The Diagnosis and Management of Neurofibromatosis 2 in Childhood

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Neurofibromatosis 2 (NF2) is an autosomal-dominant condition that causes multiple benign nervous system tumors, especially vestibular schwannoma. Although frequently confused with the more common neurofibromatosis 1, NF2 presents a distinct set of diagnostic, genetic, and management issues. The presentation and natural history of NF2 differs in children and adults, with eighth nerve dysfunction often overshadowed by the effects of other tumors on the nervous system. Molecular diagnostics is an important tool for early recognition of NF2, and when performed in the context of appropriate counseling and follow-up, may lead to a better final outcome of the disease. Further research into the molecular genetic etiology of NF2 promises to broaden the possibilities of therapy for this devastating disorder.

NEUROFIBROMATOSIS 2 (NF2) is a severe autosomal-dominant disorder causing the appearance of multiple benign nervous system tumors. Although classically considered a disease of adults, many NF2 patients are retrospectively found to have had subtle signs of the disorder in childhood and most are symptomatic by adolescence. Recent studies have better defined the clinical manifestations and natural history of NF2. In addition, the cloning and characterization of the NF2 gene is leading to a better understanding of the molecular pathophysiology underlying tumor development in this disease. These advances promise to increase the therapeutic options available to NF2 patients and improve the prognosis of the disease, especially when recognized early in its course.

Historically, NF2 (previously known as bilateral acoustic neurofibromatosis or central neurofibromatosis) has frequently been confused with the more common neurofibromatosis 1 (NF1, also known as von Recklinghausen disease or peripheral neurofibromatosis).[1-4] Gardner and Frazier,[5] studying a large family with 38 affected members over five generations, were the first to persuasively argue that bilateral vestibular tumors can be clinically and pathologically distinguished from both von Recklinghausen neurofibromatosis and from sporadic tumors. Kanter et al[6] expanded these observations using a larger cohort of affected individuals and kindreds and were the first to point out several key features of the disease including the lack of malignant transformation, risk of drowning and accidental death, and frequent misdiagnosis encountered even by classically affected patients. In 1987, the National Institutes of Health held a Consensus Development Conference that proposed formal diagnostic criteria for both NF1 and NF2 (Table 1).[7] Molecular cloning of the genes for NF1[9,10] and NF2[11,12] have confirmed the fundamental pathogenetic difference between the two disorders.

NATURAL HISTORY OF NF2 IN CHILDREN

Our original study of NF2 in children pointed out many of the differences in presentation and natural history that are unique to the pediatric population.[13] We have now expanded this cohort to a total of 23 individuals who have been given the diagnosis of NF2 before age 16 years from the Neurological Department of the Klinikum Nord Ochsenzoll. Five of the 23 were completely asymptomatic and were diagnosed on the basis of a positive family history with subsequent molecular diagnosis as noted in the section that follows. Clinical characteristics of the remaining 18 symptomatic individuals are presented in Table 2. Most adult NF2 patients come to diagnosis when they present with symptoms referable to vestibular schwannoma causing eighth cranial nerve dysfunction with auditory symptoms prevailing over vestibular.[14-16] We found that children were much more likely to present with other neurological symptoms, primarily those of spinal cord compression or visual dysfunction. Headache and seizure are distinctly uncommon modes of presentation amongst both children and adults (Table 2).[14-16] As has been documented in adult

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Table 1. NIH Consensus Criteria for NF2

The diagnostic criteria for NF2 are met if a person has either of the following:
Bilateral eighth nerve masses seen with appropriate imaging techniques (ie, computerized tomographic or magnetic resonance imaging)
A first-degree relative with neurofibromatosis 2 and either unilateral eighth nerve mass or two of the following:
Neurofibroma
Meningioma
Glioma
Schwannoma
Juvenile posterior subcapsular lenticular opacity

The Clinical Care Committee of the National Neurofibromatosis Foundation has proposed revisions that include a separate category of presumptive NF2.[8]

Data from Mulvihill et al[7] and Gutmann et al.[8]

cohorts,[15] there was often a discouraging and prolonged delay between presentation with significant neurological symptoms and the correct diagnosis of NF2 in these affected children.

