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The neurofibromatoses: more than just a medical curiosity

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ABSTRACT Until modern methods of clinical and scientific research were applied to neurofibromatosis (NF) over the last 30 years, the disease was largely regarded as a medical curiosity. In 1987, a NIH consensus conference agreed a disease classification system and diagnostic criteria for the two main forms. They are defined by the presence/absence of specific nervous system tumours (neurofibromas in NF1, schwannomas in NF2), skin pigmentation, and ophthalmological features. The recognition of the different types is not just an academic exercise (and one geneticists are fond of!), because the natural history and management of each type is distinct.

One important feature in both forms of neurofibromatosis, and indeed in other phakomatoses like tuberous sclerosis, is that the different disease features develop at different ages. For example in NF1, the café-au-lait spots develop during the first two years of life but dermal neurofibromas are unusual before the late teens or early twenties. Despite developments in molecular diagnosis it is probably still more cost effective to refer unusual patients to a specialist clinic prior to testing.

LIST OF ABBREVIATIONS Ezrin–Radixin–Moesin (ERM), GTPase-activating protein (GAP), malignant peripheral nerve sheath tumours (MPNST), National Institutes of Health (NIH), neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2)

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SUMMARY

Historically, no distinction was made between the different forms of neurofibromatosis and they were lumped together under the umbrella term 'von Recklinghausen's disease'. We now recognise that the neurofibromatoses are a group of conditions characterised by tumours of the nervous system and characteristic skin pigmentation. The type of peripheral nerve tumour (neurofibromas versus schwannoma), the presence/absence of café-au-lait spots and skin-fold freckling, and the presence of particular ophthalmic features characterise each form. As clinical and genetic research has advanced, it is clear that the two main forms (NF1 and NF2) are distinct at a clinical and molecular level. There is little problem in distinguishing the types on clinical grounds, except in the rare cases of severe NF2 where occasionally there can be overlapping features. Clinical diagnostic criteria have been developed for both types. The recognition of the different types is important since the natural history and management considerations are distinct for each form.

Inheritance of both types is autosomal dominant and in each, about half of the cases presenting are the first case in the family. Both genes act as tumour suppressors. The *NF1* gene is on chromosome 17 and encodes for the protein neurofibromin, which acts as a GAP for p21 ras. The *NF2* gene codes for Merlin/Schwannomin and is part of the ERM sub-group of the protein 4.1 family. Genetic testing has been part of the routine care of NF2 families for several years. The large size of the *NF1* gene and lack of demand for prenatal or presymptomatic testing has delayed the introduction of *NF1* gene testing. Testing is now more straightforward and is being introduced into clinical practice.

Neurofibromatosis type 1 is one of the most common dominant disorders with a birth incidence of around 1 in 3,000. The major disease features (café-au-lait spots, cutaneous neurofibromas, and Lisch nodules) are not associated with major problems other than cosmetic issues. There are a large number of complications affecting all body systems and so patients with NF1 can present with disease-related complications to almost any medical specialty.

In contrast, the hallmark of NF2 is the occurrence of bilateral vestibular schwannomas. This term is now preferred to acoustic neuromas as the tumours are schwannomas histologically and arise on the vestibular branch of the eighth nerve. Many patients will also develop

meningiomas and other cranial nerve and spinal root schwannomas. It is essential that NF2 patients are followed in a specialist clinic, as management decisions are complex. The long-term hope is that through understanding the pathogenesis, medical treatments will be developed. Of particular importance in this respect has been the development of good mouse models of neurofibroma and schwannoma/meningioma development.

