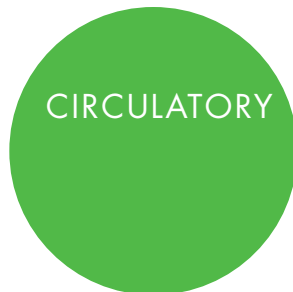




NEUROFIBROMATOSIS:



A DISTURBING



AND ELUSIVE DISEASE



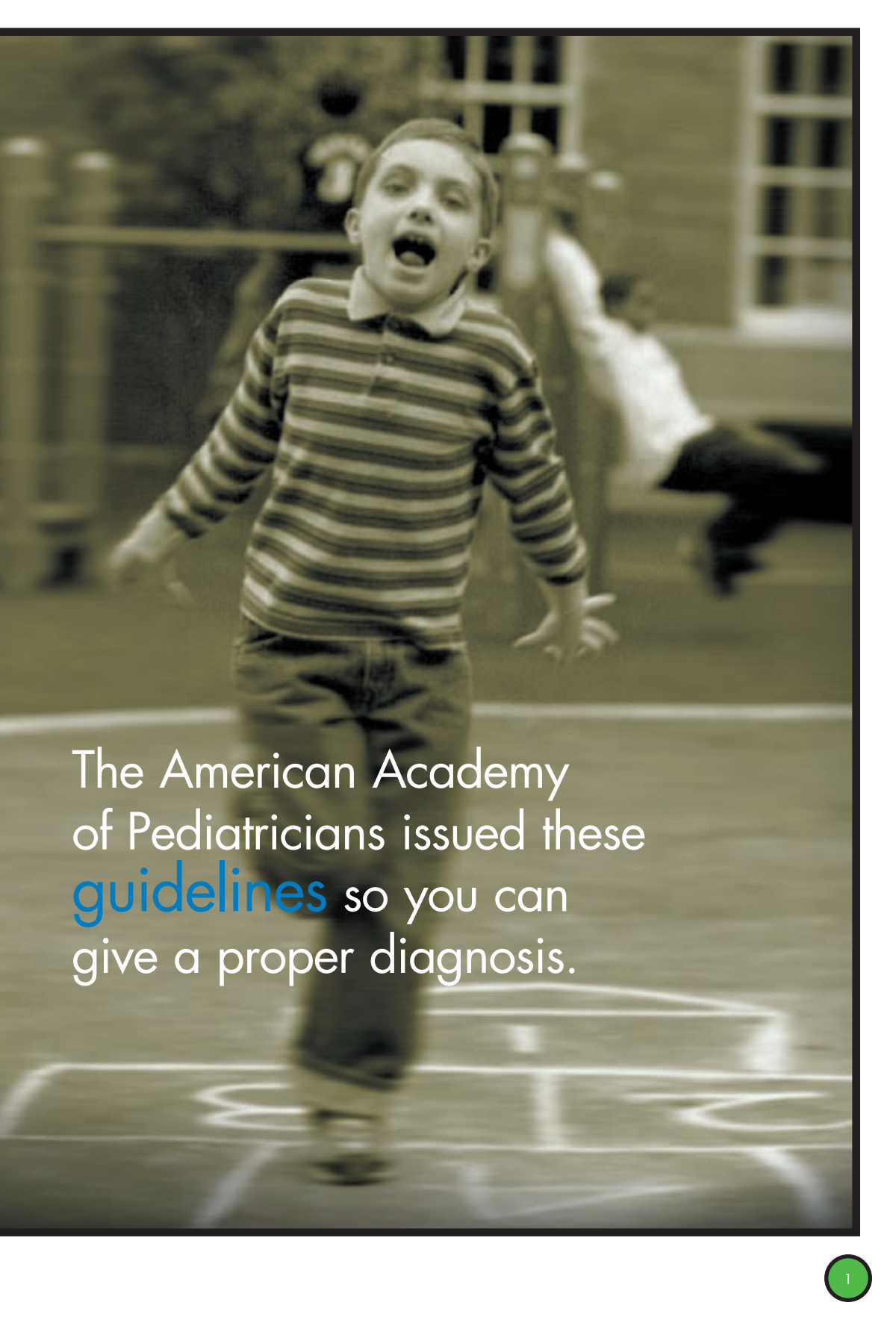
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● A SERIOUS AND MISUNDERSTOOD DISORDER

Although neurofibromatosis has been known to the medical community since 1882, there has been widespread misinformation and a lack of precise medical management guidelines available to both physicians and patients until recently.

Pittsburgh's NF Clinic serves as a beacon of information and medical expertise for thousands of families in the region. At its founding, in 1989, access to medical specialists and diagnostic testing and technology was sporadic, at best. In the 15 years since, physicians, geneticists, social workers, diagnostic technicians, nurses and other service providers have focused their clinical efforts and research interests, resulting in the highest possible care and guidance for NF patients and their families.

The highly unpredictable nature of NF requires a level of cross-specialty coordination and communication unlike that of most disorders. This brochure serves as a base reference for primary care givers who can provide the first and most important intervention by recognizing the early warning signs that lead to early diagnosis.

A young boy in a striped polo shirt and jeans is running on a basketball court. He has his mouth wide open as if shouting or calling out. In the background, another person is visible, possibly a player or coach, in a white shirt and dark pants, also in motion. The court has white chalk lines on it. The overall tone is energetic and focused on the child's action.

The American Academy
of Pediatricians issued these
guidelines so you can
give a proper diagnosis.

● PEDIATRIC GUIDELINES FOR NF1

The American Academy of Pediatrics issued the following guidelines for the medical supervision of a child diagnosed with NF1. The guidelines underscore the need for ongoing assessment and periodic review throughout a patient's life.

