Clinicopathologic Assay of 15 Tumor Resections in a Family with Neurofibromatosis Type 2

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Abstract

Keywords

- neurofibromatosis type 2
- NF2 associated tumors
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- meningioma
- quality of life
- ethics

The objective of this study is the management of multiple family members with multiple neurofibromatosis type 2 (NF2) related tumors of the skull base that can be challenging, on purely technical, decision-making, and ethical levels. These issues are addressed in this manuscript based on an experience treating an unique large family with NF2. A retrospective chart review was performed, reviewing clinical, radiological, surgical, and pathological data. A unique family of 17 siblings, whose father was the proband as a sporadic mutation is reported. Over a 4-month period, five of eight affected siblings underwent 12 procedures for resection of 15 different NF2-related tumors. This single family experience of NF2-related skull base tumors underscores the importance of preservation of function and quality of life as the major determinants of treatment success.

Neurofibromatosis type 2 (NF2) is an autosomal-dominant syndrome caused by mutation of the NF2 suppressor gene on chromosome 22.¹ NF2 affects 1 in 33,000 to 40,000 people,² with ~50 to 60% of cases representing sporadic de novo mutation, and those patients have no family history of NF2.³ The hallmark of the disease is the development of bilateral vestibular schwannomas. In addition, affected individuals with NF2 frequently develop schwannomas at other locations, meningiomas, and ependymomas.^{3–6} The tumors are benign and slow growing, however, their location often within the central nervous system can have neurological effects resulting in significant morbidity and mortality. Posterior subcapsular lens opacities that rarely progress to a visually significant cataract are the most common ocular findings and may be the first sign of NF2.⁷ Mononeuropathy that occurs in childhood is an increasingly recognized finding.⁸

In many instances, the intracranial tumor burden of individual patients can be substantial with associated limitations

in functional status and quality of life. Surgical management is aimed at preservation of function to maintain long-term quality of life. The management of patients with giant skull base tumors and/or relatively advanced neurological impairment raises several ethical issues relevant to the treating neurosurgeon. Over a 4-month period, a large family with advanced NF2 was evaluated and treated at Harborview Medical Center in Seattle, Washington. We describe the operative and nonoperative cases with a review of the pathology encountered and functional outcomes, then review the ethical issues surrounding the treatment of families with NF2.

Methods

We retrospectively reviewed the hospital charts of six members of a family affected with NF2, including clinical and operative reports, radiology, and neuropathology findings. Follow-up data, including functional outcome, was conducted

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Figure 1 Genetic pedigree of the large neurofibromatosis type 2 (NF2) family treated at our institution. The proband (arrowhead) developed sporadic onset of NF2. Of 17 children (age in years indicated in figure), there were 8 affected (red) and 6 unaffected children (white). Three younger siblings have not been formally evaluated but clinically appear to have the phenotype (question mark).

via a telephone to family members as well as recent assessments in person if a recent clinics follow-up was conducted. The family history of NF2 was obtained and pedigree constructed in compliance with published reporting guidelines.⁹ Institutional Review Board approval was obtained for the review and publication, and permission was also obtained from the affected siblings.

Results

A pedigree of this affected family is presented in ► **Fig. 1**. The father was the suspected proband died at the age of 47 years from pneumonia secondary to intracranial tumor burden and associated mental status decline. He had seventeen children aged 7 to 26 years, and once the first affect child was identified, a diagnosis of NF2 was made. In total, eight children were identified having the clinical phenotype. In three patients, the clinical phenotype was suspicious for NF2, but the patients were not yet screened radiologically due to young age. Six children thus far were referred for evaluation by the senior author (LNS), and two other siblings known to have tumors related to NF2 are pending clinical evaluation. Of these, five patients with multiple large and symptomatic-NF2 related tumors underwent 12 procedures for resection of 15 different neoplasms at our institution. These interventions are summarized in ► **Table 1**. One patient (Patient 2) was not recommended to have any treatment given the extent of tumor burden and preoperative functional impairment. All affected children referred to our institution were noted to have an advanced intracranial tumor burden, which was due to the poor outcome of the first sibling who had been treated initially at an outside institution. As such, the other siblings were initially not referred for any treatment until their symptoms were advanced, and only after Patient 1 was referred to and treated at our institution did the other affected siblings seek surgical treatment.