In retrospect, many NF2 patients are found to have symptoms or signs before their diagnosis, the significance of which was not recognized. Subtle skin tumors (Fig 1) and small posterior capsular cataract are especially important clues to the presence of NF2. At the time of presentation to our unit, 12 symptomatic children had skin tumors (60%). Before age 10 years, these tumors were characterized by small, well-circumscribed lesions often found on the trunk or face. After age 10 years, tumors often became roughened with overlying course hair. Unlike NF1, few additional skin tumors developed and existing tumors rarely grew during the years of follow-up. Cataract was observed in 13 children (24 eyes) at the time of presentation and 2 additional cataracts (in 2 patients) developed during the period of follow-up. Five children (patients 10, 12, 13, 19, and 20) had been given a diagnosis of "idiopathic" strabismus before the development of other neurological symptoms that prompted a diagnosis of NF2. Childhood onset strabismus and amblyopia has frequently been reported in adult NF2-affected individuals, and further work is needed to fully understand this association. Cafe au lait macules, similar to those seen in NF1, are probably more prevalent in NF2 patients than in the general population, but in this cohort and in other reports,[15] they do not reach the size or numbers seen in NF1 patients.

The clinical course of NF2 is extremity variable

Table 2. Natural History of NF2 in 18 Patients Presenting Before Age 16 Years

Patient Number*	Current age†	Presentation‡		Vestibular Tumors		Other Findings				
		Age	Symptom(s)	Age Radiographic Detection§	Age Hearing Loss‖	CNS Tumor¶	Spinal Tumor	Skin Tumor	Cataract/ Retinal Change	Family History
G1	11	2	Paraplegia	11	–	–	+	–	–	+
G2	17	6	Diplopia	14	–	+	+	–	–	+
G3	22	2	Skin tumor	(16)	20	+	+	+	+	+
G5	23	4	Skin tumor	15	–	+	+	+	–	+
G6	17	10	Skin tumor	(10)	(11)	+	+	+	+	–
G7	17	9	Neck pain	(11)	10	+	+	+	–	–
G8	21	15	Seizure	(15)	16	+	+	+	+	–
G9	20	10	Cataract	16	(18)	+	+	–	+	–
G10	19	14	Oculomotor	14	15	+	+	+	+	+
G11	7	3	Cataract	–	–	+	–	–	+	+
G12	24D	13	Epiretinal hamartoma	19	24	+	+	–	+	–
G13	10	2	Epiretinal membrane	9	–	+	+	+	+	–
G14	2D	1	Hearing loss	1	1	–	+	+	–	–
G16	20	9	Back pain	16	16	–	+	+	+	–
G17	20D	6	Oculomotor and skin tumor	11	15	+	+	+	+	–
G19	11	5	Paraparesis	9	–	+	+	+	+	–
G20	12	12	Skin tumors	(12)	12	+	+	+	+	–
G21	7	7	Cataract	–	–	–	+	–	+	–

*Patients 1 through 9 were previously reported by Mautner et al.[19]

†D, age deceased.

‡In retrospect, many children without positive family history had subtle skin tumors and several had oculomotor or visual acuity abnormalities of unrecognized significance.

§Large tumors (>2 cm) that may have been detectable earlier are marked are marked in parentheses.

‖Hearing loss that occurred postoperatively is marked in parentheses.

¶Other than vestibular schwannoma, includes both meningioma and other cranial nerve schwannomas.