1. Evaluate the child for new neurofibromas and progression of lesions. Examine the skin carefully for signs of plexiform neurofibromas that may impinge on or infiltrate underlying structures.
2. Check the child's blood pressure. Because renal disease (particularly renal artery stenosis), aortic stenosis, pheochromocytomas (more common in adults) and adrenal tumors may occur, regular and careful blood pressure measurements are important. A variety of vascular hypertrophic lesions may be found.
3. Evaluate neurodevelopmental progress.
4. Evaluate the child for skeletal changes. Look for scoliosis, vertebral angulation, and limb abnormalities. Sometimes localized hypertrophy of a leg, arm, or other part of the body results from plexiform neurofibromata.
5. If any complications occur or if neurocutaneous lesions appear to be rapidly advancing, refer to the appropriate specialist.
6. Recommend available resources for patients with NF1 (eg, NF clinics, support groups, and individual NF1 families).

● MANIFESTATIONS OF NF

NF and other major genetic disorders affect 13 million Americans

Manifestations of NF2

Neurofibromatosis 2 (NF2), also called Bilateral Acoustic Neurofibromatosis (BAN) or Central Bilateral Acoustic NF, is a rare (1 in 40,000 persons) type of NF characterized by multiple tumors on the cranial and spinal nerves. Other lesions can also impinge on the brain and spinal cord. Persons with NF2 are at a high risk for developing brain tumors and almost all affected individuals develop tumors on both nerves to the ears (also called the eighth cranial nerve). Tumors affecting both of the auditory nerves are the hallmark. See page 16 for more on NF 2.

Manifestations of NF1

Although most cases of NF1 are mild to moderate, no two NF patients share the same clinical history. Neurofibromas grow on and near nerves, and therefore can be found throughout the body, NF1 can also impact any of the major human organ systems. The multiorgan occurrence of neurofibromas and other non tumor complications requires close scrutiny and cooperation among a variety of medical and surgical specialists.

Nervous System

About 15 percent of children with NF 1 have thickening or swelling of the optic nerve (optic nerve glioma) which exits the back of the eye and conducts the visual impulse back into the brain. Gliomas also occur on the optic nerve chiasm where the impulses of both optic nerves are blended before the impulse is transmitted to the brain.

Skeletal System

Kyphosis or scoliosis (curvatures of the spine) can occur with or without neurofibroma growth along the spinal column. Pseudoarthrosis, a thinning, bowing and sometimes breaking of the long bones of the legs and arms, can require bracing and casting. Short stature is common in NF1 and must be differentiated from independent

endocrine or familial causes. Macrocephaly is also common (up to 45%) and may be relative rather than absolute among those who are short. The larger head size is not associated with increase risk of CNS related causes such as hydrocephalus.

Endocrine System

Precocious puberty can be seen 1) in the setting of hypothalamic/chiasmatal gliomas or 2) without obvious cause requiring regular assessment of maturation.

Clinical evidence suggests that neurofibromas (cutaneous and plexiform) may develop or grow at times of hormonal fluctuation, particularly with increases in sex steroid hormones (infancy, puberty, pregnancy). Growth of larger internal plexiform neurofibromas can injure tissues, such as spinal cord and orbit, due to compression. Growth of external plexiform neurofibromas can be very disfiguring, and in all cases surgical resection is limited by concerns regarding permanent nerve or other tissue damage.

Respiratory System

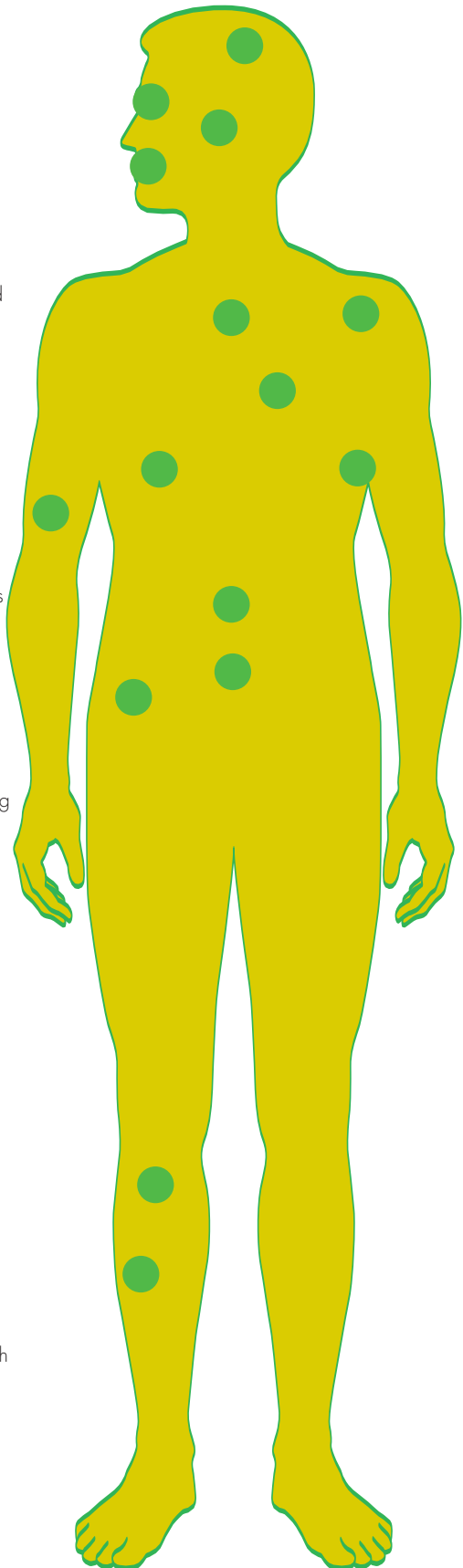
Compromises to the spinal column can weaken associated movement of the rib muscles and diaphragm that diminish pulmonary function.

Circulatory System

Cardiovascular effects of NF1 are not well understood but renal artery stenosis, coarctation of the aorta, and other restrictive lesions in major arteries have been uncommonly described. Hypertension is recognized mostly among adults in association with NF1 even in the absence of renal artery stenosis and can occur independently from other risk factors for Hypertension.

Digestive System

Neurofibroma growth along the digestive tract, stomach and small intestine may cause difficulty swallowing, pain, vomiting, chronic constipation or diarrhea.





