Diagnosis and Management of Hereditary Meningioma and Vestibular Schwannoma

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Abstract

Bilateral vestibular schwannomata and meningiomata are the tumours most commonly associated with neurofibromatosis type II (NF2). These tumours may also be seen in patients with schwannomatosis and familial meningioma, but these phenotypes are usually easy to distinguish. The main diagnostic challenge when managing these tumours is distinguishing between sporadic disease which carries low risk of subsequent tumours or NF2 with its associated morbidities and reduced life expectancy. This chapter outlines some of the diagnostic and management considerations along with associated evidence.

Keywords

Vestibular schwannoma · Meningioma · Neurofibromatosis type II · *NF2* · Schwannomatosis

Contents

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1 Introduction

The main focus of this chapter is neurofibromatosis type II (NF2). Other genetic conditions that can potentially cause meningioma or vestibular schwannoma (VS) are also discussed, but these are rare and the predominant diagnostic challenge faced by the clinician is distinguishing between sporadic occurrence of meningioma and/or VS, and NF2, particularly in its mosaic form where only a proportion of the body's cells are affected. NF2 is most appropriately managed in specialist centres with multidisciplinary input, due to the complex needs of the patients, high morbidity and multiple available treatment modalities, all with significant associated risk of complication. Suggestions for which patients with an apparently sporadic VS or meningioma should be investigated for NF2 are provided.

Meningiomata are typically benign tumours arising from arachnoidal cap cells of the meninges and are the most common primary brain tumour in adults accounting for a third of such. Around 90 % occur in the cranium, with the remainder affecting the spine. Malignant meningioma is rare, but occurs in around 2 % of cases. The incidence of meningioma in the USA is estimated to be 1.8 and 4.2 per 100,000 for men and women, respectively. True incidence may be higher due to under-reporting, and one Finnish study calculated the incidence to be 2.9 and 13.0 per 100,000 for men and women, respectively (Larjavaara 2008). Risk factors for sporadic meningioma include exposure to radiation, age and female gender. Meningioma is rare in childhood and can occur at any age in adulthood, but is most common over the age of 50 years.

Vestibular schwannomata (VS) are benign tumours arising from the eighth cranial nerve and account for 10 % of primary intracranial tumours in adults. Sporadic VS are typically very slow growing and may present as incidental findings on brain imaging. A retrospective review of over 46,000 brain MRI scans (requested for reasons other than to investigate auditory/vestibular symptoms) detected VS in 0.02 % (Lin 2005). Symptomatic VS are less common and are estimated to occur in 1–2 per 100,000 (Stangerup 2010). Sporadic VS are rare in childhood, and most occur over the age of 50 years with a median age of diagnosis of 59 years (Carlson 2015).

Hereditary phenotypes that can be associated with meningioma and/or VS include NF2 (OMIM 101000), meningioma, familial susceptibility to (OMIM 607174), and schwannomatosis (OMIM 162091). In diagnostic practice, the degree of overlap between these conditions is limited. Constitutional or mosaic mutations

in *NF2* most commonly present with bilateral VS, with meningioma and/or ependymoma, an additional feature in up to 50 % of patients. In majority of families reported with a susceptibility to meningioma, the genetic aetiology is currently unknown. Although familial meningiomata are a feature of NF2, this diagnosis is extremely unlikely in the absence of VS. Of the two other genes associated with familial susceptibility to meningioma, mutations in *SUFU* have only been described in a single Finnish family, and mutations in *SMARCB1* are associated with spinal meningiomata rather than intracranial disease. Schwannomatosis is typically associated with multiple peripheral schwannomata development, with VS and meningioma occurring infrequently.

2 Risk Assessment

2.1 Meningioma

When assessing a patient with meningioma, consideration should be given to past medical history (previous meningioma, schwannoma, neuropathy, cataract, poor vision) and family history of neurological tumours (Table 1).

Although overt cataracts occur in NF2, milder posterior subcapsular lens opacities are more common and frequently asymptomatic. Vision may also be impaired in NF2 patients due to retinal hamartomata, epiretinal membrane and papilloedema from raised intracranial pressure. Detailed examination by an experienced ophthalmologist is therefore recommended.

A family history of hearing loss, balance disturbance, neurological tumours or unexplained neurology symptoms should be explored. A large proportion of cases of NF2 occur due to a *de novo* mutation in the *NF2* gene, and so the absence of a family history does not rule out the diagnosis if other criteria are met (Table 3).

