Current Concepts in Management of Vestibular Schwannomas in Neurofibromatosis Type 2

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Abstract Neurofibromatosis type 2 (NF2) is an autosomal dominant condition resulting in multiple benign intracranial and spinal tumours including bilateral vestibular schwannomas. The management of vestibular schwannomas in NF2 is particularly challenging, given the young presentation of many patients, the natural history of the disease that often leads to complete loss of hearing in both ears and the burden of other tumours. Specialists from multidisciplinary NF2 teams describe current concepts in the management of vestibular schwannomas in NF2.

Keywords Neurofibromatosis type 2 · Vestibular schwannoma · Multidisciplinary

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal-dominant inherited tumour predisposition syndrome caused by mutations in the *NF2* gene on chromosome 22 [1]. NF2 is estimated to occur in 1 in 35,000 live births [2], but disease prevalence is around 1 in 60,000 [3] people due to late recognition and reduced life expectancy. Affected individuals develop both intracranial and spinal schwannomas (benign nerve sheath tumours) typically involving both vestibular nerves. The natural history of this disease often leads to complete deafness, reported by patients as the greatest impediment to their quality of life [4, 5]. When compared with sporadic unilateral vestibular schwannomas (VS), VS in NF2 tend to demonstrate a more aggressive phenotype, presenting at a younger age with a more rapid growth rate. These tumour characteristics, in combination with the tumour burden from additional schwannomas

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often found in close proximity (trigeminal, facial and lower cranial nerves around the jugular foramen), and the potential for complete hearing loss make the management of VS in NF2 particularly challenging. A multidisciplinary NF2 team is required to manage these patients effectively. This includes neurologists, neurosurgeons, otolaryngologists, neuroradiologists, neuro-oncologists, audiologists, plastic surgeons, ophthalmologists and specialist nurses. Specialists from multidisciplinary NF2 teams in England describe current concepts in the management of VS in NF2.

Diagnosis

Genetics

50–60 % of patients with NF2 present as *de novo* mutations [6], with as many as 33 % of these mosaics for the underlying disease-causing mutation [7]. Mosaicism is due to the mutation not being present at conception but occurring in early embryogenesis, leading to two populations of cells, the majority with normal NF2 genes and a minority with an NF2 mutation that may not be detectable in blood lymphocytes [7]. This means that the usual transmission rate of 50 % can be substantially reduced if a mutation is not identified in blood [8•]. Mosaic patients often present with asymmetric disease and may present under 30 with an apparently sporadic vestibular schwannoma [9, 10]. Truncating mutations (nonsense, frameshift insertions or deletions) are the most frequent germline events and cause the most severe disease, whilst single and multiple exon deletions are common and are usually associated with milder NF2 [11]. Children presenting with NF2 usually have a severe genotype and typically do not present with symptoms due to vestibular schwannoma, but rather symptoms due to meningiomas, spinal or peripheral schwannomas and mononeuropathy [2].

Genetic Counselling

Genetic counselling is the process of facilitating adaptation to and understanding of the medical, psychological and familial implications of a genetic disorder. At the point of diagnosis with NF2, a three-generation pedigree is taken, to establish whether the condition is *de novo* or inherited, and to determine which family members may be at risk. Genetic concepts are explained, so the patient understands the implications for relatives before consenting for diagnostic genetic testing.

If a mutation is identified in an affected patient, predictive genetic testing can be offered to relatives. Informed decision-making is promoted by non-directive discussion

including family and reproductive issues, strategies for coping with an adverse result and implications for future employment and insurance. Current guidelines for predictive genetic testing in children recommend that this is only performed when results will affect clinical management during childhood [12], which applies in NF2 where screening begins around the age of 10. Ideally, testing is offered from around the age of eight, when the child is able to participate in the process. However, some parents may wish to know earlier, and this may be appropriate following discussion.

Consideration of reproductive options begins with an exploration of how a couple feel about having a child affected by NF2, and whether or not termination of pregnancy is acceptable to them. Some couples are accepting of the chance of their child inheriting NF2, particularly if the condition is relatively mild in their family. Some opt for prenatal diagnosis by invasive testing such as chorionic villus sampling. This can be done from approximately 12 weeks of pregnancy, with results usually available within a week. If the pregnancy is affected by NF2, then termination is offered. Others choose preimplantation genetic diagnosis, where testing occurs at the blastocyst stage and an unaffected embryo is implanted [13]. However, this is quite a lengthy procedure and current success rates are in the region of 30 % per cycle started and 50 % per embryo transferred.