OPTIC GLIOMAS HEADACHES NEUROFIBROMAS TUMORS



● NEUROFIBROMATOSIS TYPE 1 *by Dr. Gulay Alper, M.D., Children's Hospital of Pittsburgh*

Neurofibromatosis type I (NF1) is an autosomal dominant genetic disorder that usually appears in childhood and adolescence. NF1 and NF2 are two separate genetic disorders, with the latter having much lower incidence. The prevalence of NF I is 1/3000 and approximately 80,000-100,000 individuals in the USA have NF.

Clinical spectrum

The clinical expression of NF1 varies even within the families. Many people with NF1 live a normal life with relatively little impact from the disease. Others have chronic debilitating disease sometimes with life-threatening medical complications. This extreme variability is one of the most striking and challenging features of NF1.

The main target of NF1 is the nervous system. It can cause tumors, mostly benign, of peripheral nerves, optic nerves, and less commonly tumors of the brain itself. Tumor growth however, in a restricted space can lead to serious neurological deficits. NF1 also can affect the development of non-nervous tissues such as bone and skin.

The NF1 gene is a tumor suppressor in some cells. Neoplastic manifestations of NF1 include:

- Plexiform neurofibromas (25-50%)
- Visual pathway gliomas (15-20%)
- Gliomas (1-6 %)
- Malignant peripheral nerve sheath tumors/sarcomas (2-5 %)
- Pheochromocytoma (1%)
- Leukemia (less than 1%)

Skin manifestations:

- Café-au-lait spot
- Cutaneous and subcutaneous neurofibromas
- Axillary and inguinal freckling

Other manifestations:

- Learning disability, cognitive deficits, ADHD
- Macrocephaly
- Headaches
- Osseous dysplasia
- Scoliosis
- Hypertension
- Seizures
- Moya Moya disease due to vasculopathy of major brain arteries
- Precocious puberty

Genetics

NF1 is transmitted as an autosomal dominant disease associated with a mutation on chromosome 17. In approximately half of the cases NF1 occurs in an individual who has no family history. Complete or nearly complete penetrance of NF1 implies that if a child with NF1 is born to unaffected parents, the child probably represents a new mutation. However, since NF1 exhibits considerable clinical variability even within a single family, a parent with NF1 may be more mildly affected than his or her child. Therefore both parents may require complete clinical and ophthalmologic

examinations before it can be concluded that they are, in fact, unaffected.

Routine molecular genetic testing of patients in whom NF1 is suspected is not currently recommended for several reasons. A definitive diagnosis can usually be made on the basis of clinical and ophthalmological examinations in most patients, especially in those over 10 years of age. The wide range of NF1 mutations and the large size of the gene have made mutation analysis difficult, with concerns regarding inadequate sensitivity for the test. However mutation analysis is now available for indeterminate cases and test sensitivity continues to improve.

Evaluation and Diagnostic Criteria

The appearance of most signs of NF1 is age-dependent. Cardinal features of NF1, such as Lisch nodules and cutaneous and subcutaneous neurofibromas are uncommon in young children and do not reach maximum frequencies until adulthood. However the frequencies of many other signs (especially skin findings of café-au-lait and axillary, inguinal freckles) increase rapidly during childhood, so that the reliability of the NIH (National Institute of Health Consensus Development Conference, 1988) diagnostic criteria improves every year as the child grows older.

Children who have inherited NF1 from an affected parent can usually be diagnosed early because the diagnosis requires just one clinical sign in addition to positive family history. That clinical sign is usually multiple café-au-lait spots, a feature seen in most NF1 at birth or in the first few years of life. Less frequently the first feature noted is a plexiform neurofibroma or anterior tibial bowing, which may also present early in life.

Symptomatic optic pathway gliomas usually present in the first 3-6 years of life but can be identified later, usually during scans performed for other reasons (headaches etc). Learning disability is the most frequent problem in school-age children. Dermal tumors may develop any

time in life but most often begin to appear in late childhood, adolescence, or even later.

NIH Diagnostic criteria for NF1:

NF1 is diagnosed in a patient who has two or more of the following signs:

1. Six or more café-au-lait macules >5mm in pre-pubertal individuals or >15 mm after puberty
2. Two or more neurofibromas of any type or one or more plexiform neurofibromas
3. Axillary or inguinal freckling
4. A tumor of the optic pathway
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of the long bones (with or without pseudoarthrosis)
7. A first-degree relative with NF1 by above criteria

Other clinical and radiological features suggestive for NF1 include presence of UBOs ("unidentified bright objects") on MRI brain scans, macrocephaly, and short stature which are frequently seen among patients with NF1. These signs do not have sufficient specificity to be useful as diagnostic criterion.

Management:

A multidisciplinary neurofibromatosis clinic can often provide an expert consultation for patients with NF1. The Neurofibromatosis Clinic is a subspecialty clinic under the Division of Child Neurology at Children's Hospital of Pittsburgh. A child neurologist, an adult neurologist, a social worker, a nurse practitioner and three clinical nurses work as a team to see patients at least once a month. Neurofibromatosis Clinic has close connections with other specialties because of frequent referrals due to the natural course of the disease (Pediatric Ophthalmology, Pediatric Neuro-Oncology, Neurosurgery, Medical Genetics, Child Development Unit, and Orthopedics).

All patients with NF1 should be seen at least annually by a physician who is familiar with them and with the disease. The assessment should include an interval history with detailed review of systems and physical examination with particular attention to signs and symptoms associated with NF1. Annual ophthalmological examination is recommended in the first decade of life, since most symptomatic optic gliomas develop within the first 6 years. Cranial MRI is indicated in any child who is suspected of optic pathway glioma. Many of these tumors are asymptomatic but require close follow up including evaluations of visual acuity, growth curves, and repeat scans. Plexiform neurofibromas, including spinal nerve tumors, are somewhat more common than optic

gliomas but can be asymptomatic. An important component of annual clinical visits is to provide anticipatory guidelines regarding features of NF1 that are developing or are likely to develop at the patient's current age.