Table 1 Differential diagnosis for patient presenting with meningioma

Potential diagnosis	Suggestive features
Sporadic meningioma	No significant family history or personal history of schwannomata
NF2	Other features include VS, ocular abnormalities[a], neuropathy, family history of NF2
Meningioma, familial susceptibility to	Significant family history of meningioma
Schwannomatosis	Multiple schwannomata

[a]Posterior subcapsular lens opacities, cataract, retinal hamartomata, epiretinal membrane and papilloedema from raised intracranial pressure

2.2 Vestibular Schwannoma

The presence of bilateral vestibular schwannomata is diagnostic for NF2. Some patients presenting with metachronous bilateral VS may not have NF2 but sporadic tumours occurring bilaterally, although this is likely to be rare. It should be considered in older patients and those in whom many years have passed before the development of the contralateral tumour.

Evaluation of the patient with unilateral VS should include consideration of the age at presentation, past history of VS, peripheral schwannoma, meningioma, ependymoma, ocular abnormalities (as per meningioma, above) and family history of hearing loss or neurological symptoms. The differential diagnosis is summarised in Table 2. Diagnostic criteria for NF2 have been published and are shown in Table 3. Genes known to be associated with genetic susceptibility to meningioma and VS are summarised in Tables 4 and 5, respectively.

Table 2 Differential diagnosis for patient presenting with vestibular schwannoma

Potential diagnosis	Suggestive features
Sporadic VS	No significant family history, unilateral VS, no history of meningioma, schwannoma, ependymoma, or ocular abnormalities[a]
NF2	Other features include meningioma, ocular abnormalities[a], neuropathy, family history of NF2 Consider mosaic NF2 in unilateral VS with other features
Schwannomatosis	Multiple peripheral schwannomata, bilateral Vestibular schwannoma rare

[a]Posterior subcapsular lens opacities, cataract, retinal hamartomata, epiretinal membrane and papilloedema from raised intracranial pressure

Table 3 Diagnostic criteria for NF2 (Baser 2002)

1	Bilateral vestibular schwannomata (VS) **or** family history of NF2 plus unilateral VS **or** any two of meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities
2	Unilateral VS **plus any two of** meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities
3	Two or more meningioma **plus** unilateral VS **or any two of** glioma, schwannoma and cataract

Table 4 Genes associated with susceptibility to meningioma

Gene	Penetrance	Comment
NF2	30–50 %	Neurofibromatosis type II Diagnosis unlikely in the absence of vestibular schwannoma
SUFU	Unknown	Single Finnish family reported (Aavikko 2012)
SMARCB1	5 %	Schwannomatosis Diagnosis unlikely in the absence of multiple peripheral schwannomata
SMARCE1	Unknown	Familial spinal meningioma

Table 5 Genes associated with susceptibility to vestibular schwannoma

Gene	Penetrance	Comment
NF2	Close to 100 %, lower for mosaic disease	Neurofibromatosis type II
SMARCB1	Low	Schwannomatosis Typically multiple peripheral schwannomata, Vestibular schwannoma rare

3 Differential Diagnosis

3.1 NF2 (OMIM 101000)

NF2 is a rare genetic condition with an estimated worldwide incidence of 1 in 33,000. It is inherited in an autosomal dominant fashion, but a high proportion of cases occur *de novo* due to an *NF2* mutation arising during meiosis. In addition, a significant number are either proven or assumed mosaic for an *NF2* mutation arising during postzygotic mitosis. In this situation, only a proportion of the patient's cells carry the mutation; these might be distributed throughout the body, restricted to an embryological tissue type, or an anatomical location. The *NF2* gene encodes the cell signalling protein neurofibromin 2 (also known as Merlin) which is expressed in all cells but has tissue-dependent function. In eighth cranial nerve Schwann cells, and in other neurological tissues, *NF2* acts as a tumour suppressor gene. Biallelic mutations can be demonstrated in DNA derived from sporadic VS tissue. Patients with NF2 have a constitutional loss-of-function mutation in the *NF2* gene, with a second-hit mutation deactivating the other allele in the tumour.

The hallmark of NF2 is the development of bilateral VS, typically becoming symptomatic between the ages of 17 and 24 years, but earlier or later presentation is common. Nearly all patients will develop symptoms before 30 years. Presentation during childhood is often due to other features such as ocular abnormalities, peripheral or spinal schwannoma, ependymoma or neuropathy. Approximately

one-third of individuals suffer reduced visual acuity in either eye due to cataract, retinal hamartoma or epiretinal membrane. A mono- or polyneuropathy causing focal weakness is the initial presenting feature in 12 % of cases (Evans 1992).

One-third to one-half of individuals develop one or more meningiomata during their lifetime. Over one half of patients develop one or more non-vestibular schwannomata, most commonly in the spine, fifth, seventh, ninth or twelfth cranial nerves (Asthagiri 2009). Ependymomata are estimated to affect around one half of individuals but are frequently asymptomatic and do not require intervention (Plotkin 2011).

