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Neurofibromatosis 1 and 2

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Neurofibromatosis (NF) 1 and 2 are multisystem disorders associated with a variety of neoplastic and non-neoplastic manifestations that typically progress in severity during the lifetime of the affected patient. The importance of appropriately diagnosing these disorders stems from the fact that the natural history of an associated neoplasm, such as a peripheral nerve tumor or an optic glioma, may be significantly different depending on whether or not the lesion arises in a person with NF. In addition, the indications for therapeutic intervention, hierarchy of treatment options and long-term management goals may differ substantially for patients with NF-related versus sporadic tumors. Finally, recognition of the diagnosis comprises an essential step for providing appropriate multidisciplinary evaluation and counseling to affected patients and their families. This article addresses the principal manifestations of these disorders and provides a contemporary review of the diagnostic and therapeutic issues that arise in children with NF1 and NF2.

Introduction

Neurofibromatosis (NF) is a descriptive term that was coined by Frederick von Recklinghausen in 1882 to characterize two patients with cutaneous tumors that were thought to be composed of a combination of neural and mixed cellular elements (1). This diagnostic category was later broadened to include patients with an array of dermatological, ocular, and nervous system manifestations. Investigators later realized that patients with NF could be categorized, based on the pattern of their manifestations, into distinct clinical groups (2). Improvements in imaging techniques and advances in molecular genetics facilitated efforts to distinguish patients with NF1 (previously known as peripheral neurofibromatosis) from those with NF2 (previously known as central neurofibromatosis or bilateral acoustic neurofibromatosis).

NF1 is now recognized to be one of the most common genetic disorders, affecting one in 3000 to 4000 people (3). The mode of inheritance is autosomal dominant, although approximately 50% of cases arise sporadically as new mutations. This syndrome results from mutations in a gene on chromosome 17q11.2 that encodes a large protein called neurofibromin. A portion of this protein is a GTPase-activator (4) that functions in signal transduction (5,6) by favoring the conversion of the active GTP-bound form of *ras* and related G-proteins to the inactive GDP-bound form.

NF2 is one-tenth as common as NF1, affecting only 1 in 50,000 people (7). The chromosomal locus for the disorder was initially suggested by cytogenetic studies of sporadic vestibular neurilemomas and meningiomas, the characteristic tumors of NF2, which frequently exhibited deletions of the long arm of chromosome 22. These observations provided a basis for detailed mapping of this region in patients with NF2, which identified a common site of mutations at 22q12 (8). The gene product, referred to as merlin (a moesin-, ezrin-, and radixin-like protein) or schwannomin, encodes a polypeptide that may be involved in linking cytoskeletal elements with plasma membrane proteins (9).

Both the NF1 and NF2 genes function as classical tumor suppressors in that loss of both alleles is needed for tumorigenesis. Because affected patients are born with only one normal copy of the gene, a single mutation or deletion that inactivates the second allele would theoretically be sufficient to favor tumor formation.

Diagnostic Criteria

Diagnostic criteria that reflect the diverse manifestations of NF1 have been proposed at a National Institutes of Health Consensus Development Conference (Table 1); they were devised, in part, for high specificity in order to achieve a low rate of false-

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Consensus Criteria for the Diagnosis of NF1 (14)

The criteria for making a diagnosis of NF1 are met if a patient has two or more of the following:

1. Six or more café-au-lait macules that have a maximum diameter of >5 mm in prepubertal patients and >15 mm in postpubertal patients
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A characteristic osseous lesion, such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
7. A first-degree relative (i.e., parent, sibling or child) with NF1 by the above criteria

Table 1.

ly positive diagnoses. Affected patients exhibit a combination of café-au-lait macules, Lisch nodules (iris hamartomas), axillary and inguinal freckling, skeletal lesions, such as sphenoid wing dysplasia and thinning of the long bone cortex, and optic gliomas, as well as an increased incidence of other central nervous system and systemic tumors (10-14).

The diagnostic criteria for NF2 are entirely different than those for NF1 (Table 2), which helps to distinguish these entities. Affected patients have a combination of eighth nerve as well as other cranial nerve neurilemomas, meningiomas, glial neoplasms, neurofibromas, and juvenile posterior subcapsular cataracts (14). Although café-au-lait macules and cutaneous neurofibromas are sometimes seen, they are typically fewer in number than in patients with NF1 (15) and are not included among the consensus criteria for diagnosis.

A distinct subgroup of patients with features of NF1 exhibit signs, such as café-au-lait macules and neurofibromas, that are restricted to certain segments of the body. This so-called "segmental" form accounts for three to five percent of patients with NF1 and appears to arise from mosaicism, in which a mutation of the NF1 gene occurs at some time after fertilization in the developing embryo (16). In cases in which the gonadal progenitors are spared (i.e., somatic mosaicism), the disorder is not genetically transmissible. A segmental form of NF2 has also been suggested for patients who have multiple peripheral neurilemomas in an extremity without other features of NF2 (17).

It has long been recognized that, even among patients with typical (non-segmental) NF1 or NF2, there is significant variability in the severity of manifestations between members of different families. In view of this diversity, Parry et al. (15) favored separating affected families with NF2 into two groups: a milder (Gardner) variant and a more severe (Wishart or Lee-Abbott) variant. The basis for this symptomatic heterogeneity is uncertain but may reflect differences in the specific site of mutations in the NF1 or NF2 genes themselves (18). Information from genetic testing of affected individuals (19,20), correlated with clinical features, should help to clarify this issue. This strategy should also help to explain the association of NF1 with other disorders, such as Noonan syndrome (21), Watson syndrome, and juvenile xanthogranuloma (22). Genetic studies should also help to resolve the diagnostic uncertainty that often surrounds patients who meet only one criterion for these disorders, such as café-au-lait macules without any other manifestations of NF1 or multiple meningiomas without other features of NF2, because these findings may reflect distinct syndromes (23,24).

Consensus Criteria for the Diagnosis of NF2 (14)

The criteria for making a diagnosis of NF2 are met if a patient has either of the following:

1. Bilateral eighth nerve masses seen with appropriate imaging techniques, such as MRI or CT
2. A first-degree relative with NF2 and either unilateral eighth nerve mass or two of the following.
   A. Neurofibroma
   B. Meningioma
   C. Glioma
   D. Neurilemoma
   E. Juvenile posterior subcapsular cataract

Table 2.

