IMAGES OF LISCH NODULES ACROSS THE SPECTRUM

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SUMMARY

The presence of melanocytic hamartomas on the iris, known eponymously as Lisch nodules, is highly characteristic of neurofibromatosis type 1 (NF1). Early recognition of NF1 is vital for optimal detection of associated tumours and for genetic counselling of family members. Although the iris nodules are probably not visible at birth, their prevalence in patients with NF1 gradually increases from birth to about 50% of 5-year-olds, 75% of 15-year-olds and 95–100% of adults over the age of 30. Iris hamartomas in NF1 are elevated, pale brown lesions that vary in appearance depending on the underlying colour of the iris. Colour illustrations are shown in this article, enabling the clinician readily to differentiate hamartomas from other iris lesions.

In 1937 Lisch[1] published his now classic paper which emphasised the association between iris nodules and von Recklinghausen's neurofibromatosis (now neurofibromatosis type 1 or NF1). Following this article these iris lesions came to be known eponymously as Lisch nodules. Almost 50 years later Lewis and Riccardi[2] described the high prevalence of these nodules in NF1 and focused medical attention on their diagnostic importance.

Although some ophthalmologists have been credited with earlier descriptions of these iris nodules,[1] surprisingly few of these turn out to be the genuine iris lesions associated with NF1. Instead, many of the earlier authors appear to be describing a different condition, that of iris elevations associated with melanosis oculi or iris heterochromia.[3–6] These iris lesions are quite different: regularly spaced small elevations described variously as 'golf-ball iris' or 'goose-skin' by Coats[4] (see Fig. 1), or a 'field of stubble or a deforested landscape where only the stumps of trees remain' by Friedenwald and Friedenwald.[6] Had the last authors been describing true iris nodules as seen in NF1, from shape alone they would perhaps have referred to the rounded tops of deciduous trees, rather than their stumps!

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At an Ophthalmological Society of the United Kingdom meeting in the early 1900s, Snell[7] presented what may have been the earliest description of true iris nodules associated with NF1. He described 'irregular yellowish markings' near the pupil margin of the iris in a patient with a plexiform neurofibroma of the orbit and associated buphthalmos. In 1913 Fuchs[8] published a description and histological illustrations of the iris nodules. Five years later Waardenburg[9] also described small wart-like growths on the iris, but he did not illustrate them or directly link them with neurofibromatosis at that time.

In 1930 Goldstein and Wexler[10] made the association between melanotic nodules on the iris and neurofibromatosis and provided histopathological illustrations. Their patient had bilateral diffuse corneal infiltration, which prevented them from identifying the iris nodules prior to microscopic examination at autopsy. Following this, Gabriélidès[11] noticed the association in 1931 in a single detailed case report. Kurz[12] presented a case of Lisch nodules in association with neurofibromatosis at a Czech congress in 1932. In the 1932 Doyne Memorial Lecture, Van der Hoeve[13] made the association between neurofibromatosis and iris 'tumours' in 3 separate patients with neurofibromatosis, including 2 from Waardenburg, but did not illustrate his article. Then in 1935, two years before Lisch's paper, Sakurai[14] in Japan published a beautifully illustrated paper linking characteristic iris nodules with von Recklinghausen's neurofibromatosis, complete with three unequivocal pictures of the iris appearances (see Fig. 2). Two years later Lisch published his famous paper with one illustration in the German literature (see Fig. 3).

THE APPEARANCES OF LISCH NODULES

Lisch nodules occur in all racial types. They vary in size and number from, in extreme cases, a single 'salt-grain' on one iris alone, barely visible by slit lamp examination, to prolific, sometimes innumerable or very large nodules, even 2 mm in diameter. Fortunately in most adults, except in very dark irides, they are easily visible either with the

