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AUDIOLOGIC PHENOTYPE IN INDIVIDUALS WITH NEUROFIBROMATOSIS TYPE 1

by

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AUDIOLOGY DOCTORAL THESIS APPROVAL PAGE

This is to certify that the thesis prepared by Laize Ferraz Dias Barcelos Corse, entitled Audiologic Phenotype in Individuals with Neurofibromatosis Type 1, has been approved by this committee as satisfactory completion of the requirement for the degree of Doctor of Audiology in the department of Audiology, Speech-Language Pathology, and Deaf Studies.

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ABSTRACT

AUDIOLOGIC PHENOTYPE IN INDIVIDUALS WITH NEUROFIBROMATOSIS TYPE 1

Laize Ferraz Dias Barcelos Corse

Neurofibromatosis Type 1 (NF1) is a common autosomal dominant multisystemic disorder. Auditory dysfunction is characteristic of Neurofibromatosis Type 2; however, some limited evidence suggested the auditory system may also be affected in NF1. One study reported patients with NF1 had elevated pure-tone thresholds and abnormal auditory brainstem response (ABRs); however, the audiologic phenotype has not been thoroughly characterized. The purpose of this study was to comprehensively describe the audiologic phenotype of NF1 and its impact on the auditory system. Forty individuals with NF1 were evaluated at the Audiology Unit of the Otolaryngology Branch, NIDCD/NIH. Results indicated hearing loss (> 15 dB HL) for the four frequency pure-tone average in 9(11.3%) ears, although hearing loss was present for at least one frequency in 29(36%) ears. Only 6(7.5%) ears had normal findings on all audiological measures. Of the 65(81.2%) ears with normal hearing sensitivity, other abnormal findings were consistent with cochlear dysfunction in 13(16.2%) ears, extra-axial pathology in 7(8.7%) ears, auditory neuropathy/dys-synchrony in 2(2.5%) ears, retrocochlear dysfunction involving VIII cranial nerve and/or the auditory brainstem tracts in 9(11.3%) ears. 15(18.8%) ears with abnormal ABRs findings were supported by findings on imaging results. These data confirmed that auditory dysfunction is often a complication in NF1. Health professionals should be aware of potential effects of NF1 on the auditory system.

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CHAPTER 1

INTRODUCTION

Neurofibromatosis Type 1 (NF1) is a progressive genetic condition caused by mutations in 17q11.2 (Barker et al., 1987; Cawthon et al., 1990; Viskochil et al.; 1990). The age of clinical onset is variable, ranging from infancy to adulthood (Huson, Harper, & Compston, 1998). It is characterized by multiple skin changes, including café-au-lait macules (brown spots on the skin), freckling in the groin and underarms, and the formation of benign tumors called neurofibromas (Riccardi, 1981). NF1 is one of the most common autosomal dominant disorders (1:3,000 births) in humans (Huson, Harper, & Compston, 1998; Mulvihill et al., 1990). It leaves affected individuals at risk for developing a variety of benign and malignant tumors (Greinwald, Derkay, & Schechter, 1996).

Auditory dysfunction is a primary characteristic of Neurofibromatosis Type 2 (NF2); however, some limited evidence suggests the auditory system may also be affected in NF1. One study reported 56% of patients with NF1 had elevated pure-tone thresholds and 48% had abnormal auditory brainstem responses (Pikus, 1995). At least one individual with NF1 has benefited from a cochlear implant (Poissant, Megerian, & Hume, 2003). Despite these reports, the audiologic phenotype has not been systematically and thoroughly characterized. In light of the paucity of literature and subsequent uncertainty in NF1 audiometric phenotype, the consensus conference of the

National Institute of Health (NIH) (Stumpf et al., 1988) does not systematically include audiologic manifestations in the classification of NF1.

The main purpose of this study was to comprehensively describe the audiologic characteristics of individuals diagnosed with NF1, in order to better elucidate the audiometric phenotype of this disorder. Secondary objectives were to characterize the audiologic abnormalities detected, to find correlations with a particular phenotype to answer the following questions: (1) considering the variability of expression and complications of NF1, is there a correlation between the severities of NF1 to hearing sensitivity? And (2) should the audiologic assessment be routine during the initial assessment of the disorder? To expand the understanding of NF1, this study analyzed how the disease impacts the auditory system to better detect, prevent, and manage the associated audiologic disorders. This study examined patients at the National Institutes of Health to gain a better understanding of the effects of NF1 on the auditory system.

CHAPTER 2

LITERATURE REVIEW

The History of Neurofibromatosis

Neurofibromatosis is not a recently discovered disease (Crump, 1981). The term neurofibroma (benign tumors arising in peripheral nerves) was introduced for the first time by Odier in his *Handbook of Medical Practices* published in Geneva in 1803 (Smith, 1849). In 1829, William Wood, a member of the Royal College of Surgeons, described the anatomic clinical characteristics of neurofibromas in 24 patients (Smith, 1849). In 1849, Robert Smith, a surgeon professor at the Dublin Medical School, described two cases of multiple neurofibromas (Smith, 1849). In 1882, Rudolph Virchow and his scholar, Friedrich von Recklinghausen, first proposed a histological classification of tumors to describe a syndrome of skin tumors and skin derived neural crest cells (group of embryonic cells from the ectoderm layer located between the neural tube and the epidermis of an embryo during neural tube formation) that he identified as neurofibromatosis (Crump, 1981). Autosomal dominant transmission was demonstrated by Preiser and Davenport in 1918.

Historically, there has been confusion regarding the relationship between Neurofibromatosis Types 1 (NF1) and 2 (NF2). It was initially thought that these two conditions represented different manifestations of the same underlying entity. In 1981, Riccardi and Mulvihill identified the existence of two distinct clinical entities: von Recklinghausen disease, or peripheral neurofibromatosis (NF1), and the acoustic or

central neurofibromatosis (NF2). Over the centuries, NF1 has been known by many names, including peripheral neurofibromatosis, von Recklinghausen disease, and, erroneously, the *Elephant Man Disease*. Another historical confusion is the belief that the *Elephant Man* had neurofibromatosis (Ablon, 1995). Joseph Merrick had a debilitating disfigurement originally presumed to be NF1. However, current knowledge suggested that Joseph Merrick had Proteus syndrome rather than NF1 (Tibbles & Cohen, 1986).

Advances in molecular biology, neuroimaging techniques, and the development of clinical investigation neurofibromatosis centers around the world have contributed to further understanding the genotype-phenotype differences between NF1 and NF2 (Viskochil, 2002). Riccardi (1982) proposed a classification for neurofibromatosis which includes seven distinct categories of neurofibromatosis (type 1 to type 7). However, Huson, Harper, and Compston (1998) mentioned that this classification has not been widely accepted among experts in the field. Since the *National Institutes of Health Consensus Development Conference Statement* on July 13-15, 1987, there has been significant progress toward a more complete understanding of the pathophysiology and the diagnostic criteria for NF1 and NF2 (Stumpf et al., 1988). The NF1 gene is located on the long arm of chromosome 17 at band 11.2 (17q11.2) (Barker et al., 1987; Cawthon et al., 1990; Viskochil et al.; 1990) while the locus for the NF2 gene is on the long arm of chromosome 22 at band 12.2 (22q12.2) (Viskochil, 2002). As a result of this consensus statement, NF1 and NF2 could be now diagnosed with confidence in the majority of the cases (Mulvihill et al., 1990; Stumpf et al., 1988). These findings marked the end of nosological confusion between the two major forms of neurofibromatosis. NF1 and NF2 are both clinically and genetically distinct entities (Ishikawa et al., 1997). The two main

forms of neurofibromatosis are NF1, or peripheral neurofibromatosis, and NF2, or central neurofibromatosis (Mulvihill et al., 1990). In 1993, the National Neurofibromatosis Foundation International Database was created with the aim of collecting the clinical characteristics of patients with NF1 and organizing multi disciplinary cooperation regarding treatment (Friedman, Birch, & Greene, 1993).

In the scientific literature, NF1 is often referred as von Recklinghausen disease, neurofibromatosis peripheral, plexiform neurofibromatosis, or neurofibromatosis classic. NF2 is also referred as neurofibromatosis central, bilateral acoustic neuroma or vestibular schwannoma.

In this literature review, NF1 case reports dated prior to the National Institutes of Health Consensus Development Conference in 1987 (Stumpf et al., 1988) were carefully reviewed since there was not a clear distinction between NF1 and NF2, and the term von Recklinghausen disease was frequently used to describe both types of neurofibromatosis disease prior to that time.

The Epidemiology of NF1

The birth incidence of NF1 is estimated at 1 in 2500- 3300 live births making NF1 almost as common as trisomy 21 or cystic fibrosis (Adekeye, Abiose, & Ord, 1984; Hirsch, Murphy, & Radcliffe, 2001; Huson, Harper, & Compston, 1998; Mulvihill et al., 1990; Rasmussen & Friedman 2000; White et al., 1986). NF1 is found worldwide, and there are no geographical or ethnic influences (White et al., 1986; Lustig & Jackler, 1996; Sobol & Tewfik, 1997). Its prevalence is 60/100,000 inhabitants and it affects approximately 100,000 people in the United States (Eldridge et al., 1989).

The Genomic Organization

The NF1 gene is located on chromosome 17 (Barker et al., 1987) in the locus 17q11.2 (Cawthon et al., 1990; Viskochil et al.; 1990) and it has one of the highest mutation rates described for human genes (Huson & Hughes, 1994). The NF1 gene contains 335 kilobases of genomic DNA (Li et al., 1995; Miyamoto et al., 1991; Viskochil, 2002; Wallace et al., 1990). The transcript of this gene is 12 kilobases and it encodes the protein, neurofibromin (Viskochil, 2002). The mode of inheritance is autosomal dominant with high penetrance (100% by the age of six) and variable expression (Huson & Hughes, 1994). Fifty percent of cases of NF1 arise *de novo* (spontaneous mutations) (Greinwald et al., 1996; Jeffrey et al., 2005). More than two hundred different mutations have been identified (Jeffrey et al., 2005; Huson & Hughes, 1994). Conventional approaches to the identification of deleterious mutations in individuals affected with NF1 have been limited, owing to the large size of the NF1 gene and the wide diversity of expressions (Huson, Harper, & Compston, 1998; Greinwald et al., 1996; Gutmann et al., 1997). Genetic testing is clinically available and identifies approximately 95% of mutations in individuals that fulfill the clinical diagnostic criteria (Messiaen et al., 2000).

The Pathophysiology of NF1

The pathogenesis of NF1 appears to be related to inactivation of neurofibromin, which is a cytoplasmic protein product known as a tumor suppressor gene (Seizinger, 1993; Theos & Korf, 2006). Neurofibromin is involved in the control of cellular growth and differentiation through the interaction of its GTPase-activating protein or GAP-related domain (regulatory proteins) with $p21^{ras}$ (cellular proto-oncogene) and tubulin (globular protein) (Li et al., 1995; Martin et al., 1990). The GAP-related domain (GRD)

has been shown to down-regulate $p21^{ras}$ by accelerating the rate of GTP hydrolysis and inhibiting $p21^{ras}$ -mediated signal transduction (Martin et al., 1990).

Neurofibromin acts as a negative regulator on the path of the oncogene $p21^{ras}$ (Li et al., 1995; Rizvi et al., 1999). Neurofibromin is expressed in many different tissues, including the brain and mutations in the GAP related domain produce hyperactivity of $p21^{ras}$, which leads to aberrant signaling for cell proliferation (Li et al., 1995; Martin et al., 1990; Rizvi et al., 1999). This may contribute to increased glial cell (astrocyte) proliferation and to enlargement of the brain in NF1 patients (Li et al., 1995; Rizvi et al., 1999). Neurofibromin deficiency induces an increase of 26 mitogenic signals transmitted to the cell nucleus, partly explaining the predisposition to tumors of patients with NF1 (Martin et al., 1990; Li et al., 1995; Rizvi et al., 1999).

In terms of embryology, neurofibromin deficiency affects all three layers: neuroectoderm, mesoderm, and endoderm (Cawthon et al., 1990; Li et al., 1995). Skin lesions and neurological disorders are caused when the neuroectodermal layer is affected (Li et al., 1995). The main production of neurofibromin is in the central nervous system, which suggests an association with learning disabilities and the occurrence of intracranial tumors (Nordlund et al., 1993). Schwann cells derived from peripheral nerve sheath tumors from individuals with NF1 are deficient for the protein neurofibromin, which contains a GAP-related domain (NF1-GRD) (Li et al., 1995). Neurofibromin-deficient Schwann cells have increased $p21^{ras}$ activation, increased proliferation in response to certain growth stimuli, increased angiogenic potential, and altered cell morphology (Li et al., 1995). Pensak et al. (1989) described alteration in the neural chemical environment produced by the proliferation of Schwann cells in patients with NF1. Bony abnormalities

occur when the mesoderm is damaged, and other organ lesions may appear when the endodermal layer is compromised (Cawthon et al., 1990).

The Clinical signs of NF1

According to Friedman, Gutmann, Maccollin and Riccardi (1999), primary features of NF1 are the major clinicopathologic manifestations of the NF1 gene. Complications of NF1 are clinicopathologic consequences of the major clinical signs' progression over time. The cardinal primary features of NF1 (major clinical signs) were described by Riccardi (1981):

- Café au lait spots: well-circumscribed pigmented macules, found throughout the body except the palms, soles, and genitalia. Their diameter is 0.5 to 50 cm. They are present in 80% of patients before the age of one-year-old (Muecke & Amedee, 1994; Tonsgard, 2006).
- Axillary freckling: these are small pale brown spots of diameter less than 5 mm. Typical locations include, in order of decreasing frequency, the axiliary folds, groin, breast, and submental triangle. They are present in 80% of cases of NF1 at the age of six years (Rubenstein & Korf, 1990; Gutmann et al., 1997; Pinson et al., 2002; Tonsgard, 2006).
- Lisch nodules (Iris hamartomas): small hamartomas (nodular growth that is composed of proliferating mature histologically normal cells) of the iris, which are pale in a child, and become more brown in adults, and are present in 90% of cases after 10 years (Carey et al., 1979; Holt, 1987). Their detection requires an examination with a slit lamp by an ophthalmologist. They are virtually

pathognomonic signs of NF1 and must be distinguished from iris naevi (a pigmented spot on the iris), common in the general population (Wolkenstein & Decq, 1998; Ruggieri, 1999; Tonsgard, 2006).

- Neurofibromas: benign tumors arising in peripheral nerves, most often during pre pubertal age (Friedman, 2002; Tonsgard, 2006).

Neurofibromas are typically multicellular in origin, composed of Schwann cells, axons, fibroblasts, mast cells, endothelial cells and perineurial cells (Peltonen et al. 1988). Schwannomas are rare in NF1 patients (Rosenbaum, Patrie & Ratner, 1997). Four types of neurofibromas are distinguishable clinically (Korf & Rubenstein 2005; Riccardi, 1981):

- Cutaneous neurofibromas or dermal neurofibromas are tumors of the nerve sheath comprised of Schwann cells, fibroblasts, perineural cells, mast cells, axons, and blood vessels (Lott & Richardson, 1981). They develop in the dermis and epidermis in the form of soft small tumors, mobile, pink, or purple color, variable in size and number, and 95% of patients present with them in adulthood (Wolkenstein & Decq, 1998). They are usually painless (Wolkenstein & Decq, 1998). Dermal neurofibromas typically begin to appear in the prepubertal period; the number and location of dermal neurofibromas are unpredictable (Riccardi, 1992).
- Subcutaneous neurofibromas are firmer and more elastic than cutaneous neurofibromas and can be tense and painful (Friedman, 2002; Tonsgard, 2006).

- Nodular neurofibromas grow on the nerves causing a fusiform (spindle-shaped) thickening of the nerve and they are present in approximately 15% of patients (Friedman, 2002; Riccardi, 1981). Its firm consistency and compression can cause paresthesia (tingling), and they can induce sensory-motor neuropathy (Friedman, 2002).
- Plexiform neurofibromas are diffuse subcutaneous neurofibromas of different lengths, which are present in one third of patients during the first year of life (Friedman & Birch, 1997). Their intra-fascicular development causes swelling of the nerve with prolapsed reaction of adjacent soft tissues (DeBella & Szudek & Friedman, 2000; Friedman & Birch, 1997). They are difficult to completely remove, tend to regrow, and there is a risk of sarcomatous degeneration (Huson & Hughes, 1994; Needle et al., 1987; Upadhyahya & Cooper, 1998; Weir & Blair, 1987).

NF1 is an extraordinarily variable condition; some patients have very mild manifestations, whereas others are severely affected (Carey et al., 1979). It is a progressive condition, with different complications occurring along a time progression, and some complications worsening over time (Carey et al., 1979; Riccardi, 1992).

NF1 Diagnosis

Despite major advances in the molecular genetics of NF1 (Messiaen et al., 2000), diagnosis remains largely based on clinical criteria (Guttman, Aylsworth, & Carey, 1997). The diagnostic criteria for NF1 were defined during the *National Institutes of Health Consensus Development Conference* in 1987, and updated in 1990 (DeBella,

Szudek, & Friedman, 2000; Guttman, Aylsworth, & Carey, 1997). A diagnosis of NF1 depends on a careful clinical examination of the patient, his or her parents and siblings, and a detailed family medical history; at times, laboratory exams are needed (Geller & Bonalumi, 2004). These NIH criteria, summarized on Table 1, specified that two or more of the following manifestations must be present for diagnosis of NF1: (1) six or more café-au-lait macules more than 5 mm in greatest diameter in prepubertal individuals and more than 15 mm in greatest diameter after puberty, (2) two or more neurofibromas of any type or one plexiform neurofibroma, (3) freckling in the axillary or inguinal regions (Crowe sign), (4) an optic pathway tumor, (5) two or more Lisch nodules (iris hamartomas), (6) a distinctive, osseous lesion, such as sphenoid wing dysplasia or thinning of the outer layer of the long bones (with or without pseudarthrosis), and (7) a first degree relative (parent, sibling, or offspring) with NF1 by the above criteria.

The most common manifestations of NF1 include café-au-lait spots, neurofibromas, Lisch nodules, and axillary or inguinal (skin-fold) freckling (Korf, 1992; Riccardi, 1991). Café au-lait spots and neurofibromas are relatively straightforward to diagnose in most affected individuals (Korf, 1992).

Complications

The clinical expression and severity in NF1 is diverse, even within families (Riccardi, 1982; 1992). The complications affect many of the body systems and range from disfigurement, scoliosis, and vasculopathy to cognitive impairment and malignancy including peripheral nerve sheath tumors, and central nervous system gliomas (Riccardi, 1992; Stine & Adams, 1989).

Table 1

Criteria for the Clinical Diagnosis of NF1 (At least two are required)

Criterion	Notes
Six or more café-au-lait macules	> 5 mm before puberty > 15 mm after puberty
Freckling	Axillary or Inguinal
Neurofibromas	Two or more neurofibromas or One plexiform neurofibroma
Skeletal dysplasia	Sphenoid or tibial lesion
Lisch nodules	Two or more iris hamartomas
Optic glioma	Detected by imaging (usually MRI)
First degree relative with NF1	Sibling or parent with NF1

Note. NIH Consensus Development Conference, 1987

Macrocephaly, short stature, and cutaneous angiomas are minor features of the disease (Huson, Harper, & Compston, 1988; Huson & Hughes, 1994; Riccardi, 1992).

The NF1 complications are related to its severity and determine the case prognosis, management, and intervention (Riccardi, 1982; 1991). Since the NF1 gene is a tumor suppressor gene in some cells, children and adults with NF1 are at risk for developing a variety of benign and malignant tumors (Bader, 1986).

Cognitive and learning disabilities are present in 40 to 60% of children with NF1 (Eldridge et al., 1989; North et al., 1994; Stine & Adams, 1989). Learning disability is the most common complication in NF1 patients (North et al., 1994; 1995; 1997). Only 3 to 8% of children with NF1 have mental retardation and an Intelligence Quotient (IQ) less than 70 (Cnossen et al., 1998; North et al., 2002). The main cognitive disabilities include difficulties in the following skills: visual-spatial orientation, hand-writing, copying letters or numbers, writing, logical reasoning and mathematical, coordination of gestures, balance, hand-eye coordination, organization, planning and strategy, short term memory, attention, school activities, articulation problems, and delayed speech and language (Lorch et al., 1999; North et al., 1997).

Thirty to 60% of individuals with NF1 demonstrate high-signal-intensity lesions (sometimes referred to as unidentified bright objects, or UBOs, or spongiform gliose) seen on long repetition time (TR) magnetic resonance images (MRI) of the brain (Hofman et al., 1994). These lesions appear as well-circumscribed, nonenhancing, hyperintense lesions without mass effect in the basal ganglia, thalamus, cerebellum, and brainstem regions (Kraut et al., 2004). According to DiPaolo et al. (1995) these hyperintense foci seen on T_2-weighted MRI appear to correspond to pathologic findings

of areas of vacuolar or spongiotic change and these lesions are not associated with mass effect. Studies have demonstrated an association between the presence of UBOs on brain MRIs and learning disabilities or low IQ scores in children with NF1 (DiMario et al., 1993; Denckla et al., 1995). However, their clinical relevance is still debatable and their pathological basis remains unclear (Kraut et al., 2004).

Children with NF1 may experience migraine headaches, nausea, and abdominal pain (Riccardi, 1991). Other conditions which occur more commonly in the NF1 population include epilepsy (Korf, Carrazana, & Holmes, 1993), aqueduct stenosis (Senveli, Altinors, Kars, Arda, Turker, Cinar & Yalniz, 1989) and hydrocephalus (Riccardi, 1981). In addition, behavioral disorders, such as impulsivity and hyperactivity, are frequently associated with NF1 and may justify treatment with psycho stimulants (Williams & Hersh, 1998; Cnossen et al., 1998; Lurch et al., 1999; North et al., 2002). If appropriate care is rapidly established, it seems that adults with NF1 are typically socially and professionally integrated (North et al., 2002).

Otolaryngologic Complications

Although Batsakis (1979) reported that 25% of all neurofibromas are found in the head and neck area, there are recent studies that reported 50% of plexiform neurofibromas occur in the region of the head and neck (Wise et al., 2005). Head and neck neurofibromas can be located on the face, nose, gingival, tongue, pharynx, larynx, temporomandibular joint, pinna, external auditory meatus, and middle ear (Hirsch, Murphy & Radcliffe, 2001; Tonsgard, 2006; Van Danme, Freihofer & De Wilde, 1996). In this location, neurofibromas have a predilection to arise in the deep planes and may interfere with the functions of surrounding anatomical structures such as respiration,

phonation, mastication, deglutition, and hearing (Tonsgard, 2006; White, Smith, Bigler, Brooke, & Schauer, 1986). Neurofibromas can cause stapes fixation and conductive hearing loss (White et al, 1986; 1991). Neurofibromas or NF1 related meningiomas may also involve the facial nerve (White et al, 1986; 1991; Tonsgard, 2006). However, little attention in the literature has been paid to the comorbidity of these conditions (Poissant et al., 2003). According to Tonsgard (2006), the psychological burden of a chronic, unpredictable, and potentially disfiguring disease all contributes to the morbidity of NF1.

The Auditory System: Peripheral and Central Auditory Nervous System

In order to describe the potential impact of NF1 on the auditory system, its anatomy, and role on the human body will be discussed. The auditory system is comprised of the peripheral and central auditory nervous system (CANS). The human hearing ability is dependent on the capability of both systems to function normally and collaboratively (Gelfand, 2001).

The ear is usually didactically described into three sections: the outer ear, the middle ear, and the inner ear (see Figure 1). The outer ear consists of the external pinna (oval-shaped appendage on the lateral surface of the head) and the external auditory meatus (also known as ear canal), which is terminated by the tympanic membrane (TM). The pinna (also known as auricle) is composed of thin skin with hair follicles, sweat glands, and sebaceous glands covering a supporting structure of elastic cartilage (Blauert, 1983). The pinna helps, to some extent, in collecting sound and contributes to the ability to determine the direction of the origin of sounds (Blauert, 1983). The direction of a sound source is the difference in sound reflection, diffraction and absorption on the

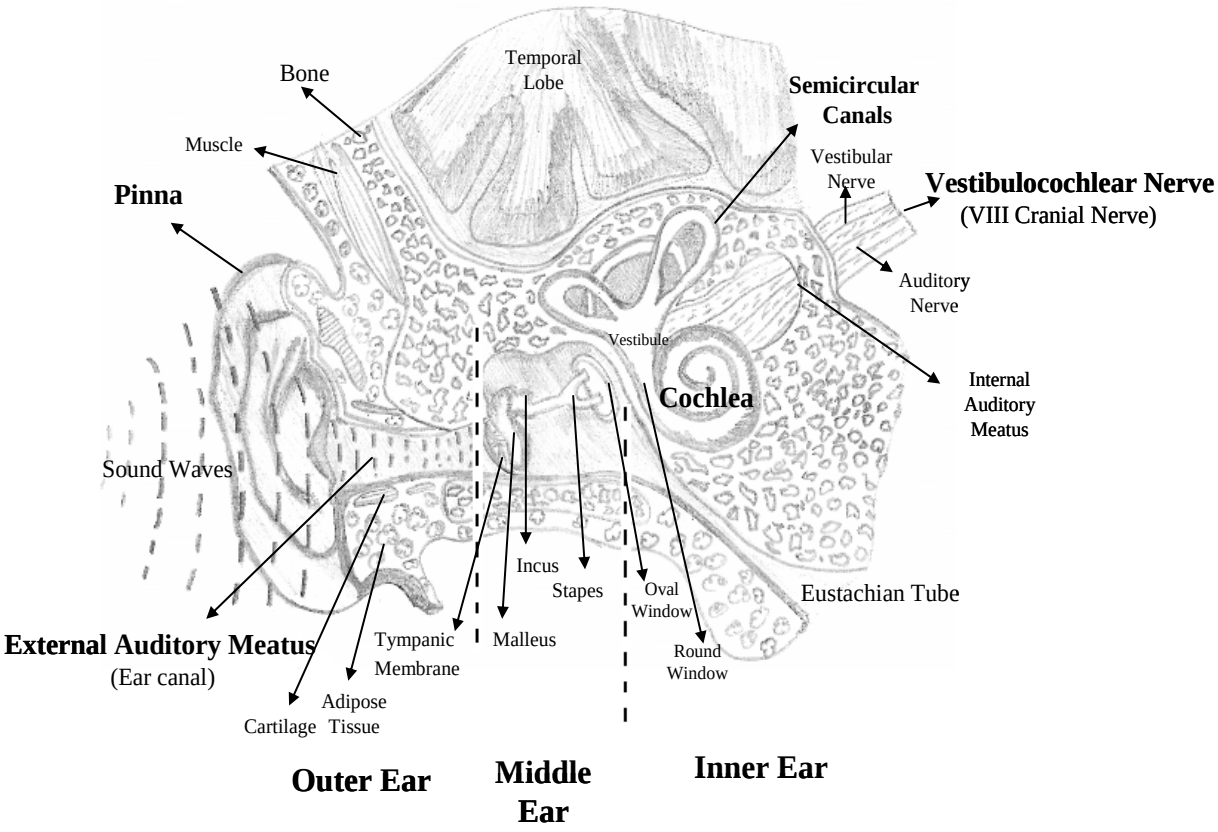


Figure 1. A schematic diagram of the peripheral part of the ear showing outer, middle, and inner regions. This picture is not to scale, and it was drawn by the doctoral student Laize Barcelos Corse for purposes of illustration. Modified from Gelfand (2001), p. 38. *Essentials of Audiology* (2nd Ed.). New York, NY: Thieme.

shoulders, head, and the folds of the pinna from both ears (Gelfand, 2001). These processes lower the intensity and change the spectrum of sound.

