Neurofibromatosis – Review of the Literature and Case Report

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SUMMARY Neurofibromatoses are genetic disorders of the nervous system that primarily affect the development and growth of neural (nerve) cell tissues. These disorders cause tumors to grow on nerves, and produce other abnormalities such as skin changes and bone deformities. Although many affected persons inherit the disorder, between 30 and 50 percent of new cases arise spontaneously through mutation in the individual’s genes. We report on seven cases of type 1 neurofibromatosis (NF1) diagnosed from 2001 to 2006 at our Department. There were four female and three male patients, mean age 46.1 and 49 years, respectively. All patients showed neurofibromas accompanied by fibromas, café au lait spots, cases showed five axillary freckling (lentigines) and one case showed five plexiform neurofibromas and pruritus belonging to NF1 category. All patients had affected first degree relatives. Systemic findings were rare and included optic glioma in one case and Lisch hamartoma nodules in three cases. In all cases, the diagnosis was established according to the National Institutes of Health criteria, including at least two of the diagnostic criteria for NF1 diagnosis. None of our cases had malignancies or gastrointestinal tract involvement.

KEY WORDS: neurofibroma; neurofibromatosis; Recklinghausen’s disease; central neurofibromatosis

INTRODUCTION

Neurofibromatosis are genetic disorders of the nervous system that primarily affect the development and growth of neural cell tissues. These disorders cause tumors to grow on nerves, and produce other abnormalities such as skin changes and bone deformities. Although many affected persons inherit the disorder, between 30 and 50 percent of new cases arise spontaneously through mutation in the individual’s genes. Once this change has taken place, the mutant gene can be passed onto succeeding generations. The following types of neurofibromatosis are distinguished: type 1 neurofibromatosis, central neurofibromatosis, and neurofibromatosis with café au lait macules only (1).

Neurofibromatosis 1

Neurofibromatosis 1 (NF1) or von Recklinghausen’s disease is a hereditary hamartomatosis, transmitted by an autosomal dominant
mechanism. It primarily affects cells of the neural crest origin and results in developmental, pigmen-
tary and neoplastic abnormalities (2). It affects both sexes with equal frequency (1:3,000).

The responsible gene is transmitted with penetrance and is located in the centromeric region
of chromosome 17 (17q11.2). At least 20 different mutations of this gene and relative clinical variants
have been reported although there are no available laboratory tests for diagnosis (3). Cutaneous
findings are café au lait macules, axillary freck-
lings, neurofibromas, plexiform neurofibroma, pig-
mentation, pruritus, juvenile xanthogranulomas, lipomas, and angiolipomas. The severity of cuta-
neous involvement in NF1 is not an indicator of the extent of the disease as internal manifestations
are common and are often more serious. Sys-
temic findings are found in the following organs:
central nervous system (optic glioma, meningio-
mas, astrocytomas, mental retardation, learning
disorders), eye (Lisch hamartoma nodules), ear
(acoustic neuromas), musculoskeletal (scoliosis,
pseudoarthrosis of long bones, sphenoid dyspla-
sia), endocrine (precocious and delayed puberty,
and vascular (renovascular hyperten-
sion, cerebral and gastrointestinal ab-
normal vessels). Neurofibroma is one of the
most common nerve sheath tumors occurring in the soft
tissue and generally occurs in NF1.

There are basically four types of neurofibromas
(tumors consisting of Schwann cells and neural fi-
broblasts), found in NF1:

- cutaneous: superficial, soft button-like tumors
  with no malignant potential;
- subcutaneous: tumors along the course of sub-
cutaneous peripheral nerves that may cause
  localized pain or tenderness;
- nodular plexiform: large network of tumors in-
  volving dorsal nerve roots;
- diffuse plexiform: invasive tumors that may in-
  volve all layers of the skin, muscle, bone and
  blood vessels.

Neurofibromas may involve spinal nerve roots and
characteristically grow through an intervertebral
foramen to produce intraspinal and extraspinal
masses (dumb-bell tumor). The intraspinal compo-
ment may compress the spinal cord. Cranial nerve
tumors include optic gliomas, which may produce
progressive blindness, and acoustic neuromas
(vestibular schwannoma), which may produce diz-
ziness, ataxia, deafness and tinnitus. The disease
is usually progressive.

The diagnostic criteria proposed by the Na-
tional Institutes of Health include at least two of
the following: (a) 6 or more café au lait skin spots
greater than 1.5 cm in diameter in the adult or 0.5
cm in the child; (b) two or more neurofibromas or
one infiltrating plexiform neurofibroma; (c) axillary
or inguinal lentigines; (d) ocular glioma; (e) two or
more Lisch nodules on the anterior surface of the
iris; (f) a discrete bone lesion or reduced thickness
of the cortex of long bones with or without pseudo-
arthritis; and (g) an affected first-degree relative
(2,4).