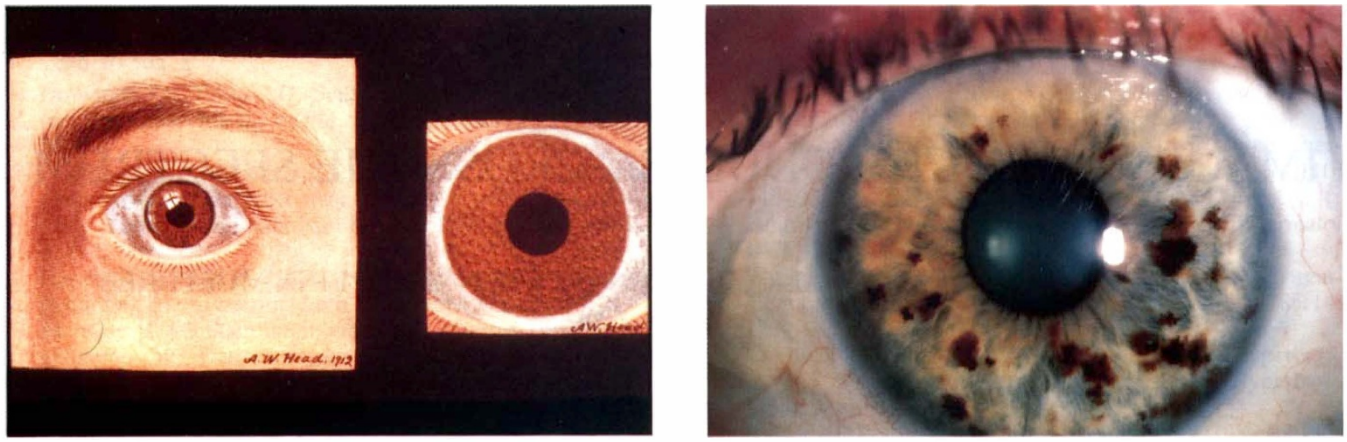

Fig. 1. *Differential diagnosis of Lisch nodules. Left: The original illustration by Coats[4] as a differential diagnosis of Lisch nodules, showing iris lesions associated with melanosis oculi. Right: Multiple iris naevi.*

naked eye or with the aid of an illuminated magnifying glass. On the other hand, declaring their absence requires slit lamp examination.

Lisch nodules vary widely in appearance depending on the background colour of the iris (see Fig. 4). In all eyes they have an elevated, fleshy appearance, best appreciated by tangential broad beam illumination. In blue and green irides they appear pale-to-medium brown with feathery margins, and in dark brown irides they are cream coloured, dome-shaped and extremely well defined. The nodules are distributed in a random fashion on the anterior surface of the iris and occasionally just in the angle, when they can be viewed gonioscopically. Although Lisch nodules have a highly characteristic appearance, there are a few iris conditions that may be similar (Table I).

HISTOLOGY AND ELECTRON MICROSCOPY OF LISCH NODULES

Fuchs in 1918 and Goldstein and Wexler[10] in 1930 published the early light microscopic appearances of the iris nodules. About 50 years later Perry and Font[15] presented electron microscopic findings of Lisch nodules from an iridectomy specimen in an NF1 patient. They confirmed that Lisch nodules were melanocytic hamartomas and were not derived from Schwann cells. In 1991 Williamson and colleagues[16] further determined by light and electron microscopy that Lisch nodules consist of a condensation of spindle cells on the anterior iris surface and are of melanocytic origin. They also found that when they are pigmented, this is because an underlying stromal naevus is present.

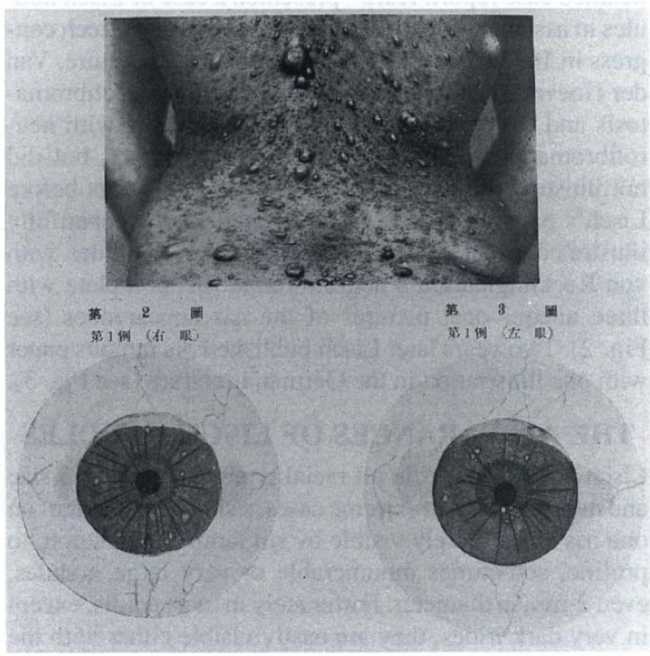

Fig. 2. *The original illustration by Sakurai.*[14]