Chemotherapy is the standard treatment for symptomatic and progressive optic pathway gliomas. Resection of plexiform neurofibromas is potentially a "curative treatment" but complete or even partial resection is often impossible due to extension of tumor into adjacent normal tissues and encasement of the nerves by the tumor. There have been ongoing clinical trials with biological response modifiers for progressive plexiform neurofibromas.



● **THE ORTHOPEDIC MANIFESTATIONS OF NF1** *by Stephen Mendelson M.D.
Children's Hospital of Pittsburgh*

Neurofibromatosis is one of the most common genetic disorders seen by pediatric orthopedic surgeons. There are two primary types of neurofibromatosis. NF1, also known as Von Recklinghausen disease, is the one commonly associated with orthopedic abnormalities. Orthopedic manifestations are seen in 50% of patients with NF1. In addition to effects on the overall rate of bone growth (macrocephaly, short stature) the most common orthopedics conditions in neurofibromatosis include scoliosis reported in up to 10-50%, pseudo-arthritis of the tibia in up

to 19%, interosseous bone lesions in up to 18-38%, protrusio acetabuli in up to 21%, and hemi-hypertrophy in up to 7%. The true incidence of skeletal and many other NF1 associated disorders has been biased due to clinic ascertainment and remains to be defined in larger population based samples.

Scoliosis, associated with NF1 is categorized into dystrophic and non-dystrophic. The etiology of dystrophic scoliosis is thought to be due to primary bone dysplasia and interspinal abnormalities that decrease the integrity of the

spinal column. This abnormality is characterized by a severe spinal deformity as well as bony abnormalities of the adjacent ribs. These deformities can become quite severe. Management is aggressive and involves early surgical instrumentation that includes a complex anterior/posterior spinal fusion in-situ with or without instrumentation. Surgery is generally recommended for any curves that have demonstrated significant progression or any curves with magnitudes greater than 45 degrees. Peri-operative complications include bleeding, infection, and neurologic compromise. Further deformity beyond the initial fused segment is also a common occurrence often requiring a revision surgery. Non-dystrophic scoliosis has a behavior pattern similar to idiopathic scoliosis. Treatment is similar to idiopathic scoliosis with observation for small curves, bracing for moderate curves, and surgical management for large curves in excess of 50 degrees. Surgery does not always require an anterior/posterior spinal fusion. However, a conversion from non-dystrophic to dystrophic scoliosis has been described and needs to be watched for during post-operative care.

Congenital pseudoarthrosis of the tibia is one of the most difficult problems faced by patients with NF1. A pseudoarthrosis is an abnormal union between two fractured bones. The exact cause is unclear. Treatment may involve a complex reconstruction utilizing any available modality to the orthopedic surgeon including internal fixation, intramedullary fixation, bone grafting, external fixation and vascularized pedicle bone transfers. A good outcome with this problem is difficult to obtain. A significant number of these patients result in amputation.

Protrusio Acetabulum is a medial migration of the femoral head in the acetabulum. Most patients have minimal symptoms and are unaware of this problem unless specifically looked for. There may be a higher incidence of osteoarthritis in adulthood. Generally, no treatment is necessary but occasionally a

fusion of the tri-radiate growth cartilage in the acetabulum can limit the severity when identified in a young child.

Hemi-hypertrophy is the overgrowth of one limb relative to the opposite side. This can involve the entirety of a limb or just a portion of the limb. This is often associated with hyperpigmentation of that extremity. Treatment is directed specifically at the local problem.

Interosseous bone lesions are found in patients with NF and appear to be fibrous in nature. They often have the appearance of fibrous cortical defects or non-ossifying fibromas. This is most often an incidental finding. Treatment is only indicated if the lesions are extremely large and involving a significant portion of a weight bearing bone. If treatment is required, a surgical excision and bone grafting is generally curative.

There are many orthopedic problems associated with neurofibromatosis 1. Once a diagnosis is made, the patient needs to be closely examined for these problems. Orthopedic conditions including scoliosis, pseudoarthrosis of the tibia, interosseous bone lesions, protrusio acetabuli, and hemi-hypertrophy are the most common. When orthopedic issues are found, it is critical that proper radiographic laboratory work-up be performed to facilitate proper treatment under the care of a pediatric orthopedic surgeon.



OPTIC GLIOMA
LISCH NODULES
GLAUCOMA
CATARACTS



● OPHTHALMOLOGIC CONSIDERATIONS FOR PATIENTS WITH NF

by Albert W. Biglan, M.D.

The ophthalmologist is part of a larger medical team that helps establish and classify the neurofibromatoses (NF) – NF1 and NF2 – two distinctly different conditions that effect tumor growth along nerves and other areas. No two NF patients present with the same symptoms or severity. This requires medical specialists to develop and monitor a unique course of treatment. Baseline visual function and status of the visual system are established and monitored as part of any ongoing assessment.

Neurofibromatosis, type 1 {NF1}

NF1 usually comes to the attention of the caregivers through the family history or by recognition of the café-au-lait spots that appear during the first year of life. Important diagnostic criteria for NF1 involve the visual system.

- **Lisch nodules:** Approximately 50% of patients with NF1 will have Lisch nodules by 9 or 10 years of age according to prevalence graphs constructed from a large sample population at the National Neurofibromatosis Foundation International database. These gradually appear on the surface of the iris as pinpoint-size raised freckles. Like freckles on the skin, they increase in number and size as children grow. The Lisch nodules require magnification to be identified. The Lisch nodule never affects visual acuity.
- **Optic nerve glioma:** The optic nerve is the nerve that exits the back of the eye and

conducts the visual impulse back into the brain. This impulse is registered and processed in the visual cortex part of the brain. About 15 percent of children with NF1 have thickening or swelling (optic nerve glioma) of the optic nerve or the optic nerve chiasm where the impulses of both optic nerves are blended before the impulse is transmitted to the brain.