The peripheral system together with the CANS create minute time differences and variations in sound pressure level at each ear so the listener can locate sound sources (Blauert, 1983; Gelfand, 2001). The external auditory meatus is composed of skin, containing hair follicles, ceruminous glands, and sebaceous glands, that covers a supporting structure of elastic cartilage (lateral one third) or bone (medial two-thirds). It has an average diameter of 6 mm and average length of 25 mm (Gelfand, 2001). The auditory canal acts a pipe resonator that boosts hearing sensitivity in the range of 2000 to 5000 Hz. Its reverberatory contribution to sound transmission is approximately 10 dB near the resonance frequency, and complete canal obstruction may lead to a conductive hearing loss as much as 30 dB (Gelfand, 2001).

The middle ear begins with the tympanic membrane, to which are attached three small bones (malleus, incus and stapes) called ossicles. The tympanic membrane, which is composed of circular and radial fibers, is kept taut by the tensor tympani muscle (Blauert, 1983; Gelfand, 2001). The TM changes the pressure variations of incoming sound waves into mechanical vibrations to be transmitted via the ossicles to the inner ear. The ossicles function as a lever, which changes the very small pressure exerted by a sound wave on the TM into a much greater pressure on the oval window of the inner ear. Another function of the middle ear is to protect the inner ear from very loud noises and sudden pressure changes (Gelfand, 2001). Since the TM makes an airtight seal between the middle and outer parts of the ear, it is necessary to provide some means of pressure equalization. The Eustachian tube, which connects the middle ear to the oral cavity,

equalizes the internal pressure of the middle ear to the atmospheric pressure (Gelfand, 2001).

The inner ear contains the vestibule, semicircular canals, and the cochlea, which are all part of one fluid-filled chamber (Blauert, 1983; Gelfand, 2001). The vestibule and semicircular canals contain the maculae and cristae ampulares (sense organs of balance), which contribute to the human balance system, and the cochlea contains the organ of Corti, which is the sense organ of hearing (Blauert, 1983). As illustrated in Figure 1, the cochlea transforms the incoming acoustic information into electrical signals that are properly coded neural impulses by the cochlear nerve (Gelfand, 2001; Talavage, Ledden, Benson, Rosen, & Melcher, 2000).

Figure 2 shows the major pathways of the ascending auditory system depart from the temporal bone through the internal auditory meatus and enter the brainstem at a location called the cerebellopontine angle (Talavage, Ledden, Benson, Rosen, & Melcher, 2000). The vestibulocochlear nerve fibers terminate in the cochlear nucleus. From there, different neural pathways are initiated; these pathways ascend through a multitude of other brainstem nuclei including the superior olivary complex and nucleus of lateral lemniscus before converging upon the inferior colliculus (Gelfand, 2001; Talavage, Ledden, Benson, Rosen, & Melcher, 2000). The colliculi (right and left) then deliver most of the input to the auditory thalamus and auditory cortex, which is located on the superior surface of the temporal lobe (Gelfand, 2001; Talavage, Ledden, Benson, Rosen, & Melcher, 2000).

The auditory system is essentially organized in a tonotopic fashion including the presence of multiple tonotopic maps with neurons arranged according to best frequency

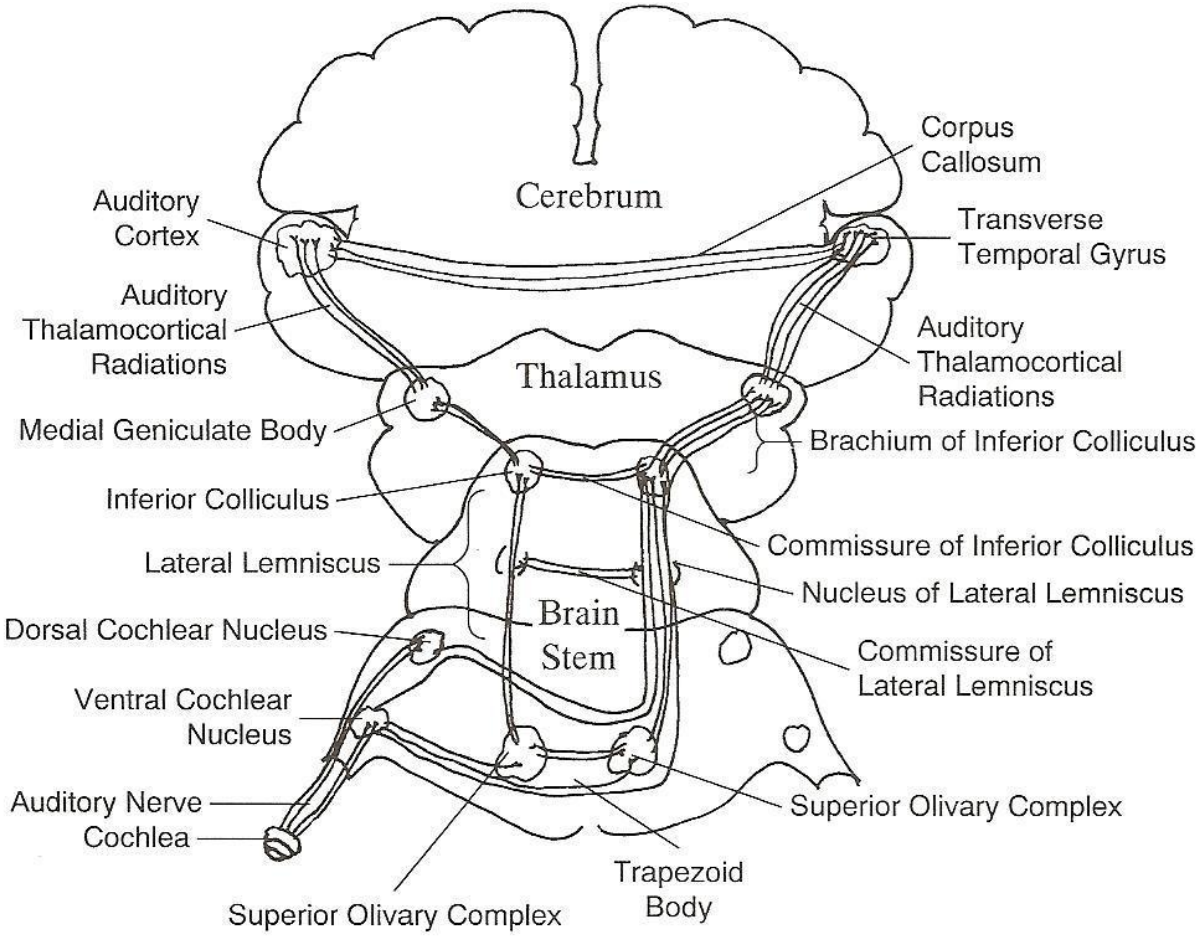


Figure 2. Central auditory nervous system pathways. From Gelfand (2001), p. 81. *Essentials of Audiology* (2nd Ed.). New York, NY: Thieme.

(the acoustic frequency to which a neuron is most sensitive) (Talavage, Ledden, Benson, Rosen, & Melcher, 2000). The tonotopy arises from the mechanical properties of the cochlea along the entire auditory neural pathway all the way to the auditory cortex (Talavage, Ledden, Benson, Rosen, & Melcher, 2000). Lesions and insults along the auditory system may affect auditory abilities (Talavage, Ledden, Benson, Rosen, & Melcher, 2000).

The Auditory System and NF1

Although hearing loss is usually described in patients with NF2 (acoustic neuroma), it is also an important complication in patients with NF1 (Pikus, 1995; Poissant et al., 2003). Pikus (1995) observed that NF1 patients are at risk of developing hearing loss, and it is noticeable within the first few years of life. Tonsgard (2006) reported that deafness occurs in about 10% of patients with NF1.

According to Pikus (1990), the hearing loss is usually unilateral and due to a variety of causes. The conductive hearing loss is most often related to the presence of neurofibromas in the external acoustic meatus (White et al., 1986; Lustig & Jackler, 1996). Neurofibromas located on the head and neck may affect the functions of the surrounding anatomic structures and cause cosmetic concerns (White et al., 1986; Lustig & Jackler, 1996). Ears are among the mostly severely affected areas of the head, and several special problems can occur such as stenosis of the external auditory meatus, disfigurement of the ear, ear infections and hearing loss (Stevenson, Zavell, & Anderson, 1986).

Table 2 presents a summary of NF1 case reports of conductive hearing loss (CHL) in the literature. Coromina (1985) described one case of a 21-year-old female with

Table 2

Summary of NF1 Case Reports of Conductive Hearing Loss (CHL) in the Literature

Case Reports of Conductive Hearing Loss in NF1			
Authors	**Number of Cases**	**Type of HL**	**Cause of CHL**
Coromina (1985)	1 case (21-year old female)	unilateral moderate CHL	stenosis of ear canal
McKennan (1990)	1 case (18-year old male)	unilateral mild CHL	stenosis of ear canal
Lustig and Jackler (1996)	7 cases of patients	unilateral CHL	pinna deformities and stenosis of ear canal
Rapado, Simo and Small (2001)	1 case (14-year old male)	unilateral mild CHL	neurofibroma in the Eustachian tube dysfunction
Ergun, Atilganoglu and Yasar (2007)	1 case (66-year old female)	unilateral moderate CHL	stenosis of ear canal
Waizel Haiat, Romo, Aguayo and Carreola (2007)	1 case (20-year old female)	unilateral CHL	neurofibroma in the ear canal and pinna
Shaida and Yung (2007)	1 case (42-year old-female)	unilateral CHL	otitis externa, large neurofibroma in the concha bowl obstructing the ear canal aperture
Abbarah and Abbarah (2009)	1 case (53-year old female)	unilateral moderate CHL	stenosis of ear canal
Geller, Darrigo Junior, Bonalumi and Ribeiro (2009)	1 case (8- year old female)	severe unilateral CHL	stenosis of ear canal
Ghosh, Chakraborty, & Barman (2008)	1 case (20-year old female)	no CHL	presence of neurofibroma in the concha extending into cartilaginous part of external auditory canal and post-auricular area

NF1, who had a unilateral moderate conductive hearing loss (CHL) due to the presence of a neurofibroma in the ear canal that appeared when she was 10 years old. McKennan (1990) reported a case of an 18 year-old male who had a unilateral mild CHL due to the presence of a nodular subcutaneous mass completely obliterating the ear canal, concha, and postauricular sulcus (benign plexiform neurofibroma) with severe otalgia in the right ear.

Lustig and Jackler (1996) reported seven cases of patients with NF1 who had unilateral CHL as a result of pinna deformities and ear canal obstruction due to the presence of plexiform neurofibroma. In addition, one of these seven patients had a collapsed ear canal that could be opened for clear otoscopy. According to these authors, the facial nerve is frequently affected by NF1, particularly in its extracranial course. Rapado, Simo and Small (2001) reported one NF1 case of a14-year-old male, who had a long standing unexplained unilateral mild CHL due to Eustachian tube dysfunction. Ergun, Atilganoglu, and Yasar (2007) described one NF1 case of a 66-year-old female presenting a unilateral moderate CHL caused by an enormous neurofibroma deforming the right outer ear and neck region. Waizel, Haiat, Romo, Aguayo, and Carreola (2007) described a case report of a 20 year-old female with NF1 and a progressive unilateral CHL in the right ear due to the presence of neurofibroma in the right external auditory canal and pinna. Shaida and Yung (2007) described a case of a 42-year-old female with NF1 and left otitis externa, swelling around the pinna, aural fullness, and CHL due to the presence of a large neurofibroma in the concha bowl area completely occluding the external auditory meatus. Abbarah and Abbarah (2009) reported one case of a 53-year-old female with NF1 and unilateral moderate CHL due to the presence of a plexiform

neurofibroma in the external acoustic meatus. Geller, Dario Junior, Bonalumi, and Ribeiro (2009) also described a case study of an 8-year-old female patient with NF1 and a severe unilateral CHL due to the presence of a plexiform neurofibroma in the left external auditory meatus, face, mandible, submandibular area and left temporal area. There was one case report found in the literature of a 20-year-old female with partially occluded left external auditory meatus due to the presence of neurofibroma in the concha extending into cartilaginous part of external auditory canal and post-auricular area of the left ear; however, pure tone audiometry showed no CHL (Ghosh, Chakraborty, & Barman, 2008).

Table 3 shows a summary of NF1 case reports of SNHL in the literature. In contrast to those previous conductive hearing loss case reports, Shambould and Grundfast (1999) described two cases of 16-year-old female patients with NF1 and sensorineural hearing loss (SNHL). The first patient had only café au-lait spots and presented a bilateral mild to moderate low frequency sensorineural hearing loss, which improved by 20 dB following steroid (Prednisolone/10 mg) treatment after a positive serum result for autoimmune inner ear disease. The second patient had severe manifestations of NF1 with a strong family history of NF1 and deafness, and also presented with a unilateral profound sensorineural hearing loss with vertiginous episodes. This former patient test results revealed abnormal ABR finding, electronystagmography (ENG) showed 19% difference in the caloric response between the ears, and MRI findings revealed normal VIII nerve and internal auditory canal. Regarding the site of the sensorineural lesion for these two patients, Shambould and Grundfast (1999) discussed that a mild NF1 case manifested mild SNHL and an advanced stage of NF1 yielded a severe SNHL, and they

Table 3

Summary of NF1 Case Reports of Sensorineural Hearing Loss (SNHL) in the Literature

Case Reports of Sensorineural Hearing Loss in NF1				
Authors	**Demographic**	**Degree of SNHL**	**Additional Audiological Findings**	**Possible Etiology of SNHL**
Kitamura, Senba and Komatsuzaki (1989)	12-year-old-male	Right unilateral moderate SNHL in the low frequencies rising to a mild SNHL in the high frequencies (.25-8 kHz)	ABRs within normal range, no gaze or positional nystagmus were observed and no bilateral caloric responses (ice water) were obtained from either ear	Bilateral IACs without the presence of tumors. Chronic intracranial hypertension? Bone tissue abnormalities? Defective development of neuroectoderm? Neural dysplasia of inner ear or VIII nerve?
Shambould and Grundfast (1999)	16-year-old female	Unilateral profound sensorineural hearing loss with vertiginous episodes	Abnormal ABR, weak caloric responses, MRI findings revealed normal VIII nerve and internal auditory canal	Advanced stage of NF1 yielded a severe SNHL
	16-year-old female	Bilateral mild to moderate sensorineural hearing loss	SNHL improved by 20 dB following steroid (Prednisolone/10 mg) treatment after a positive serum result for autoimmune inner ear disease	Mild stage of NF1 manifested mild SNHL
Poissant, Megerian & Hume (2003)	40-year-old male	Bilateral progressively profound SNHL from 750 Hz and above	AU= Clear Canals, Normal Tymps, normal IAC and VIII nerve revealed by MRI findings, and normal CT findings of the brain. Chiari I malformation. Absent OAEs	Cochlear Pathology
Pensak et al. (1989)	44 NF1 (2-22 years old)	*Unknown cases of SNHL*	ARTs performed in 35 Individuals= 25 Normal and 10 abnormal. ABRs performed in 44 Individuals= 35% (14/44) conduction delays, and 7 of the 14 abnormal ABRs also had abnormal ARTs.	Retrocochlear= neural conduction delays in ABRs reflected alterations in the neural chemical environment produced by the proliferation of Schwann cells
Pikus (1995)	43 NF1 (5-20 years old)	24/43 (56%) individuals had abnormal pure-tone thresholds (poorer than 20 dB). *No singular audiometric configuration?*	10/43 (23%) presented abnormal tympanometry, 19/43 (44%) had abnormal acoustic reflexes, and 16/33 (48%) presented abnormal auditory brainstem responses.	No discussion about possible etiology? Just mentioned that nobody in her sample had acoustic neuroma, and most of them had different tumor formations in the brain.

speculated the idea that NF1 disease spans between two ends of a spectrum due to involvement of NF1 lesions at the brainstem or higher levels. Additionally, Poissant, Megerian & Hume (2003) reported one NF1 case of a 40-year-old male with bilateral progressively profound SNHL from 750 Hz and above, which was first noticed in 1988. Diagnostic assessment revealed clear ear canals with normal tympanic membrane bilaterally, normal tympanometric results bilaterally, normal internal auditory canal and VIII nerve revealed by MRI findings, and normal computed tomography findings of the brain; however, otoacoustic emissions (OAEs) results were absent bilaterally indicating damage to the outer hair cells.

Despite the fact that Poissant et al. (2003) noted on MRI findings the presence of Chiari I malformation which could result in a neural or more central hearing loss, the authors claimed that their study data mostly supported a peripheral component to the hearing loss (absent OAEs) due to an absence of neural abnormalities. According to Poissant et al. (2003), this patient subsequently had cochlear implantation in the left ear with a very successful outcome confirmed by speech perception measures and electrical auditory brainstem responses at one and seven months after activation.

Thus far, Pensak et al. (1989) and Pikus (1995) studies are the only ones to describe in the literature the audiologic profile in individuals with NF1 using a fairly large sample size. All other reports are essentially case studies.

Pensak et al. (1989) performed ABR and acoustic reflex testing in 44 individuals with NF1 (2-22 years old) to evaluate the auditory neural conduction in the pediatric population. Mean three frequency pure tone average (500, 1000, and 2000 Hz) for 44 individuals was 8 dBHL. Of the 44 individuals analyzed, three (6.8%) individuals had

CHL $\geq$ 20 dBHL with abnormal tympanometric findings. Speech audiometry was performed in 33 individuals (mean speech scores=98%). Acoustic reflex testing was performed in 35 individuals. Of those, 25 had normal results, one individual had absent reflexes due to VII cranial nerves involvement, one individual had abnormal reflexes due to acoustic tumor, two individuals had negative middle ear pressure, and six individuals (19%) had elevated or absent acoustic reflexes with normal middle ear and facial nerve function. Acoustic reflex latency test (ARLT) was obtained in 26 individuals. Three participants had long rise times. None of them had prolonged onset latencies. ABR was performed in all 44 individuals, and 32% (14/44) had significant conduction delays in the ABR, and seven of the 14 patients with abnormal ABRs also had abnormal ARTs.

Pikus (1995) examined 43 children from age five through age 20 years diagnosed with NF1. The routine audiologic battery in that study included immittance, pure tone, and speech audiometry. ABR was completed in only 33 children. Twenty-four (56%) individuals had abnormal pure-tone thresholds (poorer than 20 dB), ten (23%) presented abnormal tympanometry, nineteen (44%) had abnormal acoustic reflexes, and sixteen (48%) presented abnormal auditory brainstem responses. Auditory brainstem response testing by Pensak et al. (1989) and by Pikus (1995) reported prolongation of central transmission between waves I and V.

These former studies presented several methodological biases. Pensak and colleagues (1989) did not mention the reason for the exclusion of those abnormal ABR responses that were affected by the three individuals with CHL; they did not confirm whether individuals' hearing thresholds were within normal limits, did not characterize the degree, configuration and etiology of CHL, did not provide information regarding

sensorineural hearing loss, did not perform otoacoustic emissions and assumed that the hearing loss was strictly retrocochlear. Pensak et al. (1989) suggested that neural conduction delays in ABRs reflected alterations in the neural chemical environment produced by the proliferation of Schwann cells. However, Pensak and colleagues (1989) did not perform otoacoustic emissions to further assess cochlear function to rule out a cochlear dysfunction; therefore, those authors cannot attribute sensorineural hearing loss in NF1 solely to alterations in the neural chemical environment in the myelin of the central nervous system. The hearing loss and ABR abnormalities could be due to cochlear pathology or to higher level portions of the CANS. Furthermore, DiPaolo et al. (1995) report that spongiform gliose are the most common intracranial lesions in NF1 (globus pallidus, cerebellum, internal capsule, and brainstem) and North (2000) reported that there is evidence associating the presence of spongiform gliose in children with NF1 with many measured cognitive impairment. However, no study was found in the literature that further investigated the association between sensorineural hearing loss and spongiform gliose. In Pikus' study (1995), there is no information regarding otolaryngologic assessment, the number of individuals excluded from her study, definition of hearing loss based on frequencies or pure-tone-average (PTA), classification of hearing loss, degree and type of hearing loss, tested frequencies, number of ears tested, type of earphone used, conditions for administering audiometric tests, normative values for immitance, probe tone test frequency used for tympanometry, definition of acoustic reflex thresholds, normative values for auditory brainstem response, reference to site of lesion, and correlation between age and severity of the disorder. In addition, Pikus' study (1995) lacks clarification about its applied terminology "handicapping hearing loss" and the type

of statistical analysis that was performed. Her study also neglects to include information about the normative values used to assess her audiometric findings. In summary, despite the large sample sizes in the Pikus (1995) and Pensak et al (1989) studies, the audiologic phenotype of NF1 has not been systematically and thoroughly characterized. Consequently, theoretical and reproducible audiological studies in patients with NF1 were warranted and were the impetus for this study.

Purpose of the Study

The main purpose of this study was to comprehensively describe the audiologic characteristics of individuals diagnosed with NF1, in order to better elucidate the audiometric phenotype of this disorder. Secondary objectives were to determine the prevalence of hearing loss in individuals diagnosed with NF1, characterize the audiologic abnormalities detected and to find correlations with a particular phenotype to answer the following questions:

(1) Considering the variability of expression and complications of NF1, was there a phenotypic correlation between NF1 and hearing sensitivity?

(2) Should audiologic assessment be routine during the initial assessment of NF1?

To expand the understanding of NF1, this study further analyzed how the disease impacted the auditory system to better detect, prevent, and manage the associated audiologic disorders. This study retrospectively examined charts from NF1 individuals seen at the National Institutes of Health from January 01, 2007 until January 21, 2010 to gain a better understanding of the natural history of NF1 on the auditory system.

CHAPTER 3

METHODS

Participants

Participants included males and females with NF1 who participated in the National Institutes of Health (NIH) National Cancer Institute (NCI) clinical trial protocol investigating the *Natural History Study and Longitudinal Assessment of Children, Adolescents, and Adults with Neurofibromatosis* (NCI-08-C-0079; Brigitte Widemann, MD, PhD, principal investigator) and that were referred by the principal investigator for comprehensive audiological assessment at the Audiology and Otolaryngology Center in the Clinical Center building of the National Institutes of Health (NIH) from January 01, 2007 until January 21, 2010. All participants had signed a volunteer consent form to participate in the NIH clinical trial protocol.

The current study retrospectively examined data (data mining) from an established database; however, the author of this thesis participated in collecting some of these data as part of the NIH Summer Research Intramural Fellowship in 2009.

Forty audiological files from 40 individuals with NF1 were reviewed. All 40 individuals with NF1 for whom data were presented in this study were evaluated from January 01, 2007 until January 21, 2010. These 40 individuals with NF1 seen at the Audiology Unit of the Otolaryngology Branch represent a subset from a larger cohort enrolled in the NF1 study. No specific referral criteria were used by the principal

investigator at the time these data were collected since audiological evaluation was not part of the original clinical trial protocol.

In order to be included in the clinical trial protocol, all the enrolled individuals were required to have a positive genetic test for NF1 or at least two positive diagnostic criteria according to the *NIH Consensus Conference* (1987). The clinical trial (NCI-08-C-0079) was open to individuals who met the eligibility requirements, regardless of where they lived in the United States. Written informed consent was obtained from each individual or parents of minor participants. The forty NF1 individuals seen at the Audiology and Otolaryngology Center had detailed clinical evaluations and genotyping to identify the specific genetic mutation at the NCI and the National Human Genome Research Institute (NHGRI). Ten individuals were seen on more than one occasion; however, only the baseline evaluation was considered for analysis in this thesis project.

Protocol and Procedures

The NF1 Audiologic Test protocol (Appendix B) was established by the Audiology Unit of the Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders (NIDCD) at the NIH. The NF1 test protocol included all the required audiologic testing and parameters to be followed by all audiologists who tested the study participants. Audiological testing was not part of the initial clinical trial protocol (NCI-08-C-0079) and therefore not all individuals enrolled in that clinical trial received audiological testing. Once audiological testing was added to the clinical trial, it was administered as often as possible based on patient and researcher availability. The test protocol included audiologic evaluations that were age- and ability-appropriate for all behavioral and objective assessments. The NF1 Audiological Test Protocol (Appendix B)

included the following testing: otoscopy, immitance (tympanometry, acoustic reflex threshold, acoustic reflex decay, and resonance frequency), speech audiometry, pure-tone audiometry (air and bone conduction), distortion product otoacoustic emissions (DPOAEs), middle ear reflectance, and auditory brainstem response (ABR) testing. All of the tests were performed consecutively in the order listed above. The audiologist instructed the individual with NF1 on how to respond during the audiological test battery.

Tympanometry was performed using 226 Hz. Tympanometric results were categorized according to tympanometric peak pressure, static compliance and equivalent ear canal volume, and compared to age- appropriate normative values established by Margolis and Heller (1987) and Hanks and Rose (1993) (Table 4). Based on the normative tympanometric data by age group presented in this table, adult individuals with static compliance findings lower than 0.3 mL (low) and greater than 1.5 mL (high) were considered abnormal. Middle ear peak pressure lower than -100 daPa or greater than +150 daPa were considered abnormal. Ear canal volume findings lower than 0.6 mL (small) or greater than 1.5 mL (large) were considered abnormal.

Acoustic reflex threshold (ART) were obtained using the GSI Tympstar. ART data obtained in this study were compared to normative data established by Gelfand, Schwander, and Silman (1990), as shown in Figure 3. The recommended criteria for normal ARTs when using a 226 Hz probe tone, is a repeatable compliance change of at least .02 ml or greater with good morphology between 85 and 100 dB SPL for pure-tones stimuli at 500, 1000 and 2000 Hz (Gelfand, Schwander, & Silman, 1990).

Speech audiometry included establishment of speech recognition thresholds (SRTs) and determination of word recognition scores (WRSs). The SRTs were obtained

Table 4

Normative Data for Tympanometric Findings

Authors	Age group	Static Compliance (mL)	Ear Canal Volume (mL)	Peak Pressure (daPa)
Margolis & Heller (1987)	3-5 years and 11 months	0.2- 0.9	0.4-1.0	+100 to -100
Hanks & Rose (1993)	6- 15 years	0.3-1.5	0.6-1.5	-100 to + 150
Margolis & Heller (1987)	20- 62 years	0.3-1.5	0.6-1.5	-100 to +150

using spondees (two-syllable words with equal stress on both syllables) presented via monitored live voice, and WRSs were obtained using the NU-6 word lists (monosyllables), ordered for difficulty, and presented via monitored live voice.