PREVALENCE OF LISCH NODULES

We combined data from six large studies[2,17–22] of the prevalence of Lisch nodules in different age groups. The techniques and advantages of meta-analysis for the purposes of integrating results have been recently reviewed.[23,24] Each study examined between 30 and 167 patients with NF1 by NIH diagnostic criteria. The total number of patients analysed was 417, with an overall age range for all the studies from 5 weeks to 83 years old. We obtained the raw data from one study.[20] In the other studies, prevalence rates were expressed in narrow age ranges, for example 1–2 years, so that the data could be combined, especially in youth where prevalence changes rapidly with age.[17,18,21] Sizes of groups were standardised by adjusting the age range limits. In adulthood, prevalence values were steady over a very large age range. For example several

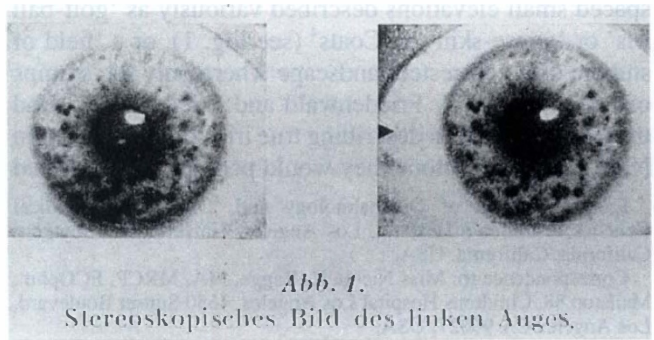

Fig. 3. *The illustration in Lisch's original article.*[1]

Table I. Differential diagnosis of Lisch nodules

Iris naevi
Multiple
Iridocorneal endothelial syndromes
Iris mammillations associated with melanosis oculi
Inflammatory nodules
Granulomatous uveitis, e.g. sarcoidosis (Koeppe and Busacca nodules), tuberculosis
Roseolae and gumma in syphilis
Iris pearls in leprosy
Tumours
Iris cyst
Iris melanoma
Tapioca melanoma
Retinoblastoma (pseudogranulomatous uveitis)

studies indicated a prevalence of 100% in adults: over 12 years of age,[17,18] over 30 years of age[20,22] or over 40 years of age.[2] In one paper,[22] all patients aged 21–35 years had Lisch nodules, but in 1 of the 8 patients aged over 35 they were not detectable. In another study, only 1 patient of 40 over the age of 30 years failed to show any Lisch nodules. In neither study was gonioscopy performed to exclude the presence of Lisch nodules in the angle alone.

The average prevalence was obtained for the different age groups. The median age of each group was used to plot the final point. The size of the groups was indicated by the diameter of a circle drawn around the point. From the graph of pooled data an approximate prevalence can be determined for different age groups.

The prevalence of Lisch nodules increases semilogarithmically with age (r^2=0.89). From this, it is likely that Lisch nodules are difficult to detect at birth. However, they are present in approximately 33% of NF1 patients aged 2.5 years, almost 50% of 5-year-olds, approximately 75% of 15-year-olds and 90% of 25-year-olds. Between 95% and 100% of those with NF1 over the age of 30 have Lisch nodules. Unlike neurofibromas, there is no acceleration in the rate of appearance of these nodules associated with puberty.[2]

DISCUSSION

Lisch nodules are melanocytic iris hamartomas,[10,15,16] and in keeping with many other pathological features of NF1 they are derived from neural crest tissue. Their importance, only recently realised,[2] cannot be emphasised too strongly. Prompt and reliable diagnosis of NF1 is critical for early detection of associated tumours and genetic counselling of family members. Until a useful genetic test is developed, they continue to be an extremely important diagnostic sign.