Patient 1

A 24-year-old man had previously undergone resection of a parasagittal meningioma in 2010 and subtotal resection of a left vestibular schwannoma in 2005. He was presented with progressive left facial weakness, followed by a rapid decline in mobility with increased somnolence and dysphagia and difficulty managing secretions, having choked on his food on two occasions in the week prior to presentation to the emergency department. Physical examination was significant for obtundation with eye opening to painful stimuli, grade 4 facial weakness on the left, and grade 2 function on the right, no hearing on the left side and moderate function on the right, diminished vocal cord movement bilaterally on direct laryngoscopy, and a right hemiparesis. CT showed ventriculomegaly. There was an improvement in mental status with spontaneous eye opening and following commands after an urgent ventriculostomy was placed. An MRI scan demonstrated giant tumors, suggestive of vestibular schwannomas bilaterally as well as kissing large cavernous sinus and petroclival tumor suggestive of meningioma (→ **Fig. 2A**). He had, additionally, multiple smaller convexity tumors suggestive of meningiomas. As the patient still had partial hearing on the right side and no hearing on the left, a planned staged subtotal debulking of the right petroclival and cerebellopontine angle tumors was planned to decompress the brainstem but preserve useful hearing, followed by maximal resection of the giant left vestibular tumor. He underwent a right subtemporal anterior transpetrosal approach with debulking of the cavernous sinus and petroclival mass. The tentorium was incised and the tumor in the petrous apex was debulked, without complications. Neuropathological examination confirmed meningioma, World Health Organization (WHO) grade 1 (→ **Fig. 3A**). Histopathology revealed cerebral cortex with glial microhamartomas characterized by multiple clusters of cells with medium-to-large atypical nuclei and eosinophilic cytoplasm immunopositive for S-100 protein

Table 1 Summary of All Interventions, in Patients Affected with NF2

Patient No.	Neurosurgical Procedure	Extent of Resection	Neuropathology	Complications
1	Right orbitozygomatic approach; resection of petroclival meningioma	Subtotal	Meningioma ^a Glial microhamartomas	None
	Left retrosigmoid and posterior transpetrosal approach; resection of giant acoustic neuroma	Subtotal	Schwannoma ^a	None
	Left posterior transpetrosal approach; resection of residual petroclival meningioma	Complete	Meningioma ^a	None
2	Right frontoparietal craniotomy; resection of giant parasagittal meningioma with superior sagittal sinus reconstruction	Complete	Meningioma ^b	None
	Midline suboccipital approach; resection of C1-C2 and spinomedullary junction intramedullary tumors	Complete	Ependymoma ^b × 2	None
	T2-T3 laminectomy and removal of large intramedullary tumor	Complete	Ependymoma ^b	Paraparesis
4	Stage 1 left extreme lateral and posterior petrosectomy approach, extradural tumor removal	Subtotal	Meningioma ^a	None
	Stage 2 left presigmoid resection of giant clival and jugular foramen meningioma	Subtotal	Meningioma ^a	None
5	Stage 1 retrosigmoid, far lateral and upper cervical exposure; removal of parapharyngeal tumor	Subtotal	Meningioma ^a	None
	Stage 2 far lateral re-exploration and removal of intradural component of tumor	Subtotal	Meningioma ^a	Delayed facial weakness, partial
	Right upper lid incision and excision of intraorbital tumor	Complete	Meningioma ^a	None
6	Right frontal craniotomy, transcortical approach and resection of giant intraventricular tumor and small convexity dural based mass	Complete	Meningioma [*] × 2	None

^aWHO grade 1.^bWHO grade 2.

NF2, neurofibromatosis type 2.