An important caveat in interpreting any genetic studies for these disorders is that the exact features of NF1 and NF2 can vary widely within a single family (in which all affected individuals should have an identical NF mutation) (25). The explanation for such pleitropy may be the involvement of disease-modifying genes or interacting environmental factors. The practical implication is that contemporary genetic testing can accurately predict the occurrence of NF1 or NF2 but not its severity or specific features. A discussion of the major non-neurological and neurological manifestations of these disorders and their diagnosis and management is provided below.

Non-Neurological Manifestations

NF1. Café-au-lait macules and axillary freckling result from abnormal collections of melanin pigment but without any neoplastic component. As such, they pose only a cosmetic concern. Similarly, Lisch nodules simply represent melanocytic iris hamartomas; although these lesions increase in frequency during childhood and are present in more than 90 percent of affected patients by the completion of puberty (26), they do not interfere with vision.

In contrast, skeletal manifestations can produce significant functional problems. Congenital bowing and/or dysplasia of the long bones, particularly the tibia, may lead to pathological fractures that resist healing. The resulting pseudoarthrosis is extremely difficult to correct, and some patients ultimately require amputation (27). Osseous dysplasia can also involve the sphenoid bone as a congenital or acquired process (28), which leads to herniation of temporal lobe contents into the orbit and, in some cases, produces pulsatile proptosis and seizures.

Although some degree of scoliosis is present in many patients with NF1 (27), the curvature is usually mild and does not require specific therapy. However, in a small percentage of cases, the scoliosis becomes severe and requires treatment (29). Because many of these patients have an associated intra- or extra-axial neurofibroma that may need to be addressed in conjunction with a spine-straightening procedure, magnetic resonance imaging (MRI) is an essential step in the preoperative evaluation. Other less serious spinal manifestations of NF1 include vertebral scalloping and non-neoplastic widening of the neural foramina from dural ectasia and meningocele formation.

An additional phenomenon that is occasionally observed in patients with NF1 is segmental hypertrophy (3). Although there is often an associated neoplastic component, the deformity is frequently out of proportion to the size of the tumor. It remains uncertain whether this reflects generalized mesenchymal dysplasia in the involved area or a trophic effect of neurogenic and humoral factors released by the tumor.

Patients with NF1 are also at risk for a variety of systemic malignancies. In particular, the relative risk

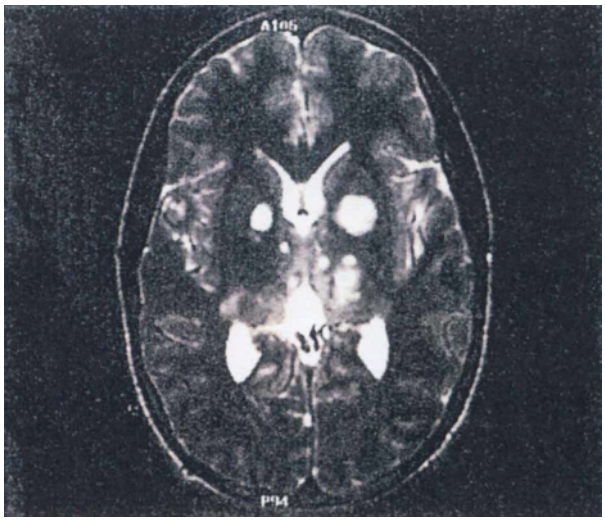

Figure 1. *This axial T2-weighted MRI demonstrates the characteristic areas of T2 signal abnormality that are commonly detected in patients with NF1 within the basal ganglia and, occasionally, within the cerebellum and other regions of the brain. Reproduced by permission of the publisher from:* Pollack IF, Mulvihill JJ. (1996) Special issues in the management of gliomas in children with neurofibromatosis. In: *Gliomas of Childhood: Current Perspectives*, Pollack IF (ed), pp. 257-268, Kluwer Academic Publishers:Boston

of chronic myelomonocytic leukemia among patients with NF1 has been been noted to be more than 200 times greater than that of the general population (30). Other neoplasms that occur with an increased frequency in patients with NF1 include neurofibrosarcoma, pheochromocytoma, rhabdomyosarcoma, adenocarcinoma of the ampulla of Vater, melanoma, non-Hodgkin's lymphoma, and lymphoblastic leukemia (3,11-13,31).

NF2. In patients with NF2, the major, serious non-neural manifestation is posterior subcapsular cataract, which is a progressive problem that affects 85 percent of patients (32). Because these lesions can threaten vision, conscientious ophthalmological follow-up is required, and surgical removal of the cataract may be indicated. In patients with unilateral visual loss secondary to one of these lesions, particular attention must be directed to monitoring and protecting vision in the contralateral eye, which includes preserving facial nerve function to maintain eye closure and corneal protection.

Neurological Manifestations

NF1. *Focal Areas of Increased T2 Signal.* The most frequent abnormalities found on MRIs in patients with NF1 are foci of increased signal on T2-weighted images without either mass effect, changes on T1-weighted images, or contrast enhancement (Figure 1), which are detected in 60 to 80 percent of NF1 children (33-35). These foci may be solitary, multiple or confluent and are seen most commonly in the basal ganglia, internal capsule, brain stem, and cerebellum.

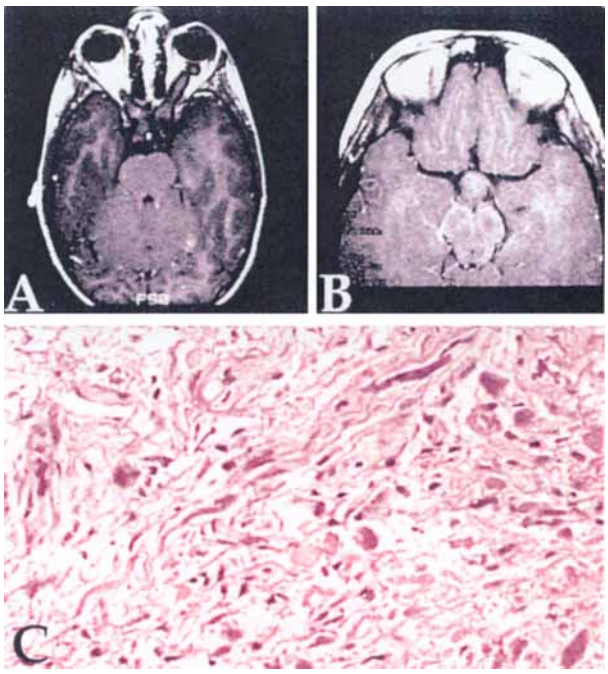

Figure 2. A. Thickening of both optic nerves is apparent in this ten-year-old boy with NF1. **B.** Globular enlargement of the optic chiasm was noted in this eight-year-old girl in association with thickened optic nerves and T2 hyperintensity along the optic tracts. **C.** H&E-stained paraffin section of a juvenile pilocytic astrocytoma. These hypocellular neoplastic lesions consist of tumor cells with long "hairlike" cytoplasmic processes. Abundant proteinaceous eosinophilic structures (Rosenthal fibers) of variable shape are scattered amongst the tumor cells.