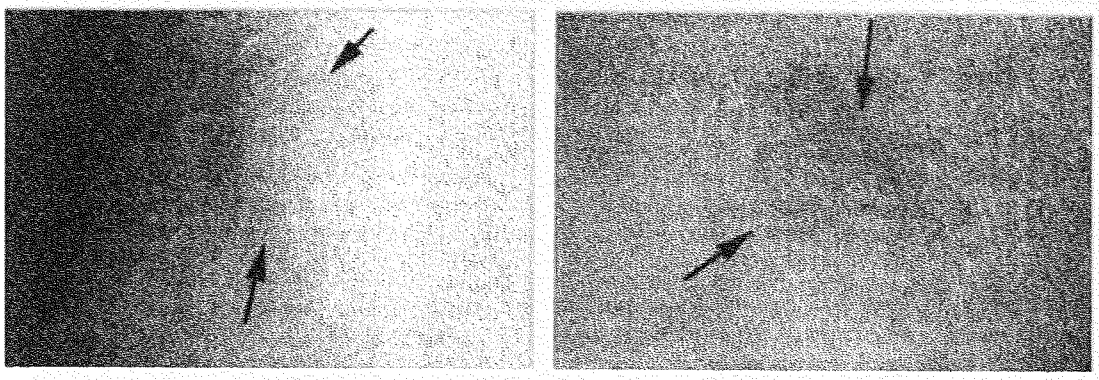

Fig 1. Appearance of skin tumors in NF2 (arrows) is shown. Cutaneous tumors in NF2 are almost always schwannomas and are much less prominent and numerous than the cutaneous neurofibromas associated with NF1. As illustrated here, these subtle tumors may best be recognized by roughening and slight darkening of the overlying skin.

and dependent on tumor burden, surgical management, and complications. The clinical course is also more fulminant in early-presenting patients than in those presenting in adulthood. Most commonly, patients exhibit a progressive deterioration with loss of hearing, ambulation, and sight along with chronic pain due to their tumor burden. The rate of deterioration from age of diagnosis may vary from years to decades, with the average survival from diagnosis in the large cohort of Evans et al[14] being 15 years. Although actuarial survival is difficult to measure accurately in a smaller cohort, it is notable that 3 of our 18 patients died during the period of follow-up at ages 2, 20, and 24 years. A number of advances in radiographic evaluation, surgical management, and potential medical therapies are on the horizon, improving the prognosis for newly diagnosed patients.

TUMOR TYPES ASSOCIATED WITH NF2

Schwannomas are the most common tumor type associated with NF2, with vestibular schwannoma being a universal occurrence (Fig 2). Other cranial nerve schwannomas occur in one fourth of the patients, with unilateral or bilateral trigeminal nerve involvement most common. With both cranial and peripheral nerve involvement, sensory nerves are more frequently affected than motor for unclear reasons. The pathology of NF2-associated schwannomas differs subtly from that of sporadic schwannomas, with a greater prevalence of lobularity and entrapment of nerve fibers.[17,18] Although

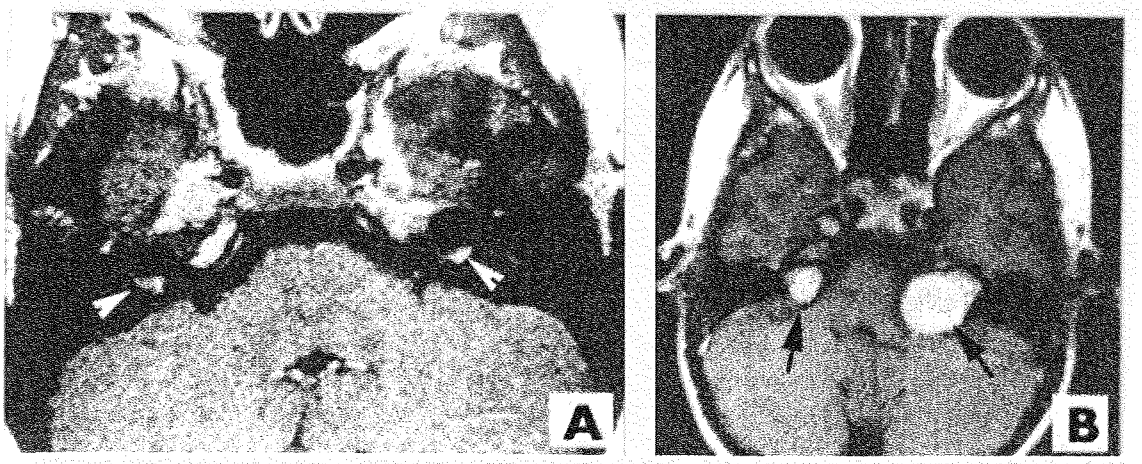

Fig 2. Bilateral vestibular schwannomas (VSs) in children are shown. (A) VSs almost always originate within the internal auditory canal. These small tumors (arrowheads) from patient 13 in Table 2 were completely asymptomatic. (B) As VSs grow, they enter the cerebellopontine angle where they eventually cause brainstem compression (arrow). This 12-year-old patient (number 20 in Table 2) had progressive high-frequency hearing loss. T1-weighted, contrast-enhanced images.

