Ophthalmic manifestations of neurofibromatosis

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SUMMARY The eyes of 64 patients known to have neurofibromatosis were examined. Lisch nodules were the commonest manifestation of the disease and were present in 95% of all patients (100% of those aged 16 years or older).

Neurofibromatosis was first described by von Recklinghausen in 1882.¹ A wide range of complications of the disease are now recognised, and it has become apparent that there are several forms of neurofibromatosis. The one described by von Recklinghausen is by far the most common and is now referred to as von Recklinghausen or peripheral neurofibromatosis. The other forms include central neurofibromatosis, the major defining features of which are bilateral acoustic neuromas with few if any cutaneous manifestations, and segmental neurofibromatosis, where the features of the peripheral form are confined to one segment of the body.²

Von Recklinghausen neurofibromatosis (NF) is an autosomal dominant disorder with a high mutation rate and a prevalence of around 30/100 000 of the population.³ There is no laboratory test for NF and the diagnosis is made on the basis of the major defining features of the disease—café au lait spots and cutaneous neurofibromas. Café au lait spots are flat light brown patches which vary in size from a few millimetres to several centimetres. They begin to develop at or soon after birth and increase in number and size throughout childhood. Some patients with NF also develop axillary freckling, a clinical sign unique to the disease. Cutaneous neurofibromas begin to appear about the time of puberty and increase in number throughout life.

Approximately 25% of patients with NF develop complications which include plexiform neurofibromas, malignancies (of which neurofibrosarcomas and embryonic childhood tumours are the most frequent), scoliosis, congenital bone defects, and tumours of the central nervous system.⁴ The complications of NF that may present to the ophthalmologist are optic gliomas, plexiform neurofibromas

which involve the orbit, congenital absence of the sphenoid wing, and congenital glaucoma. These are all rare and occur in approximately 5% of patients with NF.⁵ Recently, however, Lewis and Riccardi⁶ have drawn attention to more frequent but asymptomatic manifestations in the irides of patients with NF.

Abnormalities of the iris in NF were first reported clinically by Waardenburg in 1918,⁷ who described small wart-like iris lesion which he presumed to be neurofibromas. Goldstein and Wexler in 1930⁸ demonstrated at necropsy multiple melanocytic tumours of the iris in the eyes of a patient with NF. In 1937 Lisch⁹ reported three cases of NF all of which had iris nodules. He concluded that they were pathognomic of the disease and that if the irides of more NF patients were examined they would be a frequent finding. The study of Lewis and Riccardi⁶ was the first prospective systematic evaluation of the ophthalmological manifestations in a large number of patients with NF.

A prevalence study of NF in South Glamorgan and Gwent has recently been carried out (Huson SM, Compston DAS, Harper PS, in preparation). The principal aim of the study was to look at the variation of the disease in a relatively unbiased population and to re-evaluate the diagnostic criteria. A proportion of the patients in the prevalence study, who had initially been seen at home, attended for ophthalmological assessment at the University Hospital of Wales. We report here our findings, with particular emphasis on Lisch nodules—their incidence in patients with NF and their role in making the diagnosis.

Materials and methods

Patients with NF were ascertained from hospital records, general practitioners, and consultants in the study area. The patients were visited at home (by SH),

Table 1 Diagnostic criteria for von Recklinghausen neurofibromatosis

In children:	≥6 café au lait spots >0.5 cm in diameter
In adults:	(1) ≥6 café au lait spots >1.5 cm in diameter (2) Multiple cutaneous neurofibromas

and a clinical assessment, including portable slit-lamp examination, was carried out on all patients and where possible their first degree relatives. The criteria used for the diagnosis of NF are shown in Table 1.

A proportion of the patients then attended the University Hospital of Wales for more detailed ophthalmological assessment (by LB and DJ). This included: (1) measurement of visual acuity; (2) examination of the periorbital; (3) slit-lamp examination of the cornea and iris (the numbers of Lisch nodules in each eye were counted); (4) direct and indirect ophthalmoscopy.

