PHYT 880 Assignment 3

**Neurofibromatosis 1**

**Introduction**

Several years ago, I briefly provided physical therapy early intervention services for a 1-year-old boy, who I will refer to AJ, with unilateral tibial pseudarthrosis secondary to neurofibromatosis 1 (NF1). Up until that time, I was unfamiliar with this disorder, and I wanted to use this assignment as an opportunity to explore neurofibromatosis (NF) further. Through this process, I have learned that NF encompasses several disorders, each with a wide variability of symptoms, that NF research has helped to answer some questions about etiology, that the consensus for clinical management guidelines continue to be in development, and that ongoing research to better manage and hopefully reverse or end NF effects are in process. I start with an overview of the etiology of the three main types of NF in order to provide a comparative overview of NF1 with the other types. The awareness of the complexity, diversity, diagnostic nuances and growing research related to the pathology and pathophysiology of NF will assist physical therapists in developing optimal interventions and communicating more effectively and expediently with the child, family, physicians, and other members of the health care and educational team.

Throughout this assignment, I will add details of my experience of working with AJ, which will be denoted by italics, as a case example of an individual with NF1.

**NF Etiology**

A neurofibromatosis disorder affects all races, ethnicities, and genders with an estimated U.S. prevalence of about 100,000; one out of every 3,000-4,000 babies has NF. 1,2 Broadly speaking, neurofibromatosis, as currently classified by the National Institute of Neurological Disorders and Stroke, describes three genetically different types of disorders that cause tumor growth in the supporting cells of the nerve and myelin sheath. NF prevents specific genes from making and regulating normal proteins that control cell production. 1 All neurofibromatoses are caused by either spontaneous gene mutation or inherited, usually from the parent as an autosomal dominant trait. Once the genetic mutation has occurred, it can be passed on to subsequent generations as an inherited trait. 1,2

• **Neurofibromatosis Type 1**: NF1, also referred to as von Recklinghaus disease, is the most common type of neurofibromatosis. NF1 is also one of the most common genetic syndromes, affecting 1 per 3,000-4,0000 individuals in the U.S, and similar to the prevalence rate for cystic fibrosis. 3  Between 50-70% of NF1 is inherited and 30-50% result from a spontaneous genetic mutation with unknown cause. 1  By the mid-90s, the NF1 gene was mapped to chromosome 17q11.2, which is a large gene that encodes and assists in the regulation of the protein neurofibromin. This protein is a component of neurons, Schwann cells, oligodendrocytes and astrocytes, and is especially present in neurons with extended projections, such as the pyramidal and Purkinje cells. Neurofibromin regulation by the NF1 gene plays a critical role in balanced cell growth and differentiation. 4  NF1 gene mutations that result in the diagnosis of NF1 are numerable, resulting in a wide spectrum of disease severity and an unknown progression and prognosis as the individual with NF1 ages. Individuals with NF1 have varying degrees of nonfunctional neurofibromin, which causes abnormal cellular growth, proliferation, and differentiation. This in turn may lead to tumor formation, particularly as a part of the supporting cell framework for nerve cells, as well as other disease manifestations detailed later in this assignment. 5

**• Neurofibromatosis Type 2:** NF2, also referred to as central neurofibromatosis or bilateral acoustic neuroma disease, is considered a rare disorder, affecting about 1 in 25,000 persons; about 50% of cases are inherited from a parent. 1,2 NF2 is caused by mutations of the tumor suppressor gene on chromosome 22q12, which encodes and assists in the regulation of the protein merlin or schwannomin. This protein has a role in cell membrane organization, cell-to cell adhesions, cytoplasm architecture and interactions within the cytoplasm, cell growth and proliferation. 5 The course of NF2 can also vary widely, but there is a tendency for inherited NF2 to follow a similar pattern among family members. NF2 signs may be present in childhood, but noticeable symptoms are more prevalent between 18-22 years of age. Bilateral hearing loss or tinnitus is the most frequent symptom, which is secondary to slow-growing tumors, called vestibular schwannomas, on the eighth cranial nerve. Deafness is a common outcome of more severe cases of NF2 as a result of the vestibular schwannomas. 1