Pure-tone threshold testing by air conduction (250 Hz to 8000 Hz) and bone conduction (250 Hz to 4000 Hz) were conducted. Pure-tone threshold data were classified for type, degree and configuration using schemes adapted from the *European Working Group on the Genetics of Hearing Impairment* (Mazzoli, Van Camp, Newton, Giarbini, & Declau, 2003). Degree of hearing loss was based on a four frequency (500, 1000, 2000 and 4000 Hz) pure-tone air conduction average (4PTA) (Mazzoli, Van Camp, Newton, Giarbini, & Declau, 2003) and the descriptor of degree of hearing sensitivity used in this current study is shown in Table 5. Type of hearing loss (conductive, sensorineural, mixed) was based on four frequency (500, 1000, 2000 and 4000 Hz) pure-tone averages for air and bone conduction thresholds (Mazzoli, Van Camp, Newton, Giarbini, & Declau, 2003) as illustrated in Table 6.

Audiometric configuration was assigned independent of degree or type of hearing loss and was based on pure-tone air conduction thresholds for the full frequency range of 250-8000 Hz (Mazzoli, Van Camp, Newton, Giarbini, & Declau, 2003). The definition of configuration used in this study was shown in Table 7.

Distortion product otoacoustic emissions (DPOAEs) were recorded in each ear in quarter octave bands over the frequency range 842-7996 Hz. L1 level was set at 65 dB (HL) and L2 was set at 55 dB (HL), with F2/F1 ratio of 1.22. DPOAE was assumed to be present when the level of DPOAE was 6 dB greater than the average estimate of noise level derived from adjacent frequency bins. According Robinette and Glattke (2007),

Table 5

Definition of Degree of Hearing Sensitivity

Average Hearing Threshold level in dB (re:1969 ANSI)	Hearing Loss Label
10-15	Normal Hearing
16-25	Slight Hearing Loss
26-40	Mild Hearing Loss
41-55	Moderate Hearing Loss
56-70	Moderately Severe Hearing Loss
71-90	Severe Hearing Loss
91	Profound Hearing Loss

Note. Adapted from Goodman (1965) and Mazzoli et al. (2003)

Table 6

Definition of Type of Hearing Sensitivity

Type	Criteria
Normal	Average AC thresholds < 15 dB HL; no A-B gaps >10 dB
Conductive	Average BC thresholds < 20 dB HL; average A-B gap >15 dB
Sensorineural	Average BC thresholds > 20 dB HL; average A-B gaps no > 10dB
Mixed	Average BC thresholds > 20 dB HL
Unknown	Average A-B gap > 15 dB HL

Note. Adapted from Mazzoli et al. (2003)

Table 7

Definition of Configuration of Hearing Sensitivity

Configuration	Criteria
Normal	All pure-tone thresholds from 250-8000 Hz < 20 dB HL
Flat	< 15 dB difference between all thresholds from 250- 8000 Hz
LF- ascending	≥ 15 dB difference between LF and better HF frequencies
Mid-frequency U-shaped	≥ 15 dB difference between worst mid-frequency (1000-2000 Hz) thresholds and those of higher and lower- frequencies
HF-gentle	15-29 difference between mean thresholds of 500 and 1000 Hz and mean thresholds of 4000 and 8000 Hz
HF-sharp	≥ 30 dB difference between mean thresholds of 500 and 1000 Hz and mean thresholds of 4000 and 8000 Hz
Atypical	Does not meet above criteria

Note. Adapted from Mazzoli et al. (2003). LF= low frequency. HF= high frequency.

OAE amplitude decreases when hearing thresholds are approximately 30 dB HL, they are absent with sensorineural hearing loss that exceeds 30 to 50 dB HL and with any degree of conductive loss, and they are expected to be present with retrocochlear pathologies.

Auditory brainstem responses (ABR) were obtained with individuals awake in a semi-recumbent position. A two channel electrode montage was used. The non-inverting electrode was placed on the high forehead at Fz, the inverting electrode on the ipsilateral earlobe (A1/A2), and the ground electrode on the nasion (Nz). Test stimuli were presented following the order as shown in Table 8. The neurological applications of the ABR in identifying a normal from pathologic ear were based on comparisons of the NF1 individuals' ABR to normative data from Schwartz et al. (1989) and Issa and Ross (1995). The normative values were established for absolute latencies (waves I, III, and V) and interpeak latencies (I-V, I-III, and III-V), interaural latency differences, rate differences, and V/I amplitude ratio. ABR absolute and interpeak latencies were interpreted using normative values obtained using 80 dB nHL broadband click stimuli with rarefaction and condensation polarities. These normative values (+2.5 SD from the mean) for individuals younger than three years (Issa & Ross, 1995) and for those between 19-36 years old (Schwartz et al., 1989) are provided in Table 9.

NF1 clinical signs (café-au-lait spots and skin freckling) data, computerized tomography (CT) and magnetic resonance imaging (MRI) (plexiform neurofibromas and spongiform gliose) data were provided by the principal investigator of the NIH clinical trial (NCI-08-C-0079), Dr. Wideman. Dr. Widemann's group analyzed the location of spongiform gliose in the brain, plexiform neurofibromas in the head and neck, and

Table 8

Parameters of Test Recording of Auditory Brainstem Responses

Order of Presentation	Intensity	Rate	Polarity	# Runs	#Sweeps
1	85/95dB nHL	8.3/sec	Rarefaction	2	1000
2	85/95 dB nHL	8.3/sec	Condensation	2	1000
3	85/95 dB nHL	63.3/sec	Rarefaction	2	1000
4	55/65 dB nHL	8.3/sec	Rarefaction	2	1000
5	0 dB nHL	8.3/sec	Rarefaction	2	1000
6	85/95 dB nHL	8.3/sec	Rarefaction	1	1000

Table 9

Normative Values for ABR Absolute and Interpeak Latencies

	Waves	Normative Values (ms)
Absolute	I	1.79
	II	4.08
	V	6.08
Interpeak	I-III	2.6
	III-V	2.26
	I-V	4.49

Note. +2.5 SD from Schwartz et al. (1989), ages 19-36 years.

hydrocephalus. These data were utilized to correlate the NF1 clinical signs to audiological findings obtained for each individual. Middle ear resonance frequency and acoustic reflex decay data were not obtained from all 40 NF1 individuals of this study cohort. Otoscopy, immitance, pure-tone and speech audiometry were obtained from all 40 NF1 individuals; however, DPOAEs were not obtained from 1 NF1 individual due to the presence of an enormous plexiform neurofibroma causing stenosis in the left external auditory meatus preventing the probe tip placement and ABRs testing were not obtained from three NF1 individuals due to equipment malfunction on the day of their audiological evaluation.

Equipment

All pure-tone threshold assessments were conducted using Grason-Stadler GSI 61 clinical audiometers in double-walled sound suites, which met the American National Standards Institute (ANSI) criteria for maximum permissible ambient noise level **(**ANSI S3.1-1999 R2008**)**. Audiometers and transducers were calibrated according to the ANSI standards (S3.6-2004; American National Standards Institute, 2004b). A Grason-Stadler GSI Tympstar Middle Ear Analyzer was used for immitance measures including tympanometry and acoustic reflex threshold testing. The Otodynamic ILO 92 system was used for recording DPOAEs. ABR testing was performed using a Grason Stadler Audera system and ER-3A inserts earphones.

Participants were tested using ER-3A insert earphones to reduce the need for masking due to the greater interaural attenuation. In cases in which neurofibromas occurred in the pinna or in the external auditory meatus, and caused stenosis, Telephonics TDH- 50P supra-aural headphones were used (Clark & Roeser, 1988; Chen, Chen &

Noordhoff, 1989; Rapado, Simo & Small, 2001). A visual inspection of the head and neck during otoscopic procedures was conducted to assure the correct transducer choice for audiological testing.

The audiometric database software (AudBase®) from the company GN Otometrics was utilized to directly import and store audiological data from GSI equipment. This software was in compliance with the Health Insurance Portability and Accountability Act of 1996 (Wilson, 2006) for security and protection of the electronic health database. The NF1 individuals were searched in this audiometric database and an appropriately encoded list was created. All obtained NF1 data were carefully examined and analyzed to prevent data entry errors.

Statistical Analysis

A pilot study was performed to develop, adapt, check this project feasibility, and to determine the reliability of measures. The results of this pilot study were presented as part of an in-house research poster session at the NIH Summer Poster Day (August, 2009).

Audiologic data in this study were examined retrospectively from data collected as part of the on-going longitudinal natural history protocol (NCI-08-C-0079) through the National Cancer Institute at the Clinical Center in the National Institutes of Health (NIH), Bethesda, Maryland. This was not an experimental design.

Data management and analysis was undertaken using Excel version 2003 and SPSS version 12.01. Descriptive statistics including measures of central tendency (mean, median and mode), measures of dispersion (standard deviation and range), and percentiles were used to describe interval scale variables such as peak compensated

acoustic admittance and acoustic reflex thresholds. The chi-square test was appropriate to determine if the relationship between two variables was significant. Research findings were analyzed using descriptive statistics and trends were examined. Dichotomous variables such as the presence/absence of acoustic reflex thresholds were expressed proportionally. Analysis of variance (ANOVA) was used to test differences between means of interval scale variables with other variables entered to the model as covariates where appropriate.

CHAPTER 4

RESULTS

Forty individuals (80 ears) diagnosed with NF1 participated in this study. Participants comprised fifteen females and twenty-five males. The mean age and standard deviation (*SD*) of the females were 15.5 (*9.14*) and of the males were 14 (*5.5*) (Table 10).

The prevalence of clinical signs such as café-au-lait spots, skin freckling, plexiform neurofibromas, and spongiform gliose in this study clinic population (40 NF1 individuals) was summarized in Table 11. Examination of this table showed that plexiform neurofibroma was the most common clinical sign with 39/40 (97.5%) of individuals exhibiting this feature. Skin freckling and café-au-lait spots also exhibited a high prevalence rate with both clinical features occurring in 37/40 individuals (92.5%). Spongiform gliose was present in 11/40 (27.5%) of individuals in this study cohort. Figure 3 showed the prevalence of plexiform neurofibroma at different body locations. Examination of this figure showed that 13/40 (32.5%) of the individuals had plexiform neurofibromas only in the trunk, 10/40 (25%) of the individuals had involvement in the head, 10/40 (25%) had plexiform neurofibromas throughout the entire body, and 3/40 (7.5%) did not present plexiform neurofibromas.

Table 12 showed the location of spongiform gliose in 11 NF1 individuals. Magnetic resonance imaging (MRI) of these 11 individuals revealed the most common location of the spongiform gliose was within the left globus pallidus (73%), followed by

Table 10

Demographics of the NF1 Cohort (N=40 NF1 individuals)

N=40	Participants n (%)	Age at Baseline (Mean, SD)	Range
Female	15 (37%)	15.5 (9.14)	5-32
Male	25 (63%)	14 (5.5)	5-45

Table 11

Prevalence of NF1 Clinical signs (N=40 NF1 individuals)

NF1 Clinical Manifestations (N=40)							
Café- au- lait spots		Skin Freckling		Plexiform Neurofibroma		Spongiform Gliose	
n	(%)	n	(%)	n	(%)	n	(%)
37	(92.5)	37	(92.5)	39	(97.5)	11	(27.5)

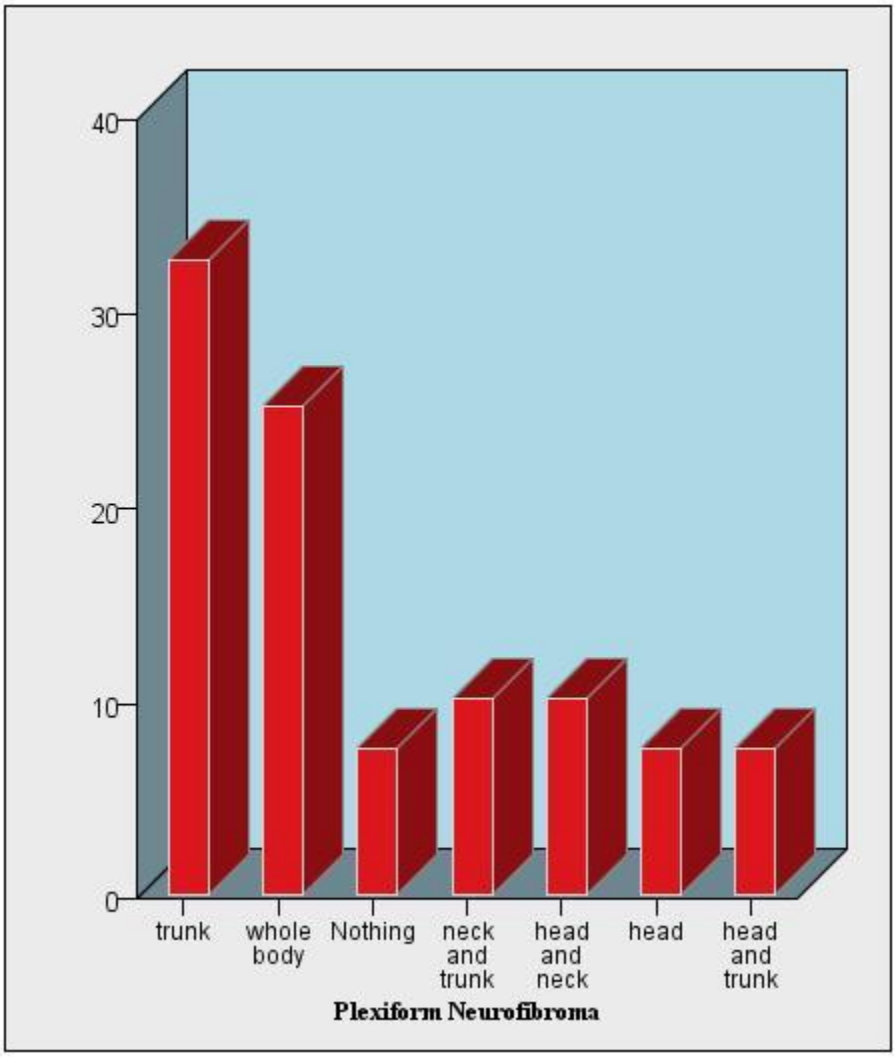


Figure 3. Location of the plexiform neurofibromas confirmed by MRI findings performed in 40 NF1 individuals.

Table 12

Description of the Location of the Spongiform Gliose in 11 NF1 individuals (N=11)

NF1 Individual Code	Spongiform Gliose
001	Central medulla, posterior pons, left globus pallidus, and right temporal lobe
008	Right and left globus pallidus
009	Right pons, right and left cerebellum, right and left globus pallidus, right thalamus, right frontal lobe
012	Right medulla and right temporal lobe
021	Right pons, right midbrain, right and left globus pallidus, right thalamus, right putamen, and right temporal lobe
026	Right and left posterior pons, right midbrain, right and left cerebellum, right and left globus pallidus and right frontal lobe
029	Right midbrain, right and left cerebellum, right and left globus pallidus
030	Right and midbrain, right and left cerebellum and left temporal lobe
038	Right midbrain
049	Right and left cerebellum, left globus pallidus, and left corpus callosum
064	Left pons, right and left cerebellum, and left globus pallidus

the left and right cerebellum (63.6%), right globus pallidus (45.4%), right midbrain/cerebral peduncle (36.3%) and right temporal lobe (36.3%) (Figure 4).

Table 13 provided a summary of the number (percentage) of ears with audiological and otological symptoms as reported by the patients during the case history conducted immediately prior to the first audiological assessment. Examination of this table shows that hearing loss was reported by study participants in 8/40 (20%) right ears and 7/40 (17.5%) left ears. Approximately 50% of ears with NF1 had a history of ear infections. This was the most reported otological symptom (52.5% and 47.5% of right and left ears, respectively), followed by dizziness (30%) and bilateral tinnitus (25%). None of the individuals reported a history of noise exposure or treatment with ototoxic medications. Twenty-two individuals (55%) reported a history of surgeries secondary to NF1-related tumors, including palate, lip, kidney, neck, coccyx, pelvis, abdomen and spine debulking surgeries. A history of NF1 related surgery was not considered an exclusionary finding; therefore, these patients were included in the analysis.

Right and left ear pure-tone air-conduction threshold means and standard deviations (*SD*) were calculated for octave and inter-octave frequencies from 250-8000 Hz, as well as for the four frequency pure-tone average (4PTA) (Table 14). The mean four-frequency pure tone average (4PTA) was similar between ears: 11.09 dB HL and 10.25 dB HL for the right and left ears, respectively. Hearing loss, as defined by 4PTA> 15 dB HL, was observed in 17.5% (7/40) of individuals with NF1 (Figure 5). Of the seven individuals with hearing loss, two had slight hearing loss, two had mild hearing loss, and three had moderate hearing loss.

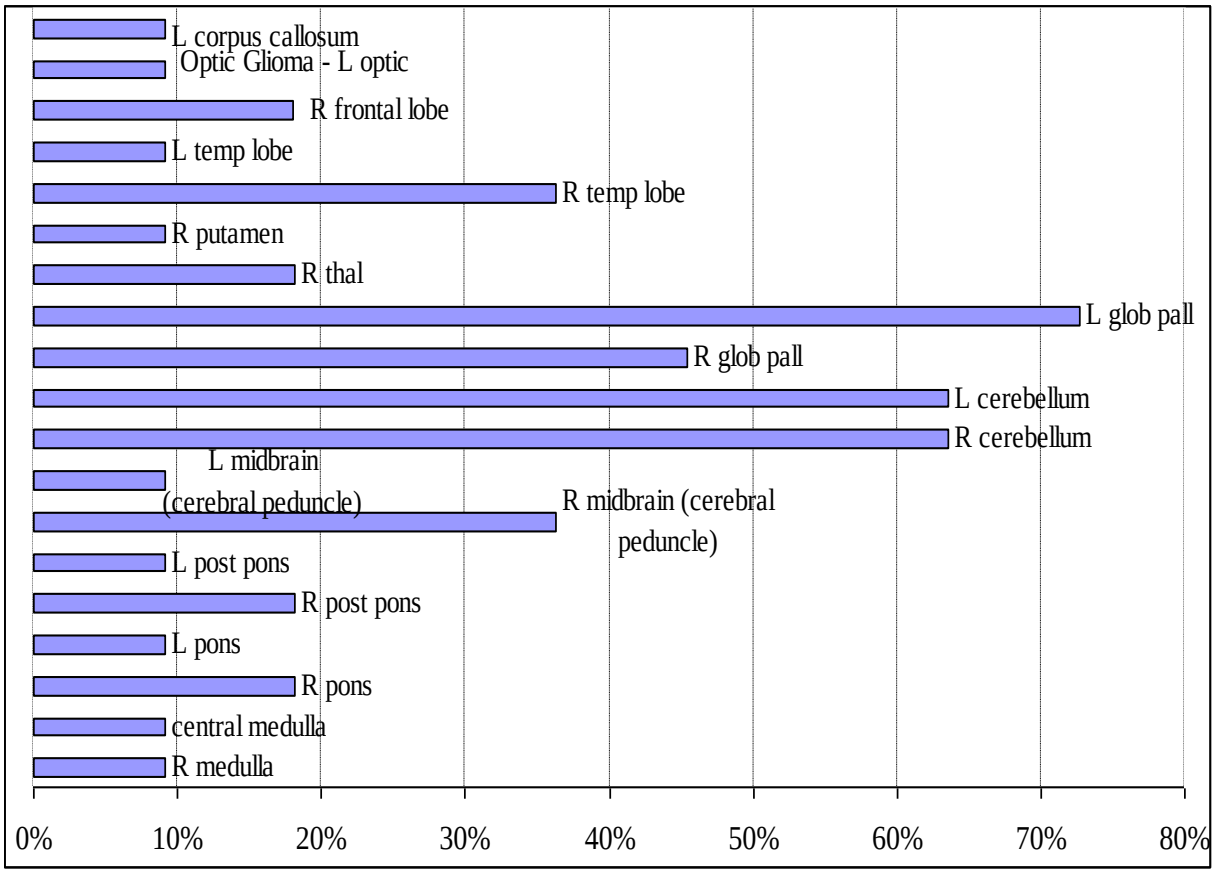


Figure 4. Prevalence rates for the location of spongiform gliose in the brain for the right and left hemisphere confirmed by MRI findings (N=11 NF1 Individuals).

Table 13

Audiologic and Otologic Characteristics of this NF1 Cohort

(N=80 ears)	Right Ear		Left Ear	
	n	(%)	n	(%)
Subjective Report of Hearing Loss	8	(20)	7	(18)
Family Hx of Hearing Loss	0	(0)	0	(0)
Noise Exposure	0	(0)	0	(0)
Hearing Aids	1	(3)	2	(5)
Tinnitus	10	(25)	10	(25)
Aural Fullness	3	(8)	2	(5)
Otalgia	1	(3)	3	(8)
Otorrhea	1	(3)	1	(3)
Hx of Ear Infections	21	(53)	19	(48)
Complete Stenotic Ear Canal	1	(3)	2	(5)
Ototoxic Medications	0	(0)	0	(0)
(N= 40 Individuals)		n		(%)
Headache		4		(10)
Migraine		3		(8)
Dizziness		12		(30)

Table 14

Mean Four-frequency Pure-tone Averages and Air conduction Thresholds for the Right and Left ears at Baseline (N=80)

		Air Conduction Thresholds (N=80)								
		PTA	.25kHz	.5kHz	1kHz	2kHz	3kHz	4kHz	6kHz	8kHz
Right	Mean	11.09	15.63	13.75	11.38	11.13	12.05	8.13	11.38	11.75
	SD	12.41	14.42	12.39	12.51	12.48	15.12	14.44	13.35	14.61
Left	Mean	10.25	15.63	13.00	10.75	10.00	8.88	7.25	10.90	8.63
	SD	8.11	10.33	8.90	10.29	9.06	8.73	8.00	9.31	10.13

Note. All numerical values represent sound level in dB HL

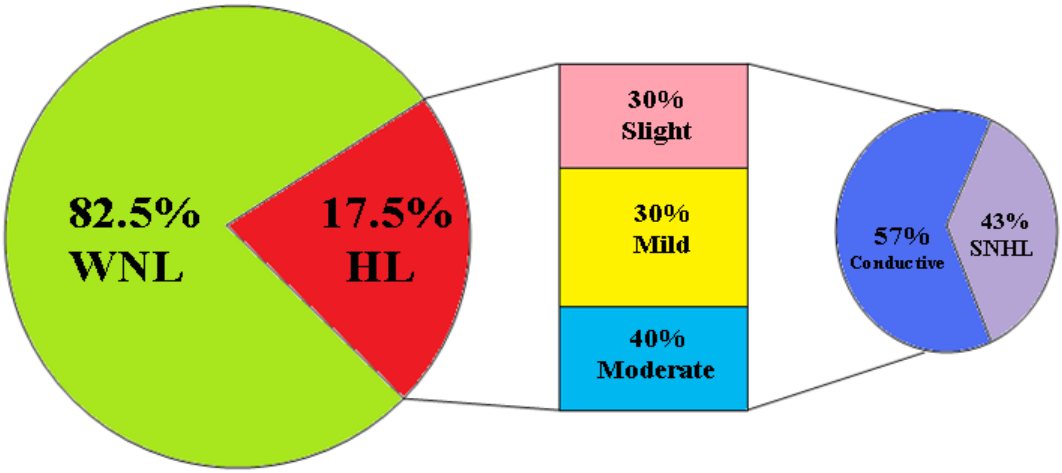


Figure 5. Audiologic profile of hearing loss based on the four-frequency pure-tone average (.5/1/2/4 kHz) for 40 individuals with NF1.

The type of hearing loss was conductive for four and sensorineural for three individuals. Of the four individuals with conductive hearing loss, three had unilateral conductive hearing loss, and one had bilateral conductive hearing loss. Of the three individuals with sensorineural hearing loss, two had unilateral sensorineural hearing loss, and one had bilateral sensorineural hearing loss. In terms of NF1 ears, hearing loss (4PTA >15 dB HL) was observed in 11.25% (9/80) of ears with NF1. Hearing loss was present for at least one test frequency in one or both ears from 250-8000 Hz (>15 dB HL) in 45% (18/40) of the individuals with NF1. When evaluated by ears, hearing loss was present in 36% (29/80) of the ears, as illustrated in Figure 6.

The prevalence of hearing loss by test frequency (n=80 ears) is shown in Figure 7. When present, the hearing loss most often occurred in the highest and lowest frequencies; specifically, it was most prevalent at 250 (35%), 500 (22.5%) and 8000 Hz (22.5%). The least affected frequency was 2000 Hz (12.5%).

The degree of hearing loss by test frequency for ears with hearing loss (N=29) is shown in Figure 8. Examination of this figure shows that NF1 ears with hearing loss most often had a slight hearing loss that occurred at 250 Hz (41.4%), 500 Hz (31%), and 6000 Hz (20.7%). Hearing loss of mild, moderate, and severe degrees occurred in a small percentage with no clear frequency effect. There were no cases of profound hearing loss in this NF1 cohort.

The type of hearing loss at the frequencies 500, 1000, 2000 and 4000 Hz for 80 NF1 ears is shown in Figure 9. Examination of this figure shows that 11 (13.8%) NF1 ears had a conductive hearing loss at 500 Hz, six (7.5%) ears at 1000 Hz, three (3.8%) ears at 2000 Hz and five (6.3%) ears at 4000 Hz. Five (6.3%) ears had mixed hearing loss

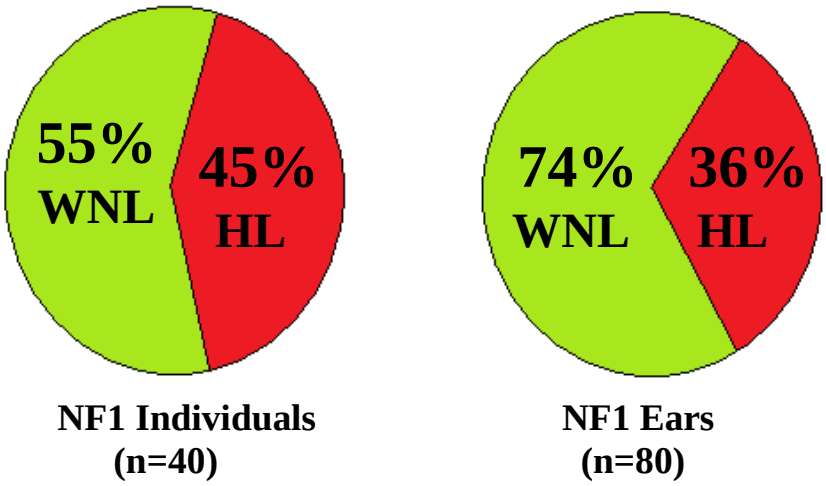


Figure 6. Audiologic profile of hearing loss based on at the presence of one or more air conduction thresholds of 20 dB HL or greater at 250 Hz- 8000 Hz. Percentages are shown for individuals (N=40) in the first pie chart and for ears in the second circle (N=80).