NEUROFIBROMATOSIS TYPE 1

Epidemiology and pathogenesis

Neurofibromatosis type 1 is one of the most common autosomal disorders in humans with an incidence of 1 in every 2,500–3,000 births. It occurs with equal frequency in all ethnic groups. Inheritance is autosomal dominant and about half of all cases are the first incidence in the family. Penetrance is 100% by the age of five, so if children born to an affected parent have no café-au-lait spots by five years then they have not inherited NF1. There are occasional rare families where affected individuals have fewer than six café-au-lait spots. This is difficult as 10% of the general population have one or two spots. In these families, unless genetic testing is used, the children need to be followed into their teenage years and monitored for the development of neurofibromas.

The *NF1* gene is on chromosome 17 and encodes for the protein neurofibromin. The best-defined function of neurofibromin is as a GAP for members of the p21 ras protein family. Loss of neurofibromin function leads to downstream cell growth activation because neurofibromin negatively regulates ras output by accelerating the conversion of active ras–GTP to inactive ras–GDP. Animal models of NF1 are now allowing dissection of the pathogenesis of neurofibroma and optic glioma formation in NF1 and the disease-associated learning problems.

Mutation testing for NF1 is complicated by the large size of the gene and the fact that there is no mutation hot spot. Although emerging technologies mean that mutations can be detected in about 95% of cases. The only genotype to phenotype correlation of clinical significance to emerge to date is the finding that patients with a whole gene deletion tend to have dysmorphic features and an increased frequency of certain disease complications.

Diagnostic criteria

The diagnosis of NF1 is usually straightforward and is made using diagnostic criteria developed in 1987 at a NIH consensus development conference (see Table 1). These criteria have stood the test of time well.

There are two rare conditions where patients could satisfy the diagnostic criteria and not have other very obvious non-NF1 features. Some cases of segmental NF1 can satisfy the criteria as they have six or more café-au-lait spots and skin-fold freckling. The distinction is made because these features are limited to one or more distinct body segments. The other relatively newly recognised condition is a recessive one caused by homozygous mutations in one of the mismatch repair genes. They may satisfy the criteria by having six or more café-au-lait spots and an affected sibling.

TABLE 1 Diagnostic criteria for NF1. Two or more of the following should be present:

- Six or more café-au-lait macules of over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals (see Figure 1).
- Two or more neurofibromas of any type or one plexiform neurofibroma.
- Freckling in the axillary or inguinal regions (see Figure 2).
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinct osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis.
- A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria.

The difficulties with mutation testing described above and the ease of clinical diagnosis in the majority of cases means that mutation testing is not routinely used for diagnostic confirmation in clinical practice, but is available for couples considering prenatal diagnosis.

Clinical features and natural history

The clinical features of NF1 are shown in Table 2. They are usefully divided into major features and disease complications. Of the major features, neither the café-au-lait spots, skin-fold freckling, nor Lisch nodules are associated with any medical problems. There are two types of peripheral neurofibroma. The common type, which develops in nearly all patients, is dermal neurofibroma. These lie within the dermis and epidermis and move passively with the skin. The majority appear as discrete nodules, are soft to palpate, and have a violatious colour (see Figure 3). Dermal neurofibromas rarely cause symptoms and are not at risk of malignant change, but they can cause considerable distress to the patient.

The other kind of peripheral neurofibroma is the nodular neurofibroma. These arise on major peripheral nerve trunks and are of much firmer consistency. They develop in only a subset of patients (around 5–10%). They frequently cause neurological symptoms and need to be removed by a peripheral nerve surgeon. Multiple nodular

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TABLE 2 Neurofibromatosis type 1: clinical features and age of onset. (Data from Huson SM *et al. Brain* 1988; **111(Pt 6):**1355–81 and Friedman JC *et al. Neurofibromatosis Phenotype, natural history and pathogenesis* 3rd ed. Baltimore; Johns Hopkins University Press; 1999.)