Table II. NIH inclusive diagnostic criteria for NF1[32]

The diagnostic criteria are met if a person has two or more of the following:
Six or more café au lait macules >5 mm in diameter pre-pubertally and >15 mm diameter post-pubertally
Two or more neurofibromas of any type or one plexiform neurofibroma
Axillary or inguinal freckling
Optic glioma
Two or more Lisch nodules
A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
A first-degree relative with NF1

Table III. Ocular findings in neurofibromatosis type 1

Presumed neurofibromas of conjunctiva
Prominent corneal nerves
Posterior embryotoxon
Lisch nodules
Congenital ectropion uveae
Heterochromia iridis
Neurofibroma of ciliary nerves
Plexiform neurofibroma of eyelid and orbit
Glaucoma
Angle anomalies
Choroidal hamartoma
Chorioretinal scar
Congenital hypertrophy of the retinal pigment epithelium
Myelinated nerve fibres
Astrocytic hamartoma
Optic nerve head glioma
Optic glioma
Strabismus

In the presence of other diagnostic features of NF1 or a positive family history, Lisch nodules confirm the diagnosis. In the absence of other signs of NF1, their presence is highly suggestive of NF1. Although the NIH diagnostic criteria (Table II) include two or more Lisch nodules, a single nodule in only one eye can contribute to the diagnosis in the presence of other signs or family history of NF1. A summary of other ophthalmic manifestations of NF1 is shown in Table III. In the paediatric population, although café au lait patches are the most common sign, Lisch nodules, if present, are highly specific for the diagnosis (more than axillary freckling or neurofibromas) and rarely may be the only sign of NF1.[27]

Lisch nodules are present in almost 100% of adults with NF1 over the age of 35 years. The prevalence increases gradually from 0 at birth, reaching 75% in the mid-teens and 90% by the mid-twenties. The nodules also occur in patients with no other features of NF1 (predecessors of affected patients with NF1[27]), or in otherwise unaffected relatives of patients with NF1[25] (Table IV). Furthermore, patients with Watson's syndrome (an allelic variant of NF1 characterised by café au lait patches, mental retardation and pulmonary stenosis[28] have these nodules. In patients with segmental neurofibromatosis, Lisch nodules may occur on the same side as the other manifestations.[29] Very rarely, and rather surprisingly in view of the different chromosome assignment of this disease, Lisch nodules have been described in isolated cases of NF2.[30,31]

Table IV. Categories of patients with Lisch nodules

Affected patients with NF1
Otherwise unaffected patients with NF1[25]
Patients with Watson's syndrome (allelic variant of NF1 characterised by café au lait patches, mental retardation and pulmonary stenosis)[28]
Patients with segmental neurofibromatosis ipsilateral to the other manifestations[29]
Very rare, isolated cases of NF2[30,31]

