Neurofibromatosis type 2 (NF2): diagnosis and management

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INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal dominant condition characterized by multiple tumors of the nervous system and meninges as well as lesions of the eyes and skin (Evans et al., 1992a; Asthagiri et al., 2009). It results from a defect in the NF2 tumor suppressor gene situated on chromosome 22q11 that encodes the protein Merlin (moesin-ezrin-radixin-like protein), also called Schwannomin (Trofatter et al., 1993; Rouleau et al., 1993). It has a very variable phenotype but the most common type of tumor to develop is the vestibular schwannoma (Fig. 54.1). These are usually present bilaterally. Intracranial meningiomas and spinal cord tumors (Fig. 54.2) are also common as are schwannomas of other peripheral and central nerves. Paradoxically, neurofibromas only occur very infrequently.

HISTORY

The first clinical description of NF2 was by Wishart in 1822 (Wishart, 1822). However, the neurofibromatoses were often confused until the nomenclature was clarified at a National Institute of Health Consensus Conference in 1987 (Seizinger et al., 1986). This confusion came about after the clinical description of neurofibromatosis type 1 (NF1) by von Recklinghausen in the late 19th century. The great Harvey Cushing then described in 1917 the association of eighth nerve tumors bilaterally in von Recklinghausen disease (Cushing, 1917). Further reports especially those of Crowe from 1956 compounded this association (Crowe, 1956). It was not until the separate localization of genes for NF1 and NF2 in 1987 that formal separation of NF2 from its more common namesake was possible.

EPIDEMIOLOGY

The apparent prevalence of NF2 has gradually increased over the past two decades because of the advent of magnetic resonance imaging and increased awareness of the condition. In 1992 the prevalence was one in 210000 (Evans et al., 1992b) whereas a recent study has suggested that the prevalence is more likely to be approximately 1 in 60000 (Evans et al., 1992c). The birth incidence has been approximated to 1 in 33000 (Evans et al., 1992c).

GENETICS

The inherited nature of NF2 was first described in 1920 by Feiling and Ward (Feiling and Ward, 1920) and its autosomal dominant inheritance was described by Gardner and Frazier in 1930 (Gardner and Frazier, 1930). Around 50–60% of patients have no family history and represent de novo mutations (Evans et al., 1992a). In de novo patients presenting with bilateral vestibular schwannomas, 70% will carry the mutation in all their cells as the mutation will have occurred prezygotically. However, in the remaining 30% the mutation occurs postzygotically and two separate cell lines develop, one with the mutation and one without (Evans et al., 2007b). This is somatic mosaicism, a phenomenon that is more common in NF2 than in almost all other inherited disorders. In de novo patients presenting with a unilateral vestibular schwannoma the incidence of mosaicism is 60% (Evans et al., 2007b). Such patients often have milder disease and have a lower than 50% risk of transmitting the disease to their offspring (Kluwe and...
The risk of transmission is dependent on the degree of mosaicism (Moyhuddin et al., 2003; Evans et al., 2007b). A de novo mosaic NF2 patient with bilateral vestibular schwannomas has a one in eight risk of passing the disease on to their children. The risk drops to 1 in 12 if the patient has a unilateral vestibular schwannoma. For affected children of de novo cases, transmission is 50% from the second generation and beyond because they carry the mutation in all their cells. Children of mosaic cases usually have more severe disease than the affected parent.

There are many different types of mutation that have been identified in NF2. These include large-scale deletions that result in no protein product, nonsense and frameshift mutations that result in a truncated protein product, and mis-sense mutations that result in a complete although abnormal protein product (Kluwe et al., 1996; Parry et al., 1996; Ruttledge et al., 1996; Evans et al., 1998; Baser et al., 2004). Splice-site mutations have also been identified (Kluwe et al., 1998; Baser et al., 2005a). Those mutations resulting in truncated protein products are associated with more severe phenotypes (Kluwe et al., 1996; Parry et al., 1996; Ruttledge et al., 1996; Evans et al., 1998; Baser et al., 2004). In nonmosaic patients and from tumor tissue in mosaic patients, the detection rate of mutations using sequence analysis and multiple ligation-dependent probe amplification (MLPA) is around 92% (Evans et al., 2007b) but the detection rate from the blood of sporadic patients is significantly lower than this.