Disease feature	Frequency (%)	Age of presentation
Major defining features		
Café-au-lait spots	>99	Birth–puberty
Freckling[1]	>99	≥ 7 years
Peripheral neurofibromas	67	Birth–puberty
Lisch nodules[1]	90–95	≥ 3 years
Complications		
Plexiform neurofibromas		
All lesions	30·0	0–18 years
Large lesions of head and neck	1·2	0–3 years
Limbs/trunk lesions associated with significant skin/bone hypertrophy	5·8	0–5 years
Intellectual handicap		
Severe	0·8	
Moderate	2·4	0–5 years
Minimal/specific learning difficulties	29·8	
Epilepsy		
No known cause	4·4	
Secondary to disease complications	2·2	Lifelong[2]
Hypsarrhythmia	1·5	0–5 years
CNS tumours		
Optic glioma[1,3]	1·5	Childhood (usually)
Other CNS tumours	1·5	Lifelong
Spinal neurofibromas	1·5	Lifelong
Aqueduct stenosis	1·5	Lifelong
Malignancy		
Malignant peripheral nerve sheath tumours (MPNST)	1·5	Lifelong
Pelvic rhabdomyosarcoma	1·5	0–5 years
Orthopaedic complications		
Scoliosis, requiring surgery	4·4	0–18 years
Scoliosis, less severe	5·2	
Pseudarthrosis of tibia and fibula	3·7	0–5 years
Vertical scalloping[1,4]	10·0	Lifelong
Gastrointestinal tumours (neurofibromas and GISTs[5])	2·2	Lifelong
Renal artery stenosis	1·5	<20 years (usually)
Pheochromocytoma	0·7	≥ 10 years
Duodenal carcinoid	1·5	≥ 10 years
Congenital glaucoma	0·7	0–1 years
Juvenile xanthogranuloma	0·7	0–5 years
Complications not seen in Welsh study but definitely associated with NF1 (presumed frequency <1%)		
Sphenoid wing dysplasia[1]		Congenital
Lateral thoracic meningocele[1]		Lifelong
Atypical forms of childhood leukemia		0–18 years
Cerebrovascular disease		Childhood (usually)
Glomus tumours in nail beds		Adults
Possible disease complications (case reports or small series but not found in large series of NF1 patients)		
Hypertrophic cardiomyopathy		Lifelong
Pulmonary fibrosis		Adults

[1]Features that are often asymptomatic and found on examination or imaging of appropriate body area.

[2]'Lifelong' indicates cases have been reported presenting in all age groups.

[3]If cranial MRI scanning performed, they are seen in 15% of cases but usually remain asymptomatic.

[4]Frequency from Friedman *et al.* 1999.

[5]Gastrointestinal stromal tumours.

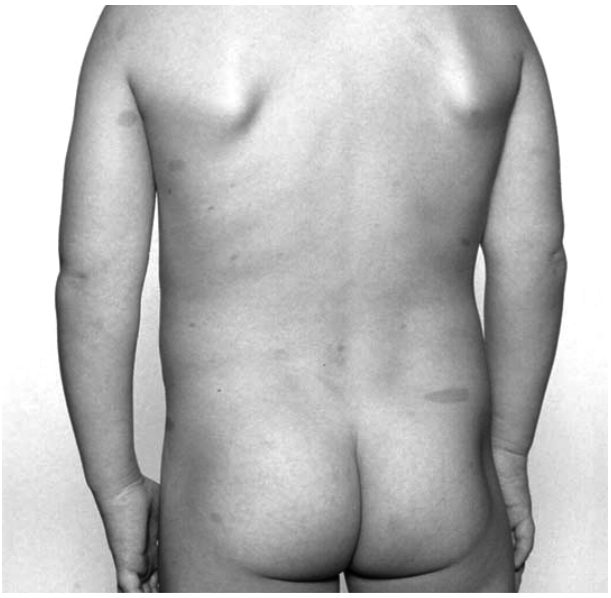

FIGURE 1 Typical appearance of café-au-lait spots in a child. (Reprinted from: Huson SM. Neurofibromatosis. In: Swash M, Oxbury JM (editors). *Chapter on The Phakomatoses. Clinical Neurology.* Edinburgh:Churchill Livingstone; 1991 with permission from Elsevier.)

