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Current topic

Recent developments in the diagnosis and management of neurofibromatosis

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The last decade has seen increasing awareness of the problems encountered in diagnosis and management of the different forms of neurofibromatosis.[1 2] Modern techniques of clinical and laboratory investigation have been applied to the disease, culminating in 1987 with the mapping of the genes for type 1[3 4] and type 2[5 6] neurofibromatosis to chromosomes 17 and 22 respectively. In the short term this means closely linked DNA markers can be used for prenatal and presymptomatic diagnosis and in the long term the cloning of the actual genes will be a major step towards our understanding of the pathogenesis of and possible treatments for the two main types of neurofibromatosis.

Nomenclature

Riccardi has suggested that there may be seven or more different forms of neurofibromatosis.[2] One of the problems addressed by the 1987 National Institutes of Health (NIH) Consensus Development Conference on Neurofibromatosis was that of nomenclature and classification.[7] The consensus panel concluded that at the present time there is sufficient evidence to clearly distinguish neurofibromatosis type 1 (previously known as von Recklinghausen or peripheral neurofibromatosis) and type 2 (bilateral acoustic or central neurofibromatosis). The diagnostic criteria for both type 1 and 2 agreed by the consensus panel are shown in table 1. The panel acknowledged previously reported cases with atypical features that would not have type 1 or type 2 by these criteria but clearly have a form of neurofibromatosis. It was felt that at the present time there was insufficient data available to justify further subclassification.

Neurofibromatosis type 1

Neurofibromatosis type 1 is the commonest form of neurofibromatosis accounting for over 90% of all cases. A recent population survey in south east Wales found a prevalence of 1/4950 ($20/10^5$) of population,[8] although the actual birth incidence may be as high as 1/2500 ($40/10^5$).[9 10] Inheritance is autosomal dominant with approximately 50% of cases representing new mutations.[9 10] Gene penetrance, in offspring of individuals with well characterised type 1, is virtually 100% by the age of 5 years.[10 11]

DIAGNOSTIC FEATURES

The diagnostic criteria for neurofibromatosis type 1 are shown in table 1. The NIH Consensus statement draws attention to distinguishing patients with McCune-Albright (polyostotic fibrous dysplasia, irregular skin pigmentation and sexual precocity)

Table 1 *Diagnostic criteria for neurofibromatosis type 1 and type 2*[7]

Neurofibromatosis type 1
The diagnostic criteria are met in an individual if two or more of the following are found:
- ≥6 Café au lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
- ≥2 Neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- ≥2 Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
- A first degree relative (parent, sibling, or offspring) with type 1 by the above criteria

Neurofibromatosis type 2
The criteria are met by an individual who has:
(1) Bilateral eighth nerve masses seen with appropriate imaging techniques (for example, computed tomography or magnetic resonance imaging)
or
(2) A first degree relative with type 2 and either: (a) unilateral eighth nerve mass or (b) two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity

and Watson syndrome (café au lait spots, dull intelligence, and pulmonary stenosis) when applying these criteria.

The major defining features of the disease are café au lait spots, peripheral neurofibromas and Lisch nodules. Café au lait spots are the first disease feature to develop and are obvious on naked eye examination by the end of the first year of life in most cases. In fair skinned people they may be extremely pale and examination is aided by the use of a Wood's lamp. The other form of characteristic skin pigmentation is axillary freckling, seen in two thirds of affected people[8] and which develops in middle childhood.

Peripheral neurofibromas, which may be cutaneous or subcutaneous, begin to appear around the onset of puberty in most cases; the youngest child the author has seen with these lesions was 6 years old. Although Lisch first described pigmented nodules of the iris in neurofibromatosis type 1 sufferers in 1937,[12] their exact frequency and diagnostic value has only recently been appreciated.[13 14] Although occasionally visible to the naked eye they are best seen by slit lamp examination. They have a characteristic dome shaped appearance, are usually brown in colour, although they can be pale or almost white in young children. Lisch nodules are present in over 90% of type 1 sufferers by the age of 5 years.

There are two minor features of neurofibromatosis type 1, which although not specific enough for diagnosis, are present in a large proportion of affected individuals. These are macrocephaly and short stature. In the Welsh study, 45% of those affected had a head circumference at or above the 97th centile and 34% had heights at or below the 3rd centile.[8] The standard deviation from normal for height for affected patients was $-1{\cdot}20$ (1·07) in affected individuals compared with $-0{\cdot}12$ (1·02) in normal siblings ($p=0{\cdot}001$).

The diagnosis of neurofibromatosis type 1 is usually straightforward; the only problem arises in assessing young children with multiple café au lait spots as their only feature and whose parents are unaffected. Although type 1 is likely the diagnosis cannot be made until other features develop, as families have been reported with café au lait spots alone segregating as a dominant disorder.[2 15] In this context slit lamp examination to look for Lisch nodules can be helpful, as they are usually present before axillary freckling or peripheral neurofibromas.