- **Plexiform neurofibroma:** This sometimes disfiguring problem affects a small number of patients with NF1. There is an overgrowth of the nerves in the eyelid and the orbit. This will sometimes cause changes in the sphenoid bone, one of the bones that make up the structure of the orbit. This condition may, in some rare situations, cause the globe (eye) to be pushed forward.
- **Thickened corneal nerves.** Sometimes the nerves that are in the cornea appear to be thicker on very high power examinations with the ophthalmologist's slit lamp. These, like the Lisch nodules, have no clinical implications.
- **Glaucoma** and problems with the sub retinal tissue, the choroid, can rarely occur.

Clinical Course: The unpredictable nature of NF means that the clinical course for any given individual is equally unpredictable. Ophthalmologic evaluations should be conducted annually to monitor the vision and course of the condition. When treatment is needed, the frequency of these examinations may be increased.

- Visual acuity is measured by the intensity and quality of the fixation response in very young children. Allen cards or the HOTV isolated letter test or the Snellen acuity chart will be used to measure the acuity in each eye as the children become more mature and responsive. A refraction will be performed to detect any optical errors in the visual system. If indicated, glasses may be prescribed.
- The ophthalmologist will use the swinging flashlight test to closely examine the pupil. The reaction of the pupil to stimulation with light will give valuable information about the function of the optic nerves.
- In older children, a baseline of color vision, testing each eye separately, will be measured. This will be tested at periodic intervals and if there is suspicion of an optic nerve or chiasm problem.
- The eyes will be dilated and the optic nerve and the retina will be examined. Optic nerve atrophy is a loss of color of the optic nerve when viewed with the ophthalmoscope. A careful nerve assessment warrants the use of the cycloplegic drops and the 30-minute wait for the drops to take effect.
- The Hertel exophthalmometer will be used to measure any proptosis (bulging forward of the eye). This instrument is gently applied to the rim of the orbits and mirrors are used to determine the position of the anterior part of the eye, the cornea.
- Visual fields are measured using special equipment (perimeter, either Goldmann or Humphries). This test requires about a half-hour of cooperation and can usually be considered in children around age 10. The test presents lights coming from the periphery of the visual field, and the child or patient will indicate when he/she is able to see the light target. It is common to perform this test every year or two if there is suspicion of a problem in the visual pathway.

Neurofibromatosis, Type 2

The diagnosis of NF2 is usually made later in life than NF1. The most frequent condition is decreased hearing due to swelling (Schwannoma) of the acoustic nerve.

Ophthalmologic features include:

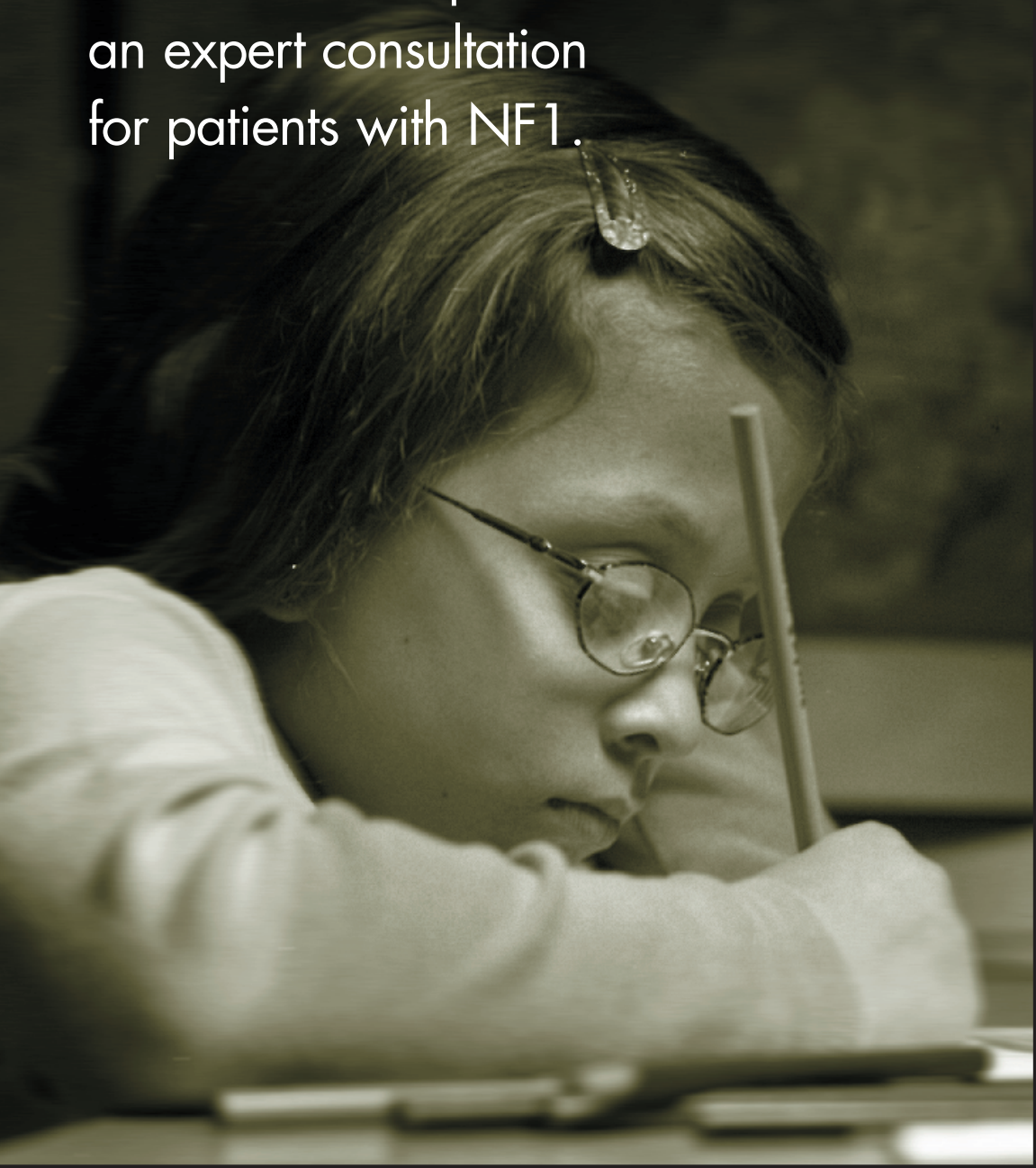
- **Posterior sub capsular cataracts.** This is a clouding of the lens that is recognized when a light is directed into the eye using a retinoscope. The cataracts are usually slow to progress, and treatment is rarely needed, unless they progress to a point where visual function is compromised.
- **Retinal hamartomas** are small growths of the retina tissue and the retinal pigmentary tissue seen through a dilated pupil. These will not affect vision unless their location is in an area critical to central vision or adjacent to the optic nerve.