On serial images in individual patients, these areas of signal abnormality often increase in frequency and number early in childhood and then regress later in childhood (34,35). This pattern supports the concept that these lesions represent age-related abnormalities in myelination. Some groups have noted that the presence and extent of these "unidentified bright objects" (UBOs) correlates with the detection of learning disabilities, which are encountered in at least 25 percent of patients with NF1 (36,37); other studies have failed to confirm this association (38). Because these lesions typically follow a benign course (34,35), their detection in an otherwise asymptomatic child does not signal the need for intervention or for frequent serial MRIs. However, this conservative management strategy should not be applied to childhood lesions with atypical MRI features, such as mass effect, T1 signal changes or enhancement; those lesions associated with focal neurological symptoms; nor to new lesions that are detected in older patients, because in such instances, the natural history remains uncertain.

Optic Pathway Lesions. The second most common imaging abnormality in patients with NF1 is optic-hypothalamic glioma, which is detected in at least 15% of affected children (33,39,40) (Figure 2). A number of characteristic lesion types may be seen either alone or in combination. The mildest abnormalities consist only of thickening of one or both optic nerves (33,39) (Figure 2A), which in some cases may represent hyperplasia of the optic nerve sheath rather than true neoplastic growth. Other patients exhibit a globular thickening of the optic nerves and chiasm (Figure 2B) that may occur in conjunction with T2 signal abnormalities streaking backwards along the optic pathways and upwards into the hypothalamus. Biopsies of such lesions have generally confirmed the presence of low-grade gliomas (Figure 2C) (40-44). Finally, a small percentage of patients are diagnosed with a large mass arising from the optic chiasm and hypothalamus that may extend upward into the third ventricle, laterally into the temporal fossa, anteriorly beneath the frontal lobe and posteriorly into the perimesencephalic region.

Optimal management of such lesions remains controversial because with the advent of sophisticated imaging technology, most tumors are now detected in asymptomatic or minimally symptomatic individuals in whom the natural history is uncertain. Several recent studies have reported the results of conservative management in patients with NF1 who had optic pathway tumors that were either asymptomatic or minimally symptomatic with mild visual loss or precocious puberty (40,41,45,46). Hoffman et al. noted that, in a series of 15 such patients who either had no therapy or only a diagnostic biopsy, 13 had stable disease at long-term follow-up (41). Similarly, Listernak et al. noted that only three of 33 asymptomatic or minimally symptomatic patients with optic pathway tumors exhibited progressive tumor growth or deteriorating vision after diagnosis with a median follow-up of 2.4 years (45). Our own experience largely concurs with the results of these studies: only 10 to 20 percent of asymptomatic or minimally symptomatic optic pathway lesions that are detected on a screening MRI either enlarge or cause clinical deterioration that merits therapy within several years of diagnosis. However, in view of the often indolent growth characteristics of these neoplasms, longer follow-up studies will be needed to define the natural history of the remaining lesions with certainty.

Because most optic pathway lesions in patients with NF1 are asymptomatic and show a low frequency of significant enlargement during a span of several years, the role of routine surveillance imaging is problematic. Many centers now limit imaging to patients with new or progressive symptoms and signs, such as nystagmus, strabismus, visual loss, visual field deficits, precocious puberty, growth delay, diencephalic syndrome, headache and other symptoms of increased intracranial pressure; the remaining patients are given annual clinical evaluations and neuro-ophthalmology examinations. One drawback

to this approach is that children younger than five years can insidiously develop significant visual impairment that eludes detection because objective testing of vision is often difficult in these young patients. Accordingly, we often obtain a baseline imaging study in children with NF1 first evaluated at less than five years of age, after which time a thorough ophthalmological evaluation can generally be performed. Subsequent MRI studies are performed every year or two if the patients are still too young to reliably cooperate with vision testing and in older children with newly diagnosed or progressive visual impairment. We no longer routinely image older children and, instead, prefer annual or semiannual clinical evaluations, which include detailed testing of visual acuity and fields, as well as a general physical and neurological examination with special attention directed toward looking for signs of neuroendocrine impairment.

However, the aforementioned guidelines do not apply to those children with severe visual compromise. In our experience, patients who exhibit significant visual loss have a high risk of further visual deterioration and require either very close follow-up (e.g., every three months) or immediate therapy. These recommendations also do not apply to children who have sizeable, symptomatic lesions on their initial imaging studies, because these patients generally require immediate intervention.

In those patients with symptomatic lesions or progression of initially asymptomatic lesions, the management options and outcome are, with several caveats, comparable to those for patients without NF1. Symptomatic chiasmatic-hypothalamic tumors in NF1 patients seem to carry a more favorable prognosis than comparable tumors in patients without NF1 (41,43,47,48). For example, Hoffman et al. noted that whereas only one of 23 patients with NF1 and optic-hypothalamic glioma died of disease progression, seven of 39 patients without NF1 died ($p = 0.045$) (41). Deliganos et al. (48) also noted that time from diagnosis to progression among children with symptomatic optic pathway gliomas arising in association with NF1 was substantially longer than for patients with sporadic tumors (8.4 years vs. 2.4 years, respectively). With an average follow-up of 10.2 years, only five of 16 patients with NF1 exhibited disease progression (48).

With increased understanding of the natural history of optic pathway lesions in patients with NF1, the indications for surgical intervention have narrowed considerably. Biopsy for purely diagnostic reasons is generally not needed because the histological identity of a given lesion is rarely in doubt. Rarely, in a patient diagnosed with an optic nerve glioma that is clearly unilateral and in whom proptosis and severe visual loss are apparent, surgical resection of the involved nerve from the globe to the chiasm may be indicated. Such lesions are uncommon because the majority of tumors in patients with NF1 also involve the chiasm and contralateral optic nerve. In these children, radiotherapy or chemotherapy, which are described in detail below, may be preferable. Such cases should be distinguished from the occasional instances of patients with an orbital plexiform neurofibroma that extends backward from the globe toward the anterior cavernous sinus, in which radical resection of the lesion may be required. Surgery has also been advocated for children with large tumors growing exophytically from the optic chiasm (41,49). However, it remains uncertain whether the duration and quality of survival that are achieved with aggressive resection represent an improvement over those obtained with non-surgical approaches (50).