In patients over the age of 20 years applanation tonometry was performed, and a limited number of patients also had gonioscopy, anterior segment and fundus photography, and fluorescein angiography. As we were particularly interested in the age at which Lisch nodules first develop, a further group of patients (all children) were ascertained through the NF Association, LINK, and their irides only were examined using a portable slit-lamp (Kowa Ltd).

During the study period 150 patients attending the general ophthalmology clinic were also examined for the presence or absence of Lisch nodules.

Results

Fifty-three people with NF attended for hospital assessment, 29 females and 24 males, age range 3–80 years. Eleven children were ascertained via LINK, five females and six males, age range 4–17 years. All the patients were of Caucasian origin. A total of 64 patients were therefore examined for the presence or absence of Lisch nodules. The diagnosis of NF was obvious from facial appearance in only 7/64 (11%) of these patients.

In 95% of the patients (61/64) Lisch nodules were present and were bilateral in 93% (57/61). The age distribution of the patients and number with Lisch nodules in each age group is shown in Fig. 1. The nodules were easily seen in all but one patient, who was aged 9 years and had only two nodules in his right iris. The appearance of the nodules was distinct. They were dome-shaped lesions found on all parts of the surface of the iris, varying in size from being barely visible with the slit lamp to up to 2 millimetres in diameter (Fig. 2). Most of them were brown in

Fig. 1 Age distribution of patients and proportion with Lisch nodules in each group.

colour but a few, particularly in children, were very pale and almost white.

We were able to count the number of nodules in all but two patients (aged 3 and 4 years). The mean number of nodules per eye was 25 (range 1 to 100). The age of the patient was compared with the mean number of nodules per eye (OS+OD)/2 by the Spearman rank correlation test. There was a highly significant correlation between age and the number of nodules per eye ($r=0.404$, $p<0.002$). For the patients <16 years ($n=24$) three had no Lisch nodules (13%) and nine (38%) had fewer than 10 nodules per eye, whereas in all patients age ≥16 years

Fig. 2 Typical appearance of Lisch nodules.

($n=40$) Lisch nodules were present and only 6 had fewer than 10 per eye (15%).

Twenty-one offspring (age range 4 to 39 years) of patients with NF, with no cutaneous manifestations of the disease, were also examined and no Lisch nodules were seen. In addition 150 general ophthalmology outpatients, 76 females and 74 males, age range 8–86 years, were examined. No Lisch nodules were seen in 149 patients. One patient had several iris naevi and two lesions indistinguishable from Lisch nodules on the periphery of one iris. She was 27 years of age and had no family history of NF. The patient and her parents underwent clinical examination. No café au lait spots or cutaneous neurofibromas were present. Slit-lamp examination was normal in both her parents.

The frequency of other ophthalmological findings in the 53 patients ascertained via the population based study is shown in Table 2. The most frequent findings were choroidal 'hamartomas,' which were present in 15/51 (29%), age range 15 to 61 years, and were only easily visible with the indirect ophthalmoscope. They appeared as discrete dark lesions, between 5 and 20 in number, 1 to 2 disc diameters in size, and were scattered around the posterior pole. Fluorography of these lesions (Fig. 3) suggested that they were choroidal naevi.

Discussion

Iris involvement in NF is regarded as rare by some authors.^{10,11} In our series of 64 patients with NF Lisch nodules were found in 96% overall and 100% of those aged 16 years or over. We would therefore agree with Lewis and Riccardi⁶ that Lisch nodules are the commonest ophthalmic manifestation of the disease and a useful clinical sign. Histologically Lisch nodules have been shown to be melanocytic hamartomas^{8,12} and therefore are presumably of neural crest origin embryonically, as are the other major manifestations of NF—café au lait spots and cutaneous neurofibromas.