MOLECULAR BIOLOGY

The defective gene responsible for NF2 was identified in 1993 (Rouleau et al., 1993; Trofatter et al., 1993). It has 17 exons that encode Merlin, a 69 kDa protein with 595 amino acids. Merlin consists of three domains, a tri-lobed FERM (4.1-ezrin-radixin-moesin) domain at the amino-terminal, an alpha-helical domain, and a carboxy-terminal domain. It exists in two isoforms, an active, closed unphosphorylated form and an inactive, open phosphorylated form (Bianchi et al., 1994; Pykett et al., 1994; Sherman et al., 1997). Phosphorylation occurs at serine 518 and is catalyzed by cyclic-AMP-dependent protein kinase A and p21-activated kinases (Kissil et al., 2002; Alfthan et al., 2004; Rong et al., 2004a). This prevents folding of the molecule with resultant inactivation and relocation. Dephosphorylation is catalyzed by myosin phosphatase-I protein phosphatase-Iβ.

Merlin is localized to the cell membrane/cytoskeletal interface (Scherer and Gutmann, 1996) and appears to have a number of different roles involving interaction
between cell membrane proteins and cytoskeletal or intracellular proteins (F-actin, β2-spectrin, Rho guanosine triphosphatase), organization of cell membrane proteins (epidermal growth factor receptor and CD44), and cell-to-cell adhesion (E-cadherin, β1-integrin) (Lee et al., 2004; Rong et al., 2004b; Ryu et al., 2005; Lim et al., 2006; Scoles et al., 2006; Curto et al., 2007). The details of these roles are unclear at present but all result in downstream regulation of cell proliferation via a number of pathways including the mitogen-activated protein kinase (MAPK) pathway and phosphoinositide-3 kinase (PI3K) pathway.

**CLINICAL FEATURES**

A number of diagnostic criteria for NF2 have been put forward but the Manchester criteria have become widely accepted (Evans et al., 2005). These are set out in Table 54.1. They are a modification of the National Institute for Health criteria (National Institute for Health, 1991) with the addition of patients with no family history who have multiple schwannomas and/or meningiomas who have yet to develop bilateral vestibular schwannomas.

NF2 usually presents in early adulthood although milder phenotypes can present much later. Penetrance is almost 100% by the age of 60 (Evans et al., 1992a). The incidence is equal between genders. The clinical features any given patient displays depends on the type and location of the pathology. Table 54.2 summarizes the types of lesion that are commonly seen in NF2.

Adults most often present with symptoms related to vestibular schwannomas whereas children more frequently present with visual disturbance, skin tumors, mononeuropathy, or symptoms related to other, nonvestibular intracranial or spinal tumors (Evans et al., 1999; Nunes and MacCollin, 2003; Ruggieri et al., 2005). Below the age of 18 years, a patient presenting with an apparently isolated meningioma or vestibular schwannoma has a 20% and 10% risk of having NF2, respectively. Over this age the rate drops dramatically (Evans et al., 2007a).

**Table 54.1**

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<thead>
<tr>
<th>Diagnostic criteria for NF2</th>
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<tr>
<td>Bilateral vestibular schwannomas or family history of NF2 plus</td>
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<tr>
<td>1) Unilateral VS or</td>
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<tr>
<td>2) Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities</td>
</tr>
<tr>
<td>Additional criteria: unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities</td>
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<td>Or</td>
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<tr>
<td>Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract</td>
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**Table 54.2**

<table>
<thead>
<tr>
<th>Table summarizing the frequency with which the common lesions associated with NF2 are seen</th>
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<tr>
<td>Neurological lesions</td>
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<tr>
<td>Bilateral vestibular schwannomas</td>
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<tr>
<td>Other cranial nerve schwannomas</td>
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<tr>
<td>Intracranial meningiomas</td>
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<td>Spinal tumors</td>
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<tr>
<td>Extramedullary</td>
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<tr>
<td>Intramedullary</td>
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<tr>
<td>Ophthalmological lesions</td>
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<tr>
<td>Cataracts</td>
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<tr>
<td>Epiretinal membranes</td>
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<tr>
<td>Retinal hamartomas</td>
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<tr>
<td>Cutaneous lesions</td>
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<td>Skin tumors</td>
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<td>Skin plaques</td>
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<td>Subcutaneous tumors</td>
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<td>From Asthagiri et al.</td>
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**VESTIBULAR SCHWANNOMAS**