Imaging

Cranial imaging in patients with NF2 or suspected NF2 is not only aimed at detecting and monitoring VS, but should also be optimised to detect other cranial nerve schwannomas, intra cranial meningiomas and orbital pathology such as optic nerve meningiomas and orbital schwannomas. The whole head should, therefore, be included in the imaging volume, and MRI is the imaging modality of choice.

Accurate assessment of tumour size is necessary to assess disease progression and response to treatment. The accuracy of both linear and volumetric measurements depends on the spatial resolution and contrast resolution of the images. High-spatial-resolution gadolinium-enhanced volumetric pulse sequences with isometric voxels that allow multi-planar reconstructions to be performed should be part of the standard imaging protocol in these patients.

Linear measurements should ideally be performed by the same radiologist on each occasion to ensure that the measurements are performed on comparable slices and encompassing the same parts of the tumour on each occasion.

Volumetric measurements are more sensitive to subtle changes in tumour size than linear measurements, but require dedicated software to aid identification of the

Fig. 1 Axial high-resolution fat-saturated T1-weighted MR image acquired after gadolinium administration. This patient is treated with bevacizumab treatment and has very large bilateral vestibular schwannomas and smaller bilateral trigeminal schwannomas. This image demonstrates the results of semi-automated segmentation of the right vestibular schwannoma (index tumour) for volumetric measurement. The *blue broken line* indicates a hand-drawn region within which the radiologist wants the segmentation tool to identify enhancing tumour. The *yellow line* represents the outer surface of the tumour as identified by the tool, while the *red line* indicates an area of necrosis identified within the tumour. The process of segmentation is automatically repeated on every slice where the tumour is present, and volumes are calculated for the entire tumour as well as for the necrotic component (Color figure online)

tumour outline (Fig. 1). This process is known as segmentation and can either be performed manually, or as an automated or semi-automated process, where the radiologist can edit the output of the segmentation tool.

Serial cranial imaging is performed annually in NF2 patients in England and three-monthly in those patients treated with bevacizumab. The presence of cochlear implants or auditory brain stem implants is no longer a contraindication to MRI, provided the manufacturer indicates that the device is MRI-conditional. A number of manufacturers now produce devices that can be scanned at 1.5 T following bandaging of the patient's head to prevent movement of the subcutaneously implanted magnet [14].

Treatment

Vestibular Schwannoma Surgery

Although the underlying surgical principles are the same for NF2 cases as they are for sporadic unilateral VS, there are a number of factors that make them considerably more challenging to manage. Not only is the patient population younger, but the dynamic nature of the disease over time requires the surgeon to be mindful of the functional consequences of tumour progression on either side after the surgical procedure. The long-term risk of bilateral loss of

cochlear, vestibular and facial nerve function, each of which carries a heavy burden for the patient, must be balanced against the potential for surgery to clear at least one side of disease whilst retaining useful hearing. An attempt at macroscopic tumour excision carries an increased risk of permanent neurodisability, and subtotal tumour excision may seem an appealing way of minimising morbidity in the short term, with the option of treatment with radiotherapy (or more recently, an angiogenesis inhibitor) for any disease progression in the remnant. However, failure of adjuvant therapy to control tumour growth is then likely to require revision surgery with a substantially higher risk of permanent nerve dysfunction than after a primary surgical procedure. Balancing all of these factors requires an experienced multidisciplinary team and a detailed patient counselling [15]. An advantage of undertaking such surgery in high-volume specialist centres is the possibility of offering brainstem implantation in suitable cases.

The primary determinants of the surgical approach in NF2 are the degree of residual hearing on the affected side, the lateral extent of the tumour and the likelihood of encountering multiple tumours. Lateral extension of VS into the cochlea is more common in NF2, and what appears to be a solitary tumour on imaging may transpire at surgery to comprise multiple tumours, including any combination of VS, facial schwannoma, meningioma and schwannomas of the adjacent cranial nerves. The presence of multiple tumours increases the risk of facial nerve injury because the nerve may no longer remain on the surface but instead becomes sandwiched between adjacent tumours. Neurophysiological monitoring should include the lower cranial nerves when operating on larger tumours.