**• Schwannomatosis:** Schwannomatosis is one of the more rare NF disorders, with an estimated prevalence of 1 in 1,000,000 individuals. 6  This disorder is only inherited 15% of the time and, unlike NF1 and NF2, it can skip generations. A mutation of the SMARCB1/INI gene has been indicated as a cause in the inherited form. The characteristic of this disorder is multiple schwannomas, which are benign nerve sheath tumor composed of Schwann cells. These schwannomas may be present on some or most parts of the body *except* the eighth cranial nerve. Chronic pain symptoms are more common with schwannomatosis, with surgical and pain management as the current treatment options. 1 Although it has been diagnosed in children, Schwannomatosis is usually diagnosed after the age of 30 years. 6

*AJ was diagnosed with NF1at 11 months of age, and inherited NF1 from his mother, who was diagnosed at the age of 10 years.*

The remaining part of this assignment will detail the pathology, clinical manifestations and physical therapy interventions for NF1 only.

**Diagnosing NF1 Pathology**

The current diagnostic criteria for NF1 was established 1987 by the National Institutes of Health. Two or more of the following are needed to diagnose NF1: 1,7,8

• ≥ 6 café au lait (light brown) skin patches measuring > 5mm in children and >16 mm in adults

• freckling in the armpit or groin area

• a parent, sibling, or child with NF1

• ≥ 2 neurofibromas or one plexiform neurofibroma (larger fibroma involving many nerves)

• Lisch nodules – unique to NF1, these are present in > 94% of individuals with NF1 by the age of 6. These nodules are asymptomatic papules on the surface of the iris detected by slit lamp examination.

• Optic pathway glioma (OPG) – OPGs are benign low-grade pilocytic astrocytomas that are usually located on the optic nerve 8

• Bony dysplasia of the sphenoid wing – this is usually recognized due to the presence of exophthalmos (eyes protruding outwards)

• Abnormal development of the spine or tibia, which may present as a pseudarthrosis

*AJ’s infant exam noted at least 6 café au lait macules 4-7mm in length with no obvious leg bowing. He was diagnosed with pseudoarthrosis of the right tibia at 11 months of age, which was then at about a 30° angle. At that time, he was formally diagnosed with NF1.*

**Clinical Manifestations of NF1**

NF1 is a progressive disorder that may affect many systems, and many individuals may not show evident clinical signs until after the first years of life. Most individuals with NF1 show evidence of diagnostic criteria by 8 years of age. Later diagnosis of NF1 may occur for individuals with spontaneous NF1 mutations due to lack of family NF history; therefore this diagnosis may not be as evident. Symptom progression of NF1 is also highly variable. 3

Milder, usually asymptomatic signs of NF1 are the café au lait spots, axillary and inguinal freckling and Lisch nodules. Café au lait macules usually develop within the child’s first year until about 4 years, and axillary and inguinal freckling develops by 7 years of age. Lisch nodules can usually be identified by 6 years of age. 3

The following information identifies some of the more serious clinical manifestations of NF1, which due to the collective systemic nature of NF1 may sometimes overlap or apply to more than one category. The approximate percentage of individuals with NF1 that are affected by these disorders, when this information is available, will be in parentheses following the specific disorder:

• **Integumentary/Peripheral Nervous System –** Cutaneous neurofibromas (99%) are common, occurring usually in young adults. They affect physical appearance and can contribute to psychological distress, including being bullied or mocked by others, but do not develop into malignancies. Subcutaneous neurofibromas and glomus tumors can cause pain and other neurological symptoms. The size of these tumors are variable and are generally controlled through surgical excision, laser treatment, or pain management. Plexiform neurofibromas (60%) are invasive subcutaneous tumors, and are more prevalent in childhood and adolescents. These may be disfiguring, affect organ functioning, interfere with bone and soft tissue growth, and cause neurological deficits. Large plexiform neuromas may be difficult to remove due to profuse bleeding and difficult wound healing. Some benign tumors, particularly the plexiform neurofibromas, may develop into malignancies, which are then called malignant peripheral nerve sheath tumors, or MPNST (8-13%). MPNSTs are treated with wide surgical excision and adjuvant therapy with a high recurrence risk and potential for metastases. With MPNSTs, there is a median survival of 20 months for children 1-17 years and 30.5 months for adults. 3,5,7