Age of first presentation of symptoms in NF2 is often remarkably consistent within families, suggesting a significant role of the specific mutation on tumour biology. Phenotype cannot be accurately predicted from the genotype of a particular individual, but associations are recognised.

Missense mutations tend to be associated with a later presentation, slower-growing VS and fewer other tumours. Nonsense and frameshift mutations (protein-truncating) are more likely to cause younger presentation and greater tumour load (Baser 2004). Mutations affecting donor or acceptor splice sites within the gene have been reported with a wide spectrum of severity. Mutations occurring towards the end of the gene and potentially producing a partially functional protein are more likely to result in milder disease with lower risk of meningioma (Smith 2011).

3.2 Meningioma, Familial Susceptibility to (OMIM 607174)

Multiple familial meningiomata is a rare entity with no recognised diagnostic criteria, or reliable estimates of incidence. The underlying molecular aetiology in the majority of families is unknown. Mutations in *SMARCE1* have been identified in four families with multiple spinal clear cell meningiomata (Smith 2013). No mutations in this gene were found in further 34 individuals with multiple cranial meningiomata. Mutations in *SUFU* were found in a single Finnish family with multiple cranial meningiomata, but no other cases with this association have been reported (Aavikko 2012). Although meningioma can occur in patients with NF2 and schwannomatosis caused by mutations in *SMARCB1*, schwannomata are more prevalent in these phenotypes (Bacci 2010). Insufficient data are currently available to draw reliable genotype–phenotype correlations.

4 Genetic Testing

When arranging genetic testing and interpreting the results, it is always necessary to consider which tissue the tested DNA is derived from and the likelihood of it being representative of the tissue affected by disease. Most routine genetic testing is performed on DNA derived from lymphocytes circulating in peripheral blood due

to the ease of sampling, but this may miss mutations that are not present in all tissues. Mutations associated with intracranial tumour development may have occurred postconception and be restricted to neurological tissue which cannot be as readily sampled.

4.1 Bilateral Vestibular Schwannomata

DNA extracted from peripheral blood lymphocytes should be sent for analysis of the *NF2* gene. If this result is normal, then consider *NF2* analysis in tumour-derived DNA if available, and if possible, from two separate tumours. Most laboratories quote improved sensitivity and specificity with analysis from DNA extracted from tissue fresh frozen in liquid nitrogen at the time of biopsy. Analysis of DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissue may be possible, and discussion with the genetics laboratory is advised in advance.

The introduction of massively parallel sequencing techniques has improved the ability to detect low-level mosaicism for *NF2* mutations over traditional Sanger sequencing. Such techniques may detect mutations present in levels as low as 5–10 % in the DNA sample analysed. Nonetheless, a normal result of *NF2* testing on lymphocyte DNA, even by this methodology, does not exclude mosaic disease as many patients are likely to have mosaicism restricted to neural tissue.

Mosaicism for *NF2* mutations appears to be very common. Up to 50 % of patients meeting diagnostic criteria for NF2 have no *NF2* mutation detectable in lymphocyte-derived DNA. To date, no other genes have been associated with the NF2 phenotype, and it is most likely that most if not all such patients are either mosaic for *NF2* gene mutations or have constitutional *NF2* gene mutations that have not been detected by current analysis methods.

4.2 Unilateral Vestibular Schwannoma

Analysis of lymphocyte-derived DNA for the *NF2* gene should be considered in patients with young age of onset, personal or family history of meningioma, or other NF2-related pathology. If there is a history of peripheral schwannoma, then consideration should be given to the diagnosis of schwannomatosis with analysis of the *SMARCB1* gene if appropriate.

4.3 Meningioma

No genetic testing is indicated for a single sporadic meningioma diagnosed over the age of 50 years. In scenarios with a young age of diagnosis, multiple primary meningiomata or multiple first-degree relatives with meningiomata, genetic testing should be considered.

If predominantly intracranial disease, consider *NF2* gene testing in lymphocyte-derived DNA, followed by *SMARCB1* and *SUFU* if available. Mutations in any of these genes are relatively unlikely given current data.

If predominantly spinal meningiomata, then testing of *SMARCE1* in lymphocyte-derived DNA may be indicated if available.

5 Management

5.1 Surveillance

NF2 should be managed within specialised services with multidisciplinary input to ideally include neurosurgery, skull base surgery/ENT, neurology, ophthalmology, audiology, mental health and medical genetics.