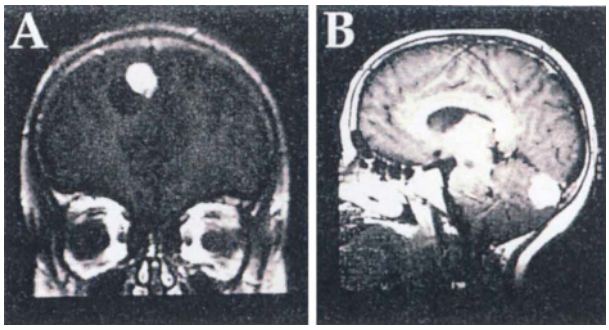

Figure 3. Cerebra **(A)** and cerebellar **(B)** low-grade astrocytomas in patients with NF1.

In contrast to the above tumors, the majority of optic-hypothalamic gliomas are clearly not candidates for excision because of their diffuse involvement of the optic apparatus and hypothalamus. Radiation therapy has long been used for the treatment of these unresectable lesions (44,47,51) and provides excellent results in terms of disease stabilization and, occasionally, regression, often leading to significant improvement in visual function. However, radiation may result in severe cognitive and endocrine deficits (44,52-54) and places the patient at risk for radiation-induced malignancies (55) and vasculopathy, such as moya moya syndrome (56).

Accordingly, in recent years, chemotherapy has been used increasingly in the management of these tumors, particularly for patients younger than five (57-59) in whom the risks of radiotherapy are particularly high. A variety of regimens have been employed with response or stabilization rates of 75 to 100% and median progression-free survivals in excess of three years (57-59). Although many children will ultimately require radiotherapy for long-term disease control, the ability to avoid or at least delay the use of radiotherapy in such children is probably of benefit in improving functional outcome.

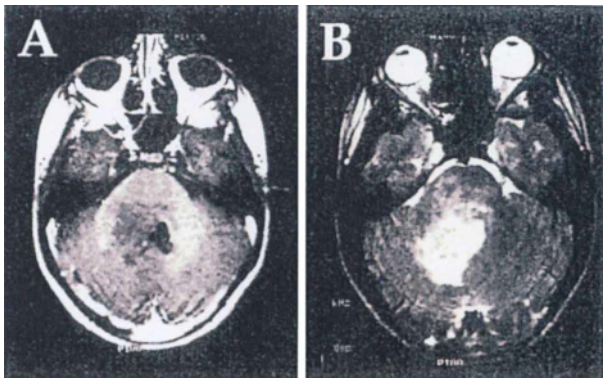

Figure 4. These MRIs demonstrate a common imaging abnormality in patients with NF1. The brain stem is diffusely enlarged with decreased T1 signal intensity **(A)** and increased T2 signal **(B)** over a wide area centered at the cerebellar peduncle, in some ways resembling the appearance of diffuse intrinsic tumors in patients without NF1. No imaging evidence of tumor progression has been detected during a follow-up interval of four years. Reproduced by permission of the publisher from: Pollack IF, Mulvihill JJ. Special issues in the management of gliomas in children with neurofibromatosis. In: *Gliomas of Childhood: Current Perspectives*, Pollack IF (ed), pp. 257-268, Kluwer Academic Publishers:Boston

Cerebral and Cerebellar Hemispheric Gliomas. A small percentage of patients with NF1 develop enlarging lesions within the cerebral (Figure 3A) or cerebellar (Figure 3B) hemispheres that differ in appearance from UBOs. The majority of such lesions are gliomas, which exhibit local mass effect and decreased signal on T1-weighted images with enhancement that may either be uniform, ring-like, in the form of a mural nodule or absent altogether. Ilgren et al. found that more than half of the NF1-associated non-optic tumors were histologically malignant (60) in a comprehensive review of symptomatic brain tumors listed in the Childhood Cancer Research Group registry and other sources from Great Britain in the era before MRI. However, our own observations in a more recent group has been that the majority of lesions are benign and amenable to complete or nearly complete resection. Accordingly, we favor aggressive excision of accessible lesions within the cerebral and cerebellar hemispheres to achieve a complete resection. Various intraoperative adjuncts, such as stereotactic guidance, have allowed resection of deep-seated lesions with minimal morbidity.

Postoperative management is guided by histopathological diagnosis. Low-grade gliomas are managed expectantly after a radiographically complete resection and, in some cases, after a radical subtotal resection. In patients with a sizeable volume of unresectable tumor and in those whose tumors recur after an initially extensive resection, adjuvant radiotherapy or chemotherapy are performed as outlined above. In carefully selected cases with well localized unresectable disease, stereotactic radiosurgery may have a therapeutic role after an initial resection, an episode of disease progression or as salvage therapy in patients with progressive disease after conventional treatment (61).

Patients with malignant gliomas are managed in the same fashion as are those patients without NF1. After an attempt at maximal surgical resection, a combination of involved field radiotherapy and chemotherapy are administered to patients older than three years of age. Younger children are initially treated with chemotherapy to defer irradiation for as long as possible. A variety of chemotherapeutic regimens have been studied in multi-institutional trials (62,63), although the optimal combination and doses of agents remains uncertain. Unfortunately, even with maximal therapy, the majority of affected patients die of progressive disease.

Brain Stem Gliomas. A number of characteristic lesion types are observed in patients with NF1. The most common abnormality is a diffuse area of brain stem enlargement associated with an increased signal on T2-weighted images (35,38,64) (Figure 4). Although such lesions have been grouped in some reports with other UBOs, these lesions are distinctive because they are substantially larger than typical UBOs, produce definite mass effect, exhibit abnormal signals on T1-weighted images, do not regress over time and are often associated with mild focal neurological deficits. Those cases that have been biopsied have been found to be low-grade gliomas (65,66); however, their behavior is even more indolent than would be expected for typical low-grade gliomas because they often remain quiescent for years without adjuvant therapy. This raises the question of whether these lesions are more appropriately classified as glial hamartomas. The generally benign behavior of these lesions mandates a correspondingly conservative approach to therapy. Thus, although these lesions may superficially resemble diffuse intrinsic tumors in patients without NF1, their prognosis generally differs drastically from these biologically malignant lesions (60,65,67). Accordingly, aggressive intervention is limited to those patients who show clear-cut clinical and/or radiographic progression.

A second group of brain stem lesions in patients with NF1 are focal-enhancing masses that are hypointense to the brain on T1-weighted images (Figure 5, A and B) and may be associated with adjacent cystic areas (64,66). This appearance suggests that these lesions are low-grade pilocytic astrocytomas, which has generally been confirmed histologically in those tumors that have been resected (Figure 5C). The biological behavior of these lesions is generally indolent but, ultimately, unpredictable. We have undertaken treatment in those children in whom progressive tumor enlargement was associated with significant local mass effect or with the development of progressive clinical symptoms.