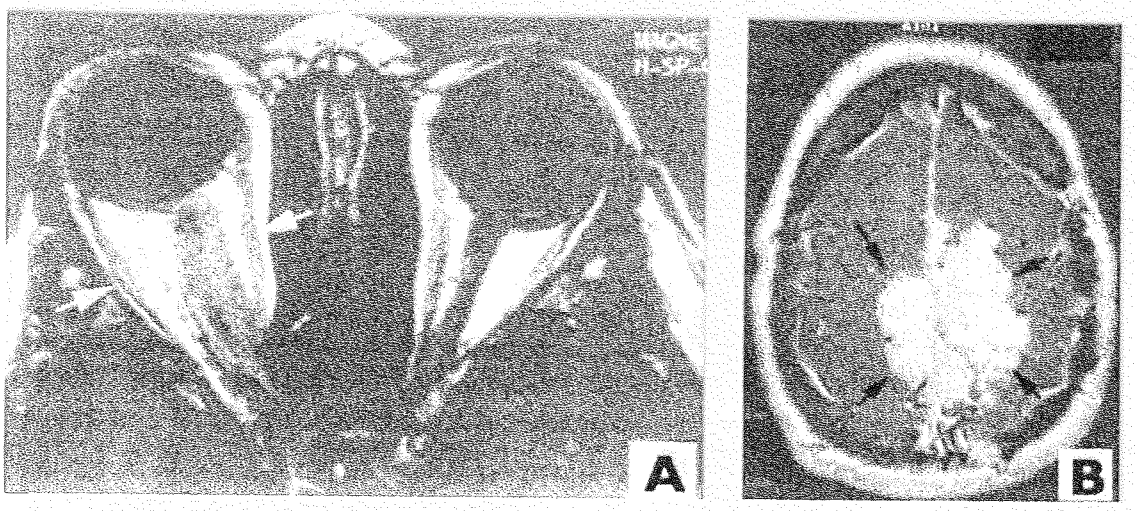

Fig 3. Meningioma in NF2 is shown. (A) On MRI, orbital meningioma (arrows) may be confused with optic nerve glioma; however, the latter tumor is seen in association with NF1, not NF2. This patient (number 13 in Table 2) had progressive proptosis and visual loss. (B) Multilobulated tumor mass (arrows) over the convexity in a patient with difficult-to-control partial seizures is shown. T1-weighted contrast-enhanced images.

neurofibromas are the hallmark tumor of NF1, they are rarely encountered in NF2 patients.[19,20]

Meningiomas occur in 50% of all NF2-affected individuals with intracranial involvement greater than spinal involvement (Fig 3). Unlike schwannomas, there is no overwhelming site of predilection for meningioma, although several sites deserve special clinical vigilance. Orbital meningioma may cause progressive loss of vision, an ominous consequence in a patient at risk for deafness (Fig 3A). Cavernous sinus involvement may lead to both vascular and cranial nerve impairment. Unlike fifth cranial nerve schwannomas, which may displace the structures of the cavernous sinus as they grow anteriorly, cavernous sinus meningiomas tend to encase the carotid and cranial nerves making surgical removal difficult. Finally, skull base meningiomas, often with an "en plaque" appearance, may become so numerous that death from brainstem compression ensues.