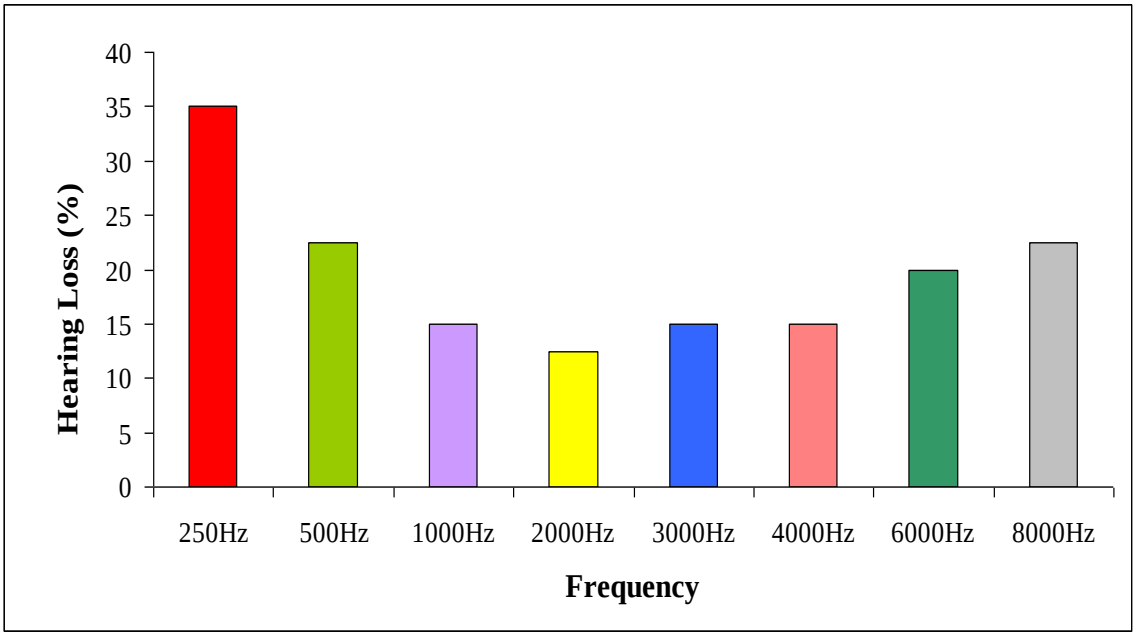


Figure 7. Prevalence of hearing loss by test frequency (N=80 ears).

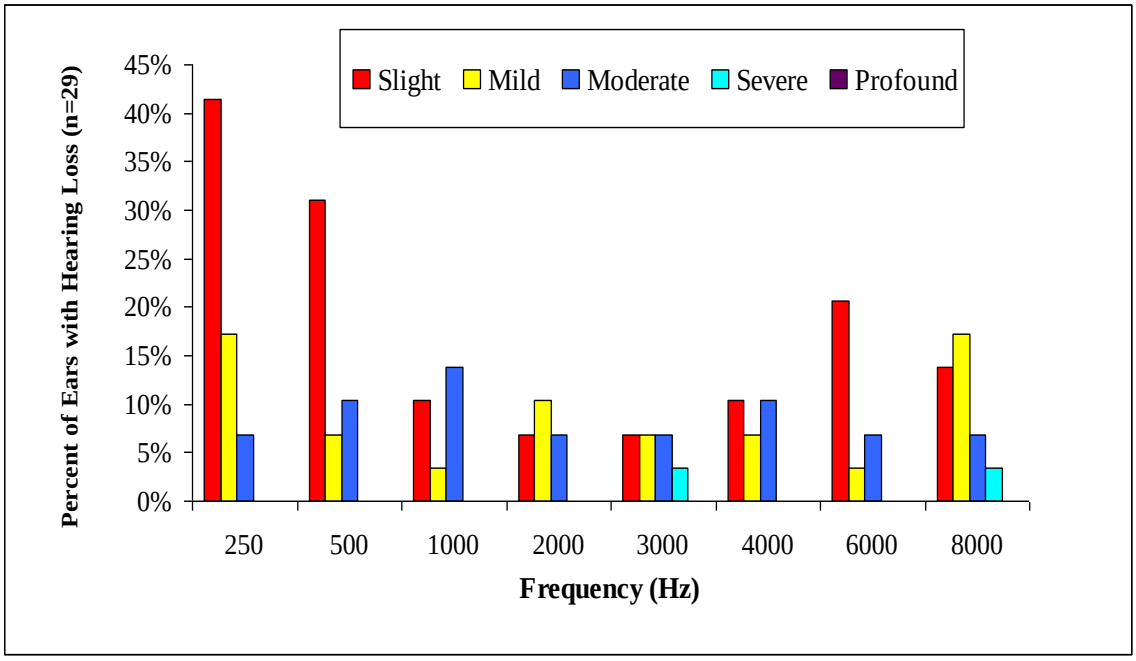


Figure 8. Degree of hearing loss by test frequency (N=29 ears).

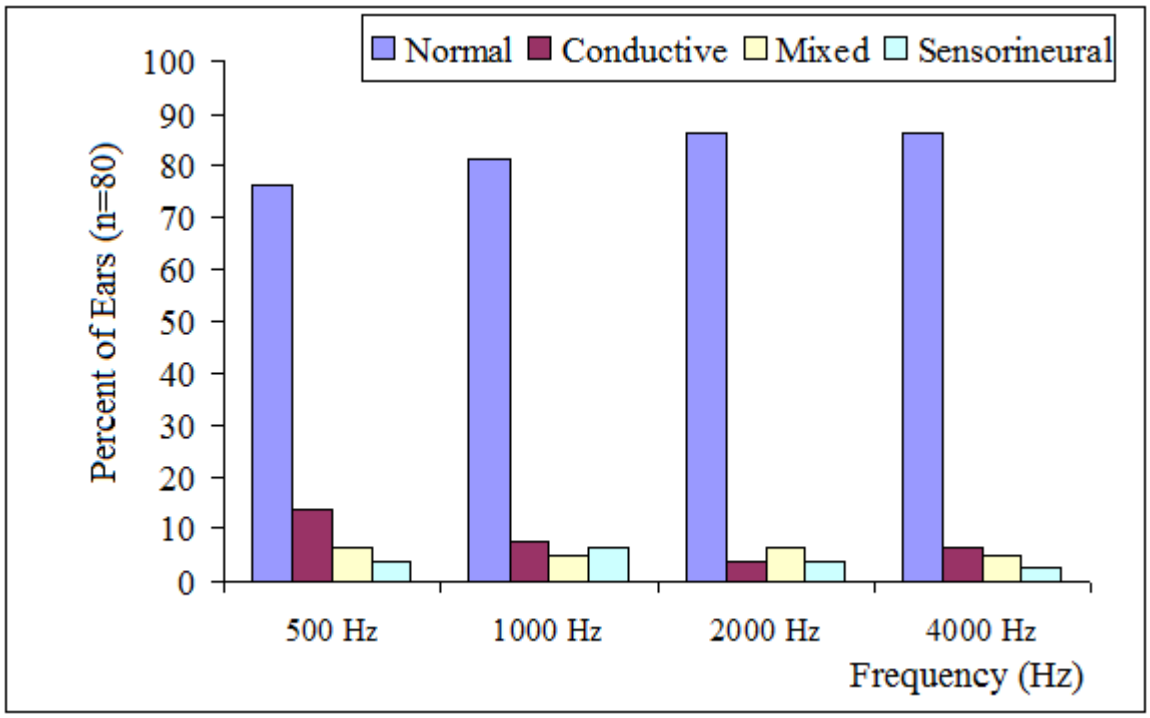


Figure 9. Prevalence of type hearing loss by test frequencies 500, 1000, 2000 and 4000 Hz (N=80 ears).

at 500 Hz, four (5.0%) ears at 1000 and 4000 Hz, and five (6.3%) ears at 2000 Hz. Three (3.8%) ears had sensorineural hearing loss at 500 and 2000 Hz, five (6.3%) ears at 1000 Hz and 2 (2.5%) ears at 4000 Hz. When hearing loss was present among the NF1 ears, conductive hearing loss was the most prevalent type of hearing loss, and sensorineural hearing loss the least prevalent.

The means and standard deviations for the 4 PTA, speech recognition threshold (SRT), and word recognition score (WRS) are presented in Table 15 (*N*=80 ears). According to the mean and *SD* values shown in the Table 15, greater than 90% of NF1 ears in this cohort presented with excellent speech recognition. Summary data for tympanometric peak pressure, static compliance and ear canal volume (N=80 ears) were provided in Table 16, and Figure 10 illustrated the distribution of the tympanometric data obtained in this NF1 Cohort. The mean (and SD) tympanometric peak pressure was -21.2 daPa (71.8) for all NF1 ears. The mean (and SD) static compliance was 0.8 ml (0.6). The mean (and SD*)* ear canal volume was 1.4 ml (0.9).

Peak compensated static compliance (ml) data for all ears (n =80) was presented in Figure 11. The mean of the right ears was not statistically significantly different from the mean of the left ears ($p > 0.05$). Normal static compliance was observed in 68 (85%) ears and abnormal compliance was identified in 12 (15%) ears. Of those 12 ears with abnormal static compliance, four had high static compliance (> 1.5 ml) with no reported history of ossicular disarticulation or scarred tympanic membrane, and eight had low static compliance (< 0.3 ml) secondary to P.E. tubes, perforation in the tympanic membrane, and fluid in the middle ear.

Table 15

Means and Standard deviations (SD) of the Four-frequency pure-tone average (4PTA), Speech recognition threshold (SRT), and Word recognition score (WRS) (N=80 ears)

		4PTA (dB HL)	SRT (dB HL)	WRS (%)
Right Ear	Mean	12.1	10.2	99.2
	SD	12.1	12.3	2.7
Left Ear	Mean	11.3	9.7	97.8
	SD	8.8	8.3	4.2

Table 16

Tympanometric Data for this NF1 Cohort (226 probe tone) (N=80 ears)

	Peak Pressure (daPa)	Static Compliance (mL)	Ear Canal Volume (mL)
Mean	-21.2	0.8	1.4
SD	71.8	0.6	0.9

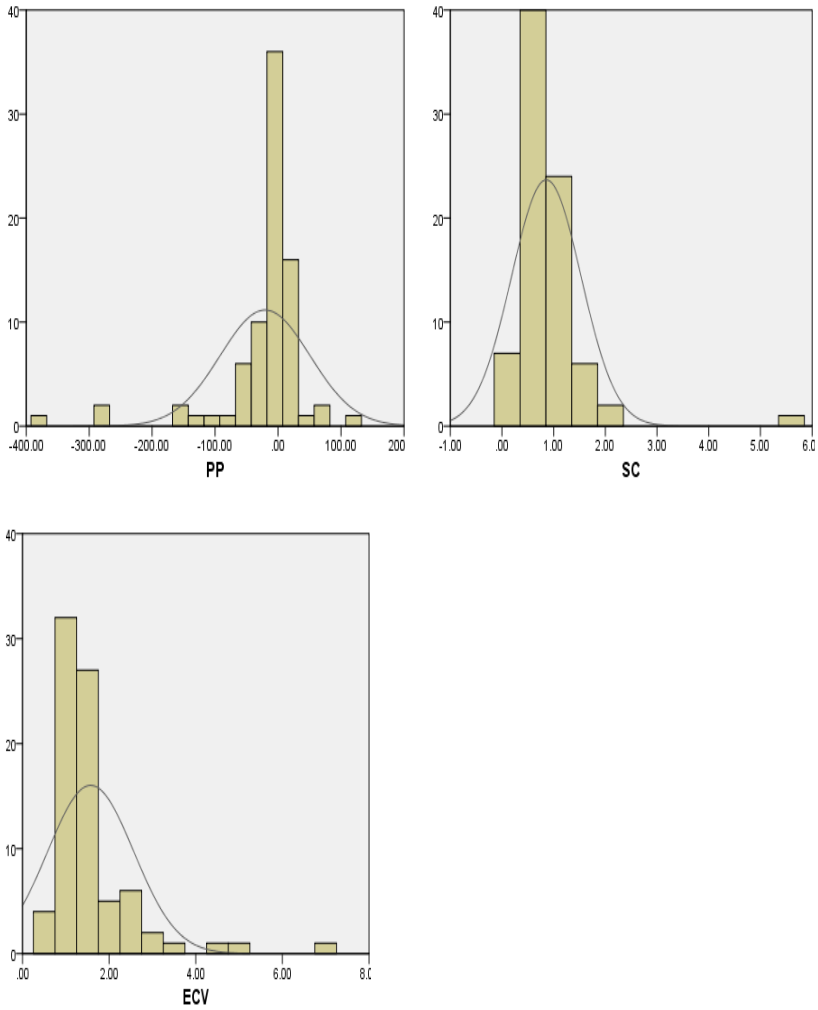


Figure 10. Tympanometric data distribution of 80 NF1 ears. PP=peak pressure in daPa. SC= static compliance in mL. ECV=ear canal volume in mL.

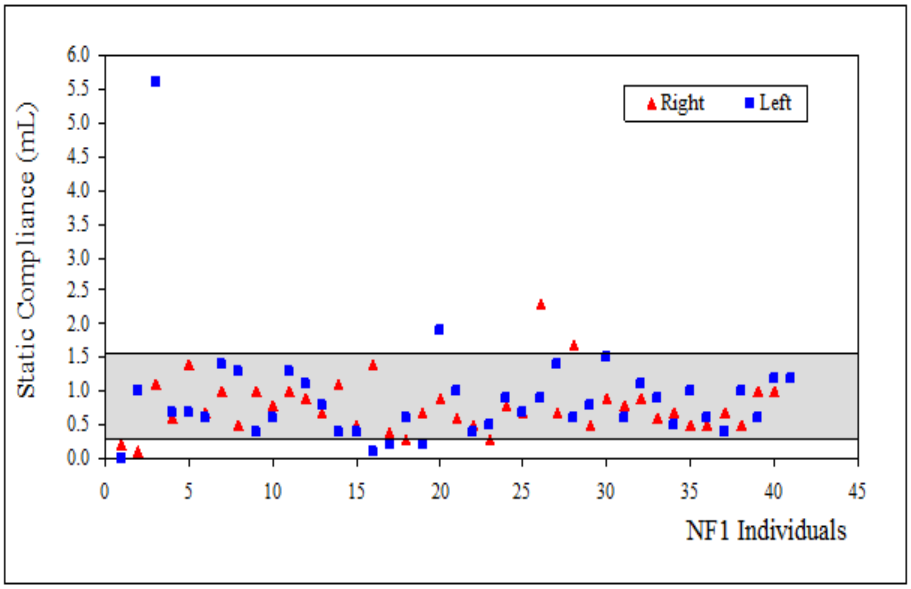


Figure 11. Tympanometric static compliance in milliliters (mL) (*N*=80 ears).

Tympanometric peak pressure (daPa) data for all ears (*n*=80) were presented in Figure 12. Normal peak pressure was observed in 74 (93%) of the NF1 ears and abnormal peak pressure was identified in six (7%) of ears. Of those six abnormal ears, five had negative peak pressure (< -150 daPa), and one had peak pressure greater than +100 daPa due to the presence of fluid in the middle ear but no reported history of Eustachian tube disorder.

Examination of Table 17 showed that 27 NF1 ears (34%) had tympanometric ear canal volume (mL) greater than 1.5 mL. Of those 27/80 (37.5%) NF1 ears, eight (29%) ears had patent pressure equalizer tubes (P.E. tubes) in place and two (7.5%) ears had perforated tympanic membrane confirmed by otoscopy, and 17 (62.5%) ears had large ear canal volume with intact TM.

Sixty-six (82.5%) NF1 ears had contralateral ARTs within normal limits at 500 Hz, 67 (83.7%) ears at 1000 Hz and 68 (85%) ears at 2000 Hz. Eight (10%) ears had elevated contralateral ARTs at 500, 1000 and 2000 Hz. Six (7.5%) ears had absent contralateral ARTs at 500 Hz, five ears (6.2%) at 1000 Hz, and four (5%) ears at 2000 Hz. Seventy (87.5%) ears had ipsilateral acoustic reflex thresholds within normal limits at 1000 Hz, seven (8.7%) ears had absent ipsilateral ARTs at 1000 Hz, and three (3.8%) ears had elevated ipsilateral ARTs at 1000 Hz. The overall mean for contralateral acoustic reflex thresholds was 92.5 (*SD*= 6) at 500Hz, 90.7 (*SD*= 6.6) at 1000Hz, and 90.9 (*SD*=6) at 2000Hz. The overall mean for ipsilateral acoustic reflex thresholds was 87.5 (*SD*= 6) at 1000Hz.

To further analyze the acoustic reflex data obtained from right and left NF1 ears, Figures 13 and 14 showed the right and left contralateral acoustic reflex thresholds for

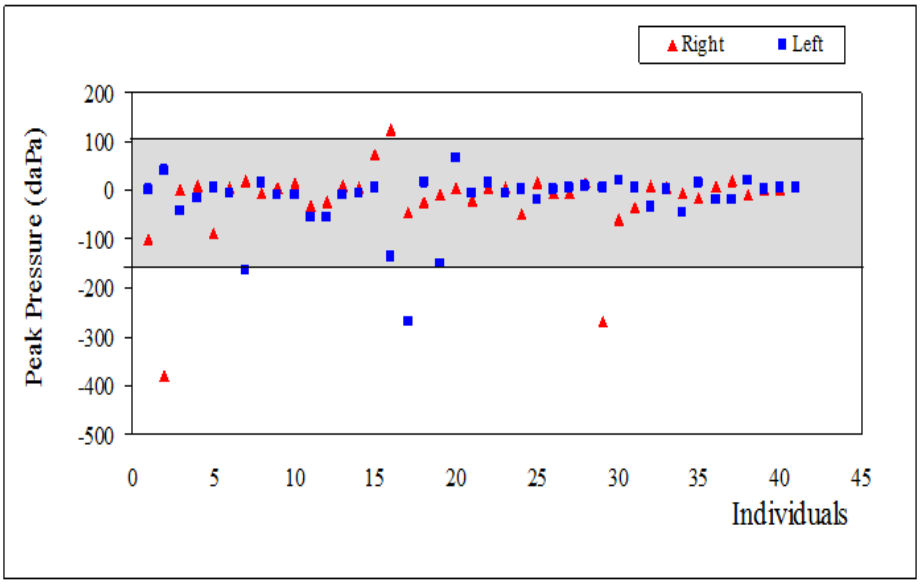


Figure 12. Tympanometric peak pressure in decapascal (daPa) (*N*=80 ears).

Table 17

Large Tympanometric Ear Volume in mL (226 probe tone) (N=27 ears)

Large Ear Canal Volume (mL)			
n (%)	Mean	*SD*	Range
27 (33.7%)	2.43	1.24	1.6-7.1

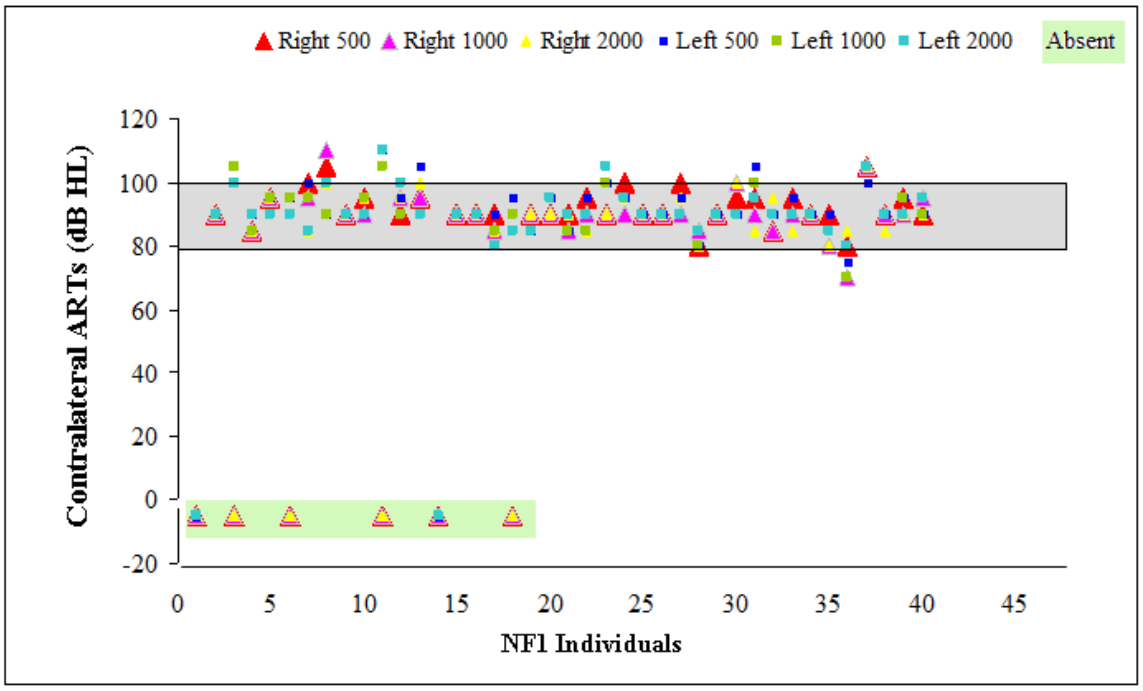


Figure 13. Contralateral acoustic reflex thresholds for 500, 1000, and 2000 Hz (226 probe tone) of 80 NF1 ears.

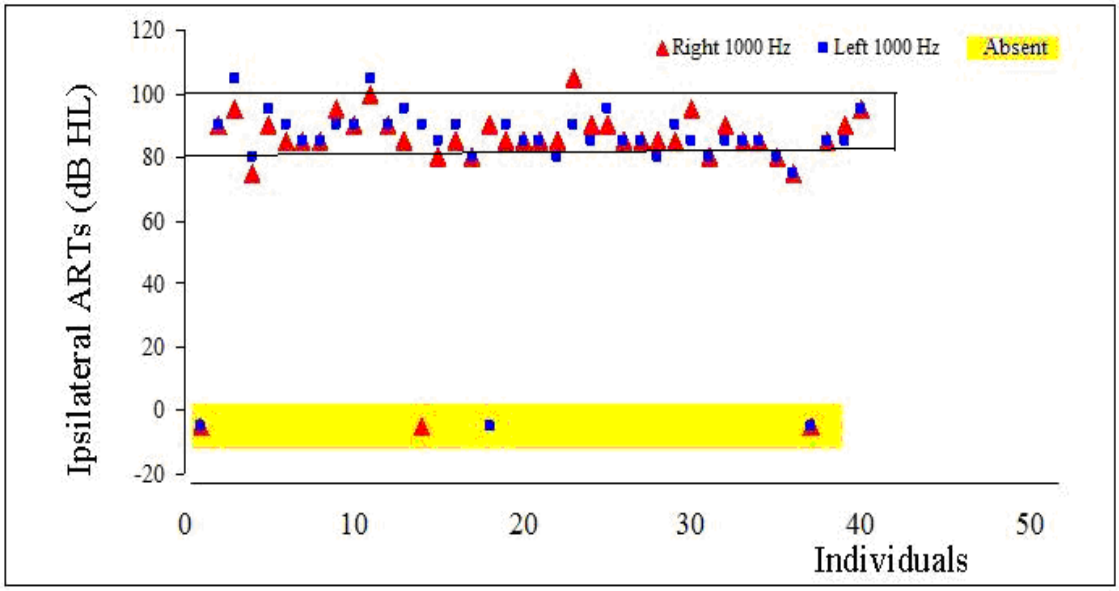


Figure 14. Ipsilateral 1000 Hz acoustic reflex thresholds (226 probe tone) of 80 NF1 ears.

500, 1000 and 2000 Hz and the ipsilateral 1000 Hz acoustic reflex thresholds for right and left ears (N=80 ears) by each individual, respectively. Figure 13 showed that 60 (75%) ears had contralateral ARTs at 500, 1000 and 2000 Hz within normal limits. Twelve (15%) ears exhibited absent right contralateral ARTs at 500, 1000 and 2000 Hz. Four (5%) ears demonstrated absent left contralateral ARTs at 500 and1000 Hz, and six (7.5%) ears presented with absent left contra ARTs at 2000 Hz. Eight (10%) ears had elevated right contralateral ARTs at 500, 1000 and 2000 Hz. Twelve (15%) ears exhibited elevated left contralateral ARTs at 500 Hz, five (12.5%) ears at 1000 Hz, and six (15%) ears at 2000 Hz. Examination of Figure 14 showed that 70 (87.5%) ears had ipsilateral ARTs at 1000 Hz within normal limits.

The relationship between contralateral acoustic reflex thresholds (ARTs) at 500, 1000 and 2000 Hz and hearing sensitivity based on the frequencies of 500, 1000 and 2000 Hz (80 NF1 ears) is shown in Figure 15.

Acoustic reflex thresholds were expected to be present when hearing thresholds were lower than 50-60 dBHL. Six ears at 500 Hz and four ears at 1000 and 2000 Hz with hearing loss had absent contralateral ARTs and two ears with hearing loss at 500 Hz had elevated contralateral ARTs. These abnormal (absent or elevated) acoustic reflex patterns were consistent with the type and degree of hearing loss. Five ears with normal hearing sensitivity had elevated acoustic reflexes that could be attributed to tympanometric findings of low static compliance, negative peak pressure, and large ear canal volume. There were 15 ears with elevated acoustic reflexes in the presence of normal hearing sensitivity and normal tympanometric measures, which could be suggestive of retrocochlear pathology (Table 18).