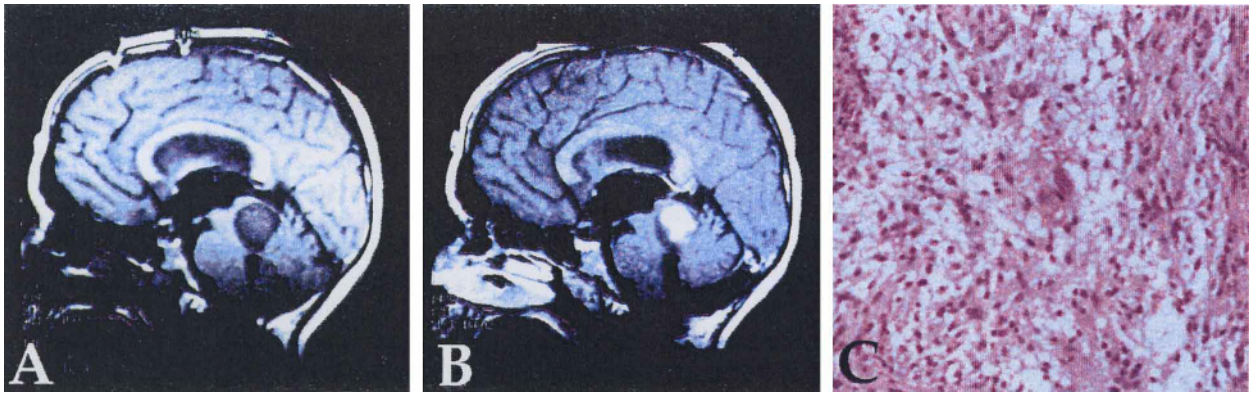

Figure 5. This large exophytic midbrain mass was detected in a 16-year-old girl who suffered from headaches and confusion secondary to obstructive hydrocephalus. **A.** The lesion is hypointense to the brain on this unenhanced T1-weighted image. **B.** Central enhancement is seen on this gadolinium-enhanced image. **C.** Histopathological examination of the operative specimen demonstrated pilocytic astrocytoma.

A final group of brain stem lesions in patients with NF1 are periaqueductal gliomas, which, unlike the above-mentioned lesions, are generally isointense to the brain on T1-weighted images and nonenhancing. These lesions characteristically produce late-onset aqueductal stenosis and are presumed to be low-grade gliomas or glial hamartomas, although biopsy confirmation has been reported in only a few cases (64,68). These indolent tumors generally remain quiescent for years without intervention, similar to the behavior of benign tectal tumors in patients without NF1 (68). We generally treat these patients symptomatically with third ventriculostomy or shunt insertions and obtain follow-up imaging on a yearly basis for five years and periodically thereafter. Biopsy and adjuvant therapy are reserved for lesions that progress symptomatically.

Neurofibromas. Paraspinal and peripheral neurofibromas are observed in the vast majority of patients with NF1. Although these tumors have been categorized in the past with neurilemomas, which are characteristic of NF2, these two groups of tumors are readily distinguished upon histological analysis (69,70). Neurilemomas characteristically exhibit alternating areas of cellular (Antoni A) architecture with palisading spindle cells that orient into Verocay bodies (71) and Antoni B architecture comprised of a loose array of spindle cells in a mucinous background. Neurofibromas, however, are comprised of spindle cells in a myxomatous stroma incorporating myelinated and unmyelinated axons (Figure 6, A and B), which are rarely seen in neurilemomas (Figure 7, A and B).

Neurofibromas are best demonstrated using MRI, which is useful for delineating the relationship between the tumor, surrounding nerve(s) and adjacent structures (72,73). Based on imaging appearance, these lesions may be categorized as either fusiform or plexiform neurofibromas. The former lesions are discrete neoplasms that involve a circumscribed area of a nerve, whereas the latter exhibit diffuse involvement of a broad extent of one or more nerves (72). These lesions may arise subcutaneously, within one or more peripheral nerves, on a major nerve plexus or on an exiting spinal nerve root.

Subcutaneous neurofibromas usually begin as raised subcutaneous masses that may enlarge and

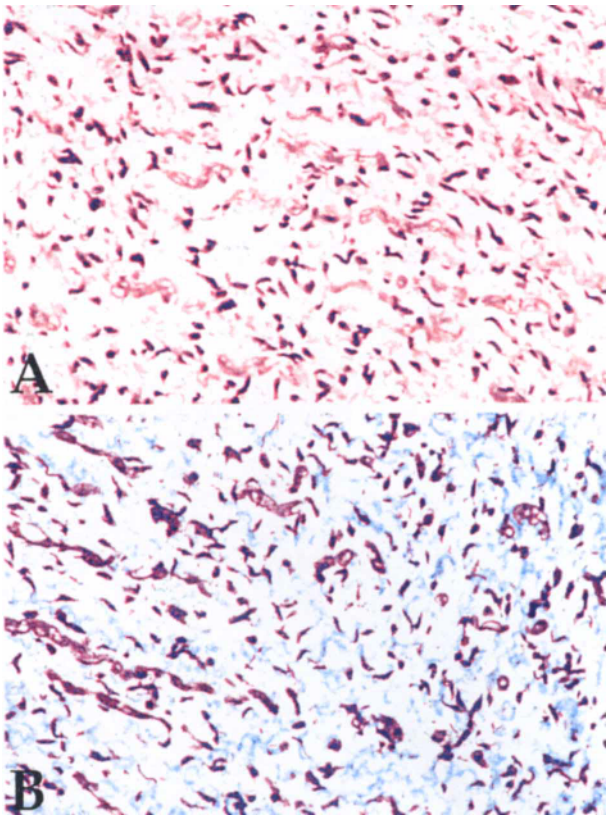

Figure 6. A. H&E-stained paraffin section of neurofibroma. A peripheral nerve twig is disrupted by a chaotic proliferation of spindle-shaped tumor cells. Residual myelin fibers mark the remaining peripheral nerve. The cytoplasm of individual neoplastic cells is difficult to resolve. Tumor nuclei are hyperchromatic and also spindle in shape. **B.** Trichrome-stained paraffin section of neurofibroma. Trichrome preparations permit easier identification of residual myelinated fibers.