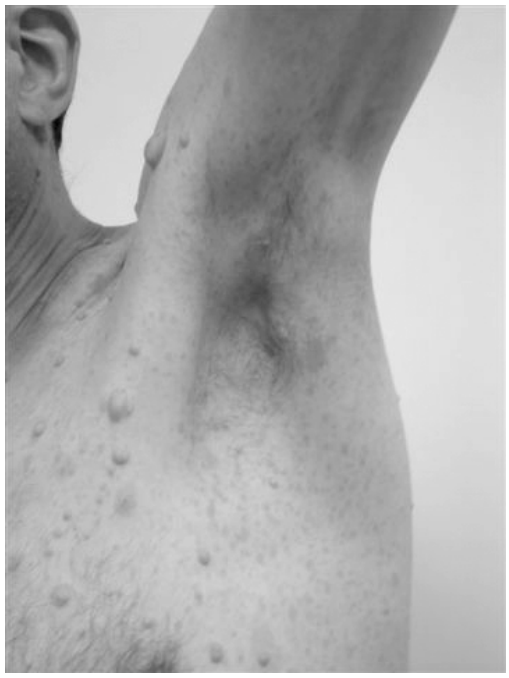

FIGURE 2 Axillary freckling.

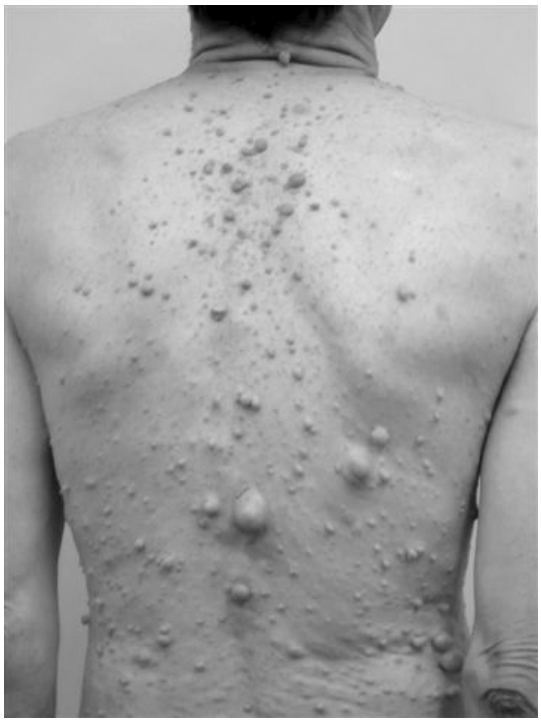

FIGURE 3 Typical appearance of cutaneous neurofibromas in a moderately severely affected adult with NF1. The lesions vary from obvious pedunculated lesions to small papules that are purplish in colour and rise just above the skin surface. When these lesions are palpated there is a sensation of the skin 'giving way'. This is described as 'button-holing'.

neurofibromas have been found to put patients at a higher risk of MPNST.

It is the complications of NF1 that cause the major part of the disease-related morbidity and mortality. The problem is that their occurrence cannot be predicted even within families. Some of the more severe complications develop in childhood or not at all. By far the most common are learning problems, and these are often associated with coordination and behavioural problems. Other than plexiform neurofibromas, the other complications each occur in around 5% or fewer of patients.

Around 50% of patients will never develop a disease complication. Death certificate studies have shown that NF1 affects mortality at all ages, but particularly so under the age of 40 years. One of the problems is often late diagnosis of a complication because the significance of the diagnosis of NF1 had not been appreciated. For example, patients reassured their sciatica would resolve only to present with cauda equina compression, or those with a history of headache and mild hypertension as warning signs of a phaeochromocytoma who then present with intra-cerebral haemorrhage.