In a patient with no serviceable hearing, we favour the translabyrinthine approach [16]. This provides a better prospect of clearing disease within the internal auditory canal and, in the case of multiple coalesced tumours or a grossly expanded internal auditory canal, provides an opportunity to identify the facial nerve lateral to the disease at an early stage. Even in a patient with no useful hearing, consideration should be given to cochlear nerve preservation, because some patients may benefit from cochlear implantation. The surgeon must at all times be mindful of balancing the goal of macroscopic tumour excision on the operated side with the risk of causing avoidable neurological injury.

Radiotherapy

There is considerable experience in the UK with single-fraction Gamma Knife stereotactic radiosurgery in the management of VS in NF2 [17]. To date, we have treated

over 190 of these tumours. It is an attractive management option, being essentially a day-case local anaesthetic treatment. In our most recent cohort, actuarial control rates (defined as freedom from salvage procedures) are 90 %, 8–10 years after treatment. This is achieved with very low facial nerve morbidity (one case of hemi-facial spasm in 71 tumours) and hearing preservation rates of 40–50 %. Whether hearing loss is due to the treatment or the natural disease process is impossible to say. Tumour volume is a major factor in determining the efficacy of the treatment, and in practice, we are reluctant to accept tumours larger than 10 cm³ [18].

Concern has been raised about the safety of using radiation in conditions with abnormal tumour suppressor genes, fearing that the radiation could induce malignancy. Using single-fraction treatments in NF2, the risks of this would appear to be low and justifies the continued use of this approach [19]. Importantly, the risks may be different for fractionated radiation treatments, although there is no comparable published experience to address this issue.

Molecular Therapeutics

Merlin is the protein product of the *NF2* tumour suppressor gene and is involved in multiple cell functions including cellular interaction and growth regulation pathways. The loss of merlin leads to uncontrolled cell growth and the characteristic tumours of NF2 including VS. Loss of the *NF2* gene has also been implicated in over 50 % of unilateral sporadic VS [6].

Numerous agents which target pathways in which merlin is involved have been trialled for the control of VS in NF2. The most successful of these has been bevacizumab, a monoclonal antibody to vascular endothelial growth factor [20].

A retrospective analysis of 31 consecutive NF2 patients treated with bevacizumab found that VS were stable or had decreased in size in 88 % of patients at 1 year and 54 % at 3 years [21••]. In addition, 90 % of patients had stable or improved hearing at 1 year and 61 % at 3 years. Two prospective trials of bevacizumab are expected to report in the coming years. Across the NF2 service in England, we have found similar results in our cohort of 60 patients treated with bevacizumab for rapidly growing schwannomas (Morris et al., unpublished data).

Epithelial growth factor receptor (EGFR) over-expression has also been observed in NF2 cellular assays. However, Erlotinib, a pure EGFR tyrosine kinase inhibitor [22], and Lapatinib, an ErbB2/EGFR inhibitor [23], have both failed to show significant beneficial tumour responses. A phase II study of the second-generation mTORC1 inhibitor, Everolimus was prematurely terminated due to a lack of volumetric response in the target VS [24].

Rehabilitation

Quality of Life Measures

Recent advances in therapy for neurofibromatosis 2 (NF2) have dictated the need for patient-reported quality of life measures to evaluate treatment, in addition to rigorous clinical, audiological and neuroradiological assessments.

Quality of life implies a state of physical, emotional, socio-economic and cultural well-being that is different for each individual and may vary with time. The NFTI-QOL (NF2 Impact on Quality of Life) was devised as a disease-specific quality of life questionnaire for adults with NF2, and is easy and rapid to complete. There are eight domains that cover balance and dizziness, hearing, facial weakness, sight, mobility and walking, role and outlook on life, pain, anxiety and depression. A free-response section allows patients to explain or amplify an answer. The maximum score is 24 and denotes the highest impact of NF2 on quality of life for an individual.

NFTI-QOL has been shown to be both reliable and capable of reflecting changes over time in 288 patients across four national NF2 centres in England [25]. It correlates strongly with generic questionnaires including SF-36 (short form 36) and Euroqol that do not focus on NF2 specifically. In the individual item scores, hearing, balance and role and outlook on life have the biggest impact on quality of life. NFTI-QOL can be used to aid individual management decisions in an NF2 clinic setting and early indications suggest that it is useful for evaluating response to bevacizumab therapy. The mean total NFTI-QOL scores decreased significantly 3 months after bevacizumab treatment in a small patient cohort Ferner et al., unpublished data). This suggests that treatment is beneficial, but larger studies are needed to confirm these findings. There is a moderate relationship between NFTI-QOL and clinical and genetic severity, underscoring the idea that NFTI-QOL probes other aspects of NF2 patient experience not covered by clinician or genetic-rated severity of disease.