Spinal cord tumors are seen in more than 80% of carefully studied NF2 patients, but most remain asymptomatic.[21] Schwannomas are the most common pathological type of spinal cord tumor and often form a "dumbbell"-shaped mass surrounding their original in the intravertebral foramen (Fig 4A). Meningiomas can usually be distinguished from spinal schwannomas by their typical radio-

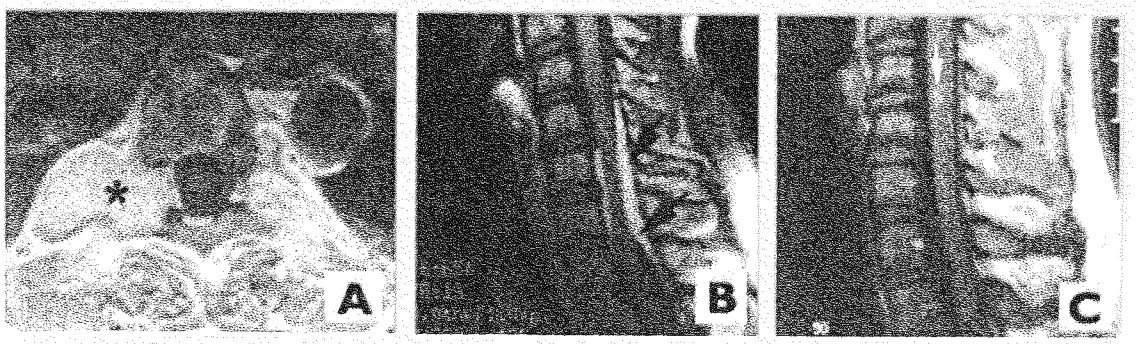

Fig 4. Spinal cord tumors in NF2 are shown. (A) Typical appearance of a spinal root schwannoma originating in the intravertebral foramen (*) and assuming a "dumbbell" configuration. (B) Spinal meningioma covering several segments of the cord (arrows). (C) Enhancing lesion (arrow) in the cervical spine consistent with an ependymoma or astrocytoma. Small intramedulary tumors that do not significantly expand the cord are rarely symptomatic in these patients and do not warrant biopsy or aggressive treatment. T1-weighted, contrast-enhanced images.

graphic appearance (Fig 4B). Glial tumors (ependymomas and astrocytomas) are radiographically common, but only rarely symptomatic in NF2 patients (Fig 4C). Spinal cord tumors may be an important diagnostic clue in the presymptomatic at risk child. In a child in whom the diagnosis has been established, intervention is rarely warranted on asymptomatic tumors, making annual studies of the spine unnecessary.

OCULAR MANIFESTATIONS OF NF2

Visual impairment is a frustratingly common complication of NF2 and is a result of a variety of disparate processes (Table 3). Estimates of visual impairment in NF2 patients vary widely from 33% to 75%, reflective of the population studied and the extent of the ophthalmological examination reported.[16,22,23] Juvenile posterior subcapsular lenticular opacity is the most common treatable lesion associated with NF2 but becomes visually significant in less then 20% of patients.[22] Retinal changes, including hamartomas and epiretinal membrane, are a marker for severe disease and may affect vision when they involve the macule or lead to retinal detachment.

Both NF2-related tumors and their surgical removal may affect vision in NF2 patients. Corneal injury is an especially common and avoidable complication of the surgical treatment of NF2.[24] Injury to both the seventh and fifth cranial may lead to a interacting combination of incomplete lid closure, decreased corneal sensation, and decreased tear production all contributing to corneal vulnerability. Postsurgical cranial nerve impairment is often transient, with greatest disability occurring in the immediate postoperative period. Temporary measures including lubricating drops and ointments and protective barriers should be aggressively applied during this time, whereas more permanent treatments may be reserved for these patients in whom facial palsy does not resolve after several weeks to months.

Table 3. Percent of NF2 Patients Found to Have Visual Axis Abnormalities

Cataract, 70% to 80%
Retinal abnormality, 22%
Juvenile amblyopia/strabismus, 12%
Corneal opacification, 11%
Orbital and optic nerve tumors, 9%
EOM abnormality, 9%

Retinal abnormalities include retinal hamartoma and epiretinal membrane. Corneal opacification is most commonly due to 5th or 7th cranial nerve damage at surgery. EOM, extra ocular movement. Data from Bouzas et al[22] and Ragge et al.[23]