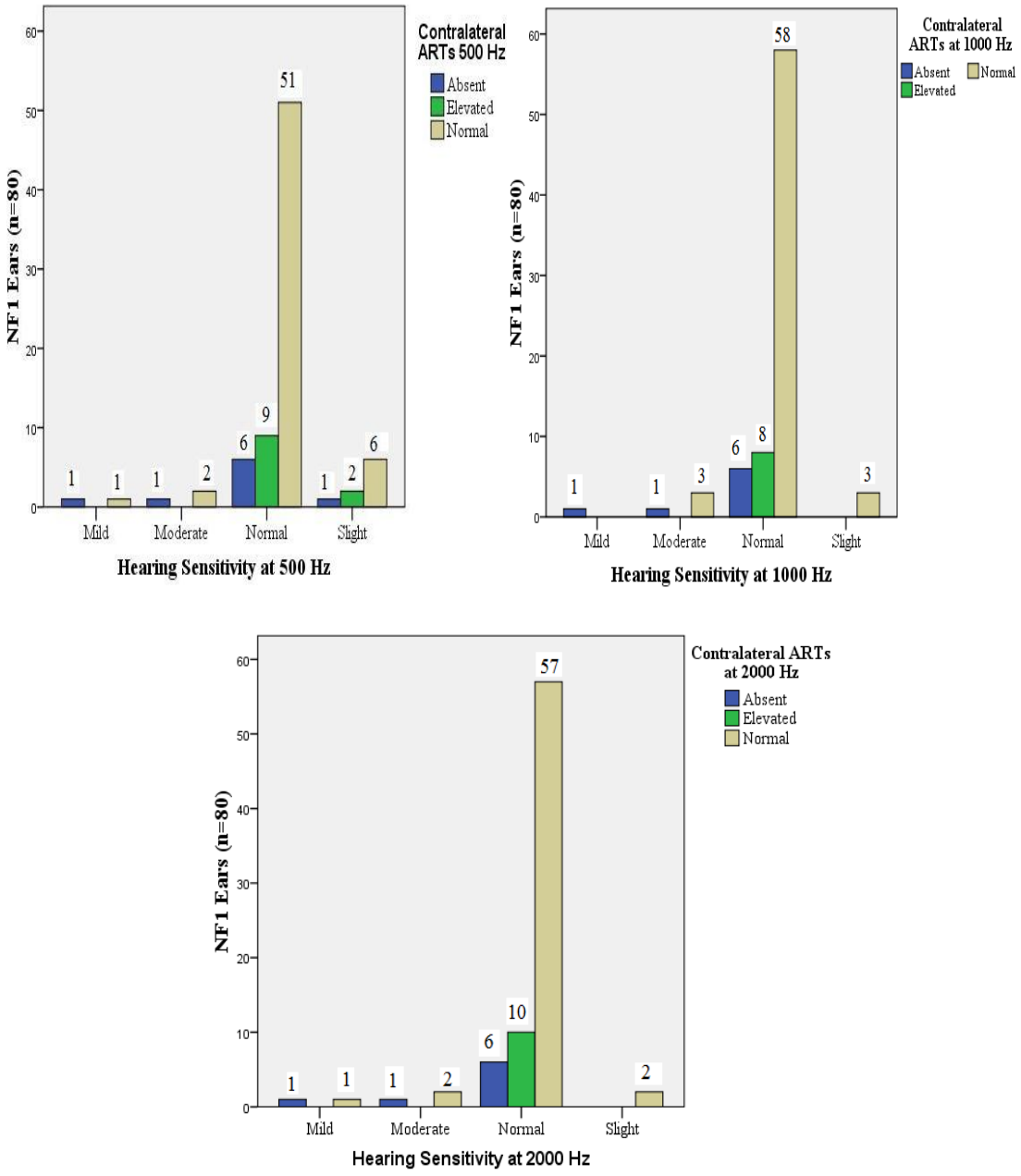


Figure 15. Relationship between contralateral acoustic reflex thresholds (ARTs) at 500, 1000 and 2000 Hz and hearing sensitivity based on 500, 1000, and 2000 Hz (N=80 NF1 ears), respectively. HS=Hearing Sensitivity. RE= Right ear. LE= Left ear. ART= Acoustic reflex threshold. RE_ART= Right Contra ART. LE_ART=Left Contra ART.

Table 18

Expected versus Observed Contralateral Acoustic Reflex Thresholds at 500, 1000, and 2000 Hz in 20 NF1 ears with Normal Hearing Sensitivity (N=18 NF1 ears)

		Contralateral Acoustic Reflex Thresholds				
NF1 Participant Code	Ear	Expected ARTs	Observed Contra ARTs 500 Hz	1000 Hz	2000 Hz	Tympanogram
001	Right	Normal	Absent	Absent	Absent	Low SC
	Left	Abnormal	Absent	Absent	Absent	Normal
003	Right	Normal	Absent	Absent	Absent	Normal
	Left	Normal	Elevated	Elevated	Elevated	Normal
008	Right	Abnormal	Elevated	Elevated	Elevated	Normal
	Left	Normal	Normal	Normal	Normal	Negative PP
009	Right	Normal	Elevated	Normal	Normal	Normal
	Left	Normal	Elevated	Normal	Normal	Normal
010	Right	Normal	Elevated	Elevated	Elevated	Normal
	Left	Normal	Normal	Normal	Elevated	Normal
015	Right	Normal	Absent	Absent	Absent	Normal
	Left	Normal	Elevated	Elevated	Elevated	Normal
031	Right	Normal	Normal	Normal	Normal	Normal
	Left	Normal	Elevated	Elevated	Elevated	Normal
033	Right	Abnormal	Elevated	Normal	Normal	Normal
	Left	Normal	Normal	Normal	Normal	Large ECV
047	Right	Abnormal	Normal	Normal	Normal	Large ECV
	Left	Abnormal	Elevated	Elevated	Normal	Large ECV
063	Right	Normal	Elevated	Elevated	Elevated	Normal
	Left	Normal	Absent	Elevated	Elevated	Normal

Note. PP=peak pressure. ECV= ear canal volume. Abnormal= elevated or absent.

DPOAEs (SNR > 6 dB) were present and robust in most ears (n=78) for all test frequencies. Presence based on a signal-to-noise ratio ≥ 6 dB, and indicate functional integrity of the cochlear outer hair cells.

In order to further analyze the presence or absence of DPOAEs with respect to expected results versus observed results based on the degree of hearing loss, the relationship between hearing sensitivity based on the frequencies 1000, 2000, 3000, 4000, 6000 and 8000 Hz and DPOAEs is shown in Figure 16 (n=78 ears). There were 14 NF1 ears with hearing loss that had DPOAEs within normal limits. Two ears with moderate and one ear with slight hearing loss had present DPOAEs at 1000 Hz. Two ears with a slight hearing loss and one ear with mild hearing loss had present DPOAEs at 2000 Hz. Four ears with slight hearing loss had present DPOAEs at 3000 Hz. Four ears with slight hearing loss had present DPOAEs at 4000 Hz. Four ears with a slight hearing loss had present DPOAEs at 6000 Hz. Four ears with a slight and six ears with a mild hearing loss had present DPOAEs at 8000 Hz.

The absence of otoacoustic emissions was analyzed in those cases (n=78) where would be expected to obtain DPOAEs (Table 19). Twenty-four NF1 ears with normal hearing sensitivity had absent DPOAEs at 1000 Hz, 27 ears at 2000 Hz, 33 ears at 3000 Hz, 30 ears at 4000 Hz, 30 ears at 6000 Hz, and 12 ears at 8000 Hz. Absence of emissions by itself was not interpretable, but only six of those cases were supported by abnormal tympanometric test results. Ten NF1 ears had absent emissions in the presence of normal hearing sensitivity (based on each test frequency) and normal tympanometric findings and abnormal contralateral acoustic reflex thresholds. This was suggestive of a cochlear dysfunction (Table 19).

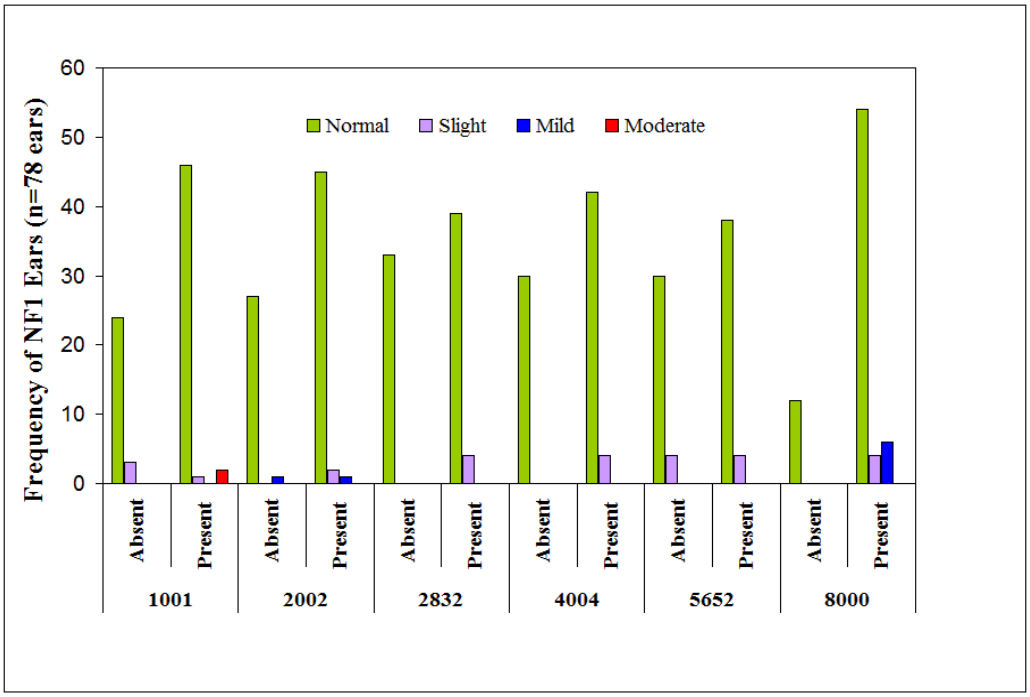


Figure 16. Relationship between hearing sensitivity based on the frequencies 1, 2, 3, 4, 6, and 8 kHz and distortion product otoacoustic emissions (DPOAEs) in 78 NF1 ears.

Table 19

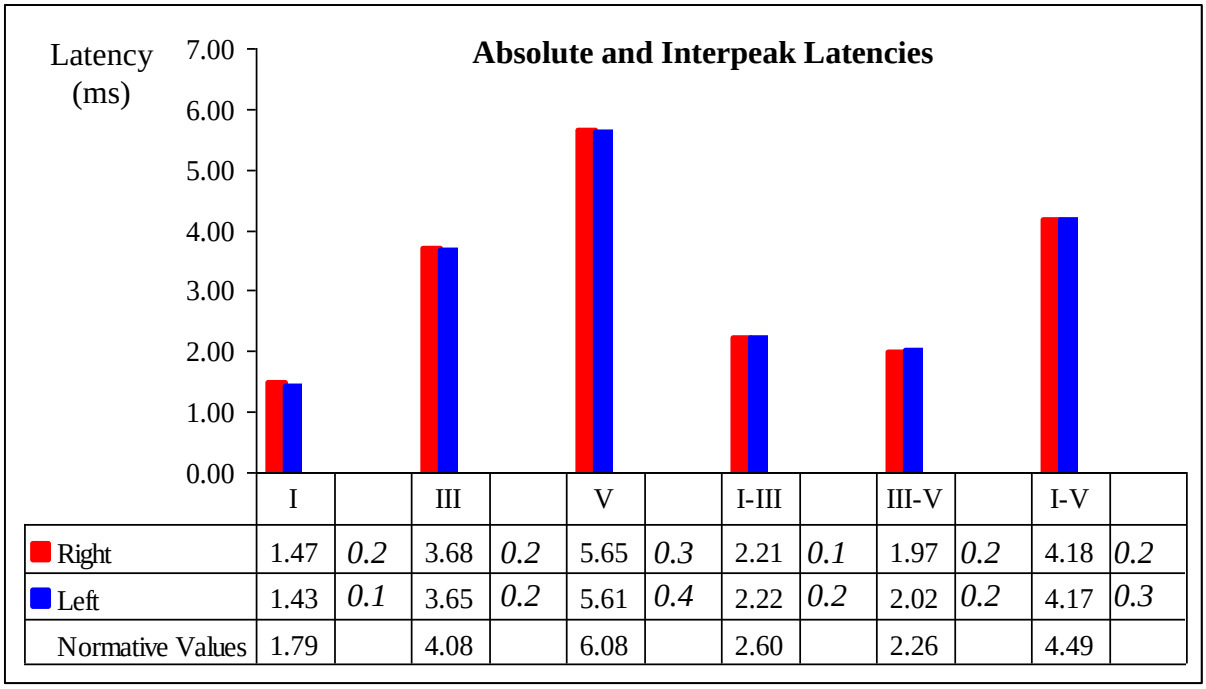
Relationship between normal hearing sensitivity (by frequency), Contralateral acoustic reflex thresholds at 0.5, 1, and 2 kHz, Normal tympanometry, and absent distortion product otoacoustic emissions (DPOAEs) in 10 NF1 ears

Individual Code	Ear	Normal Hearing	Contralateral Acoustic Reflex Thresholds			Tympanogram	DPOAEs
			500 Hz	1000 Hz	2000 Hz		
001	Left	Normal	Absent	Absent	Absent	Normal	Absent
003	Right	Normal	Absent	Absent	Absent	Normal	Absent
	Left	Normal	Elevated	Elevated	Elevated	Normal	Absent
009	Right	Normal	Elevated	Normal	Normal	Normal	Absent
	Left	Normal	Elevated	Normal	Normal	Normal	Absent
010	Right	Normal	Elevated	Elevated	Elevated	Normal	Absent
	Left	Normal	Normal	Normal	Elevated	Normal	Absent
015	Right	Normal	Absent	Absent	Absent	Normal	Absent
	Left	Normal	Elevated	Elevated	Elevated	Normal	Absent
033	Right	Normal	Elevated	Normal	Normal	Normal	Absent

Auditory brainstem response (ABR) mean absolute and interpeak latencies for waves I, III, and V were shown for the right and left ears (n=74 NF1 ears) in Figure 17. Examination of this figure showed the comparison between ABR data from the right and left NF1 ears to normative values.

Fifty-two (70%) NF1 ears had absolute latencies (I, III, V) and interpeak latencies (I-III, III-V, I-V) within normal limits, and 22 (30%) had abnormal auditory brainstem responses (prolonged or absent). The prevalence of NF1 ears (n=74) that exhibited prolongations of the absolute and interpeak latencies and/or absence of waves from auditory brainstem responses are illustrated in Figure 18. Eight (11%) ears had I-V interpeak latencies prolonged and six (8%) ears had prolonged V latency.

Figure 19 showed the association between the ABRs and the contralateral ARTs obtained from 74 ears. These data show that of the 52 (70%) ears with ABRs within normal limits, 36 (69%) had contralateral ARTs within normal limits, 11 (21%) had elevated contralateral ARTs, and 5 (9%) had absent contralateral ARTs. Twenty two (30%) ears that exhibited abnormal ABR findings, 15 (28%) had contralateral ARTs within normal limits, 4 (18%) had absent contralateral ARTs, and 3 (13%) had elevated contralateral ARTs.



	I		III		V		I-III		III-V		I-V	
Right	1.47	*0.2*	3.68	*0.2*	5.65	*0.3*	2.21	*0.1*	1.97	*0.2*	4.18	*0.2*
Left	1.43	*0.1*	3.65	*0.2*	5.61	*0.4*	2.22	*0.2*	2.02	*0.2*	4.17	*0.3*
Normative Values	1.79		4.08		6.08		2.60		2.26		4.49	

Figure 17. Mean (SD) absolute (I, III, V) and interpeak latencies (I-III, III-V, I-V) from auditory brainstem responses (N=74 ears). Normative values are mean +2.5 SD from Schwartz et al. (1989). All numerical values represent latencies in milliseconds (ms).

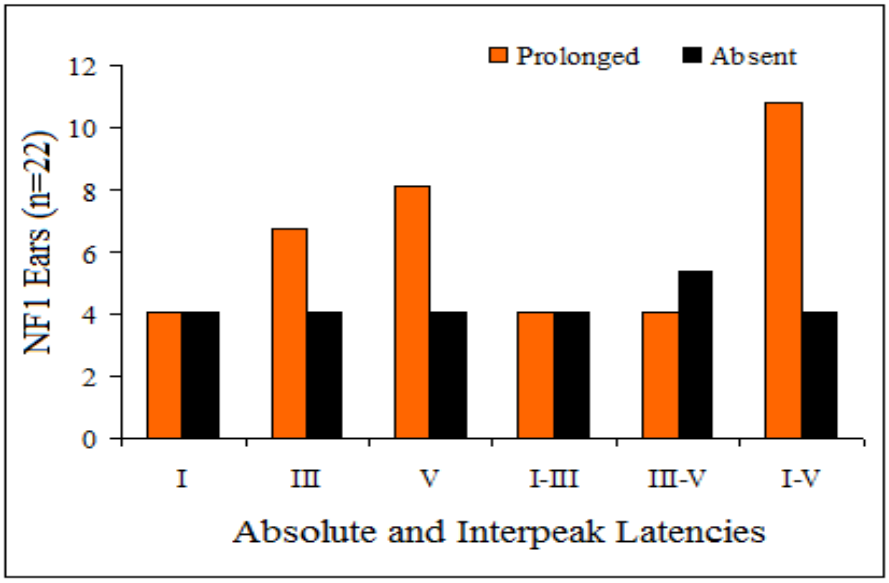


Figure 18. Percentage of NF1 ears that exhibited prolongations and absences of the absolute (I, III, V) and interpeak latencies (I-III, III-V, I-V) from auditory brainstem responses (N=74 ears).

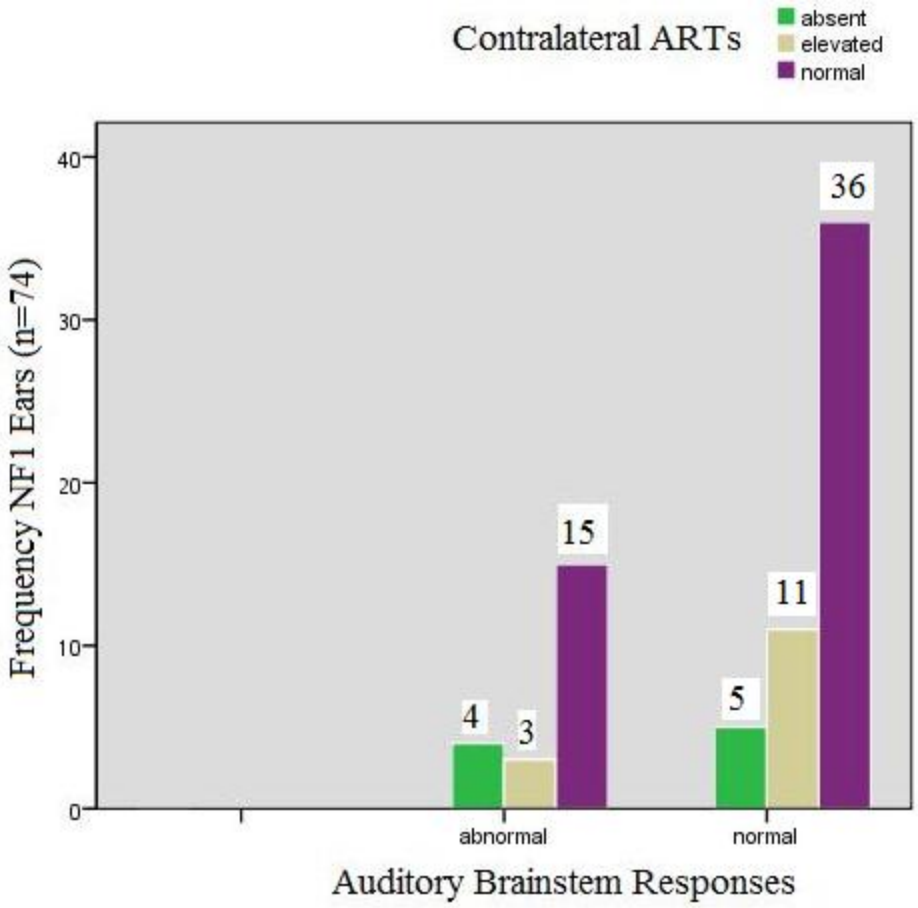


Figure 19. Relationship between auditory brainstem responses (ABRs) and contralateral acoustic reflex thresholds (ARTs) (N=74 ears).

In order to further analyze those 11 ears with normal ABRs and abnormal ARTs, these findings were compared to other audiological data (Table 20). Examination of Table 20 showed that of those 11 ears with normal ABRs and elevated contralateral ARTs, 4/11 ears had present DPOAEs, normal tympanometry, normal ipsilateral ARTs, and normal hearing sensitivity, which is suggestive of intra-axial brainstem pathology; 5/11 ears had absent DPOAEs, normal tympanometry and normal hearing sensitivity, which was suggestive of cochlear pathology; 2/11 ears had absent DPOAEs, abnormal tympanometry, and conductive hearing loss due to outer and middle ear pathology. Of those five ears with normal ABRs and absent contra ARTs, 2/5 ears had present DPOAEs, normal tympanometry, normal ipsilateral ARTs, and normal hearing sensitivity, which is suggestive of intra-axial brainstem pathology; 2/5 ears had normal hearing, normal tympanometry with absent DPOAEs absent ipsilateral ARTs, which is suggestive of cochlear pathology; 1/5 had a conductive hearing loss, abnormal tympanometry and absent DPOAEs due to outer and middle ear pathology.

In order to further analyze those ears with abnormal ABRs and abnormal contralateral ARTs, these findings were compared to other audiological data (Table 20). Examination of Table 20 also showed that four ears with abnormal ABRs and abnormal contralateral ARTs had normal hearing sensitivity at each tested frequency (0.25 – 8 kHz), normal tympanometric results, and absent DPOAEs, which is suggestive of a cochlear pathology finding. Two ears with normal hearing sensitivity, presented with abnormal ABRs (large cochlea microphonic), abnormal contralateral ARTs, normal tympanometric results, and DPOAEs within normal limits, which is suggestive of auditory neuropathy/dys-synchrony (AN/AD).

Table 20

Relationship between ABRs, Hearing Sensitivity (by each frequency), Tympanometry, Contralateral Acoustic Reflex Thresholds, and DPOAEs (19 NF1 ears)

NF1 Participant Code	Ear	Normal Hearing Sensitivity	Contra ARTs	Tymps	DPOAEs	ABR
001	Left	Normal	Absent	Normal	Absent	Abnormal
003	Right	Normal	Absent	Normal	Absent	Abnormal
	Left	Normal	Elevated	Normal	Absent	Abnormal
009	Right	Normal	Elevated	Normal	Absent	Normal
009	Left	Normal	Elevated	Normal	Absent	Abnormal
063	Right	Normal	Elevated	Normal	Present	Abnormal
	Left	Normal	Absent	Normal	Present	Abnormal
047	Right	Normal	Elevated	Normal	Present	Normal
031	Left	Normal	Elevated	Normal	Present	Normal
033	Right	Normal	Elevated	Normal	Present	Normal
038	Right	Normal	Elevated	Normal	Absent	Normal
018	Right	Normal	Elevated	Normal	Absent	Normal
010	Right	Normal	Elevated	Normal	Absent	Normal
	Left	Conductive	Elevated	Abnormal	Absent	Abnormal
019	Right	Normal	Absent	Normal	Present	Normal
024	Right	Conductive	Absent	Abnormal	Absent	Normal
015	Right	Normal	Absent	Normal	Absent	Normal
008	Right	Normal	Absent	Normal	Absent	Normal
045	Right	Conductive	Elevated	Normal	Absent	Abnormal

The description of ABR findings, computed tomography (CT) and magnetic resonance imaging (MRI), for the 21 (29%) NF1 ears that exhibited abnormal ABRs were presented in Table 21.

In addition, a description of ABR findings related to other audiological data for 21 NF1 ears was shown in Table 22. In two cases, abnormal ABR findings could be attributed to peripheral hearing loss (conductive). In 11 NF1 ears, ABR findings were consistent with cochlear pathology. In the remaining eight NF1 ears, ABR findings were consistent with retrocochlear auditory dysfunction involving CNVIII and/or the auditory brainstem tracts. Fifteen cases of abnormal ABR findings were supported by findings on imaging results. One NF1 ear, with normal MRI findings, had abnormal ABRs attributed to a moderate conductive hearing loss. Six ears with abnormal ABR findings did not have imaging data available.

Computed tomography and MRI T_2-weighted scan images illustrated the location of spongiform gliose in the brain, plexiform neurofibromas in the head and neck, stenotic ear canals and hydrocephalus, as shown in Figures 20 to 27.

Table 21

Description of ABR, CT and MRI findings in Fourteen Individuals with NF1

	ABR Findings	Hearing Status	Imaging Results	Interpretation of ABR findings
001	Prolonged I-V interval left ear, delayed wave III right ear	RE: Slight sensorineural hearing loss LE: Normal hearing	Spongiform gliose in central medulla, left globus pallidus, right posterior pons and temporal lobe; hydrocephalus	Abnormal left ear
002	Absent waves right ear and normal left	RE: Mild sensorineural hearing loss LE: Normal hearing	Spongiform gliose in right brainstem	Abnormal right ear
003	Prolonged I-V interval bilaterally	Normal hearing bilaterally	Spongiform gliose right brainstem and left globus pallidus	Abnormal bilaterally
004	Absent wave V left ear. Asynchronous activity in the right ear, waves I, III and V not identifiable	Normal hearing bilaterally	Spongiform gliose in cerebellum, high brainstem, and hypothalamus	Abnormal bilaterally
022	Delayed absolute latencies I,III, V right ear	RE: Moderate conductive hearing Loss LE: Normal hearing	Normal brainstem	Abnormal right ear
009	Delayed wave V, and prolonged I-V interval left ear	Normal hearing bilaterally	Spongiform gliose in the right frontal lobe, pons and thalamus; cerebellum and globus bilaterally.	Abnormal left ear
040	Delayed wave V, and prolonged III-V and I-V interval bilaterally	Normal hearing bilaterally	No data available	Abnormal bilaterally
013	Delayed wave V, and prolonged I-V interval bilaterally	Normal hearing bilaterally	Spongiform gliose in brainstem	Abnormal bilaterally
049	Small amplitude of wave V bilaterally	Normal hearing bilaterally	Cerebellum bilaterally, right globus pallidus, and left corpus callosum	Abnormal bilaterally
021	Large I/V amplitude ratio bilaterally	Normal hearing bilaterally	Spongiform gliose right pons, midbrain, thalamus, putamen, and temporal lobe; globus pallidus bilaterally.	Abnormal bilaterally
045	Delayed waves I, III, and V left ear	RE: Normal hearing LE: Moderate conductive hearing loss	Plexiform tumor attached to CN8 on left side, spongiform gliose on right hypothalamus	Abnormal left ear
063	Delayed waves I, III, and V bilaterally and prolonged I-III interval bilaterally	RE: Slight sensorineural hearing loss LE: Normal hearing	No data available	Abnormal bilaterally
076	Small amplitude of wave V bilaterally	Normal hearing bilaterally	No data available	Abnormal bilaterally

Note. ABR=Auditory Brainstem Responses CT=Computed Tomography (CT). MRI- Magnetic Resonance Imaging.

Table 22

Relationship between ABRs, Hearing Sensitivity (by 4PTA), Tympanometry, Contralateral Acoustic Reflex Thresholds (ARTs), ipsilateral ARTs, and DPOAEs (21 NF1 ears)

NF1 Participant Code	Ear	Normal Hearing Sensitivity 4PTA	Tymp	Contra ART	Ipsi ART	DPOAE	ABR
001	Left	Normal	Normal	Absent	Absent	Absent	Abnormal
002	Right	Mild SNHL	Normal	Normal	Normal	Absent	Abnormal
003	Right	Normal	Normal	Absent	Normal	Absent	Abnormal
	Left	Normal	Normal	Elevated	Elevated	Absent	Abnormal
004	Right	Normal	Normal	Normal	Normal	Absent	Abnormal
	Left	Normal	Normal	Normal	Normal	Normal	Abnormal
022	Right	Moderate CHL	Abnormal	Normal	Abnormal	Absent	Abnormal
009	Left	Normal	Normal	Elevated	Normal	Absent	Abnormal
040	Right	Normal	Normal	Normal	Normal	Normal	Abnormal
	Left	Normal	Normal	Normal	Normal	Absent	Abnormal
013	Right	Normal	Normal	Normal	Normal	Absent	Abnormal
	Left	Normal	Normal	Normal	Normal	Absent	Abnormal
049	Right	Normal	Normal	Normal	Normal	Absent	Abnormal
	Left	Normal	Normal	Normal	Normal	Absent	Abnormal
021	Right	Normal	Normal	Normal	Normal	Normal	Abnormal
	Left	Normal	Normal	Normal	Normal	Normal	Abnormal
045	Left	Moderate CHL	Abnormal	Elevated	Normal	No Data	Abnormal
063	Right	Slight SNHL	Normal	Elevated	Absent	Normal	Abnormal
	Left	Normal	Normal	Elevated	Absent	Normal	Abnormal
076	Right	Normal	Normal	Normal	Normal	Normal	Abnormal
	Left	Normal	Normal	Normal	Normal	Normal	Abnormal

Note. No data=DPOAEs (distortion product otoacoustic emissions) not performed. Tymp=Tympanometry. ABR=Auditory brainstem responses. ART= Acoustic reflex thresholds. Contra=Contralateral. Ipsi=Ipsilateral.