Vestibular schwannomas are the commonest tumor to occur in NF2 and are usually present bilaterally although they are often of different sizes and one usually predates the other. Similarly, intracranial meningiomas, spinal tumors, or cutaneous tumors may present prior to the development of vestibular schwannomas and these account for around 20–30% of presentations (Parry et al., 1994; Mautner et al., 1996). Hearing loss due to vestibular schwannomas is the presenting symptom in 60% of adults and 30% of children (Evans et al., 1999; Nunes and MacCollin, 2003; Ruggieri et al., 2005). It is often unilateral at presentation although bilateral hearing loss often develops over time. This may be present because of the tumor itself or because of surgical intervention. The severity ranges from mild to profound and is sensorineural in nature. Hearing usually deteriorates over time at a rate of around 5 dB per year on average (Fisher et al., 2009) although this varies considerably between patients and there are some that have rapidly progressive or sudden hearing loss. In the majority, hearing may be reasonably well preserved during the initial year or two following diagnosis (Masuda et al., 2004). Rate of hearing loss is not related to tumor size or growth (Fisher et al., 2009). Other otoological symptoms include tinnitus and imbalance. This may manifest as a chronic disequilibrium or episodic vertigo although the latter is more unusual with vestibular schwannomas due to NF2 than with sporadic tumors.

Vestibular schwannomas initially develop at the neurilemmal/neuroglial junction within the internal auditory
canal (IAC). They expand out of the IAC and into the cerebellopontine angle (CPA). Over a 4-year period, the vast majority of tumors demonstrate significant growth with 82% growing by at least 5 mm³/year (Baser et al., 2002; Mautner et al., 2002). This is more aggressive behavior than that of their sporadic counterparts. Similarly, younger patients tend to have more aggressive disease than older patients (Baser et al., 2005b). Multiple tumors may be present and it is sometimes difficult to differentiate schwannomas of other nerves, particularly the facial and lower cranial nerves from those originating from the vestibular nerves.

**INTRACRANIAL MENINGIOMAS**

These are the second most common tumor type found in NF2 patients and may occur anywhere within the cranial cavity but are particularly common on the convexities. These can become large before producing any symptoms, the most common being headache. They may also occur around the skull base and optic nerve region where much smaller tumors can cause compressive symptoms particularly of the optic nerve and lower cranial nerves. They tend to behave more aggressively than their sporadic counterparts (Perry et al., 2001).

**SPINAL TUMORS**

Up to 90% of patients have spinal tumors. Extramedullary meningiomas and schwannomas are the most common tumor types. These may cause compressive symptoms including muscular weakness, paresthesia or pain. It is common to find a moderately large schwannoma at the level of C1.

Ependymomas of the spinal cord are also frequently seen. These are intramedullary, may be multiple, and are often minute. They may be found throughout the spinal cord. They are almost always asymptomatic (Patronas et al., 2001; Dow et al., 2005).

**NEUROPATHY**

In adulthood, 3–10% of patients may develop a severe polyneuropathy although up to 40% of adults show evidence of polyneuropathy on nerve conduction studies even in the absence of any neural compression by tumor (Hagel et al., 2002). Mononeuropathy may be the presenting feature of NF2 in childhood and most often affects the facial nerve, although other cranial nerve roots can be affected especially the oculomotor and trigeminal roots. Children may also present with a polio-like illness with irreversible wasting of muscles in the lower limb most frequently causing a unilateral foot drop. Loss of muscle function may also affect the upper limb causing wasting of the thenar or hypothenar eminence. The pathogenesis of the neuropathy is unclear but may be due to Schwann cell proliferation amongst the axons of nerves in the absence of frank tumor (schwannosis), the local toxic effect of tumor cells, or cellular dysfunction due to Merlin deficiency (Sperfeld et al., 2002). Nerve conduction and imaging studies will help differentiate a tumor-related cause from a mononeuropathy.

**OCULAR DISEASE**

Loss of visual acuity is often seen in patients with NF2 and has several possible causes. This includes optic nerve meningiomas, cataracts, and retinal hamartomas. Cataracts affect up to 80% of patients and may be subcapsular lenticular opacities or cortical wedge opacities (Evans et al., 1992a; Parry et al., 1994; Bosch et al., 2006). Epiretinal membranes are also seen. Unexplained amblyopia is also very common in NF2 usually dating to early childhood.