WHAT NF2 ISN'T

Unlike the many protean manifestations of NF1, NF2 patients develop little pathology outside of their tumor burden. Specifically, the defining dermatological features of NF1, such as large numbers of cafe au lait macules, generalized hyperpigmentation, and freckling, are not seen in NF2 patients. NF2 patients do not have the associated cognitive problems, such as mental retardation and learning disability, that NF1 patients have. Although both NF1 and NF2 patients develop nerve sheath tumors in a variety of locations, careful pathological examination will show those associated with NF1 to be neurofibromas, whereas those associated with NF2 are nearly always schwannomas. Neither NF1 nor NF2 patients are at high risk for malignancy during childhood, but NF2 patients continue to carry a low risk of malignant transformation of their tumors or *de novo* malignancy throughout adulthood.[14] Despite considerable confusion in the literature, there is essentially no overlap between NF1 and NF2 patients when a thorough examination is done in conjunction with application of the National Institutes of Health (NIH) criteria.

The relationship of single tumors to NF is an interesting one. The pathology[18] and molecular biology[25] of sporadic tumors differs only in subtle ways from that of NF2. Because many NF2-associated tumors are common in adults, a search for NF2 is probably not warranted in the otherwise asymptomatic patient with a single tumor over age 35 years. Conversely, sporadic meningiomas and vestibular schwannomas are rare in children and should prompt a more through investigation with an assumption that the child is affected until adulthood proves otherwise.

Several outlying phenotypes to NF2 exist, the importance of which lies in their different clinical courses, natural history, and genetic risks. Multiple meningiomas without other tumor types has been described as a distinct autosomal-dominant disorder, which in at least some cases segregates independently from the chromosome 22 locus encoding NF2.[26] More commonly, multiple meningiomas are a sporadic occurrence due to noncontiguous spread of a single tumor or independent genetic events with no risks to the next generation.[27] Multiple

schwannomas may also rarely occur without the defining feature of bilateral vestibular schwannomas leading to the designation "schwannomatosis."[28] Finally, cases of "mosaic" inactivation of the NF genes are being increasingly recognized, only a portion of which cause classic "segmental" disease.[29,30] Because of the rarity of these conditions and the time-dependent occurrence of vestibular schwannoma in NF2, diagnosis of an outlying phenotype should be viewed with caution in the pediatric age range.

GENETICS OF NF2

NF2 is a rare disorder with a birth incidence of 1 in 40,000 individuals.[31] Consistent with the observation that half of all cases are sporadic and due to new mutation, there is no ethnic predilection. Vestibular schwannoma is a common tumor that affects older adults with an incidence of about 1 per 100,000 per year.[32] Less then 5% of individuals with unilateral vestibular schwannoma will go on to develop bilateral tumors and NF2.

NF2 shows autosomal-dominant transmission with nearly full penetrance as measured by development of NF2 associated tumors by age 18 years. NF2 also shows remarkable intrafamilial homogeneity (unlike NF1) with great similarity in age of onset and severity of disease within kindreds,[15] an observation that limits the need to screen the asymptomatic parents of a classically affected individual. Although somatic mosaicism in NF2 appears to be relatively common, germline mosaicism is sufficiently rare as to make screening of siblings of a sporadic patient unnecessarily.

The location of the NF2 gene on the long arm of chromosome 22 was predicted by both linkage and loss of heterozygosity studies. The gene itself was identified in 1993 by two groups[11,12] and encodes a novel member of the protein 4.1 family of cytoskeletal associated elements.[33] Current molecular methods enable detection of causative mutation in two-thirds of all classically affected individuals, with increased detection rates seen in severely affected persons and negligible detection in very mildly affected individuals.[34-36] In persons with atypical disease for any reason, mutational analysis may best begin in tumor rather than unaffected tissues such as blood.[28,30] Until detection rates for mutations in this gene improve or greater phenotype genotype certainty is realized, mutational analysis cannot refute a clinical impression of NF2 and is only rarely useful in confirming an impression of NF2 in an affected child.

MOLECULAR DIAGNOSTICS IN CHILDREN AND ADOLESCENTS

Molecular diagnostics is an important clinical tool for the detection of early NF2 in children at risk for the disorder by virtue of a classically affected parent. Ascertainment of affected presymptomatic children allows the detection of small vestibular tumors and preserves many therapeutic options not open to older adolescents and adults. Presymptomatic molecular analysis also reduces the cost of care to affected families and reduces the burden of unnecessarily clinical testing on unaffected individuals.

