Neurofibromatosis Type 1: Diagnostic and Therapeutic Radiologic Imaging

Elizabeth Brouillette
Abstract

Neurofibromatosis Type 1, also called von Recklinghausen’s Disease, is an autosomal dominant genetic disorder that involves tumors along the nerves and affects multiple systems throughout the body. The areas most prominently affected include the skeletal, cardiovascular, neurological, endocrine, and ocular systems with some of the most common clinical features of NF1 being short stature and macrocephaly. The tumors can be malignant or benign and result in a variety of symptoms. A diagnosis requires the presence of two or more major following clinical manifestations: six or more café-au-lait spots on the skin (must be at least 0.5 cm in diameter in pre-pubertal individuals and 1.5 cm in post-pubertal patients), axillary or inguinal freckling, two or more cutaneous neurofibromas, one plexiform neurofibroma, characteristic bony lesions, an optic glioma, two or more iris Lisch nodules, or a first-degree relative with NF1. In order to aid in the diagnosis process and therapeutic treatments, genetic testing and numerous radiologic imaging modalities are utilized. Radiography, Computed Tomography, and Magnetic Resonance Imaging help with the diagnosis and regular monitoring of tumors, whereas Radiation Therapy can be an appropriate treatment.
Introduction

Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic disorder that affects multiple systems throughout the human body and involves benign or malignant tumors along the nerves. NF1, also called von Recklinghausen’s Disease, occurs in approximately 1 in 3,000-4,000 people worldwide and an estimated 100,000 Americans have this condition.\(^1\) NF1 results in a variety of clinical manifestations and multiple criteria must be met before there is a true diagnosis of NF1. Patients undergo genetic testing and radiologic imaging exams to aid in the diagnostic process, to regularly monitor the tumors, and for potential treatment procedures. With a diagnosis by the average age of ten, patients with NF1 are exposed to numerous imaging procedures at a young age and continue to have these exams done throughout their lifetime.\(^2\)

Methodology

Research was obtained through literature databases and online search engines. A majority of the information came from 15 journal articles through electronic literature databases. Primary databases utilized were Medline via PubMed and EBSCO, Cochrane Library, and CINAHL. Other online sources and journal articles were retrieved using Google Scholar and one book and four websites were used for their information. The key search subject was “Neurofibromatosis Type 1” and primary search terms included: “NF1 and neurofibromas,” “NF1 and etiology,” “NF1 and diagnostic criteria,” “NF1 and symptoms,” “NF1 and genetic testing,” “NF1 and radiologic imaging,” “NF1 diagnosed on radiographic films,” “NF1 and Computed Tomography,” “NF1 and Magnetic Resonance Imaging,” “NF1 and prognosis,” “NF1 and treatment,” “NF1 and Radiation
Therapy,” and “NF1 and mortality.” Most of the searches were refined to less than 10 years, however four of the cited sources used were written in the early 2000’s and one in 1998 and were therefore older than the 10-year mark.

Discussion

Neurofibromatosis is the general term for a nervous system disorder in which normal cell growth is disrupted and the result is the formation of tumors on nerve tissue. NF1, Neurofibromatosis Type 2 (NF2), and Schwannomatosis are three distinct disorders that are categorized as forms of neurofibromatosis. All of the tumors originate in the supporting cells that make up the nerve and myelin sheath that protects the nerves, rather than the cells that actually transmit information. Each of these three disorders involves tumor growth in the nervous system, but the type of tumor depends on which cells are affected. Neurofibromas, which are tumors of the peripheral nerves, are most commonly associated with NF1 and usually are located on or just under the skin. Neurofibromas are not encapsulated and can appear as solitary tumors or as part of neurofibromatosis when there are many. These tumors show proliferation of nerve sheath cells intermixed with thick, wavy collagen bundles and there may be signs of myxoid degeneration, which is when surrounding connective tissue turns into a mucus-like substance. On the other hand, Schwann cell tumors, known as schwannomas, are mostly identified with NF2 and Schwannomatosis. These tumors tend to be encapsulated, with the nerve fibers stretched around the tumor as opposed to nerve fibers running through neurofibromas in NF1.