**CUTANEOUS DISEASE**

Around 70% of patients have some skin involvement in NF2 although only 10% have more than 10 lesions. The lesions may be intracutaneous, plaque-like lesions that are usually slightly hyperpigmented and may be covered in excess hair (Fig. 54.3). Alternatively, they may be more nodular subcutaneous fusiform tumors (Fig. 54.4) in which case they are usually schwannomas of peripheral nerves.

**DETERMINANTS OF DISEASE PHENOTYPE**

One of the interesting aspects of NF2 is the variation in phenotype (Evans et al., 1992b; Parry et al., 1994). This manifests in differences in age of onset of disease, speed of progression, and extent of disease. Within a family, disease severity tends to be similar. However, between...
families phenotypic severity may vary considerably. Historically, two phenotypic groups have been identified. Those with more aggressive disease have been termed “Wishart” type. Those with milder disease have been termed “Gardner” type.

There have been several papers documenting a relationship between phenotype and genotype. The type of mutation is one of the most important determinants. As outlined above, mutations that result in a truncated protein are associated with more severe disease (Kluwe et al., 1996; Parry et al., 1996; Ruttledge et al., 1996; Evans et al., 1998; Baser et al., 2004). This includes nonsense or frameshift mutations. Conversely, large deletions (which result in no protein product) and missense mutations (which result in a complete protein product) are associated with milder disease. Splice-site mutations are associated with variable disease severity with mutations within exons 1 to 5 being more severe than those within exons 11 to 15 (Kluwe et al., 1998; Baser et al., 2005a). These differences also translate to differences in survival (Baser et al., 2004).

Mosaicism also influences phenotype. The proportion of cells carrying the mutation is related to the severity of disease. Thus, those patients with fewer affected cells are likely to have milder disease and may even have asymmetrical or localized disease.

Despite the findings of the studies outlined above, there is also considerable evidence that determination of phenotype is not simply related to mutation type and degree of mosaicism. This is particularly true with respect to individual tumors. This is clearly illustrated by differences in the behavior of each vestibular schwannoma of any given individual (Fisher et al., 2009) and by poor correlation between behavior of vestibular schwannomas and other indices of clinical severity such as tumor load (Baser et al., 2002).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of NF2 is schwannomatosis (Baser et al., 2006). Patients with this condition develop multiple schwannomas without vestibular schwannomas or intracutaneous (plaque) or ocular involvement. It can be caused by mutation of the SMARCB1 tumor suppressor gene (Hulsebos et al., 2007), although it is likely that another genetic mechanism also exists. In the past, patients in this position have often been told that they have both NF1 and NF2. If there are multiple cutaneous lesions and features of NF2 then this is likely to be the case. However, the number of cases where an individual inherits both diseases is extremely small. NF2 patients do have more frequent cafe au lait patches than the general population (Evans et al., 1992c) and in children with cutaneous tumors this may give rise to diagnostic difficulty. However, only about 1% of NF2 patients have the required six cafe au lait patches for a formal NIH criterion for NF1 (Evans et al., 1992c). Multiple meningiomatosis may also have some overlap with NF2 as occasional mosaic NF2 patients present with just meningiomas. Most cases of multiple meningiomatosis occur in isolation with no other NF2 features and no family history of meningioma disease.

MANAGEMENT

NF2 presents significant challenges in terms of its management and there is strong evidence to suggest that it is best managed by a multidisciplinary team involving genetics, neurosurgery, otolaryngology, ophthalmology, neurology, radiology, pathology, and audiology. There is a clear increase in survival if NF2 patients are managed in specialist centers. The fundamental aim of management should be to maintain function and therefore quality of life whilst managing the tumor load.

Special role of the neurologist

NF2 patients may present in childhood with a mononeuropathy, often a facial palsy that does not fully recover unlike most Bell’s palsies. Foot drop is also a frequent presenting symptom. These presentations are usually in the absence of frank tumor disease. Recognizing these as potential features of NF2 and instigating a full cutaneous and ophthalmological examination is important. Recognizing NF2 plaques or retinal hamartomas in the presence of a childhood mononeuropathy makes NF2 almost certain and this will usually be confirmed by genetic analysis of a blood sample.

