Neurofibromatosis Type 2

D. Gareth R. Evans, MB, BS, MRCP, Rodney Harris, BSc, MD, FRCP

For most of the last 100 years since the reports of von Recklinghausen the majority of the medical profession have believed that patients with bilateral vestibular schwannomas (acoustic neuromas) suffered from von Recklinghausen’s neurofibromatosis. The situation has now been completely resolved with the discovery of two separate genetic loci: neurofibromatosis type 1 (NF1) on chromosome 17 and neurofibromatosis type 2 (NF2) on chromosome 22. The latter, NF2, is a dominantly inherited disorder with a high spontaneous mutation rate affecting approximately 1 in every 35,000 births. It is characterized by the development of bilateral vestibular schwannomas from the second decade and also in some affected families multiform tumour disease with cranial meningiomas and spinal meningiomas and schwannomas. Skin features are not prominent, but cataracts are a useful disease marker. In view of the marked morbidity and early mortality associated with the disease there is likely to be a strong demand for the DNA predictive diagnosis which is just becoming available.

Keywords: Neurofibromatosis type 2. DNA diagnosis. Cataracts. Bilateral vestibular schwannomas.


The first probable recorded case of NF2 was that of Wishart in 1820. However, this was not recognized as a distinct entity and after the definitive description of type 1 neurofibromatosis (NF1) by von Recklinghausen, various reports of patients with bilateral vestibular schwannomas (VS) were lumped in with NF1 as part of von Recklinghausen’s disease. Although there continued to be reports demonstrating the lack of skin tumours or cafe au lait patches in patients and families with bilateral VS, the final separation of NF1 and NF2 only came some 167 years after Wishart’s description. This came with the discovery in 1987 that the gene for NF1 was localized to chromosome 17 and NF2 to chromosome 22 by genetic linkage analysis. Partly as a result of this and the increasing clinical evidence to suggest two separate disorders, the National Institutes of Health Consensus statement formally separated them in the same year. It is still widely believed that VS occur in excess in NF1, but there is now clear evidence that this is not the case. The confusion still exists as previous reports of NF1 were contaminated with NF2 cases.

An autosomal dominant inherited disorder, NF2 predisposes affected individuals to the development of VS, schwannomas of the other cranial, spinal and peripheral nerves, meningiomas both intracranial...

From the Department of Medical Genetics, St Mary’s Hospital, Hathersage Road, Manchester M13 0JH, UK

D. G. R. EVANS, R. HARRIS
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Table 1

Diagnostic criteria for NF2

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NF1 Series</th>
<th>NF2 Series</th>
<th>Evans et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral vesicular schwannomas OR family history of NF2 plus</td>
<td>155</td>
<td>73</td>
<td>120</td>
</tr>
<tr>
<td>1. Unilateral acoustic or</td>
<td>73</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td>2. Any two of: meningioma, glioma, neurofibroma,</td>
<td>0</td>
<td>20.4 (of 59)</td>
<td>45</td>
</tr>
<tr>
<td>schwannoma, posterior subcapsular lenticular opacities.</td>
<td>0%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>1%</td>
<td>18%</td>
<td>45%</td>
</tr>
<tr>
<td>1. Cerebral calcification</td>
<td>2%</td>
<td>?</td>
<td>25.8%</td>
</tr>
<tr>
<td>2. Unilateral acoustic + 2.</td>
<td>0%</td>
<td>20.4 (of 59)</td>
<td>22.2</td>
</tr>
<tr>
<td>Multiple meningioma (two or more) + unilateral acoustic or any two of:</td>
<td>0%</td>
<td>32% (73)</td>
<td>68%</td>
</tr>
<tr>
<td>glioma, neurofibroma, schwannoma, cataract, cerebral calcification.</td>
<td>100%</td>
<td>10% (100)</td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology

The birth incidence of NF2 is approximately 1 in 35 000. However, as many cases do not develop features of the condition until the third decade or later and many other cases die before this time the actual diagnostic prevalence is only 1 in 200 000. The disease affects all races11 and as the mutation rate is high the UK incidence and prevalence probably holds true for the rest of the world. Actuarial survival from diagnosis has been calculated in a series of 150 patients as being 15 years.12