Clinical course: As with NF1, the course of NF2 is variable from individual to individual. Central nervous system problems may require the ophthalmologist to assist in monitoring the progress of the problem or its treatment.

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A multidisciplinary
neurofibromatosis
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an expert consultation
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● **PSYCHOLOGICAL ASSESSMENT** *by Hilary Feldman, PhD, Psychologist*
Child Development Unit, Children's Hospital of Pittsburgh

Neurofibromatosis Type I can be associated with learning and attentional problems. It is important that parents, medical professionals, teachers, and other individuals working with the child be aware of the possibility of developmental or learning issues. Both children and adults should be able to obtain specific specialized services when needed.

Not all children have learning difficulties, but research has shown that a greater percentage of individuals with Neurofibromatosis have learning problems as compared with their siblings who do not have Neurofibromatosis. Studies have shown that up to 50-60% of individuals may have some learning problems which range in severity from mild to severe. This includes individuals with specific learning disabilities (e.g. significant problems in reading, math, or spelling) or milder learning problems, attentional problems, or visual-perceptual difficulties. Children may have specific speech, language, gross and fine motor difficulties, which may include buttoning, snapping, tying shoes, writing, or drawing. Individuals may have problems with specific subjects or problems with specific skills. Individuals may also have difficulty paying attention and there is a greater percentage of individuals who have a specific diagnosis of Attention-Deficit/Hyperactivity Disorder.

Fortunately, there is help for individuals who may have these difficulties, particularly if they are evaluated and identified by qualified professionals. Children may qualify for early intervention services when they are infants or toddlers if they need help with early developmental skills such as walking, talking, and developmental skills. Preschool children may qualify for help through the Intermediate Unit or their school district and school-aged children can qualify for help in elementary and secondary school programs.

Children need to be evaluated by a qualified professional, through the school district, an early intervention program, or an outside agency. Discuss questions with your child's primary care-physician and particularly with the social workers, doctors, and other professionals through the Neurofibromatosis Clinic. School districts provide psycho-educational evaluations, which determine the child's strengths and weaknesses. Other agencies, psychologists, or educators can provide evaluations of specific skills.

Children who qualify can obtain an Individualized Educational Plan where specific recommendations are made about how to help a child in school. Individuals may also obtain counseling services or medical treatment if they have significant attentional difficulties which may make it difficult for them to learn or participate in activities. Children can also discuss feelings associated with having Neurofibromatosis and counseling services can be available for the child and the family.

It is important to be aware of any difficulties that a child may be having and talk with the parent or primary caregiver. The doctors, social workers, and other medical staff in the Neurofibromatosis Clinic will be looking at the child's development as part of their evaluation. The professionals in the clinic are available to discuss any concerns and to help to recommend evaluation and services as needed. Sometimes parents are reluctant to talk about these issues. However, parents and caregivers find it very beneficial when problems can be identified and addressed and when the child is able to get the help that they need. Because more children with Neurofibromatosis have developmental, learning, attentional, or other problems, it is very important to obtain this help and to work on any areas of difficulty.



DEAFNESS TUMORS LOSS OF BALANCE NUMBNESS



● NF-2 CLINICAL ASPECTS AND MOLECULAR PATHOPHYSIOLOGY

by Kathy Gardner, M.D., Children's Hospital of Pittsburgh VMAC & UPMC neurologist

Both neurofibromatosis type 2 (NF2) and neurofibromatosis type 1 (NF1) are autosomal dominant, highly penetrant genetic disorders with a mutation interrupting a tumor suppressor gene on Chr22 (NF2) or Chr17 (NF1). Ultimately the most serious and obvious result of such loss of function is unrestricted growth of gene-specific tumor types, though usually at a slow rate. Tumor size can vary or remain static for long periods of time, leading to uncertainty for patients, families, and physicians regarding the timing of interventions or treatments. The mechanisms of action for the disrupted NF2 schwannomin/merlin gene are still poorly understood, given it's unexpected similarity to cytoskeletal proteins such as moesin, ezrin, and radixin-like proteins which help form the scaffolding or structural framework of the cell.

NF2 is ten times less common than NF1 and is often confused with NF1. In both disorders the spontaneous mutation rate is 50%, therefore sporadic case presentations are common. Though cutaneous findings are the hallmark of NF1 (see Table), NF2 more characteristically involves tumors of the central nervous system with minimal or no café-au-lait or skin lesions. However small peripheral skin tumors/schwannomas can occur and may be overlooked before the correct diagnosis is actually made. Bilateral vestibular schwannomas (VS) or "acoustic neuromas" are the hallmark of NF2 and present with early asymmetric hearing loss.

Deafness has long been the inevitable outcome though it remains to be seen whether early resections by experienced surgical teams can abort or significantly slow progression to complete hearing loss. Alternatively, the long-term response and complications rate, timing, and appropriate selection of NF2 patients for radio-surgery is not yet firmly established. NF2 patients are advised to learn sign language early, since it is much easier to learn while they can still hear. Other less frequent signs and symptoms associated with heavy tumor load along the posterior fossa and/or spinal cord include loss of balance, facial paralysis or numbness, and variable signs of cord compression.