(→Fig. 3B), and immunonegative for glial fibrillary acidic protein. He subsequently had placement of a ventriculoperitoneal shunt and planned tracheostomy. Since his neurological condition did not improve, he underwent a left retrosigmoid craniotomy and subtotal resection of the giant acoustic tumor. Histopathology confirmed a schwannoma and an atypical meningioma (WHO grade 2) with increased mitotic activity, areas of small cells, and sheeting. Over the ensuing week, he became increasingly somnolent despite stable ventricular size and radiologic improvement in the degree of brainstem compression. Given the residual com-

pression by the left tentorial notch mass on the upper brainstem, we elected to proceed with complete resection of the residual apical tumor via a posterior petrosectomy approach. The tumor was removed completely (→Fig. 2B), and neuropathology revealed schwannoma (→Fig. 3C). He subsequently had progressive improvement in mental status and motor function. By 2 weeks postoperatively, he was alert, with partial hearing on the right, and communicating verbally despite hoarseness and ataxic speech. He had 3 to 4/5 strength in all extremities. He had placement of a percutaneous feeding tube, and was transferred to a rehabilitation

Figure 2 (A) Axial T1 magnetic resonance imaging with contrast of Patient 1 demonstrating giant right cavernous and petroclival tumor, and bilateral giant acoustic tumors with severe mid and upper brainstem compression. (B) Postoperative imaging after a right frontotemporal anterior transpetrosal debulking of the petroclival meningioma, and staged left retrosigmoid and posterior petrosectomy approaches and removal of the left acoustic neuroma. Note the brainstem has been decompressed. This patient had unilateral hearing on the right side only preoperatively, and this was preserved.

facility. By 6 weeks, he was beginning to ambulate with assistance and tolerating a full oral diet.

Patient 2

This 23-year-old man suffered a generalized seizure in the hospital while visiting his brother mentioned above. An MRI demonstrated a giant right parasagittal tumor (►Fig. 4A). He additionally had a holocord cervical syrinx and two enhancing lesions at the cervicomedullary junction and another larger lesion occupying the T2 to T3 spinal cord (►Fig. 4B) and bilateral vestibular schwannomas. Physical examination was notable for clear signs of myelopathy, including decreased dexterity, apraxic gait, and increased deep tendon reflexes. He was placed on antiepileptic medication. Subse-

quently, he underwent a right bifrontal and parasagittal craniotomy with near total removal of the giant parasagittal tumor (►Fig. 4C). The tumor was invading the superior sagittal sinus, and it was removed from the sinus which was then reconstructed primarily with 6–0 Prolene sutures (Ethicon, Somerville, NJ). Histopathology revealed atypical meningioma (WHO grade 2) characterized by numerous hypercellular clusters of neoplastic cells showing small cell change, loss of secondary architecture, and increased mitotic activity. The patient did very well postoperatively and was discharged home after 7 days. Given the extensive holocord syrinx and associated myelopathy, a recommendation was made to remove the known cervicomedullary and thoracic tumors. As such, 6 weeks after his initial surgery, the patient

Figure 3 Pathohistological findings in patients in our series affected with neurofibromatosis type 2. (A) Meningioma (World Health Organization [WHO] grade 1) in Patient 1 showing a meningeothelial cell neoplasm composed of cells forming a syncytium due to ill-defined cytoplasmic borders, and arranged in whorls (arrow) and nests interspersed with variably coarse collagen. Dystrophic calcification is identified (the asterisk indicates sectioning artifact). (B) Glial microhamartomas in Patient 1 revealing circumscribed clusters of S-100 protein immunopositive cells with medium-to-large atypical nuclei and scant cytoplasm (arrows). (C) Schwannoma (WHO grade 1) diagnosed in Patient 1 showing interdigitating fascicles of spindle cells with variably hyperchromatic elongate nuclei. Vague areas of nuclear palisading surrounding acellular eosinophilic tissue (so-called Verocay bodies, arrowheads) and scattered areas of paucicellular myxomatous background are identified (arrow). (D) Ependymoma (WHO grade 2) in Patient 2 demonstrating perivascular pseudorosettes consist of neoplastic cells arranged radially around the hyalinized vessels with perivascular anuclear zones of fibrillary processes (arrow) H&E stain in A, C, and D; Magnification A - 40x; B, C, D - 20x.