A total of 33 families with 68 at risk children under age 18 years have been offered the option of genetic testing in the Neurofibromatosis Clinics of Massachusetts General Hospital and the Klinikum Nord Ochsenzoll. Two families have declined testing for all children. In 8 families, mutational analysis of the proband was unsuccessful in identifying a causative alteration, and no other affected family members were available for linkage analysis. Among the remaining families in whom a causative mutation was identified, 11 remain in the process of presymptomatic counseling, some for over 2 years. In many of these families, complex medical problems of the proband have prevented their proceeding with the time-consuming process of testing of their children.

Twelve families have completed a presymptomatic diagnostic protocol on a total of 23 at-risk children. This protocol involves counseling of the immediate family and the child at an age-appropriate level with regards to possible psychological, intrafamilial, and social ramifications of testing. In addition, families with older children and adolescents were made aware of possible insurance and job discrimination issues. All children underwent pretesting neurological and dermatological evaluation, which was abnormal in six children, all of whom then tested positive. Four other children also tested positive, whereas 13 children tested negative.

Further radiographic and audiological testing was immediately performed on the 10 children testing positive (Table 4). Six of 10 children had vestibular tumors at age 6 to 18 years, and most ears had audiological abnormalities. Resection of

Table 4. Results of NF2 Testing Protocol in Gene Positive Individuals

Patient Number	Age Testing Completed	Physical Findings at Testing	Radiographic Findings at Testing	Current Status
1	18	None	BVS, cervical spine tumor	Complete RVS resection, full hearing, and facial function preserved
2	15	Strabismus, cataract	BVS	Subtotal RVS resection, full hearing, and facial function preserved
4	19	None	None	Neurologically normal
11	8	Strabismus, hearing loss	BVS	Subtotal LVS resection with subsequent unilateral deafness and facial palsy
12	6	Skin tumor, areflexia	BVS, jugular fossa tumor, meningioma	Progressive dysphagia
G4	13	Skin tumor	BVS, trigeminal schwannoma	Subtotal LVS and RVS resections with subsequent hearing loss and facial paresis
G15	8	Skin tumor, cataract	RVS, spinal tumor	Neurologically normal
G18	10	Cataract	Spinal tumor	Neurologically normal
G22	13	None	None	Neurologically normal
G23	6	None	None	Neurologically normal

BVS, bilateral vestibular schwannoma; RVS, right vestibular schwannoma; LVS, left vestibular schwannoma.
Patient G4 was previously reported in Mautner et al.[13]

vestibular tumors has been attempted in four children with variable results. Follow-up of the children who tested negative revealed that the families were pleased with the testing protocol; no obvious psychiatric or psychosocial problems related to testing were observed.

MANAGEMENT OF THE CHILD WITH NF2

All children known or suspected of having NF2 should undergo a comprehensive initial evaluation including detailed dermatological inspection, neurological examination, cranial MRI with thin cuts through the internal auditory canals, and neuro-ophthalmological examination with slit lamp (Table 5). If the diagnosis remains unclear after this evaluation, spinal cord imaging, review of pathological specimens, and molecular analysis may be helpful. When a diagnosis is established by the NIH criteria, patients should undergo audiological evaluation and spinal cord imaging. Families of all children with vestibular schwannomas, regardless of size or symptoms, should discuss surgical options with a skull base surgeon because removal of small tumors may provide better final outcome. Unless patients present with a neurological emergency, surgical intervention for nonvestibular tumors is best deferred until their growth pattern can be established. Frequent re-imaging and re-examination in the year after diagnosis may be required, although subsequent management of neurological stable children can usual be accomplished on an annual basis.