• **Central Nervous System**  - CNS disorders include Chiara 1 malformation and aqueduct stenosis and due to glial cell proliferation (1.5%). Epilepsy (6%) may be diagnosed in childhood and middle age and are considered mild and mainly complex partial seizures. Headaches (20%) are common, and most are not associated with intracranial lesions; MRIs are recommended for severe or recurrent headaches. Cognitive impairments are primarily learning disabilities (60%) with deficits in visual spatial disabilities, executive function, attention, working memory, speech and language, and emotional regulation. IQ is primarily in the low average range with about 5% with an IQ <70. Optic pathway gliomas (OPGs) (5-25%) are usually located on the optic nerve but can also occur elsewhere on the optic pathway or hypothalamus. They are usually diagnosed <6 years of age. Over half of OPGs are asymptomatic, 40% may require treatment. OPGs may cause unilateral proptosis, visual loss, visual field defects, strabismus, relative afferent pupillary defect, optic disc edema, or atrophy. Precocious puberty may be a presenting symptom in chiasmal tumors due to pressure on the pituitary gland. OPGs are usually slower growing and less aggressive than OPGs in other populations. 3,5,8

**• Cerebrovascular and Cardiovascular -** The vascular endothelium and smooth muscle are also influenced by neurofibromin regulation. Individuals with NF1 are therefore at higher risk for high blood pressure, congenital heart disease, renal artery stenosis (1%), moya moya syndrome (blockage of cerebral arteries), cerebral aneurysm, and internal carotid and cerebral artery stenosis or occlusion (2-5%) 5,7

• **Bone –** Reduced bone mineral density (50%) and short stature are more common for individuals with NF1. Long bone dysplasia and pseudarthrosis (3-4%), particularly of the tibia, is usually present in infancy, presenting as an anterolateral bowing or spontaneous fracture with delayed healing and subsequent non-union formation of a false joint. Current recommended guidelines are protected bracing until at least 5 years of age, followed with corrective surgery and internal stabilization. Secondary leg defects may also have to address leg length discrepancies and ankle valgus. Lower limb amputations may be indicated for severe cases. Vertebral deformities (10%-33%) are more common, and may contribute to a dystrophic or non-dystrophic scoliosis. A dystrophic scoliosis is based upon vertebral and rib dysplasia and malformation and often associated with paraspinal or other internal neurofibromas affecting the vertebrae, with a more rapid and severe progression to possible neurological impairment. 3,9

*At 11 months of age AJ received a bivalve plastic brace from the PT at a regional NF clinic, with instructions for LE weight bearing as tolerated. He had approximately 30° of anterolateral bowing of the right tibia.* *His mom reported that he may have leg surgery “to put a rod in the leg’” when he is 3 years old.*

**Physical Therapy Interventions**

Similar to my experience with AJ, one of the first physical therapy interventions for the infant with NF may be through an early intervention program, with an emphasis on age-appropriate gross motor skill development. A longitudinal analysis of 124 infants, preschool age children and school age children (0-8 years of age) with NF1 by Wessel et al 10 found greater delays in school-age children in gross motor, fine motor, self-help, reading, and writing development. Gross motor delays were observed in all three age groups, with recommendations for more sensitive screening for developmental disabilities and early intervention services for this at-risk population in order to improve their potential for academic success. Physical therapy early intervention works closely with the child and the primary caregivers in providing education, demonstration and practice to explore objects, interact with others through interaction with objects, and develop and support sitting and locomotion behaviors. These interventions, in turn, promote basic support and attending skills needed for the eventual classroom environment. 11 *Safety instructions for AJ was provided in brace use and weight-bearing precautions for AJ’s right leg due to his pseudarthrosis, which was also reinforced by the PT at the hospital clinic. Support equipment included a small sturdy cubed chair with arm support for stable seating for activities and transitional skills. A Star car, which is a riding toy that supports the legs and the wheels are maneuvered with the hands, was also provided for recreational mobility and a neighborhood activity.*