Management

Many of the complications of NF1 develop in childhood, and so children with NF1 should have an annual review with a paediatrician, and examination should be geared to the complications that could present at a particular age. The Clinical Advisory Board of the UK NF Association has produced management guidelines, which are available from the association. In my own practice I do not advocate any screening investigations but rely on a detailed history and examination. Because of the problems of visual examination in young children some authorities recommend regular paediatric ophthalmology checks in young children.

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For adults with NF1 by far the most important thing is patient education so that they know to ask if unusual symptoms could be disease related. Some adult patients appreciate an annual review, but at a minimum they should have their blood pressure checked annually by their general practice team.

Some centres have specialist neurofibromatosis clinics, often coordinated by a clinical geneticist, neurologist or paediatrician. They are particularly useful around the time of first diagnosis for patients with unusual features or severe complications.

Referral for genetic counselling is often helpful for families when the diagnosis is first made in their child, and for young adults as they consider their reproductive options. Both prenatal and pre-implantation diagnosis are available for the majority of families, but are dependent on identifying the disease-causing mutation or using DNA markers. For this reason genetic referral before pregnancy is preferable. Because of the variability of the condition, and the lack of ability to predict severity, many couples decide to have a family without testing.

Mosaic NF1

Some patients have features of NF1 limited to one or more body segments. This is due to somatic mosaicism for the *NF1* gene. The recognition of segmental or localised NF1 is important for two reasons. First, there is a very small chance of a disease complication and, secondly, the recurrence risk is much less than 50%, as gonadal tissue may not be involved.

NEUROFIBROMATOSIS TYPE 2

Epidemiology and pathogenesis

Neurofibromatosis type 2 has a birth incidence of 1 in 33,000–40,000, with a diagnostic prevalence of 1 in 210,000. The prevalence is much lower as many patients are not diagnosed until they are adults. Also, there is considerable disease-associated mortality.

Like NF1, NF2 is an autosomal dominant disorder and about half of cases are the first in the family. What is different is that NF2 tends to affect family members in a similar way. There is inter-family difference, with families tending to fall into two broad categories of severe and mild disease.

The *NF2* gene is on chromosome 22 and is a tumour suppressor, it encodes for the protein Merlin (also called schwannomin). Merlin is part of the ERM subgroup of the protein 4.1 super family. Merlin functions as a negative growth regulator; the molecular mechanisms that underlie this process are gradually being elucidated. Loss of Merlin function is likely to lead to a loss of recognition of certain cell-to-cell signalling pathways and to the failure to downregulate cellular growth. Current methods can identify the mutation in about 95% of patients, providing they are not genetic mosaics. There is genotype to phenotype correlation, with severe disease being associated with non-sense or frameshift mutations and mild disease with large deletions or mis-sense mutations. Phenotype is more variable with splice site mutations.

TABLE 3 Manchester criteria for diagnosis of NF2. A diagnosis of NF2 can be made in an individual with any one of the following combinations.

- Bilateral vestibular schwannomas.[1]
- First degree family relative with NF2 and unilateral vestibular schwannoma or any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities.[2]
- Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities.[2]
- Multiple meningiomas (two or more) and unilateral vestibular schwannoma or any two of: schwannoma, glioma, neurofibroma, cataract.[2]

[1]The diagnosis of bilateral vestibular schwannomas is usually made on gadolinium-enhanced MRI. There have been rare reports of mis-diagnoses of NF2 relying on bilateral CP angle lesions alone, with the lesions subsequently turning out to be secondary malignancy or choroid plexus papilloma.

[2]'Any two of' refers to two individual tumours or cataracts.

Diagnostic criteria

The diagnostic criteria agreed at the 1987 NIH consensus conference on neurofibromatosis were too stringent for routine clinical use. Gutmann *et al.* suggested a modification in 1997, but the most specific and sensitive criteria are the Manchester criteria. (See Table 3.)