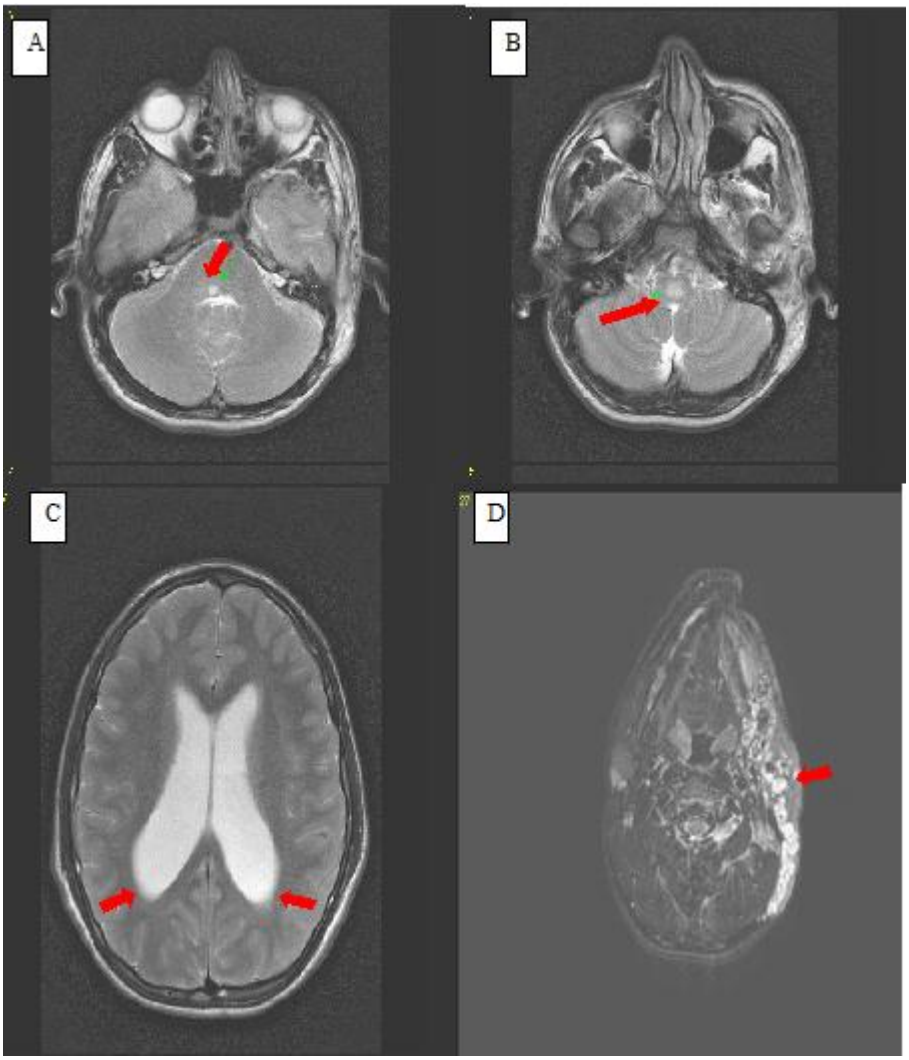


Figure 20. MRI scan (axial view) showing spongiform gliose in the brainstem (A; B) and hydrocephalus (C); plexiform neurofibroma in the face (D) (NF1 Individual Code 001).

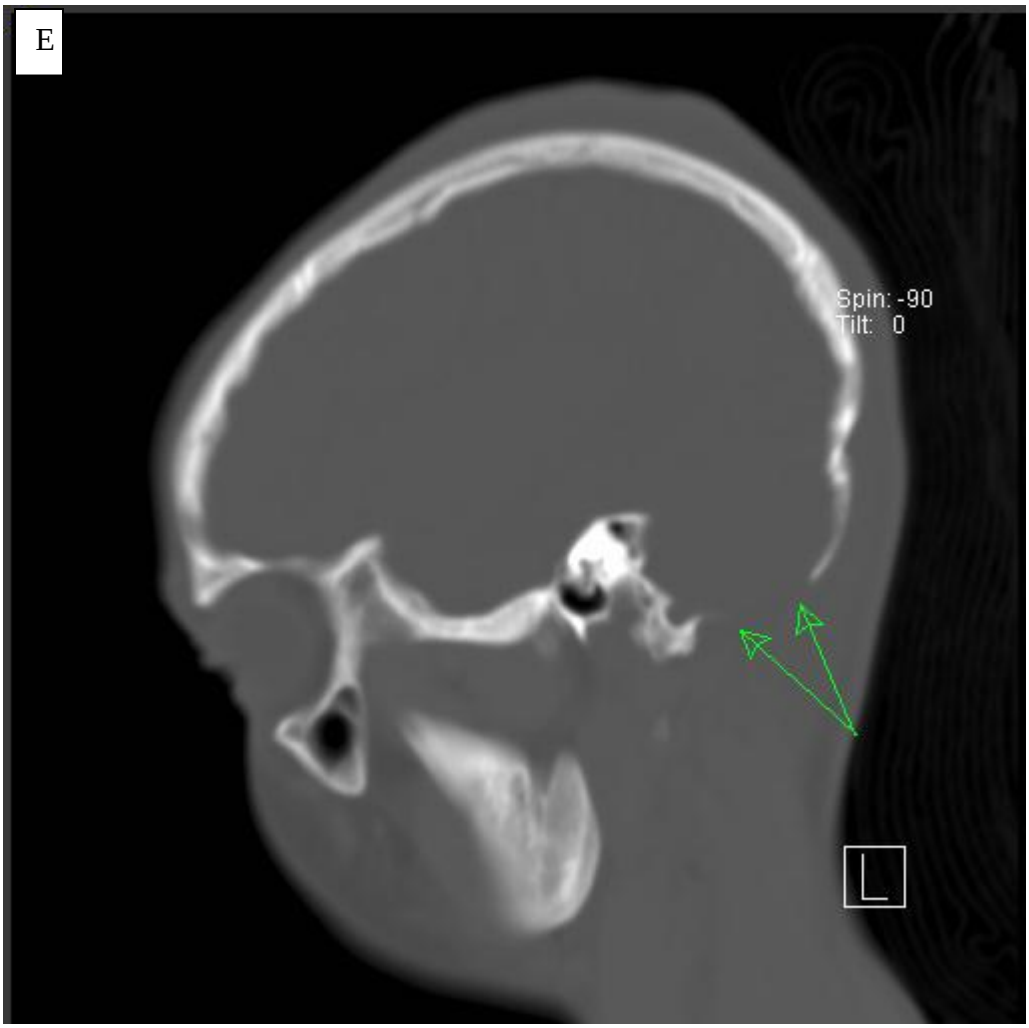


Figure 21. Computerized tomography (CT) scan (sagital view) showing post-craniotomy of the left occipital bone (NF1 Individual Code 002).

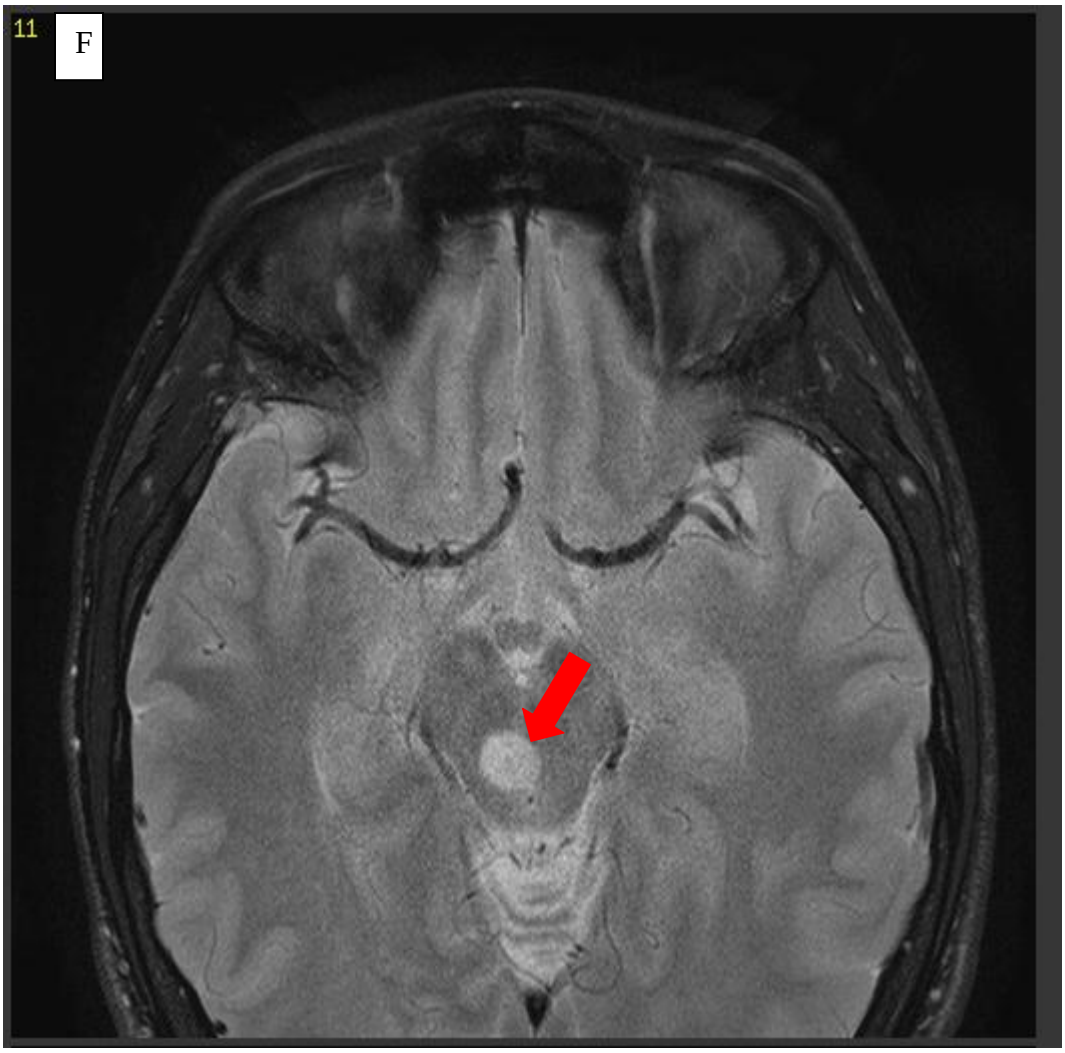


Figure 22. MRI scan (axial view) showing spongiform gliose in the globus pallidus (NF1 Individual Code 003).

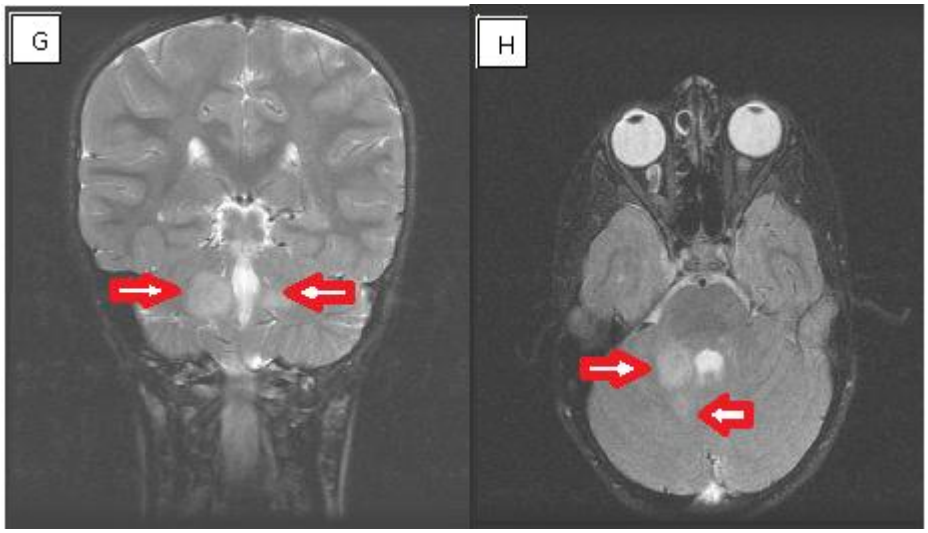


Figure 23. MRI scan (coronal view; G) showing a spongiform gliose in the cerebellum, high brainstem, and (axial view; H) hypothalamus (NF1 Individual Code 004).

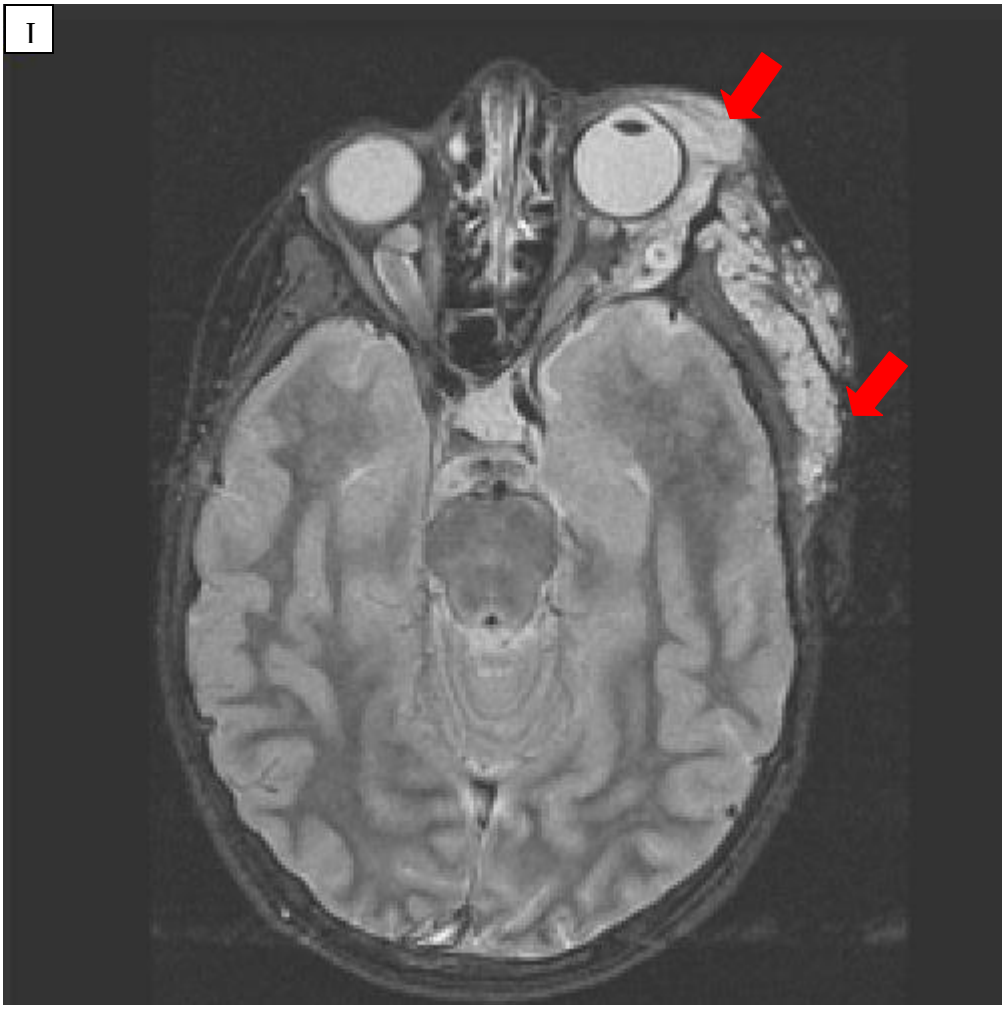


Figure 24. MRI scan (axial view) showing optic glioma and facial plexiform neurofibroma (H) (NF1 Individual Code 013).

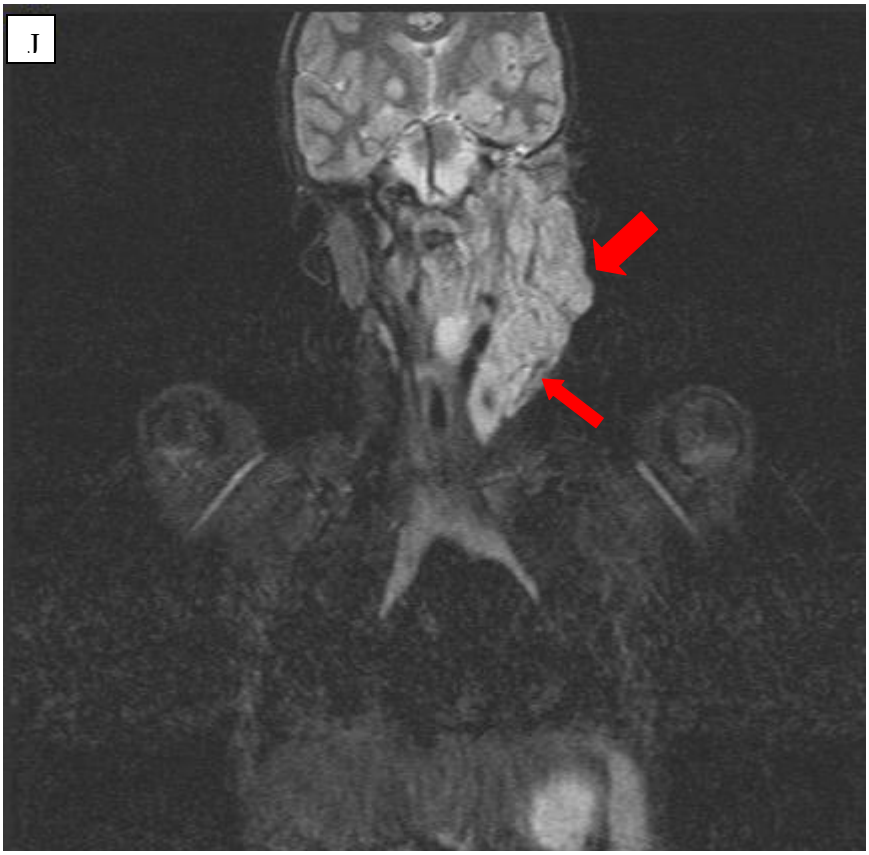


Figure 25. MRI scan (coronal view) showing head and neck neurofibroma with stenotic left ear canal (NF1 Individual Code 045).

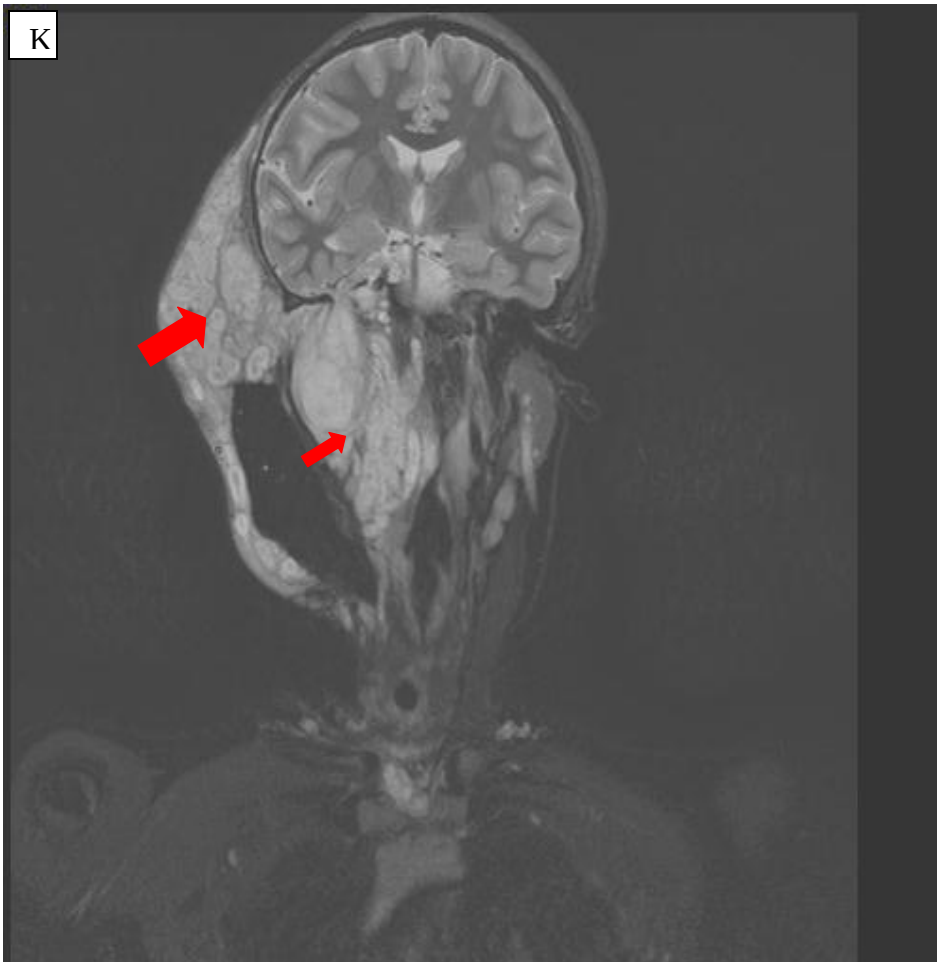


Figure26. MRI scan (coronal view) showing a stenotic right ear canal due to head/neck neurofibroma (NF1 Individual Code 022).

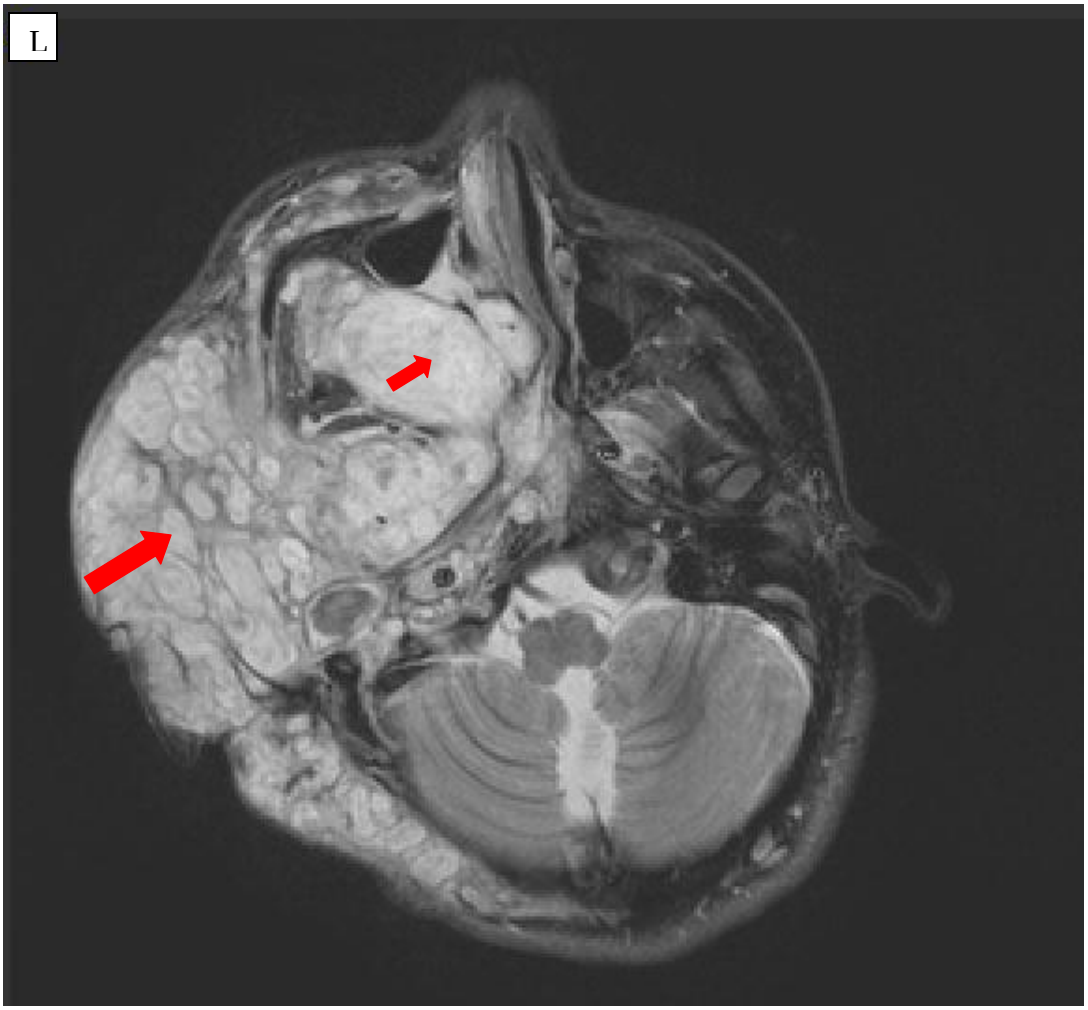


Figure 27. MRI scan (axial view) facial plexiform neurofibroma with stenotic left ear canal (L) (NF1 Individual Code 026).

A general summary of all correlated audiology findings obtained in this series of 80 NF1 ears and suggestive diagnosis was displayed in Figure 28. It should be noted that the term “normal” refers to normal audiological findings based on established normative criteria, and the term “abnormal” refers to audiological findings that are not within normal range established by normative criteria. The prevalence of hearing loss (4PTA > 15 dB HL) in this NF1 cohort was low (11.25%); however, this study revealed that 81.25% of the NF1 ears with normal hearing sensitivity with at least one audiological measure with abnormal audiological findings (not within established normative criteria). Examination of the Figure 28 is described below.

Six (7.5%) of the 80 NF1 ears had normal findings on all measures (normal hearing sensitivity based on 4PTA, immitance, reflexes, DPOAEs and ABRs).

