Chapter 5

Neurofibromatosis type 2

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INTRODUCTION

Type 2 neurofibromatosis (NF2) was probably first described by Wishart in 1822. He described a man with multiple intracranial tumors including what Wishart described as bilateral seventh nerve neuromas, but which Worster-Drought et al. (1937) later suggested were probably eighth nerve tumors (previously called acoustic neuromas but now more accurately labeled vestibular schwannoma). However, following reports of patients with type 1 neurofibromatosis (NF1) by von Recklinghausen (1882), various reports of NF2 cases around the turn of the century were lumped together with von Recklinghausen’s disease. Probably the most responsible for the prolonged co-classification of NF1 and NF2 was none other than Harvey Cushing (1917).

Although many reports emphasized the lack of skin tumors or café-au-lait patches in patients and families with bilateral vestibular schwannomas (Gardner and Frazier, 1930; Worster-Drought et al., 1937; Young et al., 1971), the final separation of NF1 and NF2 and their delineation only came in 1987. In that year the gene for NF1 was localized to chromosome 17 (Seizinger et al., 1987) and NF2 to chromosome 22 (Rouleau et al., 1987) by genetic linkage analysis. As a result of this and the increasing clinical evidence to implicate two distinct disorders (Kanter et al., 1980), the US National Institutes of Health (NIH) Consensus Statement published that year (NIH Consensus Development Conference Statement, 1987) formally separated them. The still widely held belief that vestibular schwannomas occur as part of NF1 has now been refuted by large population-based studies of the more common type 1 disease (Huson et al., 1988; McGaughran et al., 1999). Previous reports of vestibular schwannomas in NF1 clearly were contaminated with NF2 cases (Crowe et al., 1956).

CLINICAL MANIFESTATIONS

NF2 is an autosomal dominantly inherited disorder which predisposes affected individuals to the development of vestibular schwannomas (usually bilateral) (Fig. 5.1), schwannomas of the other cranial, spinal and peripheral nerves, meningiomas both intracranial (including on the optic nerve) and intraspinal, and some low grade CNS malignancies (ependymomas, and rarely low grade gliomas). Three large clinical studies now have confirmed the clinical picture (Kanter et al., 1980; Evans et al., 1992a; Parry et al., 1994).

Our own published diagnostic criteria for NF2 (Evans et al., 1992b) are shown in Table 5.1. The original NIH criteria have been expanded to include patients with no family history who have multiple schwannomas and or meningiomas, but who have not yet developed bilateral eighth nerve tumors. These criteria have been shown to be more sensitive and no less specific than the original NIH criteria which acted as the template (Baser et al., 2002a). Individuals may present with cranial meningiomas or a spinal tumor long before the appearance of a vestibular schwannoma (Evans et al., 1992a, 1999a). As at least 50–60% of cases represent new dominant mutations (Evans et al., 1992c) the criteria are more inclusive, but are still extremely unlikely to include chance associations (see below under genetics).

The results of the three major clinical studies (Kanter et al., 1980; Evans et al., 1992a; Parry et al., 1994) are shown in Table 5.2. The majority of individuals with NF2 present with hearing loss, which is usually unilateral at onset. This may be accompanied or preceded by tinnitus. Occasionally vestibular schwannomas may cause dizziness or imbalance as the first symptom. A significant number of patients present initially with a cranial meningioma, spinal tumor, or cutaneous tumor (20–30%). Indeed the more severe multitumor disease
is often manifested first in early childhood with a non-eighth cranial nerve tumor. Pediatric presentation is thus quite different to that in adulthood with vestibular schwannoma accounting for as little as 15–30% of initial symptoms (Evans et al., 1999b).

There is also a tendency for mononeuropathy, particularly affecting the facial nerve to cause a Bell’s-like palsy which often does not fully recover. Facial palsy may occur years before a vestibular schwannoma. Some children present with a polio-like illness with wasting of muscle groups in a lower limb, which again does not fully recover. About 3–5% of adults develop a more generalized polyneuropathy, often associated with an “onion bulb” appearance on nerve biopsy (Thomas et al., 1990; Evans et al., 1992a). The pathogenesis of this is related to an important function of the NF2 protein merlin (Schulz et al., 2013). This neuropathy can progress, leading to severe muscle wasting and even death.