Genetics

Many studies have confirmed the autosomal dominant inheritance of NF2. The gene has a high degree of penetrance in that it is nearly always expressed by the late fifties.13 The first clue to the whereabouts of the gene came with the discovery of chromosome 22 abnormalities found in meningiomas on cytogenetic analysis.14 This was tested at the molecular level in several different tumours from an NF2 patient, again showing loss of genetic material on chromosome 22.15,16 This lead to the belief that the NF2 gene was acting as a tumour suppressor. One large American family was then shown to have linkage to markers on the long arm of the chromosome6 and further studies have shown that the NF2 phenotype is probably caused by a single gene on 22q.17 This gene has been further localized by the discovery of a germline deletion in an NF2 family which has involved the Neurofilament Heavy Chain Gene.18 Predictive diagnosis using flanking probes is now possible in suitable families (containing two or more living affected individuals). Prenatal diagnosis is also feasible, but as the probes are only close to the gene, recombinational events are still possible. Therefore only a 95–99% certainty can be attained. However, with predictive tests in adults combination of the DNA tests with a life curve,11

Table 2

Age at onset, and frequency of clinical manifestations and tumour types in NF1 and NF2

<table>
<thead>
<tr>
<th></th>
<th>Huson et al.</th>
<th>Kanter et al.</th>
<th>Evans et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>155</td>
<td>73</td>
<td>120</td>
</tr>
<tr>
<td>Number of families</td>
<td>73</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td>Isolated cases</td>
<td>0%</td>
<td>20.4 (of 59)</td>
<td>22.2</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Vestibular schwannoma</td>
<td>1%</td>
<td>18%</td>
<td>45%</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>2%</td>
<td>?</td>
<td>25.8%</td>
</tr>
<tr>
<td>Spinal tumours</td>
<td>100% (&gt; 20 yrs)</td>
<td>32% (73)</td>
<td>68%</td>
</tr>
<tr>
<td>Skin tumours</td>
<td>100% (&gt; 40 yrs)</td>
<td>?</td>
<td>10% (100)</td>
</tr>
<tr>
<td>Café au lait spots</td>
<td>0%</td>
<td>42% (31)</td>
<td>43% (100)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>90%</td>
<td>?</td>
<td>2%</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>2%</td>
<td>?</td>
<td>4.1%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>0%</td>
<td>?</td>
<td>2.5%</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>0%</td>
<td>?</td>
<td>4.1%</td>
</tr>
<tr>
<td>Optic sheath meningioma</td>
<td>0%</td>
<td>?</td>
<td>4.1%</td>
</tr>
</tbody>
</table>
can reduce the risk to an unaffected 30-year-old with a normal scan to extremely low levels. There continues to be evidence that the condition may be worse if the disease is maternally inherited.\textsuperscript{7,12} This may result from modification of the gene perhaps by a process known as imprinting.\textsuperscript{19} There is also some evidence to support a general worsening of the disease with successive generations (anticipation).\textsuperscript{3,11} On the whole the disease nonetheless appears to breed true in families. Some families with mild disease have a late onset and few if any CNS tumours other than VS. Other families have a more virulent course with early onset and death due to multi-tumour disease.\textsuperscript{11,20}

**Presentation**

The majority of cases of NF2 present with symptoms caused by VS; most with deafness and or tinnitus, but others with symptoms such as imbalance or vertigo. The majority of these cases (75\%) have unilateral symptoms initially.\textsuperscript{11} However, at least 20\% of cases present with complications of a cranial meningioma or spinal tumour. Occasionally a skin tumour removed in childhood may lead to a mistaken diagnosis of NF1. Only about 1\% of NF2 patients fulfil the diagnostic criteria for NF1 and even these can be excluded after careful consideration.\textsuperscript{14} A childhood cataract is also common and may be present in over 10\% of NF2 cases before the presence of any tumour. An isolated cataract is unlikely to alert a clinician to the diagnosis, but in the presence of a family history or in a young patient presenting with bilateral deafness or a unilateral VS it should arouse a high degree of suspicion. After careful slit lamp examination a posterior lenticular opacity is found in up to 80\% of NF2 cases.\textsuperscript{21} Patients may also develop a peripheral neuropathy which is not due to known spinal or other CNS tumours but may be caused by a general proliferation of schwann cells around peripheral nerves.\textsuperscript{11}

**Diagnosis**

Once the criteria in Table 1 are fulfilled NF2 can be diagnosed. There are several groups of individuals who should be considered at risk and investigated further. These include persons with a family history of NF2, patients under 30 years of age presenting with an apparently sporadic unilateral VS or meningioma, patients with multiple spinal tumours and individuals with minimal skin features of neurofibromatosis, but insufficient features or family history for a diagnosis of NF1. The ‘gold standard’ in terms of diagnostic precision is the MRI scan with gadolinium enhancement, for completeness this should probably include the entire spine as well as the cranium. However, a careful skin and eye examination is also of great diagnostic importance.