A mutation in the neurofibromin 1 gene on chromosome 17 results in the production of these nervous system-associated tumors. The NF1 gene provides
instructions for making the protein, neurofibromin, which acts as a tumor suppressor and prevents cells from growing too quickly or uncontrollably. When there is a defect in this gene, the neurofibromas associated with NF1 can form throughout the body along the nerves. This genetic mutated gene that results in NF1 has an autosomal dominant pattern of inheritance. However unlike most other autosomal dominant conditions, two copies of the NF1 gene must be altered to trigger tumor formation in NF1.\(^1\) People affected with this disorder are born with one mutated copy of the NF1 gene in each cell while the second mutated copy of the gene can occur spontaneously throughout a person’s lifetime in the cells surrounding the nerves, resulting in the tumors in 50% of cases.\(^4\)

The diagnosis of NF1 is based upon clinical manifestations and genetic testing. Diagnosis requires the presence of two or more of the following major criteria: six or more café-au-lait spots on the skin (must be at least 0.5 cm in diameter in pre-pubertal individuals and 1.5 cm in post-pubertal patients), axillary or inguinal freckling, two or more cutaneous neurofibromas, one plexiform neurofibroma, characteristic bony lesions, an optic glioma, two or more iris Lisch nodules, or a first-degree relative with NF1.\(^5\) In some situations, the diagnosis can be made at birth but it can take several years for enough signs to emerge to confirm a diagnosis on other patients. NF1 is a progressive condition therefore different complications occur at various times throughout lifetime and some may become worse. The café-au-lait spots (see Figure 1) and cutaneous neurofibromas occur in at least 95% of patients, whereas other features occur in less than 1%.\(^6\)
Symptoms associated with the skin are often most noticeable at birth. Neurofibromas become apparent between the ages of 10-15, whereas other symptoms usually have typical onsets by a certain age (see Table 1). For 15 percent of individuals with NF1, the symptoms can be debilitating.

Genetic testing is an alternative method used to diagnose NF1 and can be helpful to achieve an early diagnosis. Testing during the prenatal period helps determine the possibility of developing NF1 based on family history of the disorder. However, genetic testing is not able to predict the severity of NF1. Genetic testing is performed by either a direct gene mutation analysis and/or a linkage analysis. The direct gene mutation analysis tries to identify the particular gene change that causes NF1. If this test does not provide enough information, then a linkage analysis is performed. This analysis involves testing blood from family members to track the chromosome that carries the disease-causing gene through two or more generations. Linkage testing is approximately 90 percent accurate and the mutation analysis is 95 percent accurate in finding a mutation for NF1.

Figure 1. Café-au-lait spots on the skin of NF1 patient.
Table 1.  *Frequency and age of onset of major clinical manifestations of NF1.*

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Frequency (%)</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café-au-lait patches</td>
<td>&gt;99</td>
<td>Birth to 12 y</td>
</tr>
<tr>
<td>Skin-fold freckling</td>
<td>85</td>
<td>3 y to adolescence</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>90-95</td>
<td>&gt;3 y</td>
</tr>
<tr>
<td>Cutaneous neurofibromas</td>
<td>&gt;99</td>
<td>&gt;7 y (usually late adolescence)</td>
</tr>
<tr>
<td>Plexiform neurofibromas</td>
<td>30 (visible) - 50 (on imaging)</td>
<td>Birth to 18 y</td>
</tr>
<tr>
<td>Disfiguring facial plexiform neurofibromas</td>
<td>3-5</td>
<td>Birth to 5 y</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>2-5 (8-13% lifetime risk)</td>
<td>5-75 y</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>10</td>
<td>Birth to 18 y</td>
</tr>
<tr>
<td>Scoliosis requiring surgery</td>
<td>5</td>
<td>Birth to 18 y</td>
</tr>
<tr>
<td>Pseudarthrosis of tibia</td>
<td>2</td>
<td>Birth to 3 y</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>2</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>2</td>
<td>&gt;10 y</td>
</tr>
<tr>
<td>Severe cognitive impairment (IQ &lt; 70)</td>
<td>4-8</td>
<td>Birth</td>
</tr>
<tr>
<td>Learning problems</td>
<td>30-60</td>
<td>Birth</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>6-7</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Optic pathway glioma</td>
<td>15 (only 5% symptomatic)</td>
<td>Birth to 7 y (up to 30 y)</td>
</tr>
<tr>
<td>Cerebral gliomas</td>
<td>2-3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Sphenoid wing dysplasia</td>
<td>&lt;1</td>
<td>Congenital</td>
</tr>
<tr>
<td>Aqueduct stenosis</td>
<td>1.5</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