Ophthalmic features are also prominent in NF2. Between 60% and 80% of patients with the disease have evidence of cataract (Kaiser-Kupfer et al., 1989; Parry et al., 1994). These are usually presenile posterior subcapsular lenticular opacities that rarely require removal. However, childhood cortical wedge opacities may be present from near birth (Evans et al., 1999b). Children may present with ophthalmic features. Optic nerve meningiomas can cause visual loss in the first years of life and extensive retinal hamartomas can also affect vision. Both problems have in my experience led to the eye being removed in the first few years of life due to misdiagnosis as retinoblastoma.

The skin is a useful aid to diagnosis, but features in NF2 are much more subtle than NF1. About 70% of NF2 patients have skin tumors, but only 10% have more than 10 (Evans et al., 1992a). These tumors appear to be of at least three different types. The most frequent is a plaque-like lesion (Fig. 5.2), which is intracutaneous, slightly raised, more pigmented than surrounding skin, and often contains excess hair. More deep-seated subcutaneous nodular tumors (Fig. 5.3) can often be felt,

**Table 5.1**

**Manchester diagnostic criteria for neurofibromatosis type 2**

<table>
<thead>
<tr>
<th>Bilateral vestibular schwannomas OR family history of NF2</th>
<th>PLUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unilateral acoustic OR</td>
<td></td>
</tr>
<tr>
<td>• Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities</td>
<td></td>
</tr>
</tbody>
</table>

**Additional criteria**

• Also cerebral calcification

Unilateral vestibular schwannomas + any two of: meningioma, glioma, neurofibroma, schwannoma, cataract, cerebral calcification

Multiple meningioma (two or more) + unilateral acoustic or any two of: glioma, neurofibroma, schwannoma, cataract, cerebral calcification

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**Table 5.2**

Age at onset, frequency of tumour, and other manifestations of neurofibromatosis type 2

<table>
<thead>
<tr>
<th>Series</th>
<th>Number of cases</th>
<th>Number of families</th>
<th>Isolated cases</th>
<th>Age at onset (years)</th>
<th>Meningiomas</th>
<th>Spinal tumors</th>
<th>Skin tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanter et al., 1980</td>
<td>73</td>
<td>17</td>
<td>0</td>
<td>20.4 (of 59)</td>
<td>18%</td>
<td>?</td>
<td>32% (73)</td>
</tr>
<tr>
<td>Evans et al., 1992a</td>
<td>120</td>
<td>75</td>
<td>45</td>
<td>22.2</td>
<td>45%</td>
<td>25.8%</td>
<td>68% (of 100)</td>
</tr>
<tr>
<td>Parry et al., 1994</td>
<td>63</td>
<td>32</td>
<td>17</td>
<td>20.3</td>
<td>49%</td>
<td>?</td>
<td>67%</td>
</tr>
</tbody>
</table>
Sometimes on major peripheral nerves. These can manifest as a fusiform swelling of the nerve with thickened nerve either side. There are also occasional intracutaneous tumors similar to those in NF1. The great majority of these tumors are schwannomas, but occasional definite neurofibromas do occur. I have seen only four patients (out of over 450) who had a plexiform tumor similar to those occurring in NF1.

Even with improvements in microsurgery and with use of radiation therapy, the great majority of individuals with NF2 become completely deaf. The tumors in NF2 are more difficult to treat as they are often multifocal, appearing “like a bunch of grapes” (Martuza and Ojemann, 1982; Evans et al., 1993, 2005), around the vestibular nerve in particular. A vestibular schwannoma due to NF2 is histologically more lobular and less vascular than its sporadic counterparts (Sobel and Wang, 1993). Patients may also be severely disabled by a combination of poor balance, visual problems, and weakness due to spinal tumors. Indeed many become wheelchair bound in early adulthood. Loss of facial nerve function is one of the most feared aspects of the condition for many sufferers, although in good surgical hands this is now much less common (Evans et al., 1993, 2005; Samii et al., 1997; Slattery et al., 1998). Mortality in NF2 was on average 15 years after diagnosis with a mean actuarial survival of 60 years pre 1990 (Evans et al., 1992a). Many patients with multitumor disease were dying in their twenties and thirties. This has improved recently but NF2 patients still have significantly reduced survival compared to the general population (Wilding et al., 2012) and survival is worst in those with constitutional truncating mutations (Baser et al., 2002b).