Clinical features and natural history

The clinical features of NF2 are listed in Table 4. Neurofibromatosis type 2 is associated with significant morbidity and mortality in all patients. Although bilateral vestibular schwannomas are a feature in all patients, the age of onset varies, as does the number of associated other tumours. The most significant predictors of disease severity are the age of presentation and the presence of meningiomas. Patients with severe NF2 tend to present under the age of 20 years, often with symptoms relating to a tumour other than a vestibular schwannoma (see Figure 4).

In the majority of cases there is no difficulty distinguishing NF1 and NF2. When there is confusion it is usually because of the presence of a few café-au-lait spots in a

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TABLE 4 Neurofibromatosis type 2: clinical features (data from Evans DG *et al. Q J Med* 1992; **304:**603–18 and Parry DM *et al. Am J Med Genet* 1994; **52(4):**450–61.)

Feature	Frequency (%) of symptomatic lesions
Tumours of the nervous system[1]	
Bilateral vestibular schwannoma	85
Unilateral vestibular schwannoma	6
Meningiomas	45
Spinal tumours(meningiomas, schwannomas)	26
Astrocytomas[2]	4
Ependymomas[2]	2·5
Peripheral neuropathy	3
Peripheral schwannomas	
Overall	68
>10 peripheral tumours (max. no.: 27)	10
NF2 plaques	48
Nodular schwannomas	43
NF1-like dermal lesions	27
Café-au-lait spots	
1–4 spots	42
6 spots	1
Ophthalmologic features	
Cataracts (overall)	81
Posterior capsular cataracts	72·4
Cortical cataracts	41·4
Both types	31·8
Retinal hamartomas	8·6

[1]A higher frequency of all tumours is found on cranial and spinal MRI, some remain asymptomatic.
[2]Usually located in brainstem and/or upper cervical cord.

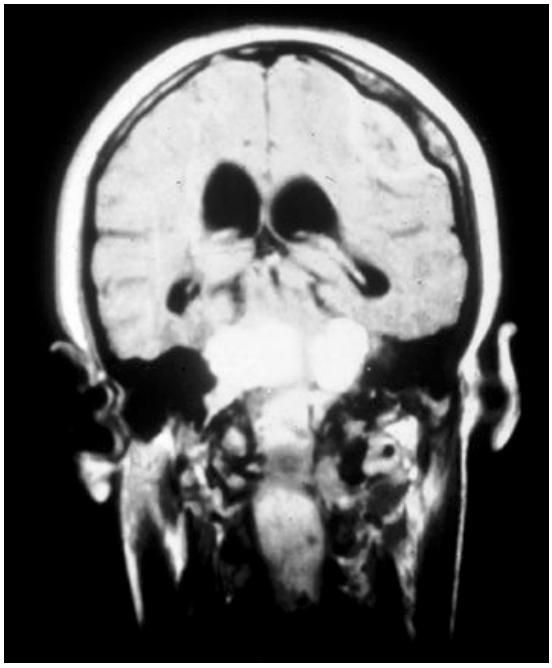

FIGURE 4 An 18-year-old with severe NF2. The scan shows bilateral vestibular schwannomas dramatically compressing the brain stem; an intrinsic lesion in the brain stem and upper cervical spine, compatible with a glioma, and a left convexity meningiomas. (Reproduced with permission from: Huson SM, Short PM, Martuza RL. Neurofibromatosis 2: Clinical features, genetic counselling and management issues. In: Huson SM, Hughes RAC (editors). *The Neurofibromatoses. A pathogenetic and clinical overview.* London: Chapman and Hall; 1994.)