COMPLICATIONS

The complications of neurofibromatosis type 1 can affect any of the body systems, and as their occurrence cannot be predicted even within families it is this aspect of the disease that is most distressing. The most frequent complications of type 1 in the Welsh study are shown in table 2.[8] The other complications seen in the study population were delayed puberty (2%), hypsarrhythmia (1%), meningioangiomatosis (1%), congenital glaucoma (1%), and bony defect of the lambdoidal suture (1%). Four previously recognised complications of type 1 were not seen in the study population even though these are part of the range of the disease: these are sphenoid wing dysplasia, pseudoarthrosis of the radius or ulna, or both, arterial disease other than renal artery stenosis, and atypical forms of childhood leukaemia. It must be assumed that their occurrence is rare in neurofibromatosis type 1 sufferers ($\leqslant$1%).

The age range of presentation of type 1 complications (unless obvious) is also shown in table 2,[16] and this can be used in planning patient follow up, both for reassurance (for example, the parents of a child with no complications at 5 years can be reassured that the child will not develop a facial plexiform neurofibroma or pseudoarthrosis) and in monitoring for complications which may yet occur.

At the present time there are insufficient data for many of the complications to define an exact age range of presentation. This will only become possible when large cohorts of children with neurofibromatosis type 1 are followed up from childhood. From such studies clinical features may emerge that predispose to some complications, such as peripheral nerve malignancy, thus highlighting a subset of patients which require closer monitoring.

MANAGEMENT

One of the problems with neurofibromatosis type 1 is that because the disease complications are so varied patients may present to many different specialists during their life and yet find no one doctor keeping an overview of their disease. In the Welsh study only 28 out of 135 (21%) of the type 1 sufferers were being regularly reviewed for their disease and this was because of complications in 16 of the 28.[8] The remaining 12, eight of whom were children, were being monitored regularly for the development of complications. Only 10 individuals had received formal genetic counselling. Many parents had been told the café au lait spots were 'just birth marks' and were unaware that subsequent problems (for example, educational difficulties, scoliosis) were related. There is therefore a need for improved patient care in neurofibromatosis type 1. Although many complications are individually rare, their combined burden is appreciable and it is likely that sufferers are not being diagnosed sufficiently early, nor receiving appropriate follow up and counselling.

Table 2 *Frequency of complications of neurofibromatosis type 1 in a population based study in south east Wales.*[8 16] *The age range at which these can occur is also presented (unless obvious)*[16]

Complication	*Frequency (%)*	*Age range of presentation (years)*
Plexiform neurofibromas:		
All lesions	26·7	0–18
Large lesions of head and neck	1·2	0–1
Intellectual handicap:		
Severe	0·8	
Moderate	2·4	
Minimal/learning difficulties	29·8	
Epilepsy:		
No known cause	4·2	Lifelong*
Secondary to disease complications	3·1	
Tumours of the central nervous system	1·5–2·2%	Optic gliomas: 0–20 Other tumours (usually astrocytomas): lifelong
Spinal neurofibromas	2·1	Lifelong
Aqueduct stenosis	2·1	0–30
Malignancy with established disease association:		
Rhabdomyosarcoma	1·5	Lifelong†
Peripheral nerve malignancy	1·5	Lifelong
Scoliosis:		
Requiring surgery	5·2	0–18
Less severe	6·3	
Pseudoarthrosis of tibia and fibula:		
Resulting in non-union and eventual amputation	2·1	0–5
Less severe forms	1	0–5
Gastrointestinal neurofibromas	2·1	Lifelong
Renal artery stenosis	2·1	Lifelong
Endocrine tumours (phaeochromocytomas and/or duodenal carcinoid)	3·1	From 10 years onwards

*'Lifelong' indicates cases have been reported presenting in all age groups.
†Although 'lifelong' risk given there is strong evidence for a subset of cases presenting with pelvic rhabdomyosarcomas in early childhood.[17 18]

The NIH Consensus Development Conference addressed these problems and recommended that neurofibromatosis type 1 sufferers should have an annual clinical assessment to monitor for complications. It was felt that screening investigations, such as cranial computed tomography, were not justified unless there were clinical indications. As many of the disease complications develop in childhood it is this author's present practise to recommend biannual review for children. Examination should be geared to monitoring for development of complications, therefore paying particular attention to blood pressure measurement and to examination of the spine and nervous system (particularly for signs of an optic glioma). As educational problems are so frequent a preschool psychological assessment seems appropriate.

There is no specific treatment for neurofibromatosis type 1 and most complications are managed in exactly the same way as when they occur in isolation. Plexiform neurofibromas, which are rarely seen as isolated lesions, are one of the most frequent complications and present a difficult management problem. They present as diffuse ill defined swellings often with overlying skin hypertrophy or pigmentation. As their margins are ill defined complete surgical removal is often impossible. Therefore unless these lesions are causing severe cosmetic problems or localised bony overgrowth conservative management is advisable.

Mast cells are a major component of both discrete peripheral and plexiform neurofibromas. Riccardi has postulated that they may play an important part in the pathogenesis of these lesions.[15] In a recent paper, Riccardi describes possible control of the growth of aggressive plexiform neurofibromas and neurofibroma associated pruritus by the use of the drug ketotifen, which blocks mast cell secretions.[19] The trial had an open label protocol, however, and involved a small number of patients, therefore larger double blind studies are necessary before firm conclusions can be drawn.