**Radiographic findings**

NF2 can be diagnosed if the criteria in Table 5.1 are fulfilled. The most precise means of diagnosis is magnetic resonance imaging (MRI) with gadolinium enhancement; this should include a complete spinal as well as cranial scan (Evans et al., 2005). MRI can now detect tumors as small as 1–2 mm in diameter on cranial and spinal nerve roots, but many tumors now being identified on spinal and cranial scans never lead to symptoms. Studies published before widespread use of spinal scanning suggested that only 25–30% of NF2 patients had symptomatic spinal tumors (Evans et al., 1992a; Parry et al., 1994). However, full spinal imaging will detect evidence of spinal tumors in 80–90% of individuals with NF2 (Mautner et al., 1996). There is also increasing awareness that intramedullary tumors in the upper cervical spine and brainstem are often associated with syringomyelia. On biopsy these tumors are usually low grade ependymomas (Hagel et al., 2012). Although these initially can be very worrying for the radiologist or treating clinician, the great majority do not progress.

An MRI can also detect schwannomas on other cranial nerves. These occur most commonly on the fifth and 12th cranial nerves (Evans et al., 1992b), but any cranial nerve except the olfactory can be affected in NF2. Nonetheless it is rare for cranial nerve schwannomas other than vestibular schwannomas to grow to a size where removal is necessitated. Meningiomas can easily be detected on MRI as enhanced areas on the meninges around the spinal cord, brain, or optic nerves. These can
form confluent areas on scan or “meningiomma en plaque”. In contrast to vestibular schwannomas, which grow on average 2 mm per year, meningiomas can grow very rapidly.

There are several groups of individuals who should be considered at risk and investigated further. These include those with a family history of NF2, patients under 30 years presenting with a unilateral vestibular schwannoma or meningioma, patients with multiple spinal tumors (schwannomas or meningiomas) or cutaneous schwannomas (Evans et al., 1992b, 1999a, 2012; Gutmann et al., 1997). MRI scanning is vital in their further assessment and full recommendations on following this group have been published (Evans et al., 2012).

An important goal is the development of more reproducible results on MRI methods to determine tumor growth. Most authors who assess the effect of either conservative (Bederson et al., 1991) or radiosurgical (Kondziolka et al., 1998) management of vestibular schwannomas rely on fairly basic measurements such as cross-sectional diameters. There is great variation from scan to scan and observer to observer with these limited measurement techniques. Use of high technology MRI with volumetric analysis is the only way in which the efficacy of nonsurgical treatment (radiation treatment, drug therapy) can be compared usefully with observation alone (Blakeley et al., 2012).

Although computed tomography (CT) scans have poor sensitivity in detecting small vestibular schwannomas (Evans et al., 1992a, b), CT can identify another feature of NF2. A proportion of NF2 patients have intracranial calcification from a young age (Evans et al., 1992a). However, this sign is not useful enough to supplement MRI with CT. Repeated CT scans should probably be avoided in individuals with NF2 due to their predisposition to tumor formation.

**PATHOLOGY**

The main tumor sites, their frequencies, and their pathologies are presented in Table 5.2. As stated before, schwannomas can occur in all locations where there are nerves with Schwann cells. The predilection for the superior vestibular branch of the eighth cranial nerve remains unexplained. Schwannomas are encapsulated tumors of pure Schwann cells that grow around the nerve. They may contain blood vessels and have areas of sheets in intertwining fascicles (Antoni A) and looser arrangements called Antoni B (Sobel and Wang, 1993). The tumors also stain for S-100 protein and vimentin. In NF2 these tumors can be multifocal and have a more lobular architecture than sporadic tumors (Sobel and Wang, 1993). Spontaneous malignant transformation of these tumors to malignant peripheral nerve sheath tumors occurs (Higami et al., 1998), but is more than 10 times as likely to happen after radiation treatment (Baser et al., 2000). The background rate of 0.5% for central nervous system (CNS) malignancy in NF2 is very much less than for NF1 (McGaughran et al., 1999).