Malignancies can appear in NF1. The two most
common malignancies are juvenile chronic myeloge-
uous leukemia (CML) and malignant schwanno-
ma, the most malignant peripheral nerve sheath
(tumor (MPNST). MPNSTs arise in the deep plexi-
form neurofibromas of NF-1. They are called neu-
rofibrosarcoma and malignant schwannoma. Most
tumors in both NF1 and NF2 are benign; however,
enlargement of a benign tumor can interfere with
vital functions. It is estimated that a person with
NF1 has a 3%-15% increased risk of developing.
The other tumors are rhabdomyosarcoma, Wilms
tumor, pheochromocytoma, carcinoid tumors, and
few cases of intestinal leiomyosarcoma and gas-

troparesis (2,5,6). There is no increased incidence
of malignant melanoma (2).

The presence of multiple juvenile xanthogranu-
lomas and neurofibromatosis is a paraneoplastic
marker of CML (7-10). There is a report on juvenile
myelomonoctytic leukemia in a child with NF1 (7).
There is also a report on multiple juvenile xantho-
granuloma, CML, and hemophagocytic lympho-
histiocytosis in patients with NF1 (9).

Although gastrointestinal (GI) tract may be in-
volved in up to one fourth of von Recklinghausen’s
disease cases, very few reports describe the dis-
ease association with intestinal leiomyosarcoma
and gastroparesis (11-13). Gastroparesis is a pos-
sible although rare paraneoplastic manifestation.
Cancers usually associated with gastroparesis as a
paraneoplastic syndrome are small cell lung carci-

toma and bronchial carcinoid (14,15). However, GI
tumors such as those of the esophagus, stomach
and pancreas have also been reported in associa-
tion with this syndrome (16,17). Recently, gastro-
paresis has also been reported in association with
retroperitoneal leiomyosarcoma (13,18). It has been
shown that the tumor-induced response may trigger
a cross-reaction against the cells of the central and
peripheral nervous system, including those in the
gut, where an alteration in the plexus of Auerbach
may be responsible for the GI dysmotility (17).
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In neurofibromatosis, other manifestations such as ataxia, orthostatic hypotension and motor-sensitive peripheral neuropathy are known to be associated with autoantibodies directed against neuronal components (13,19).

Neurofibromatosis 2

Neurofibromatosis 2 (NF2) or central neurofibromatosis is inherited in autosomal dominant pattern. The gene is located on chromosome 22q. Variable expressivity is much less common than in NF1. Clinically, one can find acoustic neuromas, mostly bilateral, meningiomas, spinal gliomas, café au lait macules, neural tumors (schwannomas, neurofibroma and overlap tumors), hyperpigmentation, hairiness, juvenile xanthogranulomas with leukemia, and juvenile posterior subcapsular cataracts. The ophthalmologist plays an important role in making the diagnosis, as several ocular manifestations may be shown during childhood, before tumors of the central nervous system have become symptomatic (20). An early diagnosis of NF2 may prevent deafness by early surgical intervention (20). Moreover, as NF2 is a distinct entity characterized by bilateral eighth-nerve schwannomas, other intracranial schwannomas and meningiomas, and multiple spinal canal schwannomas, meningiomas and gliomas screening of the entire neural axis is mandatory because of the incidence of asymptomatic lesions. Magnetic resonance imaging (MRI) is the technique of choice, particularly employing contrast-enhanced, T1-weighted sequences in multiple image planes.

Treatment

There is no cure for NF. The main goal of treatment is to monitor its development and intervene when necessary. Healthy children with NF should be followed-up and examined every 6-12 months by a pediatrician.

Neurofibromas that become large and painful can be cut out to reduce the risk of malignancy and other complications. Surgery can help prevent some NF1 bone malformations and remove painful or disfiguring tumors; however, there is a chance that the tumors may grow back and in greater numbers. In the rare instances when tumors become malignant, treatment may include surgery, radiation, or chemotherapy.

Genetic counseling and education about NF are important. One concern that should not be overlooked is the risk of isolation or loneliness in people with NF. People with NF are often anxious about future complications, and disfiguring lesions may sometimes lead to withdrawal from the society. Prenatal diagnosis of familial NF1 or NF2 is also possible utilizing amniocentesis or chorionic villus sampling procedures.

CASE REPORT

We report on seven cases of NF1 recorded at our Department between 2001 and 2006. There were four female and three male patients, mean age 46.1 and 49 years, respectively. All cases showed neurofibromas accompanied by fibromas, café au lait spots, while 5 cases showed axillary freckling (lentigines) and one case showed 5 plexiform neurofibromas and pruritus, all belonging to NF1 category (Table 1). All had an early onset of NF1 and were treated by surgical intervention for numerous neurofibromas. All patients had some first degree relatives affected with the disorder. The responsible gene for NF1 in the centromeric region of chromosome 17 (17q11.2) was proven in case 4. The severity of cutaneous involvement was similar in six of our patients. Systemic findings were rare and included optic glioma in one case and Lisch nodules in three cases. The diagnosis was established in all cases according to the National Institutes of Health criteria, and included at least two of the diagnostic criteria for NF1 diagnosis proposed. None of our patients had, and there was no gastrointestinal tract involvement.

CONCLUSION

Although there is no cure for NF, surgical treatment is recommended in all cases with painful and large neurofibromas and those with malignant alteration. All our cases were followed-up for five years and underwent surgical treatment. Until now, they are in good condition and free from malignant alteration.

References