Five (6.25%) of the 80 NF1 ears had conductive hearing loss based on the 4PTA. One ear with conductive hearing loss had normal ABRs, elevated contralateral ARTs, absent DPOAEs, abnormal tympanogram due to the presence of facial plexiform neurofibroma in the right side of the head. One ear with a conductive hearing loss had normal ABRs, absent contra ARTs, abnormal tympanogram and absent DPOAEs that could be attributed to the presence of fluid secondary to abnormal Eustachian tube dysfunction compromised by the presence plexiform in the right ear, in and around right carotid artery and periauricular region. One ear with a conductive hearing loss had normal ABRs, absent contra ARTs, abnormal tympanogram and absent DPOAEs due to head and neck plexiform neurofibromas narrowing the external acoustic meatus. Two ears with conductive hearing loss had abnormal ABRs, absent contra ARTs, abnormal

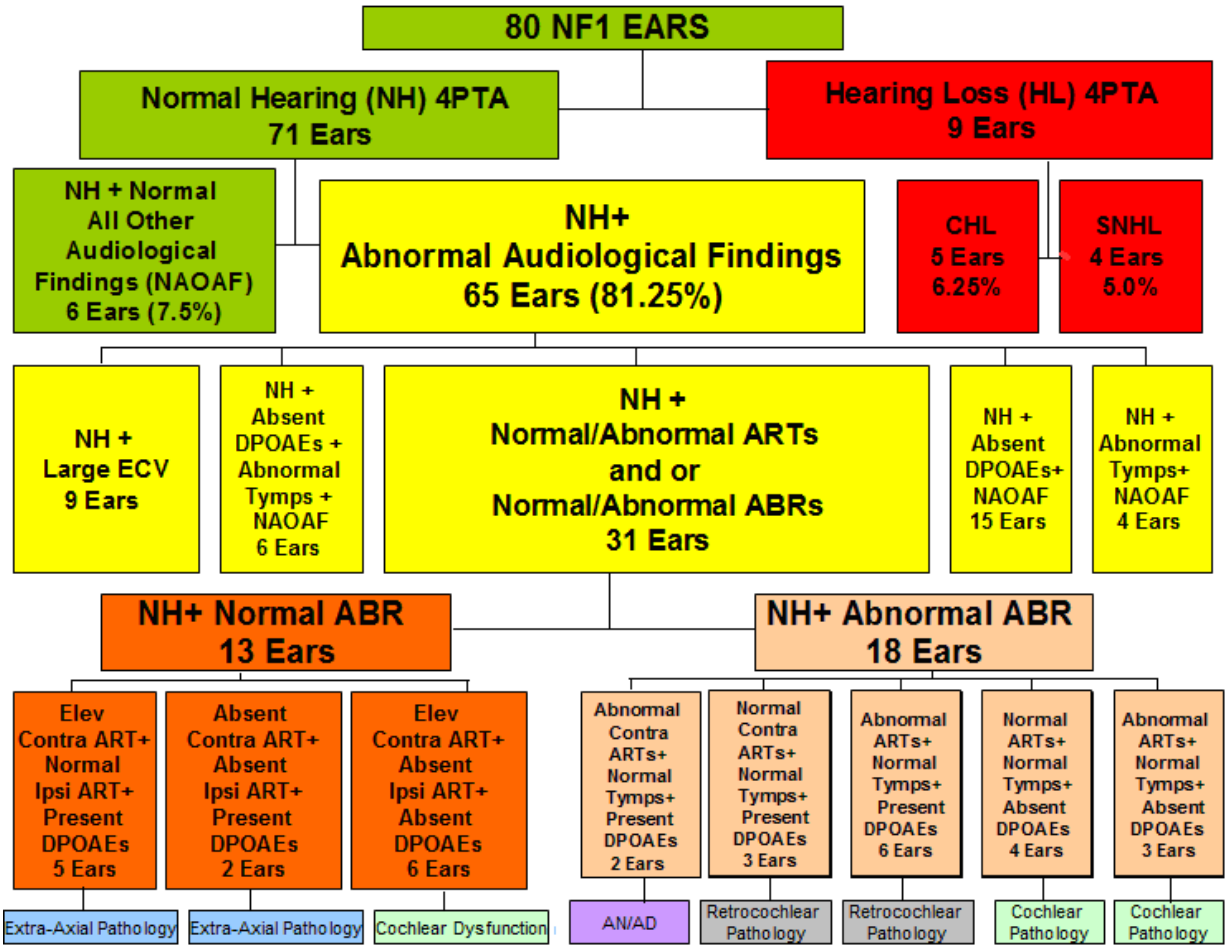


Figure 28. General summary of all correlated audiological findings (audiometry, immitance, DPOAEs, ABRs) and suggestive diagnosis in this cohort of 80 ears with NF1. Normal= normal audiological findings based on established normative criteria. Abnormal= audiological findings that are not within established normative criteria. NH= normal hearing based on the four frequency pure-tone average (4PTA). NAOAF=all other audiological findings were normal. DPOAEs=distortion product otoacoustic emissions. ABR=auditory brainstem responses. Contra ART= contralateral acoustic reflex thresholds. Ipsi ART=ipsilateral acoustic reflex threshold. Tymps=tympanograms. CHL=conductive hearing loss. SNHL=sensorineural hearing loss. AN/AD= auditory neuropathy/auditory dys-synchrony. Elev= elevated.

tympanogram and absent DPOAEs due to the presence of head and neck plexiform neurofibromas completely narrowing (stenosis) the external acoustic meatus.

Four (5%) of the 80 NF1 ears had sensorineural hearing loss based on the 4PTA. One ear of these four cases had normal ARTs, normal ABRs, large ear canal volume, and absent DPOAEs, which were consistent with peripheral hearing thresholds. One ear had absent ARTs, normal tympanogram, normal ABRs and absent DPOAEs, this finding was suggestive of cochlear dysfunction. One ear had absent ARTs, large ear canal volume with intact tympanic membrane, normal ABRs and absent DPOAEs; this finding was suggestive of cochlear dysfunction. One ear with sensorineural hearing loss had absent ARTs, abnormal ABRs, present DPOAEs and normal tympanogram, which was suggestive of retrocochlear pathology.

Sixty-five (81.25%) of the 80 NF1 ears had normal hearing sensitivity based on the 4PTA accompanied by other audiological findings that were not within normal range (abnormal).

Fifteen ears of these 65 cases had normal hearing sensitivity based on the 4PTA with absent DPOAEs, normal ABRs, normal ARTs, and normal tympanograms, due to possibly high ambient noise floor levels or decreased cochlear vascular supply by the presence of plexiform neurofibromas in the head.

Nine ears of these 65 cases had normal findings on all measures except for large tympanometric ear canal volume with intact ear tympanic membrane. Six ears of these 65 cases had normal hearing sensitivity based on the 4PTA with absent DPOAEs, normal ARTs, and normal ABRs due to abnormal tympanograms.

Four ears of these 65 cases had normal hearing sensitivity based on the 4PTA with normal DPOAEs, normal ARTs, normal ABRs, and abnormal tympanograms.

Thirty-one ears of these 65 cases had normal hearing sensitivity based on the 4PTA accompanied by abnormal audiological findings such as ARTs (normal, elevated or absent) with normal ABRs (13 NF1 ears) and or abnormal ABRs (18 NF1 ears). Five of these 31 cases had normal hearing sensitivity, elevated contralateral ARTs, normal ipsilateral ARTs with present DPOAEs, normal ABRs and normal tympanograms. These audiological findings were suggestive of extra-axial pathologies. Two of these 31 cases had normal hearing sensitivity, absent contralateral and ipsilateral acoustic reflex threshold with present DPOAEs, normal ABRs and normal tympanograms. These audiological findings were suggestive of extra-axial pathologies. Six of these 31 cases had normal hearing sensitivity and normal ABRs, elevated contralateral ARTs, elevated or absent ipsilateral ARTs, and absent DPOAEs. These audiological findings were consistent with cochlear dysfunction.

Eighteen NF1 ears of these 65 cases had normal hearing sensitivity and abnormal ABR findings:

- Two ears of these 18 cases had normal hearing sensitivity with abnormal ABRs (large cochlea microphonic), abnormal contralateral ARTs, normal tympanometric results, and present DPOAEs, which was suggestive of auditory neuropathy/dys-synchrony (AN/AD).
- Three ears of these 18 cases had normal hearing sensitivity with abnormal ABRs, normal contralateral ARTs, present DPOAEs, and normal tympanometric results,

which was suggestive of retrocochlear pathology with auditory dysfunction involving CNVIII and/or the auditory brainstem tracts.

- Six ears of these 18 cases had normal hearing sensitivity with abnormal ABRs, abnormal ARTs (elevated or absent), present DPOAEs, normal tympanograms, which were suggestive of retrocochlear pathology with auditory dysfunction involving CNVIII and/or the auditory brainstem tracts.
- Four ears of these 18 cases had normal hearing sensitivity with abnormal ABRs, normal contralateral and ipsilateral ARTs, normal tympanometric results, and absent DPOAEs, which was suggestive of cochlear pathology.
- Three ears of these 18 cases had normal hearing sensitivity with abnormal ABRs, abnormal contralateral ARTs (elevated or absent), abnormal ipsilateral ARTs (elevated or absent), absent DPOAEs, and normal tympanometric findings, which was suggestive of a cochlear dysfunction.
- Of these 18 cases of normal hearing sensitivity and abnormal ABRs, 11 cases were supported by findings on imaging results.

CHAPTER 5

DISCUSSION

The goal of this research was to describe the audiometric phenotype of Neurofibromatosis Type 1. Secondary objectives were to determine the prevalence of hearing loss in individuals diagnosed with NF1, characterize the audiologic abnormalities detected, and to investigate possible relationships between audiometric findings and other clinical manifestations of NF1.

Previous studies have reported that NF1 is inherited in an autosomal dominant fashion with an incidence rate of 1:3,000 live births. Variable expression of the clinical phenotype is found worldwide and is noted to be unbiased by racial, ethnic, gender and geographic predilections (Holt, 1978; Huson, Harper, & Compston, 1988; Kimmelman, 1979; Tonsgard, 2006; White et al., 1986; Young, Hyman & North, 2009). However, this study sample was characterized by more male individuals (63%) than females (37%), which was not consistent with equal gender incidence.

Considering the high incidence of NF1 and its innumerable manifestations in the head and neck, it is likely that many audiologists and otolaryngologists will encounter these patients in their clinical practice (DiPaolo, 1995; Holt, 1978; Huson, Harper & Compston, 1988; Kimmelman, 1979; Kraut et al., 2003; Mckennan, 1991; Rapado, Simo & Small, 2001; Tonsgard, 2006; White et al., 1986). It has been previously reported that café-au-lait spots occur in 90% of individuals with NF1, with skin fold freckling and plexiform neurofibromas occurring in 85% and 50% of individuals with NF1 respectively

(Friedman & Birch, 1997; Huson et al., 1988; Riccardi, 1992; Tonsgard, 2006). In this cohort of individuals with NF1, plexiform neurofibromas were present in 97.5%, and it was the most common clinical sign of NF1 among the 40 participants evaluated. This prevalence was slightly higher than previously reported (Friedman & Birch, 1997; Huson et al., 1988; Riccardi, 1992; Tonsgard, 2006). Café au-lait spots and skinfold freckling represented the second most prevalent clinical sign of NF1 in this study at 92.5%. This prevalence was similar to previously reported prevalence rates. Spongiform gliose was present in 27.5% of our cohort participants and was most often present in the globus pallidus (73%). This prevalence rate was in agreement with the literature that has reported occurrence of spongiform gliose in about 30% to 60% of the NF1 population (Hofman et al., 1994).

According to Tonsgard (2006), plexiform neurofibromas can be located throughout the body involving small peripheral or large nerve fibers causing compression of adjacent tissue structures, bone demineralization and proliferation of blood vessels associated with some tumors. Plexiform neurofibromas in the head and neck can cause facial disfigurement and a myriad of problems such as headache, seizures, stroke, dizziness, spinal cord compression, facial paralysis, speech impairment, visual impairment, learning disabilities, and hearing loss (Ergun, Atilganoglu, & Yasar, 2007; Tonsgard, 2006; Riccardi, 1982; Wise et al., 2005; White et al., 1986). Previous studies have reported that plexiform neurofibromas occurring in the external auditory meatus caused stenosis (complete narrowing of the ear canal) and a variety of symptoms in addition to conductive hearing such as otalgia, excessive cerumen accumulation, recurrent otitis externa, and cosmetic deformity (Abbarah & Abbarah, 2009; Collins,

Newell & Randolph, 1969; DiPaolo, 1995; Kimmelman, 1979; McKennan, 1991; Pensak et al., 1989; Pikus, 1995; Rapado, 2001; Shaida & Yung, 2007; Stevenson, Zavell, & Anderson, 1986).

In contrast to a normal outer ear with all its major anatomical landmarks (Figure 29), the face with plexiform neurofibromas could be disfigured, the outer ear could be deformed, the auricle could be dislocated, the external auditory meatus could be narrowed or obstructed (stenosis), and hearing impairment could result from this obstruction and narrowing of the external auditory meatus or invasion of the middle and inner ear by neurofibromas (Chen, Chen & Noordhoff, 1989; Rapado, Simo & Small, 2001).

In agreement with the literature, plexiform neurofibromas were found at different body locations (25%) in this cohort; however, the trunk (32.5%) was the most prevalent location followed by the head (25%). Head and neck plexiform neurofibromas causing stenotic ear canals were identified in three individuals with NF1, and history of ear infections was the most reported otological symptom in approximately 50% of ears with NF1. These same three individuals with stenotic ear canals also reported subjective hearing loss in the affected ears and history of otitis externa. The presence of an enormous plexiform neurofibroma mass in the head and neck of those three individuals were also visible in MRI scans (See Figures 25, 26, and 27).

The peripheral and central nervous system are affected in NF1, and dizziness could also be a symptom described in individuals with NF1 (Créange et al., 1999; Tonsgard, 2006). In this cohort, dizziness (30%) was the second most common otologic symptom reported by NF1 individuals. Among the 12 NF1 individuals that reported

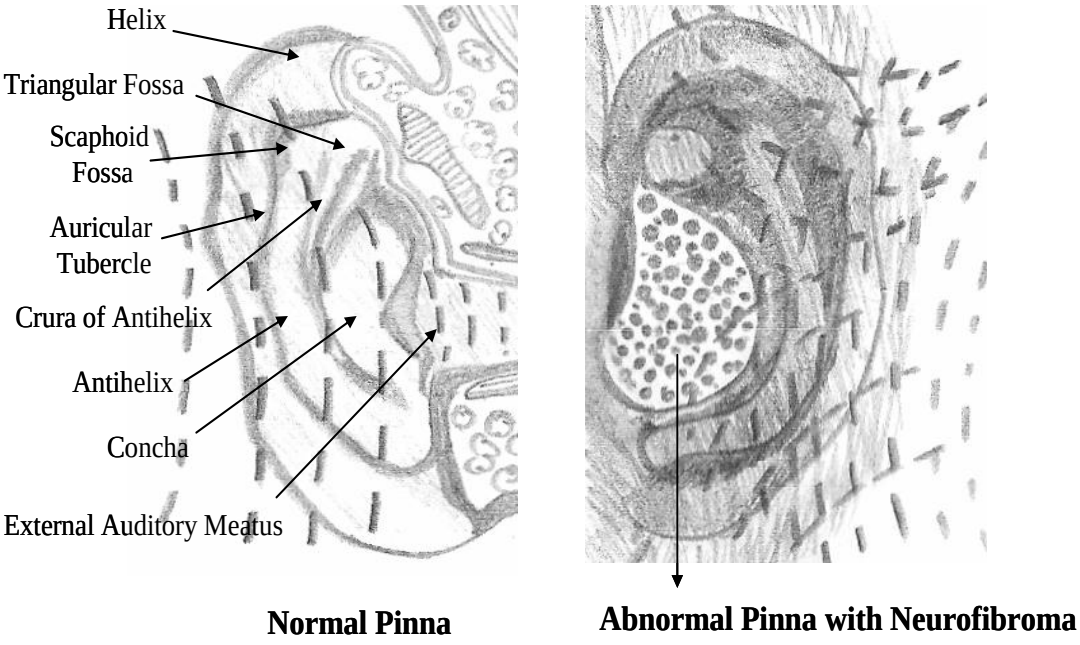


Figure 29. A schematic diagram of a normal right human pinna showing its major anatomic landmarks versus a left abnormal pinna with neurofibroma located in the concha bowl area of the pinna. This neurofibroma mass effect prevent sound waves from traveling down the external auditory meatus impacting hearing sensitivity in the affected ear and all other major functions of the outer ear. This picture is not to scale. It was drawn by the doctoral student (Laize Barcelos Corse) for purposes of illustration.

symptoms of dizziness, there were three NF1 individuals with other co-morbid disorders. There was one individual with Moyamoya disease, one individual with Chiari I malformation, and one individual with hydrocephalus. According to the literature, NF1 could be associated with co-morbid diseases such as hydrocephalus and vasculopathy disorders including vascular stenoses, aneurysm, Moyamoya disease, and Chiari I malformation, which might result in a variety of cerebrovascular complications; dizziness has been reported also as a common symptom among these disorders (Battistella, Perilongo & Carollo, 1996; Brandt & Strupp, 2005; Brookler, 2005; Hallemeier et al., 2006; Horwich, Riccardi & Francke, 1983; Kandori et al., 2002; Rosser et al., 2005; Sperling, Franco & Milhorat, 2001; Ushikoshi et al., 1999).

Simons, Ruscetta and Chi (2008) reported that Chiari I malformation might be associated with sensorineural hearing loss; however, the participant with Chiari I malformation in this NF1 cohort presented with normal hearing sensitivity. In addition, Poissant et al. (2003) reported one sensorineural hearing loss case of NF1 associated with Chiari I malformation; however, these authors believed that the etiology of the sensorineural hearing loss was cochlear due to absent OAEs in the presence of normal tympanograms, normal ABR and normal MRI and CT findings.

Hearing loss was observed in 11.25% (9/80) of ears with NF1 (4PTA > 15 dB HL). If hearing loss was based on at least one frequency greater than 15 dB HL, 36% (29/80) of the NF1 ears exhibited hearing loss. In terms of individuals, 17.5% (7/40) of the NF1 individuals had hearing loss (4PTA >15 dB HL). If hearing loss was based on at least one frequency greater than 15 dB HL, 45% (18/40) of the NF1 individuals had hearing loss in one or both ears. Although the prevalence of hearing loss reported in this

NF1 study group was much lower than previously reported by Pikus (1995; 56% prevalence), her study provided little detail regarding classification of hearing loss, precluding direct comparison with this study results. Conversely, the prevalence (17.5%) of hearing loss in this cohort was greater than reported by Pensak et al. (1989; 6.8% prevalence; 3PTA > 20 dB HL). However, Pensak and colleagues (1989), similarly to Pikus (1995), failed to provide details regarding type, classification, and configuration of hearing loss, preventing further comparisons with this NF1 cohort.

It has been observed that when hearing loss was present among these 40 NF1 individuals, unilateral (75% of the ears with hearing loss) hearing loss was the most common presentation and conductive (57%) impairment was the most predominant type of hearing loss. Slight (30%) to moderate (40%) hearing loss was the most predominant degree of hearing loss. These findings were in agreement with the reviewed literature that described more NF1 case reports with conductive than sensorineural hearing loss (Abbarah & Abbarah, 2009; Coromina et al., 1988; Ergun, Atilganoglu & Yasar, 2007; Lustig & Jackler, 1996; Geller, Darrigo Junior, Bonalumi & Ribeiro, 2009; Ghosh, Chakraborty, & Barman, 2008; McKennan, 1991; Rapado, Simo & Small, 2001; Shaida & Yung, 2007, Shamboul & Grundfast, 1999; Waizel Haiat, Romo, Aguayo & Carreola, 2007).

In addition, conductive hearing loss was the only type of hearing loss that Pensak et al. (1989) reported in 6.8% (3/44) of the NF1 individuals. The visual and otoscopic examination was important to identify the presence of neurofibromas along the pinna, pre and post-auricular areas, external auditory meatus, head and neck regions for all of these single case reports of conductive hearing loss as well as for this NF1 cohort.

In this NF1 cohort (see Table 23), conductive hearing loss was attributed to the presence of fluid secondary to abnormal Eustachian tube dysfunction compromised by the presence of plexiform in the right ear, in and around right carotid artery and periauricular region (*n*=1 ear), stenosis of the outer ear by the presence of enormous head and neck plexiform neurofibromas mass completely obstructing the external acoustic meatus (*n*=3 ears), and the presence of facial plexiform neurofibroma in the right side of the head compressing ear structures (*n*=1 ear).

Previous case reports in the literature have also stated that conductive hearing loss was due to the presence of plexiform neurofibromas in head and neck compressing the ear canal, middle ear neurofibromas, or Eustachian tube obstruction secondary to pharyngeal neuroma (Abbarah & Abbarah, 2009; Coromina et al., 1988; Ergun, Atilganoglu & Yasar, 2007; Geller, Darrigo Junior, Bonalumi & Ribeiro, 2009; Ghosh, Chakraborty, & Barman, 2008; Lustig & Jackler, 1996; McKennan, 1991; Rapado, Simo & Small, 2001; Shaida & Yung, 2007, Shamboul & Grundfast, 1999; Waizel Haiat, Romo, Aguayo & Carreola, 2007).

In contrast, Pikus (1995) reported that no particular audiometric degree and configuration could be attributed to NF1 when hearing loss was present. Additionally, Pensak and colleagues (1989) did not discussed the etiology of the three cases of conductive hearing loss found in their study and also omitted those cases from their study analysis precluding further comparison to this NF1 cohort.

In this cohort, one individual with NF1 who had head and neck plexiform and presented in the clinic with subjective complaint of hearing loss had her pure-tone and speech audiometry obtained initially with inserts and then with supra-aural headphones. It

Table 23

Summary of Conductive Hearing Loss (CHL) in this NF1 Cohort (N=5 NF1 ears)

Cases of Conductive Hearing Loss in this NF1 Cohort			
Demographics	**Degree of CHL**	**Other Audiological Findings**	**Possible etiology of CHL**
14-year-old male	Right slight CHL	normal ABRs, elevated contralateral ARTs, absent DPOAEs, abnormal tympanogram	facial plexiform neurofibroma in the right side of the head
7-year-old male	Right mild CHL	normal ABRs, absent contra ARTs, abnormal tympanogram and absent DPOAEs	abnormal Eustachian tube dysfunction compromised by the presence plexiform in the right ear
15-year-old female	Right moderate CHL	abnormal ABRs, absent contra ARTs, abnormal tympanogram and absent DPOAEs	stenosis of the outer ear by the presence of enormous plexiform neurofibromas
15-year-old female	Left moderate CHL	normal ABRs, elevated contralateral ARTs, absent DPOAEs, abnormal tympanogram	presence of enormous plexiform neurofibroma in the head and neck
9-year-old male	Left moderate CHL	abnormal ABRs, absent contra ARTs, abnormal tympanogram and absent DPOAEs	stenosis of the outer ear by the presence of enormous plexiform neurofibromas

should be noted that precautions were taken to prevent collapsing of ear canals. Her conductive hearing loss was only revealed with the use of headphones. The use of insert earphones in those NF1 individuals with large head and neck plexiform neurofibroma could potentially lead to a testing error. In the presence of obliterated ear canals by plexiform neurofibromas located in the head and neck, it is important to obtain threshold measurements with another type of transducer besides inserts to obtain valid results. Therefore, pure-tone thresholds and speech audiometry in NF1 individuals with massive head and neck plexiform neurofibromas should be obtained with the use of inserts and in sound field testing, and audiological results should be compared to evaluate the impact of massive head neck plexiform neurofibroma could potentially exert on the auditory system.

The prevalence of sensorineural hearing loss (SNHL) was observed in 5% (4/80) of ears with NF1 (see Table 24). The first case was a 15-year-old with a right unilateral mild sensorineural hearing loss in the high frequencies with normal ARTs, normal ABRs, large ear canal volume with intact tympanic membrane, and absent DPOAEs, which were consistent with peripheral hearing thresholds. Additionally, this individual reported bilateral tinnitus, right ear aural fullness, headaches, and dizziness symptoms. Dizziness seemed to be triggered by movement from a supine to an upright position. This individual was found to have a posterior craniotomy of the occipital bone confirmed by CT scan due to previous surgery to cover an occipital bony defect. This individual had undergone multiple surgeries between three months and nine months of age. These surgeries were to debulk plexiform neurofibroma from the left temporal area and to correct ear position, repair a cleft lip, and to repair the palate. This individual was also found to have

Table 24

Summary of Sensorineural Hearing Loss (CHL) in this NF1 Cohort (N=4 NF1 ears)

Case Reports of Sensorineural Hearing Loss in this NF1 Cohort				
Demographic	**Degree of SNHL**	**Additional Audiological Findings**	**Symptoms**	**Possible Etiology of SNHL**
15-year-old	Right unilateral mild SNHL in the higher frequencies	Normal ARTs, normal ABRs, large ear canal volume with intact tympanic membrane, and absent DPOAEs	Bilateral tinnitus, right ear aural fullness, headaches and dizziness symptoms	Cochlear Pathology
45-year-old	Right unilateral slight SNHL in the higher frequencies	Absent contra and ipsilateral ARTs, abnormal ABRs, normal DPOAEs and normal tympanogram	Bilateral tinnitus, headaches, dizziness, and migraines	Retrocochlear Pathology
17-year-old	Bilateral moderate SNHL in the low frequencies rising to a mild SNHL in the higher frequencies	Left ear=absent ipsilateral ARTs, normal contralateral ARTs, large ear canal volume with intact tympanic membrane, normal ABRs and absent DPOAEs	Subjective hearing loss, headaches, dizziness	Cochlear Pathology
		Right ear=abnormal contralateral and ipsilateral ARTs, normal ABRs, normal tympanogram, and absent DPOAEs		Cochlear Pathology

plexiform neurofibromas in the left side of the head. The large ear canal volume found in this individual could be due to bone abnormalities related to NF1 or to surgeries to remove plexiform neurofibroma from the head and neck.

The second case of SNHL was of a 45-year-old with NF1 who had a right unilateral slight sensorineural hearing loss in the higher frequencies with absent contra and ipsilateral ARTs, abnormal ABRs, normal DPOAEs and normal tympanogram. These audiological findings were suggestive of retrocochlear pathology. This individual reported bilateral tinnitus, headaches, dizziness, and migraines.

The third case of SNHL was of a 17-year-old with NF1 who had a bilateral moderate sensorineural hearing loss in the low frequencies rising to a mild- slight sensorineural hearing loss in the higher frequencies. The left ear had absent ipsilateral ARTs, normal contralateral ARTs, large ear canal volume with intact tympanic membrane, normal ABRs and absent DPOAEs, this finding was consistent with peripheral hearing thresholds. The right ear had abnormal contralateral and ipsilateral ARTs, normal ABRs, normal tympanogram, and absent DPOAEs, which were consistent with cochlear dysfunction. This individual reported bilateral subjective hearing loss, headaches, dizziness, and had worn hearing amplification for ten years. This individual did not have plexiform neurofibroma in the head or neck, only in the trunk.

Cochlear pathology was the most prevalent (75% of the ears with sensorineural hearing loss in this NF1 cohort) etiology in this NF1 cohort, and similar cochlear pathology findings were reported by Poissant, Megerian and Hume (2003). Kitamura, Senba, and Komatsuzaki (1989) also reported a patient with a low-frequency ascending configuration similar to the third SNHL case of this NF1 cohort. Other studies (Pensak et

al., 1989; Pikus, 1995; Shambould & Grundfast; 1999) did not describe their audiological findings in detail preventing a direct comparison to this NF1 cohort.