underwent a midline suboccipital craniotomy, C1 laminectomy, and removal of two tumors at the C1-C2 and cervicomedullary junction, also without complication (►Fig. 4D). Neuropathological examination confirmed two ependymomas, WHO grade 2. One month later, the patient underwent a third procedure, consisting of a T2 to T3 laminectomy for removal of the larger thoracic spinal cord tumor and histopathology also confirmed ependymoma, WHO grade 2 (►Figs. 3D and 4D). Intraoperatively, motor-evoked potentials of both legs deteriorated, during dissection of a poor surgical plane between the tumor and the dorsal spinal cord. Following surgery, he was found to have new onset left worse than right leg weakness, with only partial recovery at the time of transfer to rehabilitation, ~2 weeks postoperatively. At 6 weeks, he is partially ambulatory with good control of bowel and bladder function.

Patient 3

This is a 26-year-old man referred for possible surgery. He had a giant left petroclival mass with severe brainstem compression and distortion of the fourth ventricle (►Fig. 5). A partial

resection of the tumor had been done in another hospital. In addition, he had bilateral large cavernous sinus tumors, neuroradiologically suspected to be meningiomas. As per the telephone discussion, the patient had decreased vision and no hearing. He was wheelchair bound, but could achieve transfers independently. Bowel and bladder control were intact. He had both a tracheostomy and a percutaneous gastrostomy, with a tolerance for soft diet only. Cognition was intact. In light of the advanced neurological deterioration experienced by the patient prior to evaluation, and the extensive nature of the petroclival tumor, a decision not to proceed with surgery was made. He is currently in assisted living with 24-hour support.

Patient 4

A 13-year-old male sibling was referred with grade 3 right-sided facial weakness as well as worsening obstructive sleep apnea and mildly decreased right-sided hearing. Laryngoscopy demonstrated almost no true vocal cord mobility preoperatively. CT and MRI demonstrated an extensive left-sided tumor extending from the foramen magnum and jugular

Figure 4 (A) Axial (left) and coronal (right) T1-weighted magnetic resonance imaging with contrast of Patient 2 revealed a giant right parasagittal mass with invasion into the superior sagittal sinus. Additionally, the patient had a large T2-T3 enhancing mass (B) and two smaller enhancing lesions at the cervicomedullary junction associated with a holocord syrinx. The patient initially underwent complete resection of the parasagittal tumor with primary reconstruction of the sinus with 6-0 Prolene suture (C). Following this the patient did very well, and he subsequently underwent a suboccipital craniectomy and C1 laminectomy with uncomplicated removal of the cervicomedullary lesions (D left). As a third stage, the patient had a T2-T3 laminectomy and removal of the thoracic tumor (D right). He developed paraparesis following this with partial recovery thus far.

Figure 4 (Continued)

foramen to the clivus, with associated hyperostosis of the cranial base (►Fig. 6A). The patient underwent a planned two-stage resection of the left foramen magnum and jugular foramen tumor. In the first stage, a left extreme lateral partial transcondylar exposure as well as a posterior petrosectomy was completed. He returned to the operating room 3 days later for a subtotal tumor resection for the goals of brainstem decompression and hearing preservation (►Fig. 6B). Histopathology confirmed a meningioma (WHO grade 1). There were no complications, and the patient remained at baseline postoperatively and slowly improved. He has fully ambulatory and his hearing and grade 3 facial weakness remained unchanged. A flexible laryngoscopy 1 week postoperatively demonstrated new small amount of vocal cord adduction, and he tolerated a full oral diet. He was discharged home 18 days from initial admission. His postoperative MRI demonstrated decrease in the extent of lower brainstem effacement, with

residual tumor at the level of the internal auditory canal. He is awaiting further surgery for resection of a right-sided large right middle fossa meningioma (not shown).