General symptoms for those affected by NF1 can cause many abnormalities in various systems of the body. The areas most prominently affected include the skeletal, cardiovascular, neurological, endocrine, and ocular systems with some of the most common clinical features of NF1 being short stature and macrocephaly. Along with these, there is increased occurrence of hypertension, central precocious puberty, diencephalic syndrome, growth hormone deficiency, and growth hormone hypersecretion. Other features range from scoliosis and bone dysplasia in the skeletal system to blood vessel dysplasia and cognitive learning problems. Learning disabilities and Attention Deficit Hyperactivity Disorder occur in 60% of all patients but overall intelligence is usually normal with less than 3% with mental retardation. Vision is also commonly affected in
NF1 with optic gliomas in 15% of patients. In addition, recent studies have shown that Lisch nodules and choroidal abnormalities are becoming new diagnostic signs for NF1 in children. According to a recent study published in 2015, 72 out of 140 pediatric patients already diagnosed with NF1 also had an abnormality in their eye. With this early detection, a NF1 diagnosis can be made before many other symptoms appear.

Besides noticeable symptoms and genetic testing, imaging plays a vital role in the diagnosis of NF1. Neurofibromas, or benign tumors, are a major component of NF1 and can be seen on radiograph if they involve the bone. They may appear as a lucent lesion within the bone and usually have well defined margins (see Figure 2).

![Figure 2. Lucent lesions on anteriorposterior (AP) radiograph of bilateral knees of patient with NF1.](image)

In addition to the tumors themselves, spinal deformities occur in up to 50% of patients with NF1 with scoliosis affecting 21% and being the most common complication. Both scoliosis and kyphosis can easily be viewed on radiographs of the spine and produce the short stature. Most common osseous spinal manifestations associated with NF1 are vertebral body wedging and scalloping, pedicle erosion, foramen
enlargement, and penciling and spindling of transverse processes and ribs (see Figure 3).\textsuperscript{(13, 14)}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3}
\caption{AP radiograph of upper chest wall demonstrating rib penciling.\textsuperscript{14}}
\end{figure}

In addition to abnormalities in the spine region, evidence of mesodermal dysplasia that ultimately results in deficient bone formation in the pectoral and pelvis girdles and bones of extremities can be seen on radiographs. Mesodermal dysplasia causes bowing of long bones, pseudoarthrosis, and fibrocystic lesions that are common in NF1 patients. Anterolateral bowing of the lower leg along with pseudoarthrosis, a fracture that cannot heal without intervention, can lead to a diagnosis of NF1. However, unlike the usual diagnostic criteria of cortical thinning, recent studies have noted that bowed bones associated with NF1 instead have cortical thickening and medullary narrowing when viewed on radiograph (see Figure 4).\textsuperscript{15} Bowing typically occurs in the tibia as one of the earliest signs of NF1 and results in limb shortening and eventually fracture.
Radiography is not the only form of imaging that is used for diagnosis of NF1. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) provide more sensitive diagnostic pictures for NF1 than plain radiography, with MR imaging being the best option. These types of imaging are utilized most often when looking for peripheral tumors, tumors in abdominal organs, and lesions in the spine or brain to help define the boundaries of the tumor and vascular supply. However, CT scans are most useful for finding issues within the bone while MRI has better capabilities to see pathology with greater soft tissue contrast resolution. Higher doses of ionizing radiation given to the patient during a CT scan must be taken into account as well, as many NF1 patients will receive numerous imaging exams throughout their lifetime. MRI on the other hand has

Figure 4. AP and lateral radiographs of the bowing of lower leg with the appearance of cortical thickening with medullary canal narrowing.15
the added advantage of using magnets and radio waves to produce images of the body and does not involve the possible harmful effects of ionizing radiation.