Retrocochlear pathology was observed in 25% of the ears with sensorineural hearing loss in this NF1 cohort. Pikus (1995) did not report the number of SNHL cases in her study and did not discuss possible SNHL etiologies in NF1. This author just mentioned that there was not a case of acoustic neuroma in her NF1 sample group and most of the individuals with NF1 had different tumor formations in the brain.

The most common configuration of hearing loss among individuals with NF1 in this study was atypical (either a low frequency hearing loss or a high frequency). Similarly, configurations were reported by Shambould and Grundfast (1999) that speculated that hearing loss in NF1 spans between two ends of a spectrum (peripheral and central) due to involvement of NF1 lesions at the brainstem or higher levels. The prevalence of low frequency hearing loss at 250 Hz (35%) and 500 Hz (22.5%) could be attributed in part to the presence of plexiform neurofibromas in the head and neck region.

The tonotopic organization of the auditory nerve fibers dictates that low frequency nerve fibers are located in the center of the auditory nerve and high frequency fibers are located along the periphery of the auditory nerve (Spoendlin & Schrott, 1989). For this reason, the higher prevalence of high frequency hearing loss at 4000 Hz (15%), 6000 Hz (20%) and 8000 Hz (22.5%) could be attributed in part to the pressure from adjacent massive plexiform neurofibromas compressing the periphery of the VIII nerve and other portions of CANS centers, or other possible NF1 abnormalities such as spongiform gliose at the high frequency portions of other CANS centers.

Additionally, the pathophysiology of high frequency sensorineural hearing loss could be in part attributed to cochlear dysfunction at the base of the cochlea caused by the pressure of massive neurofibromas, or demineralization of bone tissue structures of the inner ear caused by pressure from adjacent plexiform neurofibromas, or vascular alterations caused by the disorganized proliferation of blood vessels associated with some tumors in the head.

Tympanometric static compliance, peak pressure, and ear canal volume within the normal range were observed in 85% (68/80), 93% (74/80), and 66% (53/80) of ears with NF1 respectively. The prevalence of abnormal tympanometric static compliance, peak pressure, and ear canal volume were observed in 15% (12/80), 7% (6/80), and 34% (27/80) of ears with NF1 respectively. Despite the fact that Pikus (1995) only considered static compliance (hyper or hypomobile) as the tympanometric measure in her study, the prevalence of abnormal tympanometric static compliance and peak pressure observed in this cohort was lower than reported by Pikus (1995; 23% prevalence). However, the prevalence of abnormal ear canal volume findings in this cohort was higher that Pikus (1995).

Although the prevalence of abnormal tympanometric findings in this cohort was higher than reported by Pensak et al. (1989; 7% prevalence), their study provided little detail regarding the classification of tympanometric abnormalities. Furthermore, Pikus (1995) and Pensak et al. (1989) did not provide their established normative criteria used to classify static compliance, peak pressure, and ear canal volume findings preventing further comparisons with this study results.

Pikus (1995) reported that the etiology of all abnormal tympanometric (static compliance) findings were uncertain since they could not be attributed to otitis media or any other middle ear pathology. Conversely, in this cohort 66% (8/12) of the ears with abnormal static compliance had low static compliance (<0.3 mL) secondary to P.E. tubes, perforation in the tympanic membrane, and fluid in the middle ear; however, similarly to Pikus (1995), 33% (4/12) of the ears with abnormal static compliance had high static compliance (>1.5 mL) with no reported history of ossicular disarticulation, scarred tympanic membrane or other middle ear disorder.

Further investigation is needed to elucidate the etiology of these high static compliance findings in this NF1 cohort. All other authors (Abbarah & Abbarah, 2009; Coromina et al., 1988; Ergun, Atilganoglu & Yasar, 2007; Geller, Darrigo Junior, Bonalumi & Ribeiro, 2009; Ghosh, Chakraborty, & Barman, 2008; Lustig & Jackler, 1996; McKennan, 1991; Rapado, Simo & Small, 2001; Shaida & Yung, 2007, Shamboul & Grundfast, 1999; Waizel Haiat, Romo, Aguayo & Carreola, 2007) who published single case reports of hearing loss in NF1 did not provide details about tympanometric middle ear status of their individuals preventing further comparisons to tympanometric results found in this cohort. It should also be noted that most of those case reports were written by otolaryngologists or other health care professionals other than audiologists.

Although all tympanometric data (peak pressure, static compliance and ear canal volume) obtained from this cohort were not significantly different from the normal population, large ear canal volume (> 1.5) was the most prevalent (34%; 27/80) abnormal tympanometric finding in this cohort. Large ear canal volume was observed in eight (29%) NF1 ears secondary to P.E. tubes and in two (7.5%) ears due to perforated

tympanic membrane confirmed by otoscopy. However, 17 (62.5%) NF1 ears with large ear canal volume had intact tympanic membrane. In agreement with the reviewed literature (Mckennan, 1991; Mulvihill et al., 1990; Riccardi, 1992; Tonsgard, 2006), head and neck plexiform neurofibroma surgeries modified the anatomic structures and the pressure of adjacent plexiform neurofibromas could cause bone demineralization. The large ear canal volume with intact tympanic membrane could be either associated with the anatomic tissue erosion caused by plexiform neurofibroma surgeries and the pressure from adjacent plexiform neurofibroma or with large ear canal volume could be a characteristic of individuals with NF1.

In order to further investigate this large ear canal volume finding in this NF1 cohort, it would be interesting to examine the relationship among ear canal volume and the number of head and neck surgeries , the volume of the mass that was removed, and the estimated volume of the plexiform neurofibroma mass remaining in the patient These data were unavailable in the current study; however, there could be relationship among them.

The analyses of the audiological evaluations in this cohort revealed that individuals with NF1 can have conductive and sensorineural hearing loss; however, mostly likely these individuals will have peripheral hearing thresholds within normal limits and their auditory abnormalities might be revealed by other audiological measures. Therefore, peripheral hearing losses per se do not characterize their auditory phenotype. Other auditory abnormalities in individuals with NF1 might be detected by additional audiological measures complementing pure-tone audiometry.

Abnormal ABRs (prolonged or absent) were observed in 30% of NF1 ears in this cohort; 11% had I-V interpeak latencies prolonged and 8% had prolonged V latency. The prevalence in this cohort was similar to Pensak and colleagues (1989). They reported that 32% of the individuals with NF1 had abnormal ABR findings, which represented significant conduction delays in the auditory brainstem. Conversely, the Pikus study reported 49% of the individuals with NF1 showed ABR abnormalities, including prolongation of I-V interpeak latencies and absent wave V. However, further analyses of this study ABR results could not be compared to Pensak and colleagues (1989) or to Pikus (1995) since they did not correlate their ABR findings to other audiological measures including peripheral hearing thresholds, immitance, and OAEs. It is uncertain if a comprehensive audiological evaluation was performed with their study individuals since they have not provided details of the association all audiological measures performed.

In this cohort, 39% of the NF1 ears with normal hearing (4PTA > 15 dB HL) were accompanied by other unexplained abnormalities (normal ABRs with elevated or absent ARTs, abnormal ABRs with normal and abnormal ARTs). These abnormal audiological findings were consistent with cochlear dysfunction in 16% of the NF1 ears, retrocochlear dysfunction involving VIII cranial nerve and/or the auditory brainstem tracts in 11.25% of the NF1 ears, extra-axial brainstem pathology in 8.8% of the NF1 ears, and auditory neuropathy/dys-synchrony in 2.5% of the NF1 ears.

According to Berlin et al. (2005), AN/AD is considered when patients demonstrate poor auditory function in at least some listening situations, abnormal function of the auditory nerve with large amplitude and prolonged cochlear microphonic,

and evidence of normal cochlear hair cell activity (present OAEs). In this cohort, the two ears with AN/AD also presented with large and prolonged cochlear microphonic, which could also suggest an auditory dysfunction in those ears. Mom, Chazal, Gabrillargues, Gilain, and Avan (2005) have also reported in the literature that VIII nerve pathology can potentially affect the cochlea since it decreases the cochlear vascular supply; therefore otoacoustic emissions can be affected.

There has been much speculation in the literature about the pathophysiologic nature of SNHL in NF1. Pensak et al. (1989) had attributed sensorineural hearing loss in NF1 to alterations in the chemical environment of the cortical lamination produced by the abnormal proliferation of Schwann cells. Shamboul and Grundfast (1999), similarly to Pensak et al. (1989), suggested that the etiology of SNHL lies at the brainstem or higher levels due to disordered cytological and chemical architecture. Kitamura, Senba and Komatsuzaki (1989) discussed other possible etiologies including chronic intracranial hypertension and NF1 related bone tissue abnormalities. Kitamura, Senba and Komatsuzaki (1989) concluded their single case report hypothesizing that SNHL is attributed to neural dysplasia of the inner ear and VIII nerve due to defective development of the neuroectodermal tissues in individuals with NF1. However, none of these authors assessed the cochlear function of their individuals with NF1. In addition, they did not report the use of otoacoustic emissions testing in their study. For this reason, retrocochlear pathology in those studies could not be confirmed unless cochlear pathology was initially ruled out, and sensorineural hearing loss in these studies could be due to several other reasons instead of solely retrocochlear pathology as those authors had claimed. Furthermore, Pensak et al. (1989) and Shamboul and Grundfast (1999)

alluded to Holt's autopsy study (1978) that revealed heterotopic gray matter within the cerebral white matter suggesting that these brain abnormalities could cause a delay of auditory transmission at higher levels of the brain. Currently in the literature, the term "heterotopic gray matter" referred by Holt (1978), Pensak et al. (1989) and Shamboul and Grundfast (1999) is known as spongiform gliose, which are vacuolar change of myelin without mass effect and are identified in MRI scans as areas of increased T2 signal intensity (DiPaolo et al., 1995; Kraut et al., 2004). Furthermore, DiPaolo and colleagues (1995) reported in their histopathological study of NF1 that demyelination was not observed in the brain of individuals with NF1 refuting prior studies speculation about the pathophysiologic process of SNHL as demyelination of cortical neurons (Pensak et al., 1989).

Similarly to DiMario and Ramsby (1998), Kraunt and colleagues (2004) reported that the foci of spongiform gliose disintegrate during late childhood; however, the latter authors found that spongiform gliose reappears in adolescence. The increase of spongiform gliose over time is mainly along major fiber bundles in the centroencephalic regions (globus pallidus and thalamus), especially during adolescence, and has a different evolution in the cerebellar white matter than the rest of the brain (DiPaolo et al., 1995; Kraut et al., 2004). Furthermore, the incidence of increased T2 signals varies from 53.5% (Zimmerman, 1992) to 79% (Sevick et al., 1992). Thus, this variation might be secondary to the difference in the age range of individuals with NF1 that were recruited to their study. In this cohort, about 70% of the eleven individuals with NF1 who had MRI scans revealed spongiform gliose in the left globus pallidus, 20% in the right thalamus, 35% in the right temporal lobe, 10% in the left temporal lobe, and 10% in the corpus callosum.

The general consensus in the literature is that spongiform gliose may represent a marker for developmental abnormalities in the brain parenchyma (Coude, Mignot, Lyonnet, & Munnich, 2006; DiMario & Ramsby, 1998; Kraunt et al., 2004; Sevick et al., 1992; Zimmerman, 1992).

In view of these studies regarding spongiform gliose, and considering the fact that the auditory thalamus is a very important area in the CANS, spongiform gliose could potentially impact the CANS structures causing a processing dysfunction of the auditory information. Surprisingly, there is a paucity of data on the neuropathology process of sensorineural hearing loss in NF1. Additional longitudinal studies considering audiological evaluations and anatomic locations of spongiform gliose on different age groups of NF1 need to be performed to further clarify the neural etiology of the auditory dysfunction.

In this NF1 cohort, abnormal ABR findings with normal peripheral hearing thresholds were observed in 23% of NF1 ears (I-V interpeak latencies prolonged, prolonged V latency, and absent wave V). Although 83% of these abnormal audiological findings (normal hearing and abnormal ABR) were supported by abnormal imaging results (MRI and CT scans) showing spongiform gliose throughout the brain, the pathophysiology of SNHL in individuals with NF1 has yet to be clearly defined with more systematic longitudinal studies.

CHAPTER 6

CONCLUSION

Brief Summary

An examination of the prevalence of audiological abnormalities in this NF1 cohort showed that lesions related to NF1 can affect the auditory system. No study in the reviewed literature investigated the association between spongiform gliose and auditory dysfunction in individuals with NF1. Although there were several reports (North, 2000) associating spongiform gliose with many measured cognitive impairments in NF1, Kraut and colleagues (2004) reported that there are still many controversies regarding the functional significance of spongiform gliose in the brain and further longitudinal studies on the neuropathology of NF1 are necessary to better elucidate the pathogenesis of spongiform gliose in the brain of individuals with NF1.

Future Research

The functional implications of the abnormal ABRs in the presence of normal peripheral hearing thresholds should be evaluated with behavioral measures of central auditory processing and considered in relation to learning disabilities and speech and language delays previously documented in this population (Coude, Mignot, Lyonnet, & Munnich, 2006; Cutting, Koth & Denckla, 2000; Hyman, Shores, & North, 2005; Mazzocco, Turner, Denckla, Hofman, Scanlon & Velluntino, 1995; Williams & Hersh, 1998).

Bamiou, Musiek, and Luxon (2001) and Chermak and Musiek (2002) reported that the incidence of central auditory processing disorders in the general population is about 3 to 5%, higher than the incidence of hearing loss. NF1 affects the nervous system in several ways (Tonsgard, 2006). Therefore, further studies in individuals with NF1 should consider evaluating central auditory processes to determine if their auditory processes are deficient compared to normal population. Furthermore, longitudinal studies with these NF1 individuals utilizing central auditory processing tests are needed to further evaluate their auditory processing abilities at different stages of their life (childhood, adolescence, adulthood, and senilescence) and different stages of the NF1 disease. Audiologists should be aware that these NF1 insults, when occurred along the CANS, might potentially degrade the acoustic signal and the processing of auditory information that allows sound localization and lateralization, sound discrimination, auditory pattern recognition, and auditory perception with competing sounds (Bamiou, Musiek, & Luxon, 2001; Chermak & Musiek, 1992; 2002).

Further studies could potentially create and validate a NF1 questionnaire to be answered by individuals with NF1 and family members including questions about their age of diagnosis, number of family members diagnosed with NF1, ethnicity, number of surgeries undergone in the head and neck, type of surgeries undergone to remove plexiform neurofibromas or any other complication related to NF1, family history of hearing loss, age of onset of the disease, any other co-morbid disorder associated with NF1, list of medications, intensive care after birth, any delay to reach developmental milestones, hearing difficulties, speech problems, school performance, language spoken at home, profession or school grade. In addition, further studies in individuals with NF1

should include auditory processing disorder questions in the NF1 questionnaire regarding handedness, whether the individual is easily distracted or has difficulty to attend sounds in the environment (attention assessment), localization ability for sound, and the ability to listen to speech in noise and follow complex directions.

Clinical Recommendations

There are several pertinent issues that audiologists should consider when clinically assessing and managing patients with NF1. The audiologist should visually inspect the head and neck region looking for NF1 clinical signs, determine the location of head and neck neurofibromas, and describe what locations of the head and neck are affected. During the audiological evaluation, the audiologist should reflect on what impact those NF1 head and neck manifestations could potentially exert on the auditory system, and what therapeutic intervention approaches should be considered when counseling families and individuals with NF1.

The routine comprehensive audiological evaluations of individuals with NF1 should include at least a thorough case history, visual inspection of the head and neck, otoscopy, pure tone and speech audiometry, otoacoustic emissions, immitance measures, auditory brainstem responses, and central auditory processing evaluation. Additionally, results of testing in clinical reports should include clinical features of NF1 that were observed during visual and otoscopic inspection, presence and size of head and neck plexiform neurofibromas, family history of NF1, cognitive development, and school performance. It should be noted that NF1 individuals with vertiginous complaints should also have their balance system assessed and case history should further investigate those symptoms. Radiological imagines such as CT and MRI scans of the brain can further

compliment the comprehensive audiological evaluation. CT scans can provide information about the bone structures from skull base to vertex showing the status of middle ears, outer ears, external auditory canals, internal auditory canals, and mastoid air cells. MRI scans can provide information about the status of the neuroanatomic tissue organization of the brain, cranial nerves, especially VII and VIII cranial nerve, and the other CANS regions helping to identify areas of spongiform gliose.

Health care professionals performing newborn hearing screenings should be aware that NF1 is common in infants (1:3,000 births), especially those with positive family history of NF1. NF1 is a progressive autosomal dominant genetic disorder with highly variable expression (Huson, Harper, & Compston, 1998; Mulvihill et al., 1990) and individuals with NF1 are at risk for hearing loss and other auditory dysfunctions. There several clinical signs of NF1 that can be seen at birth; however, the manifestations usually appear during adolescence (Riccardi, 1981; Mckennan, 1991; Tonsgard, 2006; Wallace et al., 1990). Audiologists should closely monitor children's auditory system because the ability to hear sounds is crucial for speech and language development, especially during the first year of life (Blauert, 1983; Gelfand, 2001; Sharma et al., 2005).

Audiologists and other health professionals should consider the importance of follow-up individuals with NF1 since complications worsen over time and plexiform neurofibromas have the potential for malignant transformation; for example, up to 5% of lesions have been found to develop into highly malignant peripheral nerve sheath tumors (Waggoner, Towbin, Gotesman & Gutman, 2000; Zoller et al., 1997).

Furthermore, educational professionals should be aware of the potential impact of NF1 in speech and language development and learning disabilities in school age-children

with NF1. Educational audiologists should consider recommending assistive listening devices, preferential seating, or other compensatory strategies in the classroom for children with NF1 in order to optimize their development of speech and language, learning, and social-communication skills.

NF1 is an autosomal dominant genetic disorder (Barker et al., 1987; Cawthon et al., 1990; Viskochil et al.; 1990); therefore, health professionals need to consider referring families with NF1 for genetic counseling since there is a chance that 50% of the descendants will become affected with NF1. Individuals with NF1 and family members should be counseled with compassionate delivery of information about the natural history of NF1 and the potential impact of NF1 on the auditory system to help them planning both their personal and professional lives. Audiologists should be aware of the psychological and emotional impact of this disorder on an individual's life, and referrals to other health professionals should be considered as needed.

In this cohort, there was one individual that reported benefits from hearing amplification. Pensak, Poissant, Megerian and Hume (2003) reported a successful cochlear implant case of a NF1 individual with cochlear dysfunction. In addition, an auditory midbrain implant has also been reported in the literature as an alternative for those individuals without an implantable cochlea or a functional auditory nerve (Lim et al., 2007). Therefore, audiologists should facilitate communication strategies and rehabilitation options for individuals with NF1 to optimize their quality of life.

Neurofibromas grow slowly over a period of decades and are found all over the body (Riccardi, 1992). According to Riccardi (1992), surgical excisions would be unnecessary for non-disfiguring and asymptomatic neurofibromas since they can

potentially regrow; however, a conservative surgery approach might need to be considered for symptomatic and cosmetically disfiguring lesions. For this reason, health professionals including otolaryngologists, neurotologists, otoneurologists, audiologists, and dentists should be aware of the potential impact of NF1 disorder that manifests in the head and neck lesions when managing patients with NF1.

In order to minimize peripheral conductive hearing loss causes by massive plexiform neurofibromas, audiologists should consider special ear molds called *canal shell uplift* with extra large sound bore as a therapeutic intervention to NF1 individuals with massive plexiform neurofibromas in the head and neck causing ear canal stenosis or collapsed ear canals, to prevent conductive hearing loss due to outer ear abnormalities secondary to NF1. These ear molds have been used mainly by people with normal hearing but who have collapsed ear canals. The vent should have as large a bore as possible in the center to allow the maximum amount of sound to reach the tympanic membrane.

Limitations of the Study

The NF1 audiological research protocol established at the Audiology and Otolaryngology Center in the Clinical Center of the NIH was implemented systematically subsequent to the inception of the clinical trial protocol investigating the *Natural History Study and Longitudinal Assessment of Children, Adolescents, and Adults with Neurofibromatosis* (NCI-08-C-0079); therefore, not all individuals with NF1 that were initially recruited for this on-going longitudinal natural history research of individuals with NF1 at the NCI/NIH received audiological evaluation. In addition, the referral procedure for audiological evaluation has improved throughout the process of the study.

The data sample of this study consisted of 40 individuals with NF1; however, there were only a small number of individuals within each age group. There was a wide range of age variability (5 to 45 years old), which prevented categorization of individuals at specific age groups and comparisons between groups.. Consequently, the phenotypic correlation between NF1 and hearing sensitivity could be better explained with larger sample studies. Longitudinal studies should consider obtaining a larger sample to further explain the impact of NF1 on the auditory system at different stages of life, which will in turn assist with the correlation of NF1 manifestations and the audiological phenotype of individuals with NF1. In addition, radiological images of the brain and skull (MRI and CT scans) were performed only in 11 individuals, which prevented better analysis and stronger correlations between brain images and ABR findings.

The case history utilized in this study had general questions regarding audiological and otological symptoms; however, specific information tailored to individuals with NF1 should have been documented more precisely for further clarification and understanding of the audiological findings obtained from the individuals with NF1. In addition, the case history format for the pediatric population should have been different from adults, so as to include more age-appropriate questions for each population.

This study confirmed that auditory dysfunction can be a complication in NF1 and health care professionals should be aware of potential effects of NF1 on the auditory system. Longitudinal studies focused on evaluating both peripheral and central auditory dysfunction are needed to describe further the natural history of the auditory phenotype in NF1.

APPENDICES

APPENDIX A

TOWSON
UNIVERSITY

EXEMPTION NUMBER: 10-0X86

To: Laize Ferraz Barcelos Corse
From: Institutional Review Board for the Proctection of Human Subjects Marcie Weinstein, Member
Date: Monday, March 08, 2010
RE: Application for Approval of Research Involving the Use of Human Participants

Office of University Research Services

Towson University
8000 York Road
Towson, MD 21252-0001

t. 410 704-2236
f. 410 704-4494

Thank you for submitting an application for approval of the research titled,
Audiologic Phenotype in Individuals with Neurofibromatosis Type 1

to the Institutional Review Board for the Protection of Human Participants (IRB) at Towson University.

Your research is exempt from general Human Participants requirements according to 45 CFR 46.101(b)(3). No further review of this project is required from year to year provided it does not deviate from the submitted research design.

If you substantially change your research project or your survey instrument, please notify the Board immediately.

We wish you every success in your research project.

CC: Diana C. Emanuel
File

APPENDIX B

NF1 Test Protocol

Patient:_____ Date:_____

☐ Baseline / _____ months from baseline

HEARING EVALUTION:

- ☐ Immittance
  - Tympanograms
    - 226 Hz
    - 1000 Hz
  - Acoustic Reflex: .5, 1, 2 kHz Contra; 1 kHz Ipsi (if not present test other frequencies)
    - Screen reflex if unable to conduct threshold search
  - Acoustic Reflex decay (.5, 1 kHz)
  - Resonance Frequency
- ☐ SRT/SAT
- ☐ Word recognition:
  - +30 dB SL re: SRT
  - 85 dB HL with 65 dB HL of contralateral masking
- ☐ Pure-tone thresholds 250-8000 Hz (AC) and 250-4000 Hz (BC)
  - If unable to condition for threshold estimation obtain startle response
- ☐ DPOAEs
- ☐ Middle Ear Reflectance
- ☐ ABR
- ☐ Other:_____

Notes/Comments why test(s) were not performed:

_____

_____

_____

_____

_____

APPENDIX C

NF1 Test Protocol

Patient:_____ Date:_____

AUDITORY BRAINSTEM RESPONSE:

Patient state: ☐ Awake ☐ Sedated

Broadband click via insert earphones. Conditions should be performed in both ears.

	Intensity	Rate	Polarity	# of Runs
☐	85/95 dB nHL	8.3/sec	Rarefaction	2
☐	85/95 dB nHL	8.3/sec	Condensation	2
☐	85/95 dB nHL	63.3/sec	Rarefaction	2
☐	65 dB nHL	8.3/sec	Rarefaction	2
☐	0 dB nHL	8.3/sec	Rarefaction	1
☐	***85/95 dB nHL*	*8.3/sec*	*Rarefaction*	*1*

***Clamp the tubing of the insert phone during the final run to ensure no electrical artifact is present.*

1.) ☐ 85 / ☐ 95 dB nHL, 8.3/sec, Ipsilateral recordings

	Polarity	Tracings	Chart	I	III	V	I-III	III-V	I-V	I/V μV
Right ear	$R_1 + C_1$									
	$R_2 + C_2$									
Left ear	$R_1 + C_1$									
	$R_2 + C_2$									
*Normative Values (ms)				1.79	4.08	6.08	2.60	2.26	4.49	

Absolute and interpeak wave latencies in ms.

Interaural wave V:_____

Comment:

_____

_____

*Normative values are +2.5 SD from Schwartz et al. (1989): ages 19-36 years; 80 dB nHL broadband click stimulus; rarefaction and condensation polarities combined; ER-3A transducer; hearing thresholds and stimulus rate unspecified

APPENDIX D

NF1 Test Protocol

Patient:_____ Date:_____

2.) ☐ 85 / ☐ 95 dB nHL, 63.3/sec, Ipsilateral recordings (add R + R)

	Tracings	Chart	V
Right ear (ms)			
Left ear (ms)			

3.) ☐ 55 / ☐ 65 dB nHL, 8.3/sec, Ipsilateral recordings (add R + R)

	Tracings	Chart	V
Right ear (ms)			
Left ear (ms)			

4.) Cochlear Microphonic

	Polarity	Tracings	Chart	Present? (Y/N)	Estimated duration (ms)	Amplitude µV	CM present during clamped run?
Right ear	$R_1 + R_2$						
	$C_1 + C_2$						
Left ear	$R_1 + R_2$						
	$C_1 + C_2$						

Notes/Comments why test(s) were not performed:

_____

_____

_____

_____

_____

APPENDIX E

NF1 Test Protocol

Patient:_____ Date:_____

Tracings:

	Ear	Level	Rate	Polarity	Ipsi/Contra		Ear	Level	Rate	Polarity	Ipsi/Contra
T1						T41					
T2						T42					
T3						T43					
T4						T44					
T5						T45					
T6						T46					
T7						T47					
T8						T48					
T9						T49					
T10						T50					
T11						T51					
T12						T52					
T13						T53					
T14						T54					
T15						T55					
T16						T56					
T17						T57					
T18						T58					
T19						T59					
T20						T60					
T21						T61					
T22						T62					
T23						T63					
T24						T64					
T25						T65					
T26						T66					
T27						T67					
T28						T68					
T29						T69					
T30						T70					
T31						T71					
T32						T72					
T33						T73					
T34						T74					
T35						T75					
T36						T76					
T37						T77					
T38						T78					
T39						T79					
T40						T80					

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- (Central) Auditory Processing Disorders
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- Pediatric and Adult Comprehensive audiological evaluation
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- Visual reinforcement and behavioral audiometric evaluation
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