A small proportion of nerve-related tumors in NF2 is pathologically delineated as neurofibroma. In these tumors there is an admixture of cell types including Schwann cells, fibroblasts, and mast cells, and the tumor usually contains identifiable axons. Neurofibromas occur mainly in the skin (where they still are outnumbered by schwannomas by a factor of 5–10) but also develop on the spinal nerve roots; they are not, however, seen in the cranium. Occasionally tumors show features of both schwannoma and neurofibroma, particularly on spinal nerve roots. In contradistinction to NF2, schwannomas and meningiomas do not occur in excess in NF1 (Huson et al., 1988; McGaughran et al., 1999).

Meningiomas are the second most characteristic tumor of NF2. The most typical sites for meningiomas are supraptentorially in the falx and around the frontal, temporal and parietal regions. Meningiomas also occur around the spinal cord, and these can be difficult to remove surgically. Although there are different histologic types of meningioma (meningothelial, fibroblastic and transitional), there is no evidence for a subdivision into NF2 and non-NF2 related tumors clinically (Antinheimo et al., 1997). Collision tumors consisting of a schwannoma and meningioma can occur particularly in the cerebello-pontine angle. A number of studies have determined the proportion of meningiomas and schwannomas due to NF2. In one series of spinal schwannomas and neurofibromas (Halliday et al., 1991), all the cases of NF1 had neurofibromas, whereas only a proportion of the spinal schwannomas were due to NF2 and one NF2 patient had a mixed tumor. Another study of all meningiomas and schwannomas from an 11-year period in the Helsinki area found that 3% of schwannoma patients and 1% of meningioma patients had NF2 (Antinheimo et al., 2000). However, a further 2% of schwannoma patients and 4% of meningioma patients had multiple tumors without fulfilling diagnostic criteria for NF2. The great majority of NF2 patients do not present with an isolated tumor, and the risk of NF2 in a person with an isolated vestibular schwannoma is small (Evans et al., 1999b), but as many as 10% of children with an apparently isolated meningioma go on to develop NF2 (Evans et al., 1999a).

Low grade ependymomas and gliomas are now being increasingly recognized in individuals with NF2 (Fig. 5.4). These are indolent tumors and rarely metastasize within the CNS. Their prime location is in the cervical spine and brainstem (Hagel et al., 2012). Malignant progression is sometimes associated with radiotherapy treatment (Baser et al., 2000).
GENETICS

Type 2 neurofibromatosis is an autosomal dominantly inherited disorder due to mutations in a single gene on chromosome 22. Individuals who inherit a mutation of the \textit{NF2} gene inevitably develop schwannomas, particularly of the eighth cranial nerve, but also other cranial, spinal and cutaneous nerves. The great majority of nerve tumors are schwannomas, but cutaneous and spinal neurofibromas do occur. Around 60% of individuals will also develop a meningioma. All these tumors occur by inactivation of the second normal copy of the \textit{NF2} gene in a single cell, although further events may be necessary for tumor progression. As expected with autosomal dominant inheritance, half of the offspring of individuals with full blown constitutional NF2 are affected.

\textit{NF2} affects about 1 in 35–40 000 people (Evans et al., 1992c, 2010). However, because many people do not develop features of the condition until the third decade or later – and many others die before this time – the actual diagnostic prevalence was only 1 in 200 000 in 1992. This has increased to 1 in 56 000 in 2010. The annual incidence rate is 1 per 2 355 000 representing about one new case per year for each health region in the UK (Evans et al., 1992c), or 100 cases per year in the USA. Individuals with NF2 have reduced genetic fitness and this is more marked in males, who may delay having families until their disease has progressed (Evans et al., 1992c). This reduction of potential gene carriers to pass on the condition is counterbalanced by the high new mutation rate, with 50–60% of patients having no affected parent.

Fig. 5.4. Ependymoma.