**Surgery**

Surgery remains the mainstay of treatment for NF2. Recent advances in microsurgical techniques have lead to great optimism about early diagnosis and surgical removal of VS in NF2.\textsuperscript{8,22} However, there has always been the feeling that the tumours in NF2 may be more difficult with which to achieve good results.\textsuperscript{23} Nevertheless, some surgeons do continue to report optimistic results for both hearing preservation and facial nerve function postoperatively.\textsuperscript{24,25} The reality for most patients is somewhat different. Outside specialist centres a large series reporting results for sporadic VS may be as poor as no hearing preservation in any patient and complete facial palsy in over 50\%.\textsuperscript{26} A recent series reporting operations throughout the UK showed very indifferent results particularly concerning postoperative facial nerve function.\textsuperscript{27} As there is likely to be reticence about publishing bad results for operations, it is very easy to expect good results from removal of VS from the available literature. A truer reflection can be gauged by the reversal in opinion of the National Institutes of Health Consensus between their statements in 1987 and 1990.\textsuperscript{28} Experience from experts in the field led the second Consensus to advocate a more watchful approach rather than early presymptomatic surgery. Some people with NF2 have very slow growing tumours that can be safely monitored for many years.\textsuperscript{29} A more aggressive stance is still needed for some cases\textsuperscript{27} and as things stand most cases will eventually come to surgery. We feel that the complex decisions in NF2 mean that there is a strong argument for the care of NF2 patients to be co-ordinated by specialist centres used to dealing with the particular problems involved—especially timing of surgery.\textsuperscript{27}

There are other options for treatment such as radiotherapy which has been found to be useful in sporadic VS.\textsuperscript{30} There are nonetheless concerns over the long-term implications in terms of tumour regrowth and initiation of further tumours. Results from 12 VS from NF2 cases we have seen have been mixed. Only five could be classified as partially successful, with some hearing preservation in three cases. Of the remaining cases one died and six needed operations within 3 years. As well as tumour regrowth treatment was complicated by immediate loss of facial nerve function and hearing in two cases. Although radiotherapy may offer a useful alternative to surgery, there are still
grounded for reservations in its use. Attempts are also being made to evaluate chemotherapy.

It is often forgotten in the course of treating the major manifestation of VS that the other complications, such as multiple meningiomas (Fig. 1) and spinal tumours may also be very troublesome. Particular care must be taken to exclude the presence of upper cervical spinal lesions which may cause problems during intubation.

Despite the disappointing results of intervention, it is still worthwhile picking up lesions such as VS as early as possible. Late presenting tumours have a poor prognosis despite being benign and early diagnosis allows all options to be used including watchful follow up of the tumour with scans. A suggested protocol for screening is shown in Fig. 2. The importance of ophthalmic assessment even at birth cannot be overemphasized in a disease likely to lead to complete deafness.

Conclusions

Two major studies have now well defined NF2.7,11 Affected individuals may present in childhood or as late as in their fifties, but death by 20 years is not unusual. The disease appears to breed true in families—which helps with genetic counselling. However, the disease is almost always accompanied by severe eventual morbidity. Complete deafness, loss of balance and visual impairment leaves individuals housebound or even bedbound. The hope is that with the localization and cloning of the NF2 gene better forms of treatment will become available. This will also lead to more exact diagnosis if a specific mutation can be found in affected families. It may also be possible to predict the course of the disease by genotype/phenotype correlation studies. This will not be as important

Suspected patient

Birth: detailed ophthalmic examination
annual from 2-12 years: history, neurological and skin examination + ophthalmoscopy
annual from 12-30 years: as before + audiological tests
at 16-18 years and 30 years or if suggestive screen: MRI scan

At first visit

history (headache, deafness)

Neurological (weakness, numbness)

Audiological (BSER)

Ophthalmological (lens opacities)

Dermatological

MRI

Vestibular schwannoma

negative MRI

glioma, meningioma

schwannoma + skin or eye signs

one criteria

two criteria — NF 2

No diagnosis

3-12 monthly appointments, regular MRI scans, operative procedures

Figure 2. Screening protocol for NF2. BSER: Brain stem evoked response.
in families where we already know the extent of the disease, but in new mutations in whom an insight into the likely speed of tumour progression and risk of other tumours would be very helpful. Although DNA predictive testing is now available in a limited form, we are not aware of any prenatal diagnoses. There may, nevertheless, be a real demand for this option. A less controversial option would be pre-implantation diagnosis and this is starting to become available in a limited sense for other diseases.

The real hope is that the discovery of the gene and its transcriptional protein product, will lead to the development of somatic gene therapy. Instinctively, the prospects for NF2 appear promising. This is because of the lack of variation in individuals with the same mutation and in the paucity of involvement of other genes in the tumours themselves. Replacement of the tumour suppressor product in the tumours, although requiring great advances in our knowledge, may be very rewarding.

References