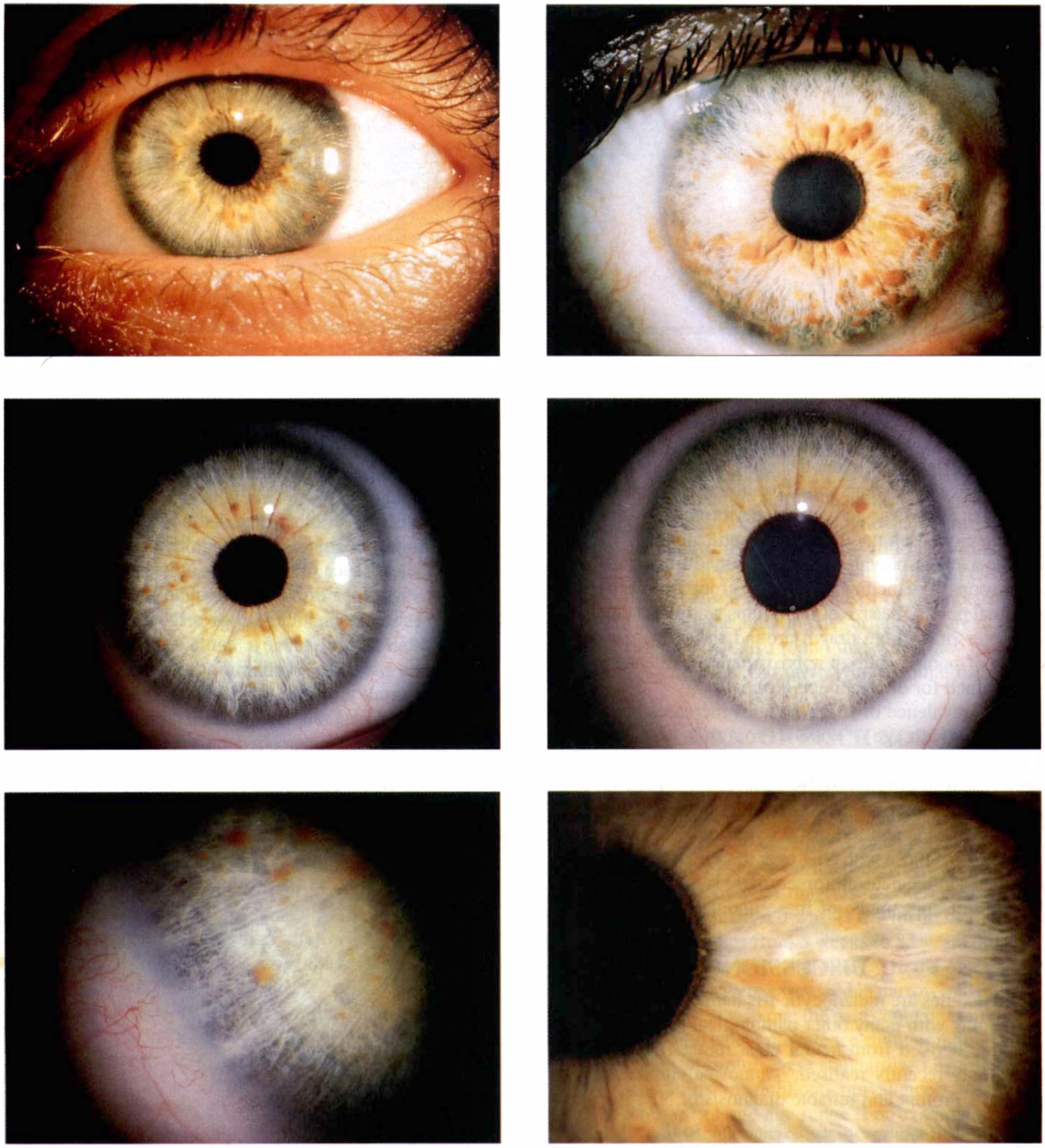

Fig. 4. *The spectrum of appearances of Lisch nodules in different coloured irides.*

The universal finding of Lisch nodules in NF1 and in apparently otherwise unaffected family members[25] is of especial interest now that the gene is cloned.[26] The gene for NF1 is situated on the long arm of chromosome 17 and is one of the largest genes to code for a single disease in man, with a protein product, 'neurofibromin', comprising 2818 amino acids. The function of the gene product is a subject under intense study at present. Exactly how this gene product will relate to the multiple and diverse manifestations of NF1 in different tissues remains to be seen.

CONCLUSION

The purpose of our paper is to provide the ophthalmologist with a firm basis for the identification of Lisch nodules in NF1 and some indication of their prevalence in different age groups. The ophthalmologist can then provide critical diagnostic information to other specialists caring for