The gene has a high degree of penetrance and is nearly always expressed by the late fifties (Evans et al., 1992c). The initial clue to the whereabouts of the gene came with the discovery of chromosome 22 abnormalities on cytogenetic analysis of meningiomas (Zang, 1982), a location that was confirmed at the molecular level in several different tumors from an NF2 patient with loss of constitutional heterozygosity for chromosome 22q markers (Seizinger et al., 1986). This provided strong evidence that the NF2 gene was a tumor suppressor, with both copies of the gene needing to be inactivated to initiate tumorigenesis (Knudson’s 1971 “two hit” hypothesis of tumorigenesis). NF2 is perhaps the best example of this mechanism, other than retinoblastoma, for which the hypothesis was made. Every Schwann cell in NF2 already carries a mutant copy of the gene and if the other copy is mutated or deleted then a tumor ensues. There is little evidence for the involvement of other genes in the formation of schwannomas. Indeed while many studies have shown direct evidence of NF2 mutation or deletion in about 60% of schwannomas, at the biological level virtually 100% show loss of NF2 protein (Huynh et al., 1997).

After the confirmation of a site of tumor loss, linkage studies confirmed that all affected members of the large Pennsylvanian family first reported in 1930 by Gardner and Frazier carried the same copy of chromosome 22 (Rouleau et al., 1987). Further studies have shown no evidence for another gene to account for the NF2 phenotype, and NF2 is almost certainly caused by a single gene on 22q (Narod et al., 1992; Ruttledge et al., 1993). The NF2 gene was further localized by the discovery of germ line deletions in NF2 families, one of which involved the neurofilament heavy chain gene (Watson et al., 1993). The gene itself was eventually isolated by the simultaneous discovery of constitutional and tumor deletions in a gene coding for a cell membrane-related protein termed merlin (Trofatter et al., 1993) or schwannomin (Rouleau et al., 1993).

Many studies have now confirmed this locus as the \textit{NF2} gene. Standard mutation techniques such as SSCP (single strand confirmation polymorphism) or DGGE (denaturing gradient gel electrophoresis) detect between 35% and 65% of causative mutations (Bourn et al., 1994a; MacCollin et al., 1994; Mérél et al., 1995; Evans et al., 1998a). The majority of these mutations are truncating mutations, leading to a smaller and probably ineffective protein product. Currently full sequencing of the coding exons and intron exon boundaries is the best method, with next generation sequencing offering a valuable rapid approach that can detect mosaicism.

There is now clear evidence of a genotype/phenotype correlation with most missense mutations, which will give rise to a complete protein product, or deletions...
giving no protein product having a mild phenotype (Parry et al., 1996; Rutledge et al., 1996; Evans et al., 1998a). Splice site mutations that may splice out a sequence of amino acids from the protein also appear to cause a mild phenotype, but this is more variable (Kluwe et al., 1998). The more severe phenotype with truncating mutations, such as nonsense and frameshift- ing changes, may be due to a dominant negative effect with mutant protein dimerizing with the normal product leaving less wild type protein for tumor suppression. Recent evidence also suggests that up to 33% of new cases of NF2 with no family history of the disease carry the mutation in only a small proportion of their cells (Evans et al., 1998b; 2007; Kluwe and Mautner, 1998). In these mosaic individuals, the NF2 gene mutation occurs after conception. If the mutation is carried by < 10% of lymphocytes, it is not detectable by standard mutation detection techniques (including sequencing), although the percentage of cells affected can vary from tissue to tissue (Bourn et al., 1994b). A higher proportion of affected neural crest cells may increase the severity of the disease, but, in general, mosaic individuals are less severely affected than would be predicted from their mutation because fewer cells receive a second hit (Evans et al., 1998b, 2013). In sporadic NF2 patients in whom a mutation is not detected in blood DNA, mutations can be identified in their tumors. An identical mutation in two tumors from the same individual is virtually certain to represent the underlying defect (Evans et al., 1998b). A further cause of the low detection rate for mutations using standard techniques is large deletions and rearrangements at the NF2 locus (Zucman-Rossi et al., 1998). Some of these can be detected by cytogenetic studies using FISH where the signal from one chromosome 22 is missing in each cell. However, others are too small for this type of detection, and techniques such as Southern blotting and PCR dosage studies need to be employed. Mosaic patients are unlikely to be detected with these methods (Zucman-Rossi et al., 1998; Evans et al., 2007).