Patient 5

This 14-year-old boy was evaluated for multiple large intracranial and parapharyngeal tumors. He additionally had developed severe proptosis with blindness in the right eye, and evidence of exposure keratopathy. He had complete palsies of the right IX and X cranial nerves, moderate right hypoglossal palsy, no hearing on the right side, and mild right-sided facial weakness. An MRI demonstrated a giant right cervical parapharyngeal tumor encasing the internal and external carotid arteries, a right retro-orbital tumor, and an extensive right posterior fossa tumor extending from the foramen magnum and jugular foramen to the tentorium (►Fig. 7A). A tracheostomy was performed preoperatively

Figure 5 (A, B) Axial T1-weighted magnetic resonance imaging (MRI) with contrast of Patient 3 demonstrating extensive left petroclival mass as well as and bilateral cavernous sinus tumors. The entire brainstem demonstrated severe compression. In light of the patient's poor presenting neurological condition, and degree of brainstem compression on the MRI, conservative management was recommended.

and subsequently, a staged resection was performed. The first stage was a right-sided temporal and retrosigmoid craniotomy with a far lateral exposure and unroofing of the vertebral artery. The cervical parapharyngeal tumor was then resected and the pathological examination of the tumor confirmed meningioma (WHO grade 1) invading fibroadipose tissue, skeletal muscles, peripheral nerves, and ganglia. As a second stage, the patient underwent re-exploration of the far lateral and retrosigmoid exposure and underwent a ~70% debulking of the posterior fossa tumor with preservation of the facial nerve (→Fig. 7B). Postoperatively the patient did very well. His third procedure was a right upper lid incision and removal of the intraorbital tumor. Neuropathology examination also confirmed a meningioma, WHO grade 1 with identical morphological features as the previously diagnosed neoplasm.

The tracheostomy was decannulated 1 week postoperatively, and oral feeding was resumed. Facial nerve function was initially intact but he subsequently developed delayed right-sided facial weakness 5 days postoperatively, which is currently recovering. His speech remained hoarse. He was otherwise fully ambulatory with complete motor function and fine finger control. He was discharged home 5 weeks after admission.

Patient 6

This is a 20-year-old male who experienced progressive left-sided weakness and hoarseness of his voice. He had previous excision of a cervical spine tumor at age 10, and strabismus surgery in childhood. At age 17, he had excision of a lumbar spine tumor at another institution. He had reasonable

Figure 6 (A) Axial and coronal magnetic resonance imaging (MRI) with contrast and noncontrast computed tomography bone algorithm of Patient 4 demonstrating large left foramen magnum and jugular foramen tumor with skull base hyperostosis and severe lower brainstem compression. The patient underwent a two-stage left posterior petrosectomy and far lateral approach with subtotal resection of the tumor, without complications. (B) Postoperative MRI demonstrating satisfactory decompression of the brainstem.

swallowing function on history, however, direct laryngoscopy demonstrated immobility in abduction of his vocal cords with absent glottal closure. On examination, he was alert, but generally slow to follow commands and respond to questioning, and a 4/5 left arm and leg weakness. An MRI of his brain demonstrated a giant right intraventricular mass measuring 7×9 cm, involving the deep venous system and causing marked compression and edema within the right cerebral hemisphere (►Fig. 8A). In addition, he had large bilateral acoustic lesions, where the right one in particular was causing substantial brainstem effacement. He underwent a cerebral angiogram with successful embolization of the posterior choroidal arterial supply to the intraventricular tumor (►Fig. 8B, C), and subsequently underwent a right frontal craniotomy with a transcortical corridor established after removal of a small convexity tumor, morphologically confirmed as a meningioma (WHO, grade 1). The intraventricular

tumor was removed in near total fashion (►Fig. 8D), and the neuropathologic examination revealed another meningioma (WHO grade 1). In the postoperative period, he was successfully extubated with improved strength on his left side, intact memory, and was beginning to ambulate with assistance. He is slated to undergo a right retrosigmoid craniotomy with removal of the larger vestibular schwannoma in 3 to 4 months' time.