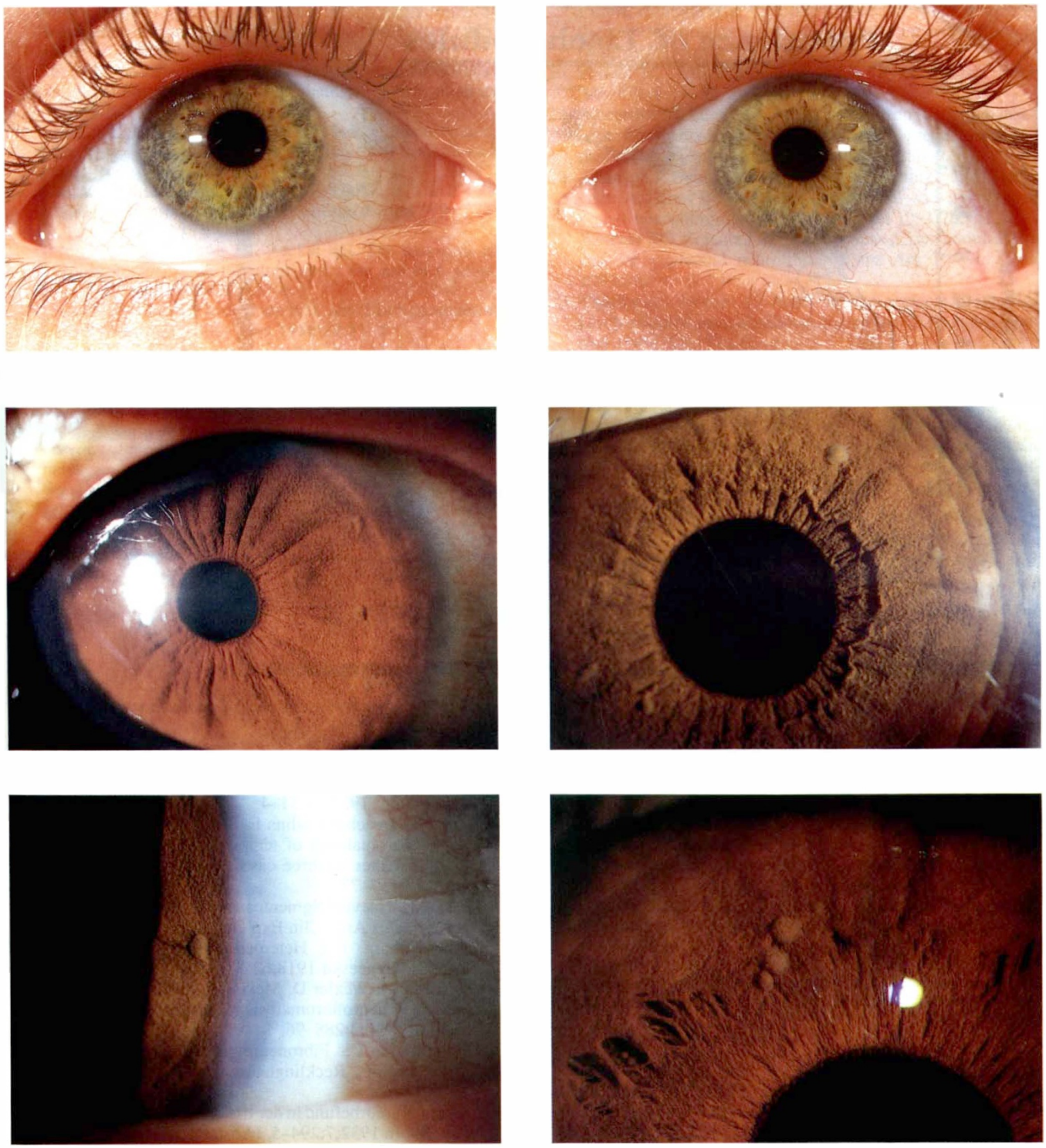

Fig. 4. *(Continued).*

patients with this diversely manifest disease. Use of an illuminated magnifying glass could assist the ophthalmic and non-ophthalmic specialist in the initial screening for these nodules, especially on young children and where no specialised equipment is available. However, in difficult cases slit lamp examination is required, including gonioscopy to answer the question definitively for the purposes of exclusion. Furthermore, in view of the other ocular manifestations seen in NF1, a full ophthalmic evaluation is recommended.

Finally we propose that Tsuya Sakurai, a Japanese physician, be given credit for her detailed and well-illustrated description of iris lesions and von Recklinghausen neurofibromatosis. We wish to rename them Sakurai–Lisch nodules in her honour.