Growth of VS in both sporadic and NF2-related disease is nonlinear, and longitudinal observation to demonstrate active growth is essential before intervention (Carlson 2015). Tumours can be very slow growing and exhibit reduction in size over time. Individuals presenting with bilateral VS may have had the tumours for many years with few or no symptoms. Surveillance interval should be decided based on tumour size, patient age, prior growth rate, symptoms and potential risk to hearing. Annual surveillance is common in adults under regular follow-up. Shorter intervals such as 3–6 months are common at initial presentation or in symptomatic paediatric patients. Older patients and those with evidence of static disease may only require reimaging every 3–5 years.

Surveillance should be by contrast enhanced brain MRI with internal auditory meatus protocols. Patients with cochlear or auditory brainstem implants with subcutaneous ferrous components require head-wrapping to reduce discomfort during MRI scanning. CT with contrast can be effective to monitor VS growth in patients unable to tolerate MRI or in whom it is contraindicated.

5.2 Therapeutic and Risk-Reducing Options

5.2.1 Vestibular Schwannoma

Surgical treatment for VS carries a high risk of profound hearing deficit, tinnitus and facial nerve damage. Other potential complications of skull base surgery include other cranial nerve damage, CSF leak, infection, headache and unexpected death. Nonetheless, surgical resection remains the treatment of choice for large VS that are unlikely to be amenable to other therapies and have already resulted in significant ipsilateral deafness.

Surgical approaches will depend on the tumour size, shape, relation to other structures, whether lobulated/multifocal, whether hearing is still present and whether a cochlear or auditory brainstem implant is to be sited. The most common surgical approach is translabyrinthine which results in the total loss of residual

hearing, but provides optimal visualisation of the facial nerve, and allows siting of a cochlear implant during surgery (Moffat 2013). A retrosigmoid approach provides a more direct approach to expose VS tumours and can be used to preserve any residual hearing, but may be associated with an increased risk of facial nerve damage.

Radiotherapy (stereotactic radiosurgery/Gamma Knife) has been demonstrated to provide effective control of tumour growth with a reasonable side effect profile, although hearing outcomes are poor and the technique is most suitable for smaller tumours (Mallory 2014).

Bevacizumab, a monoclonal antibody to the vascular endothelial growth factor (VEGF), emerged as a potential treatment for NF2 due to VEGF receptor expression in VS tissue (Plotkin 2009). Ten patients were subsequently treated with 5 mg per 5 kg of body weight for a median of 12 months, with concomitant tumour shrinkage in 9. Further studies to validate these findings in larger populations are ongoing. Questions remain surrounding the optimum length of treatment and long-term effects. Proteinuria and hypertension are known associations, but in most patients, toxicity appears to be relatively mild (Slusarz 2014). Additional barriers to continuous treatment are that bevacizumab is contraindicated during pregnancy and perisurgery, and emerging evidence suggests that other tumours occurring in NF2 are unlikely to show a similar response (Nunes 2013).

Given the almost inevitable hearing loss seen in NF2, and the high risk of dual sensory impairment due to visual loss,hearing preservation or rehabilitation is a significant component of clinical management. Pre-emptive measures include presymptomatic learning of sign language and lip reading in patients known to be at risk. Similarly, restoration of limited or primitive auditory sensory input from cochlear implants and auditory brainstem implants, respectively, can potentially improve quality of life.

5.2.2 Meningioma

Meningioma management in NF2 is similar to that of sporadic meningioma except that additional complications from concurrent tumours and comorbidities may limit surgical options and outcomes. Meningiomata in NF2 may follow a saltatory growth pattern (Dirks 2012), so clear evidence of active tumour growth, attributable symptoms and likelihood of good neurological outcome is needed before surgical intervention. Radiotherapy may be considered when surgery is not considered suitable, but there are limited data on outcomes.

5.3 Ongoing Research and Future Developments

Much focus in NF2 research is currently given to trials of experimental medical treatments in the light of increasing understanding of the molecular pathophysiology and the initial studies of anti-VEGF therapy. Further trials of bevacizumab therapy are ongoing. Initial reports of everolimus therapy in NF2 are disappointing

(Karajannis 2014) but other studies are ongoing. Other novel chemotherapeutic agents such as lapatinib and axitinib are in trial (Karajannis 2015). The importance of inclusion of quality of life measures in research outcomes must be stressed, due to the complex symptom profile, progressive nature and reduced life expectancy (Ferner 2014).

6 Summary

The majority of meningiomata and vestibular schwannomata that present as single lesions are likely sporadic occurrences that do not appear to have a familial basis. Multiple primary tumours in the same individual or a family history of such tumours are suggestive of a genetic susceptibility. NF2, familial meningioma and schwannomatosis are the only genetic conditions currently recognised with these phenotypes. Management of these conditions is complex, requiring multidisciplinary input. Genetic testing can be a helpful component of management, but diagnosis and management are mostly dependent on clinical considerations.

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