The neurologist also has a vital role in symptom identification. NF2 patients may have upper limb symptoms that could be due to extra-axial spinal tumors, an intra-
axial ependymoma, or a brachial plexus tumor. Brainstem compression may also cause long tract signs. A patient’s symptoms may also be primarily due to peripheral neuropathy that will not be improved by removing a spinal tumor.

Vestibular schwannomas

For vestibular schwannomas, the management options include conservative management, surgical excision, radiotherapy, usually in the form of stereotactic radiosurgery or, more recently, medical therapy. The decision-making process regarding which modality to offer and at what point to offer it is very complex. Considerations when deciding whether to actively manage a vestibular schwannoma include tumor size, tumor growth rate, and degree of hearing loss not just in the ear under consideration but also the opposite ear. Patient preference and the presence of comorbidity are also influential factors.

Patients are managed conservatively when possible and this allows an assessment of the behavior of the tumors and avoids unnecessary surgery in patients with stable or slow-growing tumors. However, surgical resection is still commonly undertaken if tumors are large or have demonstrated growth. The decision to remove a vestibular schwannoma takes account of the need to balance preservation of function with surgical morbidity (facial and other lower cranial nerve palsies) that increases with increasing tumor size. In the UK, the cumulative proportion of patients with excised bilateral vestibular schwannomas is 1% by the age of 20 years, 3% by the age of 25 years, and 37% by the age of 50 years (Baser et al., 2005b). The most frequent approaches are translabyrinthine and retrosigmoid although some centers also use the middle fossa approach. Each has its proponents but most centers in the UK use the translabyrinthine approach as this allows good control of the canicular portion of the tumor, excellent access without the need for brain retraction, and visualization of the facial nerve both proximally and distally. Hearing preservation surgery via a retrosigmoid approach may be considered if the tumor is below 20 mm and there is cerebrospinal fluid at the lateral end of the IAC. Preservation of serviceable hearing is possible in 30–65% of cases (Samii et al., 1997; Brackmann et al., 2001). In some centers, the middle fossa approach has also been used with preservation of serviceable hearing in 50% of cases, where it was deemed possible beforehand (Slattery et al., 2007).

NF2-related vestibular schwannomas tend to be more difficult to excise than sporadic vestibular schwannomas. They are more lobulated, tend to wrap around neurovascular structures, and are often more adherent to adjacent structures (Jaaskelainen et al., 1994). As a result, the facial nerve preservation rate in patients with NF2 are poorer than in patients with sporadic tumors with the structural integrity of the nerve preserved in around 85% in experienced hands (Samii et al., 2008). Most surgeons also have a lower threshold for leaving small tumor remnants in order to protect facial function. Thus, in most series, the residual tumor rate is higher than that quoted for sporadic tumors.

Radiotherapy, usually in the form of stereotactic radiosurgery, has been widely used to manage vestibular schwannomas in NF2. However, its role is controversial. It successfully controls tumor growth in 66–100% of cases over a 5-year period (Linskey et al., 1992; Subach et al., 1999; Kida et al., 2000; Mathieu et al., 2007; Vachhani and Friedman, 2007; Meijer et al., 2008; Rowe et al., 2008; Phi et al., 2009). It also carries a 33–57% chance of preserving serviceable hearing over a 5-year period (Linskey et al., 1992; Subach et al., 1999; Kida et al., 2000; Mathieu et al., 2007; Meijer et al., 2008; Rowe et al., 2008; Phi et al., 2009). There is a 0–10% risk of significant permanent facial weakness although 10–17% of patients develop at least a transient weakness (Linskey et al., 1992; Kida et al., 2000; Mathieu et al., 2007; Meijer et al., 2008; Rowe et al., 2008). Whilst these results are poorer than those seen in sporadic vestibular schwannomas, the morbidity in the short to medium term is less than that of surgery in NF2.

However, there are concerns regarding radiotherapy relating to the possibility of malignant change following treatment. There have been nine cases of malignancy in NF2 patients following radiotherapy over the last 13 years four of which have not been formally reported (Carlson et al., 2010; Comey et al., 1998; Noren, 1998; Thomsen et al., 2000; Bari et al., 2002). These include malignant peripheral nerve sheath tumors, malignant meningiomas, a rhabdomyosarcoma, and a malignant ependymoma. This is a seven times greater risk than in patients with NF2 who have not had radiotherapy (Baser et al., 2000). Increased pleomorphism may be seen in vestibular schwannoma tissue that has been removed following radiotherapy (Manchester NF2 Group).