FIGURE 5 Neurofibromatosis 2 plaques. Clinically, they are slightly raised and the skin appears thickened and there may be hypertrichosis. (Reproduced with permission from: Huson SM, Short PM, Martuza RL. Neurofibromatosis 2: Clinical features, genetic counselling and management issues. In: Huson SM, Hughes RAC (editors). *The Neurofibromatoses. A pathogenetic and clinical overview.* London: Chapman and Hall; 1994.)

patient with peripheral nerve tumours that are clinically indistinguishable from those seen in NF1. The nodular schwannomas and some of the dermal lesions look exactly like their equivalents in NF1. However, histologically they are nearly always schwannomas. Useful distinguishing points clinically are that NF2 patients do not get skin-fold freckling and have a unique skin lesion, the NF2 plaque. These are discrete, well circumscribed, slightly raised lesions, usually <2 cm in diameter (see Figure 5). The other helpful distinguishing features are the distinct ophthalmologic features (see Table 4).

Management

Neurofibromatosis type 2 patients should be treated in specialist centres, with a multidisciplinary team comprising neurosurgeon, otolaryngologist, neurologist /geneticist, specialist nurse, and audiologist. In a UK study of factors influencing mortality, treatment in a non-specialist centre was found to be associated with increased mortality. Advances in surgical technique and auditory rehabilitation with cochlear or auditory brain stem implants are improving outcomes for NF2 patients. Minimal interference, maintenance of quality of life, and conservation of function or auditory rehabilitation are the cornerstones of NF2 management. A recent UK consensus document on NF2 management is included in *Further reading*.

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The ophthalmological features can be present from infancy, and so children at risk of NF2 should be monitored from birth. Screening MRI scans are usually commenced around the age of 10 years, depending on the age of onset in the family. Genetic testing of at-risk offspring is now available for nearly all families. The timing of the testing is usually discussed in depth with the family. Some parents prefer to have the children tested in infancy whilst others prefer it when the child is older and can join in the decision-making process. Prenatal and pre-implantation diagnosis is available.

Mosaic NF2

About one-quarter of people who are the first case of NF2 in their family are somatic mosaics. In a few of these individuals this will be suggested clinically by disease being localised to one side of the brain. More commonly, however, it is impossible to distinguish mosaic patients clinically. Recognition of this has important clinical implications. In these cases the gene mutation is often not identified on analysis of DNA from a blood sample, but can be identified on tumour analysis. Therefore it is important to obtain fresh frozen samples for analysis. The risk of mosaic patients transmitting NF2 to their children is lower than 50%. Although the parent may have mild disease, this may not be the case for the offspring who will have the mutation in all their cells.

OTHER FORMS OF NEUROFIBROMATOSIS

These are rare even in specialist practice and no other form has yet been added to the numerical classification. If a patient does not fall into a clear category of NF1 or NF2 it is worth referring them to a specialist NF clinic.

The most significant other form is Schwannomatosis, where patients are predisposed to multiple nodular and spinal schwannomas but no other NF2 disease features. Although there are some dominant families, many cases are sporadic. In familial cases the gene maps to chromosome 22 but appears to be distinct from the *NF2* gene.

There are rare families with only multiple café-au-lait spots segregating as an autosomal dominant. Some of these families have mutations in the *NF1* gene and the reason for the mild phenotype is not known.

KEYPOINTS

- There are two main types of neurofibromatosis (NF1 and NF2). NF1 is one of the commonest autosomal dominant disorders in humans.
- The diagnosis of both NF1 and NF2 is usually straightforward using established diagnostic criteria. Unusual cases benefit from assessment in a specialist neurofibromatosis clinic.
- Patients with NF1 can present to almost any medical specialty but the significance of their underlying diagnosis to presenting symptoms may be missed.
- Patients with NF2 present with problems related to tumours of the nervous system and should be managed in specialist multidisciplinary clinics.
- The genes for NF1 and NF2 have been cloned and pathogenetic insights from animal models provide the possibility of future medical treatments.

FURTHER READING

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- UK Neurofibromatosis Association. http://www.nfauk.org/ This useful website details the services offered for patients and the literature offered. NF1 management guidelines are available.