NF2 Tumor Types

Specific types of tumors are associated with type 1 neurofibromatosis and type 2 neurofibromatosis (see Comparison Table, page 15). With NF2, the most commonly associated tumor types are schwannomas of cranial nerves (especially 8th/vestibulocochlear), spinal nerves, or peripheral nerves. Additionally ependymomas, sometimes with spinal drop metastases, or meningiomas can occur around the brain or around spinal cord. There is some debate regarding the occurrence of glioma in NF2. If the glioma does occur, the incidence is likely very low. Neurofibromas do not occur in NF2, except possibly with rare exceptions. Radiographically, plexiform neurofibromas

cannot be readily distinguished from schwannomas along spinal nerve roots, however the specific tumor type can be predicted accurately based on the type of NF diagnosis (NF1 = neurofibromas, NF2 = schwannomas).

Screening for new cases of NF2 in family members at risk

Full expression of a mutant NF2 schwannomin/merlin gene on Chr22q likely requires a “second hit” or interruption of a second tumor suppressor gene or pathway before tumor develops in an individual carrying the mutation. The age at which this first occurs is not always easily predicted however within a family of affected individuals carrying the same NF2 mutation, the age of onset tends to occur at about the same time. Nevertheless ascertainment bias and real differences in disease onset within a family can make screening to detect newly affected members among those at risk an ongoing, cumbersome, yet necessary process. MRI scans with gadolinium and 3mm axial and coronal cuts through the internal auditory canals are done on a yearly basis as the gold standard. Other measures for detecting early disease or follow-up may include brainstem auditory evoked potentials (BAER’s) which can be done with the MRI and audiogram to increase sensitivity. If a family history regarding disease onset is available for guidance, a slightly more relaxed schedule or alternation between BAER’s and MRI may be considered. The screening should be guided by a physician or team quite familiar with the importance of early detection and with the limitations of the diagnostic and treatment methods. Mutational analysis of the schwannomin gene is not routinely offered because of the low sensitivity (average 70%) using the current method of a protein truncation test. The size of the gene and possibility of non-coding sequence mutations prohibit direct sequencing as a molecular approach to diagnosis. The diagnosis therefore remains a clinical one with a few exceptions. The NIH Consensus Development Criteria for clinical

diagnosis requires detection of either bilateral vestibular schwannomas (VS’s) or a single VS under age 30 with additional positive family history or other NF2 associated tumors such as meningiomas, ependymomas. Early detection of VS’s may enhance success in the delicate surgical treatment for preservation of hearing if performed by one of the handful of specialized surgical treatment centers around the world. The risk of sudden, permanent damage to the eighth nerve (deafness) is thought to be higher in NF2 related vs as opposed to sporadic vs, whenever surgical or (to a lesser extent) radiosurgical treatment is attempted.

Screening for recurrent tumors

After the diagnosis of NF2 is made by detection of bilateral VS or a single VS under age 30 with one or more associated features or family history, the affected individual will require annual imaging studies and audiogram for the remainder of their life, even if tumors have been completely resected. The mutation is found in every tissue and cell of the body and presents a lifelong risk for recurrence and growth.

Spinal root schwannomas or meningiomas can result in significant cord compression yet present with only minimal pyramidal tract signs due to a propensity for depressed reflexes, due (presumably) to tumor infiltration and axonal loss of nerves in the spinal reflex arc. At least one imaging study of the spine is therefore needed during the course of workup. Repeat spinal imaging thereafter may be warranted based on the development of new myelopathic signs or symptoms.

Difficult treatment options for vestibular schwannomas and other tumors

The treatment of vestibular schwannomas is most controversial and associated with risk of serious side effects such as of immediate or hastened onset of deafness and other deficits such as facial numbness or paralysis. Options are to wait and follow the tumor, resect the tumor early and repeatedly, undergo radiosurgery, or some

combination of the above. Following the tumor with scans and audiograms may be safe in the short term since the tumors are often slow growing, however hearing loss is inevitable with insidious tumor growth. The risk of an immediate poor outcome (deafness, facial nerve paralysis) is highest with the surgical approach though this can be moderated reasonably by the experience of the surgical team and by the size of the tumor at time of surgery. In general the likelihood of good surgical outcome decreases as the tumor size increases (as happens with late detections or prolonged delay to interventions). For instance, resection of <1.5 cm VS tumors have the best outcome as reported by the House Clinic in Los Angeles, which is a major NF2 referral center with a team approach to the delicate surgery they perform routinely. Given the rareness of NF2, only a few surgical centers in the world have operated on large enough numbers of NF2 patients to offer a reasonably low surgical risk, or accurate prediction of risk based on tumor size thus justifying attempts to actually remove tumor rather than palliate. Radiosurgery on the other hand is recommended either as a single dose (gamma knife) or fractionated dose with lessened risk of subacute immediate deafness or facial paralysis. There can be post-radiation swelling, which tends to be more severe with larger tumors and this can potentially increase speed of progression to hearing loss, facial weakness, numbness or imbalance. Several case reports have also described an increase in tumor growth after radiosurgery resulting in brainstem compression and death, always in the setting of heavy tumor load. Theoretically, radiosurgery could provide the "second hit" needed for tumor progression in this tumor suppressor disorder and there are growing concerns regarding risk of malignant transformation. Nevertheless some cases can be stabilized with radiosurgery and at a significantly lower risk of immediate neurologic worsening than conventional surgery. Finally,

radiosurgery can increase, probably more so than conventional surgery, brainstem scar tissue and gliosis thereby decreasing the effectiveness of an Auditory Brainstem Implant device that might be used to supplement hearing in those who have become severely impaired. The not so easy choice from the options above must therefore be individualized to the needs, age, and sensibilities of the patient. It is best to present all sides of an argument that cannot always be won in the setting of real risks, regardless of our knowledge base for an individual patient.