In addition, surgery following failed radiotherapy may be more difficult than primary surgery (Pollock et al., 1998; Shuto et al., 2008). There may also be greater morbidity and indeed mortality following surgery after stereotactic radiosurgery. This is a significant issue in NF2 as up to 25% of tumors may continue to grow despite treatment and will require surgery. The perioperative mortality may be as high as 18% in patients who have had previous radiotherapy (Manchester NF2 Group).

Hearing rehabilitation is an important consideration in patients with NF2. The disease itself as well as surgical intervention to remove disease both result in hearing loss
and many patients become bilaterally profoundly deaf over time. In those patients who have a moderate to severe loss, a hearing aid may suffice. However, those with profound bilateral hearing loss may benefit from a cochlear implant or an auditory brainstem implant (ABI). Cochlear implantation is an option if the cochlea is intact and the cochlear nerve is intact and functional (Trotter and Briggs, 2010; Lustig et al., 2006; Neff et al., 2007). This is the case in patients who have not had surgery or have had surgery with preservation of the cochlear nerve. In most series, patients gain significant benefit in speech perception following implantation.

For those who have had the cochlear nerve divided auditory brainstem implantation is the only implant option available (Colletti, 2006; Grayeli et al., 2008; Schwartz et al., 2008; Maini et al., 2009). This device is similar to a cochlear implant but the electrode array is placed on the cochlear nucleus on the brainstem. The outcomes of ABI are significantly worse than cochlear implantation. They provide an aid to lip reading in the majority of cases although there is a nonuser rate of around 20%. The best users, however, are able to hear without the need to lip read although this is very unusual. Most ABI centers will implant patients during removal of the first vestibular schwannoma even if the opposite ear still has serviceable hearing. This so-called “sleeper device” may be switched on periodically to provide some auditory input into the implanted side. This may maintain neural plasticity and optimize outcomes once the patient becomes profoundly deafened on the opposite side and needs to start using the implant on a regular basis. More recently, attempts at midbrain implantation have been made. These devices stimulate the auditory pathway at the level of the inferior colliculus (Colletti et al., 2007; Lim et al., 2009). The very early results of these devices have been disappointing.

Auditory implants in patients with NF2 present significant challenges in terms of tumor monitoring for a number of reasons. The magnets that they contain may dislodge whilst within the magnetic field of the MRI scanner (Deneuve et al., 2008) potentially causing injury to the patient and preventing correct functioning of the implant. The magnetic field of the implant magnet causes considerable distortion of the image obtained during scanning (Majdani et al., 2009). The magnet of the implant may become demagnetized whilst within the scanner (Majdani et al., 2008) and the device itself may be damaged by the magnetic field of the scanner. However, modern devices are safe when used in a 1.5 Tesla machine (Gubbels and McMenomey, 2006) and displacement of the magnet can be prevented through firm wrapping of the head (Crane et al., 2010). Whilst the distortion induced by the implant is unavoidable it is possible to reduce the size of the distortion by rotating the head of the patient such that the magnetic field of the implant magnet is in a similar plane to the magnetic field of the scanner (Wackym et al., 2004). The alternatives are to remove the magnet under local anesthetic prior to scanning and then replace it (this risks infection of the device which is disastrous) or to perform computed tomography imaging (this provides compromised resolution compared to MRI scanning).

**Meningiomas**

Convexity meningiomas are usually straightforward to remove completely although this is not necessary unless they are causing considerable compression or are symptomatic. In contrast, those meningiomas involving the skull base are difficult to completely remove and have a higher risk of postoperative neurological morbidity. Radiosurgery is less effective for the management of meningiomas than vestibular schwannomas (Kondziolka et al., 1999).

**Spinal tumors**

Spinal schwannomas and meningiomas may require excision if they are causing compressive symptoms. Approximately 30% of NF2 patients will require spinal surgery in their lifetime although this is usually straightforward. Ependymomas very rarely require surgical intervention as they do not usually cause any neurological compromise.

**Management of other manifestations of NF2**

Peripheral neuropathy can be difficult to treat and involves symptomatic control, in particular, the use of neuropathic medications. Most of the ocular manifestations of NF2 do not require treatment although cataracts may require extraction.