Predictive diagnosis using markers flanking the NF2 gene has been possible for 20 years in the vast majority of families containing two or more living affected individuals by linkage analysis (Rutledge et al., 1996; Evans et al., 1995a). Once a mutation has been identified in an affected individual, a 100% specific test is available for that family. However, blood mutation analysis may not reveal the causative mutation. As such, tumor analysis is a vital step in sporadic cases so that a mosaic mutation can be identified (Evans et al., 2007). Mutation analysis can be undertaken on the child of a sporadic NF2 patient (Evans et al., 2012). By combining this with a cumulative age at onset curve (Evans et al., 1992b; updated in Fig. 5.5), the risk to an unaffected 30-year-old with a normal scan and favorable DNA result would be infinitely small. Complete confidence can still be attained only with the identification of family-specific mutations.

Age at onset curves aid genetic counseling. For example, for an asymptomatic at-risk 20-year-old individual, their risk of having inherited NF2, prior to screening, will have dropped to 25%. As more families are followed prospectively a curve for age at diagnosis, with screening, will become available. At-risk individuals can be discharged if they have been shown not to have inherited the mutated NF2 gene. Uptake of presymptomatic genetic tests for NF2 are high (Evans et al., 1997a), with around 90% of asymptomatic individuals at 50% risk opting for genetic tests.

The main diagnostic dilemma with NF2 is patients with isolated multiple noncranial schwannomas. Some of these patients may well go on to develop NF2 (Evans et al., 1997b) and all require a cranial MRI scan. Some patients prove to be mosaic for an NF2 mutation (Jacoby et al., 1997; Evans et al., 1998b). A small group of patients with tumors largely confined to the peripheral nerves and spine, with sparing of the eighth nerve do not to have an identifiable NF2 mutation (Jacoby et al., 1997). These individuals have schwannomatosis and may pass the condition on to their children, and in families where this occurs there is still linkage to the NF2 locus (Evans et al., 1997b; Jacoby et al., 1997). Two genes centromeric to NF2 on chromosome 22 have now been found and account for about 70% of familial and 20% of sporadic schwannomatosis patients: SMARCB1 (Hulsebos et al., 2007; Smith et al., 2014) and LZTR1 (Piotrowski et al., 2014; Smith et al., 2015).
Patients with unilateral vestibular schwannoma and other schwannomas may have a LZTR1 mutation (Smith et al., 2015). Patients may also present with multiple meningiomas with no other features of NF2. The key feature in both these related conditions is the absence of other NF2-related tumors such as intracutaneous schwannoma and ependymoma or cataracts.

Modifying factors

There is evidence that NF2 may be worse if it is inherited from the mother (Kanter et al., 1980; Evans et al., 1992c). However, this could also be due to decreased genetic fitness in males, with only the less severely affected men having children (Baser et al., 2001). As there is no evidence of genomic imprinting on chromosome 22q, the previous reports of a maternal gene effect may be spurious. General worsening of the disease with successive generations (“anticipation”) has also been suggested, but objective evidence for this is lacking. Some authors strongly believe that females are more severely affected than males and women become worse during pregnancy (Allen et al., 1974). However, a more complete analysis suggests that this effect applies mainly to meningiomas rather than schwannomas (Evans et al., 1995b).

On the whole, the disease course of NF2 does breed true in individual families. Some families have a mild disease course with late onset and few if any CNS tumors other than vestibular schwannomas. Other families have a more virulent course with early onset and death due to multitumor disease. The evidence of a genotype/phenotype correlation is encouraging and may provide insight into the disease process. Nonetheless, much will depend on stochastic events such as loss of the second NF2 allele, because the disease course is not identical even in monozygotic twins (Baser et al., 1996).