For an older child, Johnson et al 12 described benefits of a individualized plyometric training program provided for 3 children with NF1 (ages 5yr-11mos, 7, and l0 years of age) with delayed motor skills as measured by the Bruininks-Oseretsky Test of Motor Proficientcy-2nd edition (BOT2). The training program was twice weekly for l0 weeks, with a gradual increase in exercise load, and a change of half of the exercises at 5 weeks. Each session consisted of a 5 minute stretching warm-up, followed by ball throw and broad jump tests, 8 plyometric exercises, and a 5-minute cool-down activity chosen by the child. Each child also established personal goals as a part of the program (Child #1: increasing speed during basketball drill, #2: Improved stability in bike riding, #3: improving consecutive jump frequency in jump rope). By the end of the training program, each child showed improvement in their personal goals as well as improvement in body coordination. Strength and agility measures improved for 2 of the children. 12  Although the study sample is small, this study is an example of appropriate physical therapy intervention that demonstrates the value of incorporating child-selected goals and activities into a family-supported exercise program and that showed measurable improvement.

For some children with NF1, an aquatic physical therapy intervention may be effective improving strength and coordination, promoting cardiovascular activity and with supporting land-based function activities. An aquatic physical therapy intervention was described Fragala-Pinkham et al 13 for 4 children with activity limitations and a variety of diagnoses; three children had limited weight bearing restrictions. This may also be applicable to a child with NF1 with weight bearing restrictions or difficulty due to bony abnormalities or soft tissue restriction, or post-surgery rehabilitation following corrective limb surgery. Therapy activities included strengthening, balance, endurance, and gait training in the pool, which also included an underwater treadmill. The episodes of care ranged from 6 weeks to 8 months with a frequency range of 2-5x/week, and at least 50% of the sessions were provided in the pool. All patients showed improvement in body function, activity, and participation. The outpatient aquatic program is a popular program with the child, families, and therapists and is in high demand at this rehabilitation hospital. 13 Similar to the previous study, this sample is small and highly individualized and additional research is needed to support and guide aquatic interventions.

**Activities and Community**

For the young child with NF1, it is important for the family, as well as the health and educational team members, to become knowledgeable in this disorder. Effective advocacy skills are essential in order to access to the best possible medical, educational, and therapeutic interventions. There are several excellent websites that can serve as a base for NF education and support for parents, older children and adults with NF, and health and education professionals. Several valuable websites include:

• The Neurofibromatosis Network ([www.nfnetwork.org](http://www.nfnetwork.org)) - founded in 1988, the NF Network is a non-profit organization whose mission is to “find treatments and a cure for neurofibromatosis by promoting scientific research, improving clinical care, providing outreach through education and awareness, while offering hope and support to those affected by NF.” 14 The NF Network website is rich with valuable resources, including downloadable educational materials, scientific research, location of qualified doctors, personal stories, chat rooms and local group information.

• Children’s Tumor Foundation: Ending NF Through Research. 15 (<http://www.ctf.org>) - CTF is also a medical non-profit organization with a complimentary mission to the NF Network. In addition to excellent downloadable educational materials for parents, older children and adults with NF and health professionals, it contains a NF registry for clinical trials, a quarterly newsletter for health professionals with research updates, chat rooms, a NF Forum for Patients and families, and information about NF camp for children ages 12-21 in Utah with scholarship applications.

• British Columbia Neurofibromatosis Web site. 16 This website provides a link and sign-up for a positive and informative magazine, called Inspire magazine, that features individuals with NF. <http://www.bcnf.bc.ca/living-with-nf/inspire-magazine/>.

For children with NF with physical disabilities, additional activities to support activity, recreation and participation might a therapeutic tricycle riding system like the AmTryke, which is offered through AMBUCSTM. The smaller AmTryke models allow the young child to pedal with both their hands and feet, and foot cups and handwraps can be used to help teach the child to pedal. The parent has a handle to push or pull the AmTryke, so it can be used for the child to be more active when the parent goes for a walk in the neighborhood. The PT would need to assist with the AmTryke evaluation (forms are available online) to place the child on the wish list to obtain one through fundraising if the family is interested.17

The individual with NF1 has an uncertain prognosis. Given continued advances in medical research, it is possible that the potentially devastating systemic effects of NF genetic disorders may one day become medically stabilized or even reversed. Staying current with research for the best treatments to address and manage impairments, educating and advocating for effective supports to ameliorate the effects of possible learning and physical disabilities, and maintaining participation in regular physical activities to support and improve physical functioning are keystones for the individuals with NF to establish and maintain an optimum quality of life.

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