**Medical therapy**

In the past few years a number of drugs targeting specific aspects of the mitogenic process have been developed. Some have shown encouraging results in early clinical trials. Bevacizumab has resulted in stabilization or reduction in size of vestibular schwannomas together with an improvement in hearing in some cases (Plotkin et al., 2009). The Plotkin study of 10 patients showed objective radiological improvement in eight vestibular schwannoma (VS) with bevacizumab (Plotkin et al., 2009). This drug is an antivascular endothelial growth factor (VEGF) monoclonal antibody that inhibits the angiogenic effects of VEGF. Other potential agents that target specific intracellular mitogenic pathways and may be of benefit in NF2 include sorafenib, erlotinib, and lapatinib (Evans et al., 2009). Targeting the ERK1, AKT, integrin/focal adhesion
kinase/Src/Ras signaling cascades, PDGFRbeta, phosphatidylinositol 3-kinase/protein kinase C/Src/c-Raf pathway, VEGF, and other pathways may provide other drug opportunities (Evans et al., 2009).

**SCREENING FOR NF2**

Whilst almost all patients can be diagnosed with NF2 at presentation based on the Manchester diagnostic criteria, it is often difficult to confirm the diagnosis genetically in those patients who are mosaic. The blood of mosaic patients does not usually contain affected cells and the only consistent way of confirming the diagnosis in these cases is to obtain tumor tissue. The most accessible tumors are usually cutaneous, if present, but vestibular schwannoma tissue is the most frequently obtained as these are the commonest type of tumor that require excision. Once the mutation has been identified in any given individual then it is possible to specifically identify whether other at risk family members carry the same mutation.

Those individuals who are first degree relatives of NF2 sufferers or those suspected of having NF2 are at significant risk of developing NF2 themselves. Similarly, some individuals who fall short of the NF2 diagnostic criteria may subsequently develop NF2. This is particularly true of patients with mosaicism. It is important to screen these “at risk” individuals on a regular basis in order to diagnose NF2 early and initiate appropriate management. For pragmatic reasons, some authors have defined “at risk” as a 1% or greater risk of developing NF2 (Evans et al., 2011).

In children of affected parents, screening may begin at birth with the search for cataracts. Formal screening should start at 10 years with cranial and spinal MRI and audiological assessment. Below the age of 20 years scanning should take place in alternate years. Beyond 20 years of age, when tumor growth becomes slower, scanning every 3 to 5 years is acceptable. Scanning may be discontinued by the age of 40. If an individual has a proven mutation but has not yet displayed any features of NF2 then cranial imaging should be undertaken annually with spinal imaging every 3 years.

Individuals with features of NF2 have a greater than 20% risk of having NF2 if there is a unilateral vestibular schwannoma under the age of 20 years, an isolated cranial meningioma under the age of 20 years, an isolated schwannoma at another site in childhood, a retinal hamartoma in childhood, or fulfilment of the Manchester criteria under the age of 50 years adding childhood mononeuropathy as one of the criteria. Those with a risk of between 1% and 19% include those with a unilateral vestibular schwannoma aged between 20 and 30 years. Investigation should include cranial and spinal MRI, audiology, and ophthalmic and dermatological assessment at baseline and at 18 to 20 years of age. Further cranial MRI should be undertaken 5, 10, and 20 years after initial assessment. If there is no evidence of NF2 at that stage then the risk of developing it is less than 1%.

Once diagnosed, annual MRI of the head is performed. The gold standard protocol is T1-weighted imaging with gadolinium-DTPA enhancement. MRI of the spine is usually performed every 3 years in patients with spinal tumors unless there are new symptoms. In those patients who have no spinal tumors, MRI should be performed every 5 years.

**SURVIVAL RATES**

The mean actuarial survival has been shown to be 62 years although more than 40% of patients in this cohort died before the age of 50 years (Evans et al., 1992a). This data was published in 1992 and survival has probably improved significantly since then due to improvements in management.

**CONCLUSION**

NF2 is a complex disease that is best treated in a multidisciplinary setting. This has proven benefits in terms of morbidity and mortality. Significant advances have been made in our understanding of the disease and its management and new modalities of treatment, particularly targeted medical therapies, have the potential to significantly improve outcomes in this condition.

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