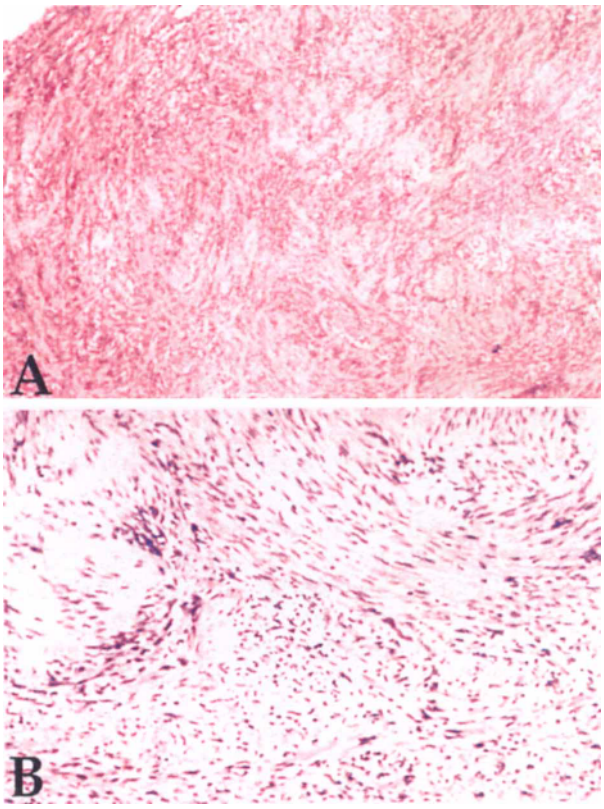

Figure 7. **A.** H&E-stained paraffin section of neurilemoma. Palisading of tumor cell nuclei with intervening cytoplasm form distinct Verocay bodies. **B.** H&E-stained paraffin section of neurilemoma. At great magnification, the spindle-shaped tumor cells are observed to grow in a disorganized mesh resembling a neurofibroma, except for the absence of entrapped nerve fiber twigs.

become pedunculated over time. Because these lesions arise from small cutaneous nerves, they may be resected without neurological deficit, although this is generally not practical because new lesions continue to arise throughout the patient's life. However, resection is clearly indicated for lesions that are painful, enlarging rapidly, or arising in an area prone to irritation, such as the belt-line. Because a small percentage of these tumors will become malignant (i.e., neurogenic sarcomas), patients are encouraged to report lesions that enlarge rapidly, become red or ulcerated or cause progressive discomfort because excisional biopsy may be indicated.

Peripheral nerve neurofibromas, if symptomatic, produce neurological dysfunction in the distribution of a major nerve with pain and paresthesias, often brought on by pressure upon the involved nerve (72). Unlike neurilemomas, which typically involve a single fascicle of a major nerve, neurofibromas often involve many or all fascicles of a nerve, thereby limiting resectability (72). The management of these lesions has been controversial, with some authors recommending biopsy and observation (74), others advocating *en bloc* resection with reconstruction of the involved nerve (75,76) and others favoring intracapsular enucleation. However, in many fusiform lesions, it is possible to resect multiple involved fascicles without sacrificing significant neural function (72). Intraoperative nerve stimulation techniques are useful to confirm that fascicles to be sectioned in order to remove the tumor are indeed nonfunctional. In some cases, complete resection is not feasible without risking neurological impairment, and a subtotal resection may be advisable. For lesions that exhibit malignant features, operative and postoperative management involve a multidisciplinary approach incorporating neurosurgical, general surgical, orthopedic, medical oncology and radiation oncology input (77,78).

For plexiform lesions, total resection is possible if only a single nerve is involved, in which case resection and reconstruction may be feasible (72,75,76,79). Complete resection is generally not practical for lesions of the brachial plexus or lumbosacral plexus and, in such locations, is usually reserved for cases with malignancy (80). Similarly, for large plexiform lesions of the thoracic and abdominal cavities and the parapharyngeal region, complete resection is not a realistic goal. Subtotal resection is often indicated to relieve pain (for plexus lesions), pulmonary compromise (for large intrathoracic lesions), upper airway obstruction (for parapharyngeal neurofibromas), abdominal discomfort or spinal cord compression (from transforaminal encroachment of a paravertebral tumor). Patients with unresectable plexiform lesions are appropriate candidates for NF1 chemotherapy protocols. The recent study of 13-cis retinoic acid and interferon-2α demonstrated efficacy of both regimens in stabilizing previously progressive disease, although objective disease regression was not observed (81). Future approaches will likely focus on inhibiting the ras pathways that are overactivated in patients with NF1 as a result of their impaired neurofibromin function. Farnesyltrans-ferase inhibitors, which interfere with ras processing, are particularly promising in this regard and have shown efficacy against other ras-dependent neoplasms (82).

Paraspinal neurofibromas are usually fusiform tumors that involve nerve roots at their entry into the spinal canal (Figure 8A). Because most lesions enlarge slowly and patients commonly have multiple lesions, intervention is reserved for tumors that progressively encroach into the spinal canal (Figure 8B). These lesions are typically approached using a laminectomy for the intraspinal component. The extraspinal component may be removed transforaminally if the tumor is small and medially located, but larger lesions require a separate, more laterally directed approach, which varies depending on the spinal level involved. Resection of the involved nerve root is often required to obtain complete tumor removal,

but this can often be accomplished without producing severe neurological impairment (83,84).

NF2. *Vestibular Neurilemomas.* Tumors of the eighth cranial nerve occur in more than 90 percent of patients with NF2 and often become symptomatic in late adolescence or adulthood; however, with proactive screening of the young children of affected adults (85,86), an increasing number of lesions are detected during childhood (Figure 9). The finding in a child of a posterior cataract or multiple spinal cord or peripheral nerve tumors without Lisch nodules, café-au-lait macules or an alternative explanation, should raise concern about a diagnosis of NF2, and such children should undergo an MRI examination for intracranial manifestations of the disorder.

There is general agreement that MRI is the optimal screening tool for vestibular neurilemomas in individuals at risk for NF2 and that periodic hearing tests are indicated for the functional evaluation of affected patients. However, the indications and preferred approaches for the treatment of these lesions, once detected, remain controversial. In a patient with a large lesion causing significant brain stem compression, the decision to proceed with surgical resection is relatively clear-cut. However, for patients with small, asymptomatic lesions, the optimal approach for preserving function is less obvious. Some surgeons recommend early attempts at radical tumor resection because the chance for preserving hearing and avoiding facial nerve injury intraoperatively is greatest when the lesion is small (87-89); in skilled hands with lesions smaller than one centimeter, the likelihood of preserving hearing exceeds 50% and that of maintaining facial nerve function exceeds 90%. However, the risks of iatrogenic hearing loss are all "up-front" and pose a major concern in patients with functional hearing in whom tumor- or treatment-induced deafness in the contralateral ear is a significant long-term risk. Among those who favor early surgery in patients with bilateral tumors, some recommend first removing the larger lesion, which is most likely to pose an initial threat of ipsilateral hearing loss, whereas others advocate removing the smaller lesion, which theoretically affords the patient the best chance of achieving both tumor removal and ipsilateral hearing preservation. Tumor resection is often combined with placement of a cochlear or auditory brain stem implant, which may provide a way for ensuring at least some hearing preservation in patients with bilateral tumors who undergo surgical intervention (90,91).