MANAGEMENT ISSUES

We have previously published protocols for screening individuals at risk for NF2 (Evans et al., 1992b, 2005, 2012). The potential for early onset symptoms (10% of cases symptomatic before 10 years of age) warrants earlier screening than generally suggested. The presence of congenital or very early cataracts necessitates detailed early ophthalmologic screening, and slit lamp evaluation and ophthalmoscopy should be done at least every 5 years. Screening for vestibular schwannomas should begin around 10–12 years of age with audiologic testing including auditory brainstem responses (ABRs) which should be performed annually. ABRs have been shown to be more useful in screening for vestibular schwannomas in NF2 than other audiologic tests (NIH Conference Statement, 1990). MRI scans are the imaging technique of choice, because they detect smaller tumors than CT and avoid the risk of radiation. Cranial MRI should be carried out annually in individuals with tumors and every 3 years in those at risk. A baseline scan should be performed aged 14 years. A normal MRI scan at 16–18 years approximately halves the risk of having inherited NF2 and will facilitate reproductive decision making. A normal scan at 30 years will make inheritance very unlikely except in late onset families and could justify cessation of formal screening. When onset has been late, screening should be continued appropriately. In view of the increasing availability of MRI, it may well replace audiologic testing altogether as a screening tool. The baseline scan should include full spinal imaging, but because the majority of asymptomatic spinal tumors would not be surgically removed, further spinal imaging should be performed as indicated by signs and symptoms. Clinical review including an annual neurologic examination should accompany any screening. Although annual review could be omitted in very mild families in the first 10 years of life, it is useful for there to be a point of contact for all at-risk individuals.

The surgical management of individuals with NF2 is complex and probably should be confined to specialized centers with experienced otolaryngologists and neurosurgeons. Data from our own group and elsewhere (Evans et al., 1993, 2005; Samii et al., 1997; Slattery et al., 1998) indicate that individuals treated at specialist centers have a better outcome. As NF2 is a relatively rare condition, in a country the size of the UK, perhaps only two or three such centers would be needed (perhaps 10 in the USA). Otolaryngologists, neurosurgeons and clinical geneticists working together could coordinate the care and follow-up of affected individuals and their at-risk relatives. Timing of surgery can be critical, and the decision to operate early or wait until symptoms develop is crucial. Availability of new techniques such as brainstem implants is only available in a few centers. The cloning of the NF2 gene may provide insights into pathogenesis and suggest possible preventative treatments. Specialist centers with vast experience in NF2 management would ensure clinical application of such developments, with careful appraisal at the earliest opportunity.

Drug therapy

One of the most significant breakthroughs in NF2 was the publication of a small pragmatic study of the use of the VEGF antibody bevacizumab in treatment of growing vestibular schwannomas (Plotkin et al., 2009). This study and a larger follow-up study showed that 2 weekly infusions of bevacizumab shrinks around 40–50% of growing vestibular tumors and controls growth in around 70%. There is also evidence of hearing improvement in a minority (Plotkin et al., 2012).
is not convincing evidence of the drug in treating NF2-related meningioma disease.

THE FUTURE

The much awaited step in NF2 was the localization and cloning of the gene. This achieved, precise diagnosis is possible if a specific mutation can be found, and this may also allow prediction of disease course by genotype/phenotype studies. This will not be as important in families where the extent of the disease is already known, but for new mutations insight into the likely speed of tumor progression and risk of other tumors would be very helpful. Although DNA predictive testing is now available with flanking markers, there is currently little demand for prenatal or preimplantation diagnoses.

The real hope was that the discovery of the gene and its transcriptional protein product merlin/schwannomin would lead to the development of somatic gene therapy. The prospects for NF2 appeared promising, because of the lack of variation in individuals with the same mutation and in the paucity of involvement of other genes in the tumors themselves. Replacement of the tumor suppressor product in the tumors through viral vectors or direct recombination of the NF2 gene, although requiring great advances in our knowledge, could be very rewarding. Nonetheless many trials of agents utilizing knowledge of the NF2 pathway such as sorafenib, nilotinib, erlotinib, lapatinib and rapamycin have been initiated and it is hoped there will soon be additional agents with proven efficacy available (Blakeley et al., 2012).

REFERENCES