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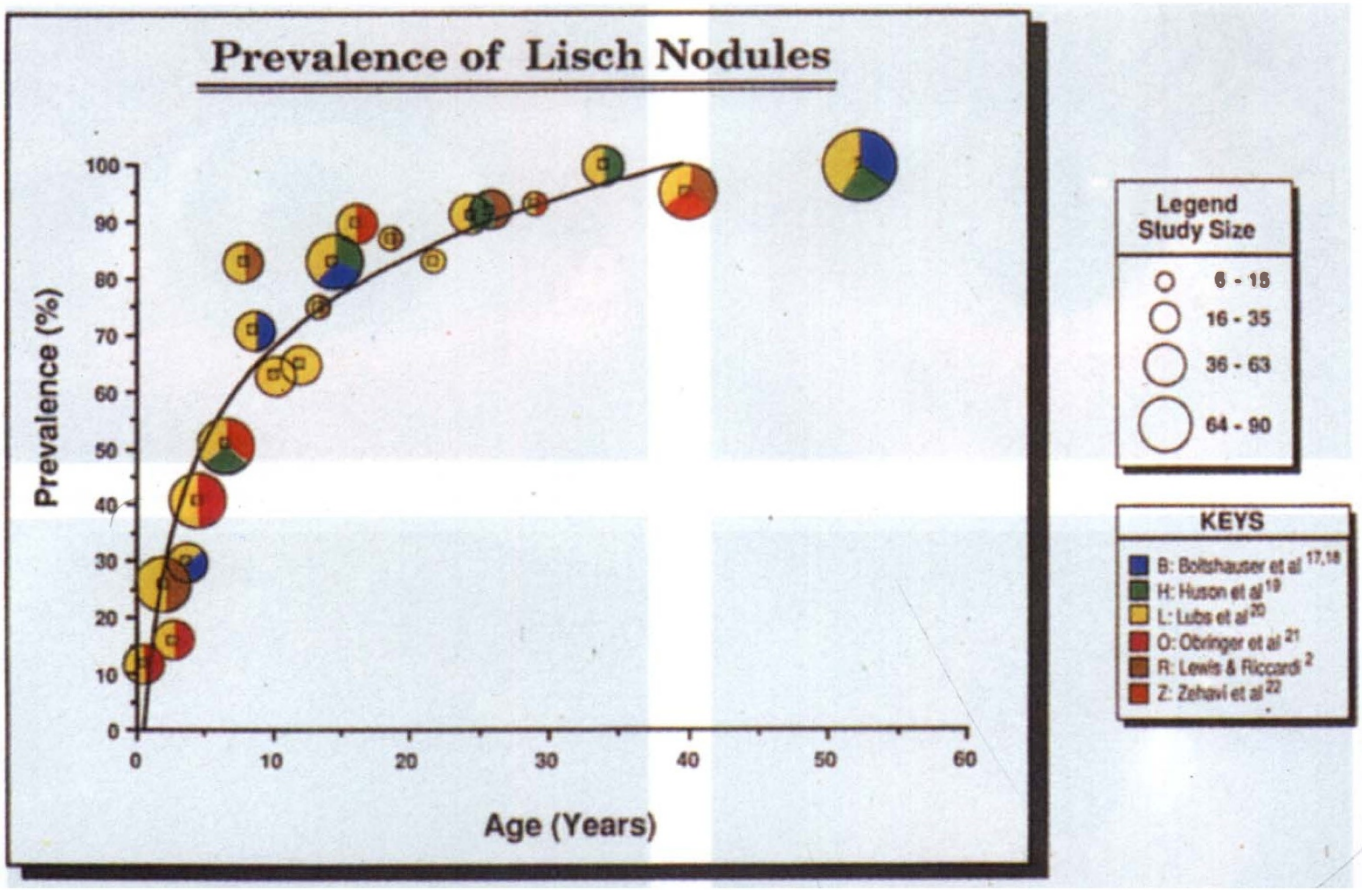

Fig. 5. *Graph showing the prevalence of Lisch nodules with age. Diameter of circles represents size of pooled data; colour coding represents studies used to construct that data point.*

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Key words: Iris hamartoma, Lisch nodules, Neurofibromatosis type 1, NF1, Ophthalmic manifestations, von Recklinghausen neurofibromatosis.

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