An equally convincing argument can be made for deferring surgery until there is objective evidence of tumor progression or hearing loss because of the variable natural history of these lesions. Stereotactic radiosurgery provides an alternative approach for the treatment of such lesions (92). Although it is uncertain whether the chances for hearing preservation are any better than those with open resection, hearing loss generally occurs in a delayed fashion, which provides the patient time to learn sign language and lip reading. Another approach that has been advocated in patients with bilateral tumors is subcapsular resection of the lesion, leaving a small amount of tumor adherent to the facial and acoustic nerves in order to minimize the risk of irreversible nerve injury (93). In the absence of objective data to support one management approach vs. another, we believe that therapeutic decision-making should be individualized, taking into account the risk tolerance of the patient, after the various management approaches with their pros and cons have been thoroughly discussed with the patient and family. Because of the complexity of the management issues involved, a supraregional approach to the care of affected patients has been advocated in order to optimize functional outcome (94).

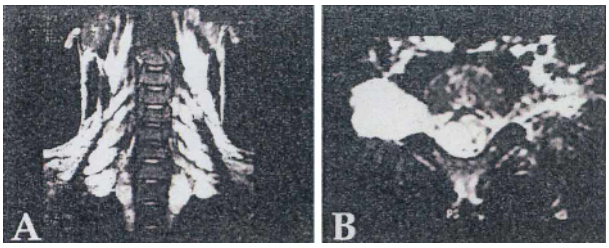

Figure 8. A. Multisegmental involvement of the exiting spinal nerve roots by neurofibromas in a patient with NF1. These lesions caused no intraspinal compression and have remained stable for more than four years without intervention. **B.** Intraspinal growth of a paraspinal neurofibroma in a nine-year-old boy caused a mild, progressive Brown-Sequard syndrome; the intraspinal and extraspinal components of this lesion were resected completely three years ago, and the patient remains free of disease progression.

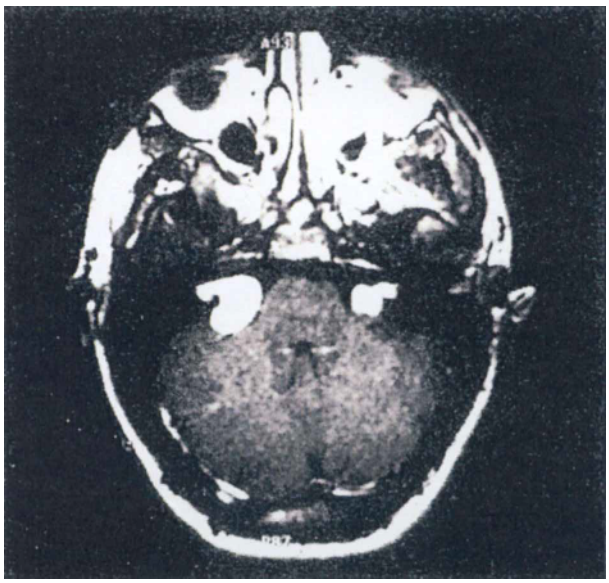

Figure 9. Bilatera vestibular neurilemomas in a 16-year-old child of a woman with known NF2.

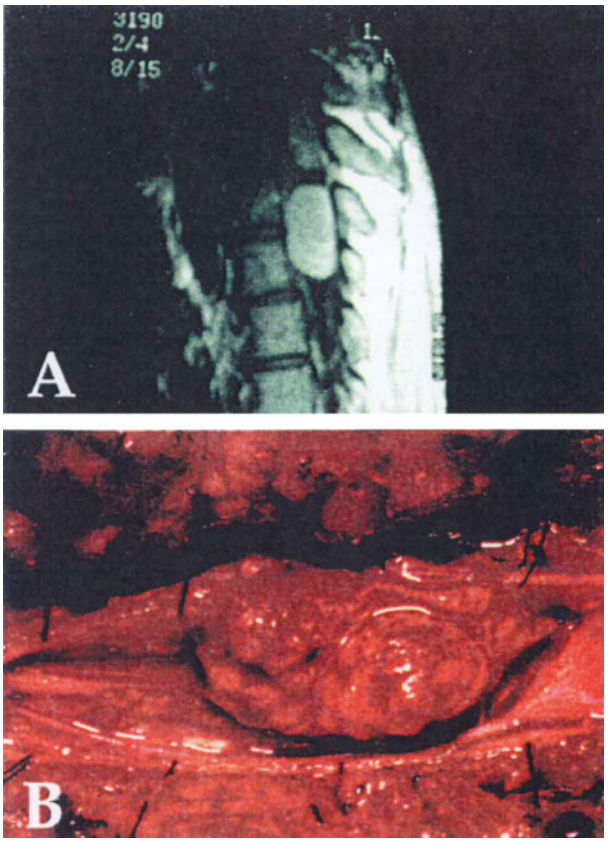

Figure 10. A child with NF2 with multiple intraspinal tumors causing progressive myelopathy. **A.** Both a meningioma and neurilemoma are apparent in this MRI. **B.** The severity of the spinal cord compression by one of these lesions is illustrated. The spinal cord, which is apparent at the right and left of the figure, is flattened to a thin ribbon that is draped around the large tumor. The child recovered normal neurological function postoperatively.

Intracranial Meningiomas and Non-Vestibular Cranial Nerve Neurilemomas. Approximately half of patients with NF2 have intracranial meningiomas, and more than 30% have multiple non-vestibular neurilemomas (15,85,86). From a therapeutic standpoint, many of the controversial issues regarding vestibular neurilemomas also apply to other intracranial neurilemomas and meningiomas. These lesions exhibit unpredictable biological behavior, with some tumors remaining quiescent for extended intervals and others enlarging rapidly. Because affected patients often develop multiple intracranial neurilemomas and meningiomas, we generally reserve operative intervention for large lesions that are causing obvious neural compression as well as those exhibiting progressive growth. However, vigilant imaging and clinical follow-up are needed for lesions that are managed conservatively. As noted above, radiosurgery or focused radiotherapy techniques may provide a useful therapeutic option for lesions that are difficult to remove without significant morbidity (e.g., cavernous sinus meningiomas), for lesions that can only be partially removed and for those that recur after an extensive resection.