Discussion

We report a unique large family with 8 of 17 offspring affected with NF2, of which 6 were referred for neurosurgical evaluation. Five siblings presented above underwent surgical treatments due to multiple schwannomas (WHO grade 1), meningiomas (WHO grade 1 and 2, respectively), and ependymomas (WHO grade 2; ►Table 1). In addition, intracortical

Figure 7 (A) Axial and coronal T1-weighted magnetic resonance imaging (MRI) with contrast of Patient 5 demonstrating extensive right petroclival and foramen magnum tumor, associated with a giant right parapharyngeal mass. The patient additionally had a right intraorbital tumor mass with proptosis and blindness. The patient underwent placement of a tracheostomy, followed by a staged right retrosigmoid and far lateral exposure, resection of the parapharyngeal tumor, and debulking of the posterior fossa tumor. The pathology for both lesions was meningioma. He later underwent removal of the intraorbital tumor. Final MRI appearance is shown in B.

glial hamartias were found in one of the reported patients. Although phenotypes within the members of the family are broadly similar, there was a marked variation between the members of the family. Meningiomas were the most commonly diagnosed neoplasm in our patients. Intracranial meningiomas are found in 50% of the patients with NF2,² and it is well known that some people who present only with meningiomas develop classical NF2.¹⁰

NF2 is the only gene known to be associated with NF2. It was identified through family linkage and tumor testing.^{4,5} The protein, *merlin* or *schwannomim*, is involved in the interaction between actin within the cell cytoskeleton and the cell membrane and appears to suppress tumorigenesis through contact-mediated growth inhibition.¹¹ The majority of the mutations on NF2 gene are truncating mutations (nonsense, frameshift insertions/deletions), leading to a smaller and probably nonfunctional protein product, while single and multiple exon deletions are common and are usually associated with milder NF2.^{12–14} About 25 to 30% of NF2 patients have a mosaic form of the disease, in which only a proportion of cells contain the mutated NF2 gene. As a result, the clinical phenotype tends to be milder. However, if

an offspring has inherited the mutation, they will have a typical phenotype and usually be more severely affected than their parent since the mutation is present in all of their cells.¹¹ Genetic testing had not been obtained in our affected family as affected siblings satisfied the NF2 diagnostic criteria. NF2 diagnostic criteria include the United States National Institute of Health (NIH) criteria, and the Manchester Clinical Diagnostic Criteria for NF2.^{8,15–19} The Manchester criteria include patients with neither a family history of NF2 nor bilateral vestibular schwannomas but who have multiple schwannomas or meningiomas because such tumors are known to occur in NF2 patients long before the appearance of vestibular schwannomas.²⁰ Patients are at increased likelihood of having NF2 if they have an affected parent or first-degree relative, have a meningioma or schwannoma diagnosed before the age of 30 years, have multiple spinal schwannomas or meningiomas, or cutaneous schwannomas.

Patients typically present in the late teens and early twenties but can also develop the clinical phenotype in middle age. The single most important predictor of clinical disease severity is the age at onset of symptoms, such that

Figure 8 (A) Axial and coronal T1-weighted magnetic resonance imaging with contrast of Patient 6 demonstrating a giant right intraventricular tumor, with partial encasement of the deep cerebral veins. Additionally, there is a large right acoustic tumor. Preoperative angiography demonstrated marked tumor blood supply via the posterior choroidal artery (B), which was successfully embolized (C). Shortly after, the patient underwent a right frontal transcortical approach and complete removal of the intraventricular tumor, without complication (D). A small noncontiguous tumor is seen in the left lateral ventricle.

symptoms occurring after the age of 25 years are associated with a favorable long-term survival.^{21,22}

There are several management considerations regarding the management of a family with NF2. Screening in children of affected parents from birth is indicated given the 50% probability of inheriting the clinical phenotype. Cataracts or

other ocular abnormalities can affect vision in early life, and other tumors such as meningiomas can occur in the first 10 years of life. Annual ophthalmological screening, neurological examination, and inspection of the skin should be done from infancy. The age of onset of symptoms in NF2 is ~18 to 24 years, with a range of 2 to 70 years.⁷ An initial

Figure 8 (Continued)

screening MRI of the brain should be performed 10 to 12 years of age or earlier in severely affected families. An MRI should be repeated every 2 years for patients less than 20 years old, after which the interval is extended to every 3 for asymptomatic patients. For symptomatic patients with established tumors, MRI is done yearly and/or in accordance to the tumor growth rate or clinical symptomatology. A spinal MRI is recommended every 3 years in at-risk individuals.²⁰ Genetic testing is necessary for all newly diagnosed individuals. For people who were not faced with the NF2 before their parents, it is sometimes difficult to undergo genetic testing of their infants and young children and some of them decide to make that decision later in children life until they will be grown up to understand.²⁰