On CT scans, neurofibromas have a homogenous, smooth, round appearance with distinct outlines and lower attenuation values of 20-25 Hounsfield units (HU) on unenhanced scans and 30-50 HU on contrast-enhanced scans (see Figure 5). Studies suggest that the amount of lipid-rich Schwann cells, adipocytes, fat, and collagen are the reasoning as to why neurofibromas show up differently on scans with contrast and ones without. CT is often used to look for NF1 complications within the thoracic, abdominal, and pelvic regions of the body. In addition, neurofibromas may look different on each scan due to the ubiquity of peripheral nerves within these areas. Neurofibromas can easily be mistaken as other pathology processes on CT scans. For example, neurofibromas in the mediastinum can resemble lymphoma, tuberculosis, and metastatic testicular cancer while an intercostal neurofibroma in the ribs can mimic pulmonary or metastatic adenocarcinoma or a pulmonary infection. For reasons like this, other tests and criteria must be met before a true diagnosis of NF1 is confirmed.
MRI is useful as well for diagnostic imaging of NF1 with the ability to pinpoint masses, tumors, deeper neurofibromas, and lesions associated with this disease. MRI is argued to do the best job out of the other imaging options as far as searching for pathology, especially in the brain and within the ocular pathway. T1 and T2 weighted scans in multiple projections are used to aid with diagnosis. One of the indications of NF1 that could potentially be seen on a T2 weighted brain MRI is a hyperintense lesion, or what is also known as an unidentified bright object. These lesions are not one of the main clinical manifestations used for diagnoses as mentioned previously, but they are becoming more prevalent in patients diagnosed with NF1. Although a brain MRI is not a routine exam for NF1 diagnosis, it has assisted in the identification of asymptomatic structural abnormalities and have given a greater definition of the symptomatic structural abnormalities. According to one study, these unidentified bright objects are typically found in the brain stem, thalamus, and cerebellar peduncles on brain MRI scans (see Figure 6).
Also, a target sign on a scan indicates a plexiform neurofibroma which is one of the diagnosis criterion for NF1. This appearance is due to a central fibrocollagenous core (T2-hypointense) surrounded by myxomatous tissue (T2-hyperintense) (see Figure 7).\(^\text{18}\)

Once a patient has been diagnosed with NF1 and their symptoms are under control, their prognosis is only slightly lower than the normal person. Studies have shown that there is an 8-15 year decrease in life expectancy for NF1 patients and there are excess deaths due to malignancy before the age of 50.\(^\text{19, 20}\) While there is only an estimated 3 to 5 percent chance that one of the benign tumors becomes malignant, unusual tumors are more likely to occur with increased frequency of NF1.\(^\text{2}\) Carcinoid, pheochromocytoma, brain tumors, chronic myeloid leukemia, and...
malignant peripheral nerve sheath tumors all have been known to occur, as well as common tumors such as breast, lung, kidney, color, and prostate. Other problems that can lead to early death in NF1 patients include acute hydrocephalus, severe seizures, progressive spinal cord intrusion by plexiform neurofibromas, unstable scoliosis, and complications from hypertension.

Not only does radiologic imaging aid in the diagnosis of NF1, but radiation therapy can be a treatment option as well. Although there is no specific treatment yet for NF1, surgery is most commonly recommended in addition to radiation therapy and chemotherapy to remove and shrink tumors. Only the tumors that are painful, result in a loss of function, or have grown quickly are likely removed during surgery. Even though radiation therapy is not the first line of treatment for NF1, it can still be utilized to shrink tumors. Many studies have shown that radiation therapy is most effective at relieving symptoms and is used in conjunction with other treatment methods.

However, it has been argued as to how beneficial radiation therapy really is for treating NF1. Some studies claim that therapy should only be performed on malignant tumors in fear that it could stimulate the growth of plexiform lesions. Other studies have been constructed to look at how radiation therapy specifically affects children with NF1 too. Optic pathway gliomas associated with NF1 are known to greatly affect vision and often undergo radiation therapy treatment to shrink these tumors. However, some results show a significantly increased risk of secondary nervous system tumors in patients who received radiation therapy treatment for optic pathway gliomas during childhood. Due to these results and mixed outcomes from other studies in regards to the actual benefits of radiation therapy, this treatment tends to be avoided unless absolutely necessary.
Conclusion

Although Neurofibromatosis Type 1 is a genetic disorder that involves multiple symptoms and parts of the body, radiologic imaging still plays a crucial part in numerous stages of this disorder. From radiographs, CT, and MRI scans throughout the diagnosis process to radiation therapy during treatment, patients with NF1 become quite familiar with many imaging modalities. Without imaging, the pathology and neurofibromas that comprise most of this disorder would not be easily diagnosed and NF1 may not be caught as early. Radiation therapy may not be the sole treatment for NF1 but radiologic imaging as a whole can help these patients in more than one way. Not only are radiologic imaging exams vital at the beginning stages of diagnosis and during treatment, but also to continuously check the progress of tumors throughout the body during the patient’s lifetime.
AMA References


4. Fortman BF, Kuszyk BS, Urban BA, Fishman EK. Neurofibromatosis Type 1: A Diagnostic Mimicker at CT. Radiographics. 2001;21(3). doi: http://dx.doi.org/10.1148/radiographics.21.3.g01ma05601