Hearing

The management of NF2-related hearing loss requires a holistic approach drawing upon a team that can manage all forms of deafness. VS cause a complex mixture of neural and cochlear loss, so surprisingly, cochlear implantation can play a role in auditory rehabilitation [26]. Maintaining or rehabilitating hearing is individualised and is dictated by the presence of a VS, tumour size and growth rate as well as contralateral hearing thresholds. The degree of deafness is often unrelated to tumour size or indeed speed of tumour growth. Patients can present with a large VS in their better hearing ear or a growing VS in their only hearing ear.

Effective management of these dilemmas forms the basis of good patient care [15].

Hearing optimisation is required for all NF2 patients and an understanding of hearing disability is required to achieve this. The English NF2 Group published a hearing scale to guide clinicians when to consider intervention [27•]. Contralateral routing of sound (CROS) aids or cochlear implantation for single-sided deafness and hearing aid optimisation for moderate and severe hearing loss are simple yet effective tools to alleviate disability in a patient group that often accepts progressive deafness as inevitable.

It is desirable to create at least one stable hearing ear, so that management of the contralateral ear is not dominated by the need to maintain hearing. In the past, early surgical intervention by performing hearing preservation surgery on small VS seemed attractive [28] but has not delivered the expected hearing or tumour control results. Timing surgery to coincide with a profound loss offers the opportunity of auditory brainstem implantation; removing a growing small tumour offers the potential for maintaining cochlear nerve function, so that cochlear implantation can be considered. Subtotal tumour removal and subsequent radiotherapy if the residual tumour grows or indeed radiotherapy alone rarely delivers long-term hearing stability, but might again offer the possibility of cochlear implantation. New chemotherapeutic regimes have demonstrated promising early tumour control rates, and recent evidence suggests that hearing can be stabilised.

Balance

An area where NF2 has one of its most significant impacts upon quality of life is in the balance domain, with up to 64 % of individuals restricted in their ability to perform routine daily activities and a further 14 % unable to perform them at all [5]. A normal sense of balance and spatial orientation relies upon accurate visual, peripheral vestibular and proprioceptive inputs to the vestibular nuclei in the brainstem. The resultant vestibulo-ocular and vestibulo-spinal reflexes provide gaze stabilisation and the ability to adapt to any sudden changes in posture. The impact of unilateral VS upon peripheral vestibular function is recognised to be inevitable but variable [29]. The impact of bilateral VS in NF2 upon vestibular function is far greater. Despite this, the decline in peripheral vestibular function with smaller tumours is often gradual and can enable physiological compensation mechanisms to provide adequate balance in day-to-day activities; although, this does not hold true in more challenging vestibular environments, such as low-light or uneven ground. Sudden loss of vestibular function through disease progression or resulting from surgical management provides significant stability challenges. The compounding impact of any spinal or

peripheral nerve tumours, in addition to any visual impairment, must also be taken into consideration. Active vestibular rehabilitation can help to improve quality of life and subjective balance perception and is an essential component in the management of patients with NF2 [30]. Without active vestibular rehabilitation, it is recognised that there is a limited prospect for recovery of vestibular function independent of age or severity of vestibular hypofunction [31].

Facial Reanimation

Facial reanimation and rehabilitation can be especially challenging in NF2 for three reasons. Firstly, the bilateral nature of the condition means that the usual motor nerve to power any proposed microvascular muscle flap may not be available (or may be in jeopardy in the future). Secondly, the availability of other cranial nerves, particularly the trigeminal nerve that may otherwise serve as a donor of motor function may not be available. Thirdly, the size and volume of the tumour load, either intra-cranially or in the spinal cord, may deter the surgeon from considering any facial reanimation procedure that has a lengthy rehabilitation period.

Whilst bilateral facial nerve impairment makes dynamic reanimation more challenging, complete loss of the oral sphincter is particularly disabling from the point-of-view of oral continence, speech and dental care. The threat to the eyes should be managed promptly with lid loading and support from the lower eyelid in the form of a lateral canthopexy or tarsorrhaphy. If there is minimal risk of impairment of the trigeminal nerve, then a temporalis myoplasty may be performed to improve both static and dynamic symmetry. If the trigeminal nerve is involved, a static sling is the next best option as it is relatively quick to perform and has a low morbidity.