Managing an entire family with NF2 can evoke significant psychological distress, as the degree of functional impairment from tumor burden can vary across family members. Patients may face rejection from their friends, suffer loss of self-esteem as well as loss of control in their lives, and parents may feel guilty. It mobilizes the whole family in their interactions, social, and financial resources. Crisci²³ analyzed a family with 7 children whose mother died in the age of 37 as

a consequence of NF2-related tumors. Five of the affected children died from disease-related causes. The youngest child, aged 22 years, was unaffected. The remaining child has yet to develop signs of NF2, however suffers from psychological distress while he “waits his turn.” One of the sisters suffered abandonment from her husband when she became ataxic at age 26 and, following neurosurgical intervention for her NF2-related tumor, she became bedridden, blind, deaf, and severely paralyzed. After discussion with involved family members in our case series, it is clear that they were grateful and pleased with their management and they would alter nothing with regards to our recommendations and management.

Although many NF2-related intracranial tumors can be followed conservatively until significant growth or the development of symptoms occur, there has been a general trend of more aggressive management of NF2-related vestibular schwannomas.^{24–26} Brackmann et al reported a 70% hearing preservation rate in 28 patients undergoing 40 middle fossa approaches for tumors ranging in size between 0.5 and 3.2 cm.²⁴ This hearing preservation rate is substantially better than a typical watch and wait approach classically adhered to

for these tumors. Furthermore, cochlear and auditory brainstem implants have contributed to hearing rehabilitation in patients with established sensorineural hearing loss.²⁵

In this particular family, affected children were referred with a substantial intracranial tumor burden and advanced symptoms. In patients with severe intracranial tumor burden from NF2, neurosurgeons must examine from the outset whether surgery is indicated and, if so, what are ethically sound goals of management. The factors which influence whether or not surgical intervention is futile in such cases can sometimes be difficult to interpret objectively. Our reported Patient 3 had prolonged impairment of bulbar function secondary to severe tumor-related compression of the brainstem. It was, therefore, agreed between the surgeon, patient, and his family that surgical resection would not be indicated based on qualitative futility, that is intervention would prolong and potentially contribute to a prolongation of unacceptable quality of life.²⁷ Furthermore, the physician's view that surgery in this patient would not achieve benefit, that is act in the best interest of the patient, was in line with the patient's autonomy and right to decline treatment after extensive discussion and education regarding the nature of his current condition and the expected outcomes with surgery.²⁸

For the remaining family members discussed above who underwent surgery, the treatment objectives were preservation of function and improvement if possible. Of 12 procedures, preservation in relevant neurological function occurred in 10 cases. This was the result of planned subtotal resection in several cases, particular for the operated acoustic neuromas. Several patients described above presented with giant petroclival tumors, often meningiomas with kissing acoustic neuromas, associated with severe brainstem compression and preoperative bulbar and lower cranial neuropathy. Unlike sporadic petroclival meningiomas, where in most cases the surgical goal is complete resection,²⁹ safely decompressing the brainstem while preserving both the lower cranial nerves and, when still functioning, the vestibulocochlear nerve within the acoustic neuroma, was accomplished by planned subtotal debulking of the acoustic neuroma and maximal safe resection of the associated meningioma.

Conclusion

The management of multiple family members with NF2-related skull base tumors is reviewed. The ethical issues regarding withholding surgical treatment in cases of overwhelming intracranial tumor burden are reviewed. For suitable candidates, the goals of surgical resection are primarily preservation of relevant neurological function and maintenance of quality of life.

