] A summary marker which combines data on the presence of both PSC and peripheral cortical opacities when compared with PSC cataract alone increases the

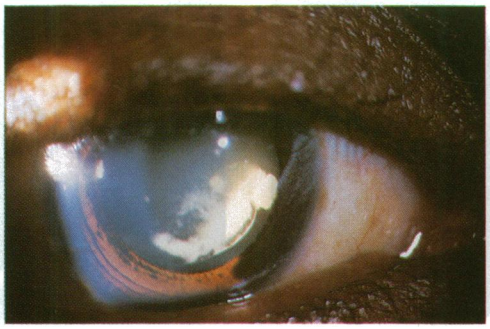

Fig 2A

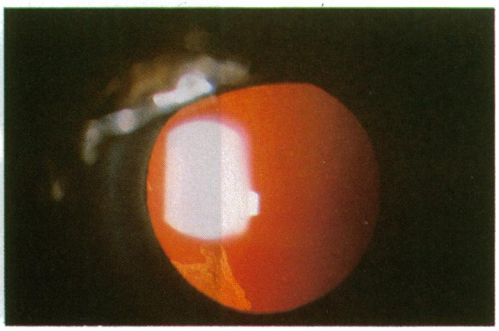

Fig 2B

Figure 2 Cortical opacities in the right eye of a 45-year-old woman (A) and the right eye of a 39-year-old man (B) with neurofibromatosis 2, viewed by direct illumination (A) and retroillumination (B).

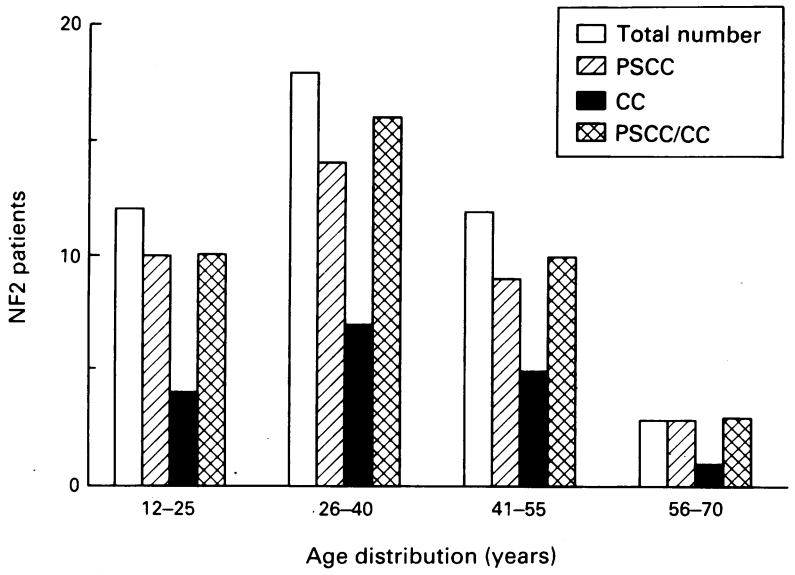

Figure 3 Distribution by age group of total number of NF2 patients, NF2 patients with posterior subcapsular/ capsular cataract (PSCC), NF2 patients with cortical cataract (CC), and NF2 patients with posterior subcapsular/capsular and/or cortical cataract (PSCC/ CC).

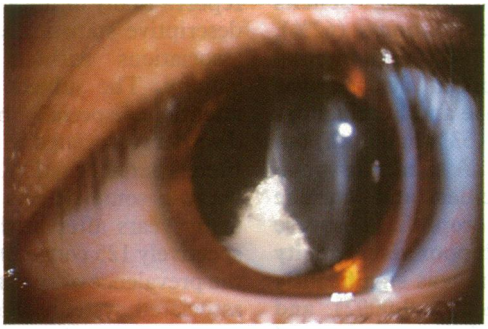

Fig 4A

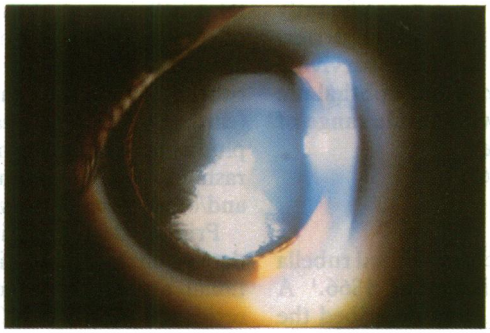

Fig 4B

Figure 4 60×Zeiss photo slit-lamp photograph of cortical lens opacity, present in the left eye of a 12-year-old girl with neurofibromatosis 2 (A). Same magnification slit-lamp photograph which shows the progression of the cortical opacity within 2 years (B).

sensitivity in screening members of families with NF2.

It is likely that most of the lens opacities were of early onset but the exact age is difficult to assess. In the present study the mean age was 35·2 and 36·8 years at the time of the diagnosis of PSC and peripheral cortical cataract respectively. Three of the patients were noted to have had a cataract since early childhood. On the other hand PSC opacities developed during the follow up period in three patients at ages 23–45 years.

This report suggests that peripheral cortical cataracts of early onset should be included, in addition to PSC cataracts, in the diagnostic criteria of NF2. Because of the size and location of the opacities a careful examination after maximum dilatation is required in all individuals suspected to have or at risk for NF2.

We wish to thank Dr Robert D Sperduto for his help in reviewing this manuscript.

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