The use the hypoglossal nerve for hypoglossal–facial anastomosis needs to be carefully considered in light of the risk of future swallowing problems due to lower cranial nerve tumours that might be affected by any loss of tongue function. An end-to-side neurotomy is preferable in order to minimise these risks. Vakharia and colleagues [32] have recently described a small series of NF2 patients who underwent microvascular reanimation with a gracilis flap coapted to the masseteric nerve and conclude that this option is suitable for selected patients. Other treatments that may be of benefit include botulinum toxin to treat synkinesis in those with incomplete nerve lesions.

Psychology

The role of clinical psychology within the NF2 service is primarily one of promoting psychological well-being. This

includes supporting individuals experiencing psychological distress, offering mental health assessments and liaising with other agencies. Many patients are met at an early stage following diagnosis in order to introduce the role of psychology and to inform them about the service. Referrals to psychology commonly include requests for help with difficulties adjusting to diagnosis, preparation for medical procedures, emotional distress (including anxiety and depression) and difficulties coping with symptoms.

NF2 can result in problems communicating within families and loss of confidence in accessing social activity. A patient who has experienced changes to their hearing and balance may find it difficult to socialise in large groups due to problems following conversations and feeling unsteady in crowded spaces. Patients who experience changes to their physical appearance as a result of facial palsy may struggle with issues around self image and confidence. This can lead to increased anxiety, social withdrawal and in some cases low mood, which in turn affect family relationships and ability to access support [33–35]. Adjustment of the wider family system can also be a cause for concern [36], which may lead to a reduction in perceived social support for the patient and thus reduced psychosocial adjustment [37].

Psychological support can offer the opportunity for patients to talk about their feelings in situations which cause them concern or distress, allowing for their experiences to be acknowledged and normalised [38], and to consider realistic goals for rebuilding confidence and activity levels. Psychology input can also be useful in promoting and supporting communication within family systems, or in supporting carers. A recurring challenge in NF2 is the management of chronic pain and disability, and the ongoing uncertainty in respect of prognosis; psychological interventions can explore these issues, increasing tolerance for uncertainty and developing stress management and coping strategies.

Nursing

Specialist nurses play a core role in the diagnosis and ongoing management and rehabilitation of patients with NF2 as part of the multidisciplinary team to provide high-quality, patient-centred, cost-effective care. The specialist nurse provides a coordinated and individualised approach for each patient across both acute and community services, providing support from pre-diagnosis to palliative care.

The specialist nurse is able to provide direct patient benefit by playing a lead role in patient education and support, and by undertaking interventions that improve health status and quality of life. An NF2 diagnosis can have a devastating effect on the patient's quality of life, with

implications for themselves, their carers and their families, and the nurse can provide personalised expert advice and care and a point of contact during this period where the patient may feel overwhelmed. Provision of education improves compliance with multiple consultations and management strategies that may be required. The specialist nurse is able to offer generic health and well-being advice, as well as recognising and appropriately referring patients for rehabilitation that may help in the home and work environments. These include hearing aid provision, balance rehabilitation and assistance with disability benefits such as access to work schemes and personal independence payments. These interventions aim to reduce the financial and psychosocial implications of a diagnosis of NF2, and to maximise patient independence with minimal stress and anxiety. In addition to direct patient benefits, the specialist nurse can benefit the service by reducing waiting times through early triage and follow-up, prevent hospital admissions and re-admissions through the provision of community care, provide nurse-led clinical appointments and provide education about the disease to other health care professionals [39].

Future Developments and Conclusions

The management of VS in NF2 has changed dramatically over the past few years due to the use of bevacizumab to treat growing VS, with encouraging data in terms of tumour growth and hearing stabilisation [21••]. As experience grows, the longer-term toxicity and rates of tumour and hearing stability will become clear [40]. Undoubtedly, the main advances in the future are likely to result from further development of molecular therapeutics. However, the main factor important in maintaining high-quality care for these patients will remain the presence of a multidisciplinary NF2 team that is able to take a holistic view on patient care in order to identify and rehabilitate all issues caused by this disease to maintain quality of life.

Compliance with Ethics Guidelines

Conflict of Interest James R. Tysome, Richard Mannion, Juliette Durie-Gair, D. Gareth Evans, Rosalie E. Ferner, Robert Macfarlane, Charles Nduka, Pieter M. Pretorius, Gabriella Rands, Amy Taylor, Neil P. Donnelly, Patrick R. Axon, Jeremy Rowe and Katrina Morris declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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- Of major importance

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