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References

- 1 Baser ME; Contributors to the International NF2 Mutation Database. The distribution of constitutional and somatic mutations in the neurofibromatosis 2 gene. *Hum Mutat* 2006;27(4):297–306
- 2 Evans DG, Huson SM, Donnai D, et al. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. *J Med Genet* 1992;29(12):841–846
- 3 Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet* 1994;52(4):450–461
- 4 Trofatter JA, MacCollin MM, Rutter JL, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 1993;75(4):826
- 5 Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature* 1993;363(6429):515–521
- 6 Mautner VF, Lindenau M, Baser ME, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. *Neurosurgery* 1996;38(5):880–885, discussion 885–886
- 7 Evans DG, Huson SM, Donnai D, et al. A clinical study of type 2 neurofibromatosis. *Q J Med* 1992;84(304):603–618
- 8 Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child* 1999;81(6):496–499
- 9 Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2008;17(5):424–433
- 10 Evans DG, Watson C, King A, Wallace AJ, Baser ME. Multiple meningiomas: differential involvement of the NF2 gene in children and adults. *J Med Genet* 2005;42(1):45–48
- 11 Evans GR, Lloyd SK, Ramsden RT. Neurofibromatosis type 2. *Adv Otorhinolaryngol* 2011;70:91–98
- 12 Evans DG, Trueman L, Wallace A, Collins S, Strachan T. Genotype/phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease associated with truncating mutations. *J Med Genet* 1998;35(6):450–455
- 13 Parry DM, MacCollin MM, Kaiser-Kupfer MI, et al. Germ-line mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. *Am J Hum Genet* 1996;59(3):529–539
- 14 Baser ME, Kuramoto L, Woods R, et al. The location of constitutional neurofibromatosis 2 (NF2) splice site mutations is associated with the severity of NF2. *J Med Genet* 2005;42(7):540–546
- 15 National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference statement. *Arch Neurol* 1988;45(5):575–578
- 16 The Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement on Acoustic Neuroma, December 11–13, 1991. *Arch Neurol* 1994;51(2):201–207
- 17 Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM. Neurofibromatosis 2 in the pediatric age group. *Neurosurgery* 1993;33(1):92–96
- 18 MacCollin M, Mautner VF. The diagnosis and management of neurofibromatosis 2 in childhood. *Semin Pediatr Neurol* 1998;5(4):243–252
- 19 Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. *J Child Neurol* 2003;18(10):718–724
- 20 Evans DG, Baser ME, O'Reilly B, et al. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *Br J Neurosurg* 2005;19(1):5–12
- 21 Otsuka G, Saito K, Nagatani T, Yoshida J. Age at symptom onset and long-term survival in patients with neurofibromatosis Type 2. *J Neurosurg* 2003;99(3):480–483

- 22 Baser ME, Friedman JM, Aeschliman D, et al. Predictors of the risk of mortality in neurofibromatosis 2. *Am J Hum Genet* 2002;71(4):715–723
- 23 Crisci C. Tribute—and a clinical lesson in bioethics and quality of life. *J Med Ethics* 1997;23(1):18
- 24 Brackmann DE, Fayad JN, Slaterry WH III, et al. Early proactive management of vestibular schwannomas in neurofibromatosis type 2. *Neurosurgery* 2001;49(2):274–280, discussion 280–283
- 25 Odat HA, Piccirillo E, Sequino G, Taibah A, Sanna M. Management strategy of vestibular schwannoma in neurofibromatosis type 2. *Otol Neurotol* 2011;32(7):1163–1170
- 26 Samii M, Matthies C, Tatagiba M. Management of vestibular schwannomas (acoustic neuromas): auditory and facial nerve function after resection of 120 vestibular schwannomas in patients with neurofibromatosis 2. *Neurosurgery* 1997;40(4):696–705, discussion 705–706
- 27 McCullough LB, Jones JW. Postoperative futility: a clinical algorithm for setting limits. *Br J Surg* 2001;88(9):1153–1154
- 28 Moulton B, King JS. Aligning ethics with medical decision-making: the quest for informed patient choice. *J Law Med Ethics* 2010;38(1):85–97
- 29 Natarajan SK, Sekhar LN, Schessel D, Morita A. Petroclival meningiomas: multimodality treatment and outcomes at long-term follow-up. *Neurosurgery* 2007;60(6):965–979, discussion 979–981