Imaging and functional testing of vestibular schwannoma in NF2-affected children deserves special mention. Imaging of the internal auditory canal (IAC) is best obtained with MRI scanning done at 3-mm slice thickness overlapping by 1.5 mm on both axial and coronal views with and without the administration of contrast material ("IAC protocol"). Standard slice thickness MRI (5-mm slice thickness), noncontrast MRI, and cranial CT scanning should not be substituted for an IAC protocol, especially in the initial evaluation of these tumors. Annual hearing evaluation is mandatory for patients with NF2 that have any functioning hearing in either ear. Evaluation should

Table 5. Initial Evaluation and Clinical Follow-Up of NF2 Patients

Initial Evaluation	Minimum Frequency of Follow-Up
Neurological examination	Annual
Dermatological evaluation	As needed
Neuro-ophthalmological evaluation	Annual
Genetic conseling	Annual
Cranial MRI with IAC protocol	Annual
Spinal MRI	Annual follow-up of intramedulary tumors, symptomatic tumors or dumbell tumors with significant mass effect on cord
Audiology	Annual if any usable hearing

In the years following diagnosis and during times of neurological change more frequent follow-up may be needed; clinically stable patients may usually be evaluated on an annual basis.

IAC, Internal auditory canal.

include both pure tone measurement of hearing sensitivity and speech intelligibility measurement of the quality of information that the child is receiving. Auditory brainstem response (ABR) is a useful adjunct to audiology as it may show abnormalities before symptomatic hearing loss; serial ABR is especially important in the presymptomatic child whose family is contemplating surgical intervention. Testing should be performed in a center experienced with vestibular tumors and should be compared with previous years' results by a certified audiologist.

Many surgical options exist for the management of vestibular schwannoma.[37-39] Children and their families should consider carefully the advantages and disadvantages of any planned approach, including that of watchful waiting. Surgical management of other NF2-associated tumors is less bound by set protocols because the tumor location is less uniform. Unfortunately, the presence of a tumor alone is often taken to be an indication for surgery. As is the case with NF1, poor timing of surgical intervention on a minimally symptomatic tumor may cause far more disability and disappointment than the tumor itself.

Regardless of management strategy, all children with NF2 are at risk for deafness during their lifetime. Strategies for facilitating communication should be introduced as early as possible. Children should receive audiological care in a center experienced in teaching lip reading skills and should acquire sign language skills early in the course of their disease. Amplification type hearing aids may preserve useful auditory function in some patients with large tumors. In those with complete or imminent deafness, referral to a center experienced in auditory brainstem implantation should be considered.[40]

Nonsurgical interventions for NF2 are more limited. There is no currently accepted medical therapy for tumors associated with NF2, although trials of anti-angiogenesis agents, hormonal manipulation, and hydroxyurea have been performed in adults with NF2 related tumors.[41-43] Anticipatory guidance is a important part of management of NF2 patients. Compassionately delivered information about the natural history of NF2 is important for families in planning both personal and education issues for their children. Children should not be allowed to swim underwater or alone because of the risk of underwater disorientation and should be discouraged from activities that require balance function, such as gymnastics. All families should be introduced to the many excellent support groups which exist for the NF community (Table 6).

Table 6. Resources for Families Affected by NF2

The National Neurofibromatosis Foundation 800 323-7938 nnff@aol.com http://nf.org/
Neurofibromatosis, Inc 800 577-8984 NFInc1@aol.com http://www.nfinc.org//nfink.html
von Recklinghausen Gesellschafter 49-40-5271-2822 VRGES@aol.com
The Acoustic Neuroma Association (404) 237-8023 ANAUSA@aol.com http://ANAusa.org/
The NF2 Review and the NF2 Crew (213) 483-4431 http://www.webcrossings.com/nf2crew/
The NF Association 44-181-547-1636 NFA@zetnet.co.uk http://www.users.zetnet.co.uk/neurofibromatosis/

FUTURE DIRECTIONS

Although NF2 is frequently a severe and relentlessly progressive disorder, current avenues of research provide hope to both patients and families that future outcomes will be better than historical ones. Investigations into genotype/phenotype relationships suggest that many of the manifestations of NF2 may be predictable from the underlying genetic mutation. This may allow the greater use of focused monitoring and presymptomatic intervention. Advances in surgical techniques, imaging techniques, and medical treatments may also yield better outcomes, especially when applied early in the course of disease. Finally, the development of rational therapies, including genetic therapy, may eventually provide a treatment or cure for this devastating disorder.

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