In their series Lewis and Riccardi⁶ found Lisch nodules in 36 (92%) of 39 patients >16 years of age

Fig. 3 Fluorescein angiogram showing the choroidal lesions seen in some patients with NF.

but in only three (23%) of 13 patients <6 years of age. Boltshauser *et al.*¹³ have recently reported their findings in 90 patients with NF, 82 (91%) of whom had Lisch nodules. They were present in all the 53 patients aged >16 years but in only 3 (33%) of 9 aged <6 years. In these three series only three patients aged >16 years did not have Lisch nodules. We therefore conclude that over 95% of adults with NF have Lisch nodules and that they begin to develop in early childhood. Both in our series and that of Lewis and Riccardi⁶ there was significant correlation between the number of Lisch nodules observed and the age of the patients.

In the 150 normal subjects we examined only one had two lesions (in the same eye) which were clinically indistinguishable from Lisch nodules. No other features of NF were found in this patient or her parents, neither of whom had Lisch nodules. It may be that this patient has these nodules as her sole manifestation of NF, for which she is a new mutation; we believe this is unlikely. The alternative explanation is that normal individuals may rarely have one or two Lisch nodules but that numbers greater than this are unique to NF. One case has been reported¹⁴ where the only manifestations of NF in the parents of two affected sons were Lisch nodules in the mother. This patient had over 100 nodules in each eye (Riccardi, personal communication).

On slit-lamp examination by oblique illumination Lisch nodules because of their smooth outline and dome-shape are easily distinguishable from iris

Table 2 Ophthalmological findings in 53 patients with von Recklinghausen neurofibromatosis

Lisch nodules	51 (96%)
Choroidal 'hamartomas'	18/51* (35%)
Neurofibromas on eyelids	9 (16%)
Presumed conjunctival neurofibroma	1 (2%)
Prominent corneal nerves	3 (6%)
Glial tissue overlying optic disc	2 (4%)
Bilateral optic atrophy due to optic glioma	1 (2%)

*Only 51/53 patients were examined with an indirect ophthalmoscope.

naevi. We did, however, observe an unusual variation of pigmentation in three patients (two normal subjects and one with NF) which could at first glance be confused with Lisch nodules by the inexperienced observer. These three patients had approximately 100 tiny nodules of dark brown pigmentation confined to the peripupillary region of the iris. The appearance was similar to the mammillations described in some cases of unilateral melanosis by Mann.¹⁵

Pigmented choroidal lesions were the second most frequent finding and were seen in 18/51 (35%) of the patients. They were best seen with the indirect ophthalmoscope and appeared as discrete areas of hyperpigmentation, dark brown-black in colour, which were flat or only minimally elevated. Fluorescein angiography demonstrated that they were avascular patches of hypofluorescence similar to multiple small choroidal naevi. Lewis and Riccardi⁶ found similar choroidal lesions in 51% of their series and referred to them as choroidal hamartomas. Cotlier¹⁶ reported two patients with these lesions and described them as 'café au lait spots' of the fundus, which seems the most appropriate term. None of the patients in this series had either choroidal melanomas or glial hamartomas, and other ophthalmological manifestations of NF were all relatively uncommon (Table 2).

In conclusion, we have found Lisch nodules to be virtually pathognomic of NF. The nodules become manifest in early childhood, are present in over 95% of adults with NF, and are easily seen on slit-lamp examination. They are therefore a useful clinical sign and under appropriate circumstances can be used to establish or exclude the diagnosis of NF. If a child with multiple café au lait spots is found to have Lisch nodules, then the diagnosis is confirmed. Conversely, if the children of a patient with NF reach the age of 5 years and have neither café au lait spots nor Lisch nodules, it is extremely unlikely they have inherited the disease.

Most clinicians perceive patients with NF as having the severe form of the disease, but in the majority of patients the diagnosis is not obvious at first glance (89% in this series). Similarly many patients are unaware of the disease complications and therefore do not think it relevant to mention their NF when

attending an ophthalmology clinic. The finding of Lisch nodules on slit-lamp examination should alert the ophthalmologist to the diagnosis of NF and the consideration that the patient's presenting symptoms may be due to one of the complications of the disease.

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