Team approach for treatment including genetic counseling for at risk family members

The management of NF2 is a lifelong and family affair requiring consistent monitoring with imaging studies, audiograms/BAER's, and neurologic exams. There are often a number of difficult decisions regarding treatment options that have to be individualized and require counseling. Discussions regarding recurrence risks are important for family planning. A team approach with input from Neurologists, Geneticists, Neurosurgeons, Neuro-oncologists, Otolaryngologists, and Ophthalmologists is essential. Social workers play a crucial role in helping orchestrate such complex care. Referral centers for neurofibromatosis are best suited for managing this devastating disorder.

Comparison of Neurofibromatosis 1 and Neurofibromatosis 2

	Incidence	Age of onset	Skin findings (after puberty)	Tumors of peripheral nerve, neural crest derivation	Tumors of the central nervous system	Other organ systems affected	Other/Ocular/Ophthalmologic Abnormalities
NF1 (Chr17, neurofibromin gene)	1/3000-4000	>95% with skin findings by age 10	6 Café-au-lait's of size 15mm, Axillary, inguinal freckling Cutaneous neurofibromas (superficial/along subcutaneous nerves)	Internal or external plexiform neurofibromas (along medium or larger peripheral nerves) Uncommon Tumor-types Carcinoid, Pheochromocytoma Malignant peripheral nerve sheath tumors Other neural crest derived tumors	Astrocyomas, including optic nerve and anterior visual pathway (visual loss)	Learning disabilities, ADHD symptoms Macrocephaly Short stature Precocious puberty Bone dysplasias (sphenoid, tibial, etc)/ scoliosis Vasculopathy/ moya moyo, renal artery stenosis	Lisch nodule/ hamartomas
NF2 (Chr22, merlin/ schwannomin gene)	1/30,000-40,000	Variable onset but average age 8-22 years (diagnosis often delayed)	Rare Café-au-lait's, hypomelanotic lesions Schwannomas (along superficial nerves)	Schwannomas of peripheral nerves, including spinal roots (some with intraneural extension, cord compression)	Schwannomas of cranial nerves (including bilateral vestibular 8th nerves, leading to deafness) Spinal root schwannomas (some with intraneural extension, cord compression) Meningiomas Ependymomas	None	Early posterior capsular cataracts, Epiretinal membranes Hamartomas Congenital amblyopia

● THE OTOLOGIC MANAGEMENT OF NF2 *by Moises A. Arriaga, M.D.*

Multiple disciplinary team management of Neurofibromatosis 2 is the key to successful outcomes. Although spinal, lower cranial nerve, and ophthalmologic manifestations are just some of the issues, the hallmark finding in Neurofibromatosis 2 is the presence of bilateral acoustic neuromas. As a result, the primary care physician should be suspicious of any patient with unilateral otologic symptoms of hearing loss or tinnitus as well as any sudden hearing loss or tinnitus occurring in an adolescent or young adult. The only successful diagnosis is with aggressive imaging of suspected patients. MRI with contrast is the key diagnostic study. Failing to include Gadolinium contrast is like not obtaining the MRI at all. The presence of bilateral acoustic neuromas (vestibular schwannomas) should initiate involvement of a multidisciplinary approach including: neurotology, neurosurgery, audiology, medical genetics, social work orthopedics, and ophthalmology.

As in any acoustic neuroma patient, management priorities begin with life preservation, preservation of facial function, hearing preservation, and preservation of lower cranial nerves. The priority of hearing preservation from the management of any acoustic tumor is heightened in NF2 because of the bilateral involvement. Accordingly, our philosophy emphasizes early tumor removal with hearing preservation surgical approaches first for the side with the larger tumor.

Our success in hearing preservation has been reviewed in a rigorous fashion with 70% of patients retaining measurable hearing and 50% retaining hearing at the preoperative functional level. If preservation is successful on the side with the larger tumor, we then address the side with the smaller tumor. Creative management is very important. Some patients have elected radiation

therapy. Although, we generally reserve radiation for older patients with medical contraindications to surgical management, we have found that even radiated tumors, in which hearing has been lost, have responded to cochlear implantation on the deaf ear with a previously radiated tumor. This strategy would delay the need for surgery while restoring hearing on the deaf side. When hearing preservation is not possible, the auditory brain stem implant offers the opportunity for hearing by direct stimulation of the brain connections of the cochlear nerve.

Our NF2 skull base team including neurotology (Drs. Arriaga and Chen) and neurosurgery (Drs. Day, Jannetta, and Wilberger) at Pittsburgh's Allegheny General Hospital have much combined experience in this procedure. Although, the auditory brain stem implant does not restore normal hearing in patients with NF2, it provides auditory information, which can be combined with appropriate speech reading and lip reading to enhance auditory oral communication.

The key to long term management is close and repeated follow up. As of yet, we are unable to cure NF2, but we can manage the manifestations to preserve life and enhance the quality of life for these patients with this difficult clinical problem.

Conclusion:

A high degree of suspicion and aggressive use of MRI with Gadolinium contrast are keys to identifying these lesions early before they have created irreversible changes of neurological function. Once NF2 has been identified, a cascade of subspecialty teams is necessary for appropriate management with emphasis on an experienced surgical team to manage the bilateral acoustic neuromas with all the modern interventions available.

● RESOURCES FOR PATIENTS, PARENTS AND DOCTORS:

NF Clinic and the NFCA

The NFCA (Neurofibromatosis Clinics Association, Inc.) acts as an information resource for health care professionals, educators, patients and the general public throughout southwestern Pennsylvania and surrounding regions. NFCA contributes funds to support social work services to the clinic and to other NF patients who call the NFCA for information and support. The NF Clinic is located in the Neurology Department at Children's Hospital of Pittsburgh. Adults and children can make an appointment by calling 412.692.5220.

How You Can Help

NF strikes equal numbers of men and women, and people in every racial and ethnic group. By learning more about this highly unpredictable disorder, you offer a life-saving first line of early detection and information for patients and their families. Although the body of basic science research and clinician investigation into the root causes and implications of NF is growing, there is still much to learn.

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