Families who are keen to gain more information about the disease and meet other sufferers may

benefit from being put in contact with the British neurofibromatosis patients association, LINK (Lets increase neurofibromatosis knowledge).*

The mapping of the gene to chromosome 17 by family linkage studies has laid open the way to applying more complex molecular techniques to clone the gene itself. Clinicians can help in this research by looking for abnormalities of chromosome 17 in unusual cases—for example, with particularly severe intellectual handicap, dysmorphic features, or more than one genetic disease. It is also now possible to examine whether the mechanism of tumour formation in neurofibromatosis type 1 is similar to that in type 2.[5] It is therefore helpful if a portion of any tumour removed from patients with neurofibromatosis type 1 can be preserved for DNA analysis.

GENETIC COUNSELLING

Genetic counselling is an integral part of the care of neurofibromatosis type 1 sufferers and their families. The 50% risk of transmission to offspring is straightforward. It is more difficult to convey the risk of complications in offspring. There is a fine balance between providing adequate information without causing unnecessary alarm. In counselling families the author has found it useful to divide the complications into groups that focus on the effects a given complication would have on an individual's life. There are (1) intellectual handicap: moderate to severe: 2%, minimal intellectual handicap or learning difficulties: 15%; (2) complications that develop in childhood causing lifelong morbidity (severe head and neck plexiform neurofibromas, orthopaedic problems): 4%; (3) complications that can occur at any time but are 'treatable' (for example, epilepsy, endocrine tumours): 8%; and (4) central nervous system and malignant tumours: 2–3%. The frequencies for each group are taken from the Welsh study and have been halved to account for dominant inheritance and rounded to the nearest whole number.[8]

Approximately 50% of all cases of neurofibromatosis type 1 are new mutations. Before parents of an apparently isolated care are fully reassured as to their own recurrence risks, however, it is important they have a detailed cutaneous and slit lamp examination. There have been several cases reported where patients with limited disease features have had affected children.[11] For example, Riccardi and Lewis have reported a case where a mother of two affected children had bilateral Lisch nodules as her only feature.[11]

*LINK, the British Neurofibromatosis Patients Association, Office BO3, Surrey House, 34 Eden Street, Kingston KT1 1ER.

Since the mapping of the gene for neurofibromatosis type 1 to chromosome 17 in 1987 there has been rapid progress. Linkage studies of chromosome 17 markers in large numbers of families have shown no evidence of non-allelic genetic heterogenity—that is, there is no evidence for a second type 1 locus not on chromosome 17.[20] There are now several DNA markers that can be used for prenatal diagnosis with an accuracy of >95%.[21] As their clinical application will depend on a 'gene tracking' approach,[22] however, it will be limited to families with more than one affected individual who are 'informative' for the marker polymorphisms. A more widely applicable DNA or biochemical marker for neurofibromatosis type 1 will only become available with the cloning of the gene itself.

Neurofibromatosis type 2

The diagnostic criteria for neurofibromatosis type 2 are shown in table 1. This form of neurofibromatosis has been recently comprehensively reviewed elsewhere.[23] Type 2 is much rarer than type 1 with an estimated prevalence of 1/50 000, inheritance is also autosomal dominant. The main features of neurofibromatosis type 2 are bilateral acoustic neuromas, which occur in over 95% of patients. Other tumours of the nervous system, particularly schwannomas and meningomas are often associated.

Patients with neurofibromatosis type 2 do, however, have a few café au lait spots (but always fewer than six) or peripheral neurofibromas more frequently than the general population,[24] and in the past the two forms of the disease were not clearly distinguished. Recent large surveys of type 1 sufferers have shown no increased frequency of acoustic neuromas.[8 13]

Neurofibromatosis type 2 does not usually present in childhood: the mean (SE) age of onset of symptoms from acoustic neuromas was 20·4 (1·1) years in one large series.[24] Cases have been reported with an earlier presentation, however, and the diagnosis should be considered in children presenting with meningeal or Schwann cell tumours in any location. In these cases the finding of lens opacities on slit lamp examination would make the diagnosis of neurofibromatosis type 2 a strong possibility.[23]

Genetic counselling is also important for type 2 sufferers and their families. As most gene carriers develop acoustic neuromas, screening for their development is justified[23]; surgery on small tumours at an early stage in their development is associated with the preservation of hearing in some cases and a noticeable decrease in other complications. A closely linked chromosome 22 DNA marker has

been identified for neurofibromatosis type 2.[25] As the linkage studies have only been done in one large family, however, heterogeneity, although unlikely, remains a possibility and the accuracy of the marker is not yet sufficiently defined for clinical application.

Neurofibromatosis clinics

Several centres in the United States have now established multidisciplinary neurofibromatosis clinics,[15] with a view to improved coordination of care particularly for neurofibromatosis type 1 sufferers. There is a need for other countries to consider following this model so that expertise can be developed in treating some of the more difficult complications that are individually rare (for example, facial plexiform neurofibromas), the assessment of unusual cases, and the application and assessment of new developments.

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