Intraparenchymal Gliomas. Patients with NF2 may develop intrinsic glial neoplasms of the brain, but such lesions are less commonly seen than with NF1. In contrast, intraspinal intramedullary tumors are more common in NF2 (85,95,96). In such patients, ependymomas are more frequent than astrocytomas, whereas the converse is observed with NF1 (97). Because ependymomas are generally well circumscribed, complete resection is often feasible and is indicated for lesions that are large and that show definite signs of progression (97).

Extracranial Neurilemomas and Meningiomas. Intraspinal growth of a combination of nerve sheath tumors and meningiomas is seen in a significant percentage of patients with NF2 (Figure 10A) (85,95). Because these tumors grow slowly and displace the surrounding neural structures, large lesions may be asymptomatic despite the severity of associated cord compression (Figure 10B). However, such patients can exhibit rapid deterioration in neurological function with small amounts of subsequent tumor growth. Accordingly, even in the absence of symptoms, we have generally advocated tumor resection for patients with radiographic evidence of pronounced cord compression. Not unexpectedly, we have observed that children who exhibit intact neurological function preoperatively maintain this function during the postoperative period, and many patients with significant deficits improve, whereas those with profound impairment fail to recover, which supports the concept of early surgery. Because some patients exhibit severe multisegmental cord compression, we generally perform a screening evaluation of the entire spine in any newly diagnosed patient with NF2 who manifests myelopathy because several lesions at different levels may need to be removed (Figure 10A) (15,85,95). We do not, however, routinely remove lesions that are producing little or no spinal cord compression and, instead, follow these tumors periodically with clinical evaluations and MRI examinations of the spine.

Because most nerve sheath tumors in NF2 are neurilemomas (70) rather than neurofibromas, these lesions generally arise from a single nerve fascicle and are well encapsulated. Complete resection of intraspinal lesions can often be achieved with minimal neurological morbidity (72) if injury to adjacent uninvolved fascicles and to minimize cord manipulation is avoided. Similarly, extra-spinal neurilemomas that arise on a peripheral nerve can usually be resected without significant loss of neural function. By identifying the involved fascicle entering and leaving the tumor and dissecting off the surrounding uninvolved fascicles, the surgeon can generally remove the tumor and leave the bulk of the nerve intact.

In general, meningiomas (Figure 11, A and B) can be removed without resecting any neural elements. However, because they often arise ventrolaterally within the spinal canal, great care must be taken to avoid excessive manipulation of the spinal cord during the course of tumor removal. We commonly use somatosensory evoked potential monitoring as a warning tool during the resection of meningiomas as well as large neurilemomas. The observation of latency shifts or deterioration in the amplitude of the recordings in the absence of an alternative explanation guides us in altering our surgical plan to minimize inadvertent cord manipulation.

Counseling

In addition to the acute evaluation and management of medical and surgical problems that arise in the context of NF1 and NF2, affected patients and their families generally benefit from a comprehensive approach to their chronic multisystem genetic disorder, which is often best provided by a clinical geneticist or genetic counselor. A clinical geneticist or genetic counselor can clarify inheritance risks for the patient or parents; discuss reproductive options, including prenatal diagnosis, gene testing and assisted reproductive procedures; offer anticipatory guidance; and conduct or expedite diagnostic examinations for other family members who may be at risk for having NF. As genetic testing becomes commercially available, the changing risks and benefits of undergoing DNA analysis of the genes for NF1 and NF2 also need to be discussed with affected or potentially affected families.

Because patients and families affected by NF1 and NF2 are faced with a lifetime of uncertainty regarding potentially debilitating or life-threatening consequences of the disorder, which may be superimposed on chronic difficulties in learning and socialization (in NF1) and cosmetic concerns (both disorders), social service or psychological support are often beneficial. Neuropsychological testing and early intervention services are particularly helpful in young patients with NF1 who are experiencing delays in cognitive development in order to define specific areas of learning difficulty and facilitate proactive educational assistance. Also, local support groups, often affiliated with one of the two NF organizations in the United States (the National Neurofibromatosis Foundation and Neurofibromatosis, Inc.), provide patients and families with an opportunity to share their experiences with others and keep abreast of new developments in the field. Finally, a geneticist, neurologist, or knowledgeable generalist, such as a family practitioner, pediatrician, or internist, should monitor the patient using published guidelines for health supervision (98,99), which complements the periodic comprehensive evaluations that are provided by a multidisciplinary NF clinic.

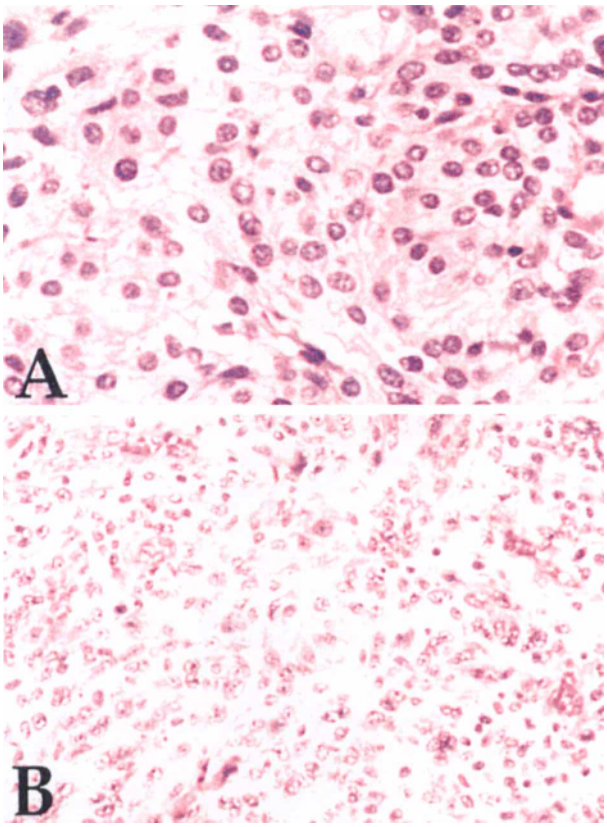

Figure 11. A. H&E-stained paraffin section of meningioma. Meningiomas have been subdivided into a variety of histopathological types of questionable prognostic significance. These figures demonstrate a meningotheliomatous subtype. Tumor cells have abundant eosinophilic cytoplasm and grow in a pavement with defined cell borders. **B.** H&E-stained paraffin section of meningioma.

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