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Neurofibromatosis – Review of the Literature and Case Report

Zrinjka Paštar, Jasna Lipozenčić[1], Dragomir Budimčić[1], Mirna Tomljanović-Veselski[2]

Health Department, Ministry of Defence; [1]University Department of Dermatology and Venereology, Zagreb University Hospital Center, Zagreb, [2]Department of Dermatology and Venereology, Dr. Josip Benčević General Hospital, Slavonski Brod, Croatia

Corresponding author:
Professor Jasna Lipozenčić, MD, PhD
University Department of
Dermatology and Venereology
Zagreb University Hospital Center
Šalata 4
HR-10000 Zagreb
Croatia
jasna.lipozencic@zg.htnet.hr

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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

Neurofibromatoses 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 neurofibromatoses, 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

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mechanism. It primarily affects cells of the neural crest origin and results in developmental, pigmentary 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 frecklings, neurofibromas, plexiform neurofibroma, pigmentation, pruritus, juvenile xanthogranulomas, lipomas, and angiolipomas. The severity of cutaneous involvement in NF1 is not an indicator of the extent of the disease as internal manifestations are common and are often more serious. Systemic findings are found in the following organs: central nervous system (optic glioma, meningiomas, astrocytomas, mental retardation, learning disorders), eye (Lisch hamartoma nodules), ear (acoustic neuromas), musculoskeletal (scoliosis, pseudoarthrosis of long bones, sphenoid dysplasia), endocrine (precocious and delayed puberty, pheochromocytoma), and vascular (renovascular hypertension, cerebral and gastrointestinal abnormal 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 fibroblasts), found in NF1:

- cutaneous: superficial, soft button-like tumors with no malignant potential;
- subcutaneous: tumors along the course of subcutaneous peripheral nerves that may cause localized pain or tenderness;
- nodular plexiform: large network of tumors involving dorsal nerve roots;
- diffuse plexiform: invasive tumors that may involve 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 component may compress the spinal cord. Cranial nerve tumors include optic gliomas, which may produce progressive blindness, and acoustic neuromas (vestibular schwannoma), which may produce dizziness, ataxia, deafness and tinnitus. The disease is usually progressive.

The diagnostic criteria proposed by the National 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 pseudoarthrosis; and (g) an affected first-degree relative (2,4).

Malignancies can appear in NF1. The two most common malignancies are juvenile chronic myelogenous leukemia (CML) and malignant schwannoma, the most malignant peripheral nerve sheath tumor (MPNST). MPNSTs arise in the deep plexiform neurofibromas of NF-1. They are called neurofibrosarcoma 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 gastroparesis (2,5,6). There is no increased incidence of malignant melanoma (2).

The presence of multiple juvenile xanthogranulomas and neurofibromatosis is a paraneoplastic marker of CML (7-10). There is a report on juvenile myelomonocytic leukemia in a child with NF1 (7). There is also a report on multiple juvenile xanthogranuloma, CML, and hemophagocytic lymphohistiocytosis in patients with NF1 (9).

Although gastrointestinal (GI) tract may be involved in up to one fourth of von Recklingshausen's disease cases, very few reports describe the disease association with intestinal leiomyosarcoma and gastroparesis (11-13). Gastroparesis is a possible although rare paraneoplastic manifestation. Cancers usually associated with gastroparesis as a paraneoplastic syndrome are small cell lung carcinoma and bronchial carcinoid (14,15). However, GI tumors such as those of the esophagus, stomach and pancreas have also been reported in association with this syndrome (16,17). Recently, gastroparesis 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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Table 1. Clinical characteristics of seven patients with neurofibromatosis type 1

Patient				Cutaneous findings					
No	Sex	Age (yrs)	Café au lait spots (diameter in cm)	Neurofibromas + plexiform neurofibromas + +fibromas	Location	Tumor size (cm)	Axillary or inguinal lentigines	Other findings	Ocular glioma
1	F	33	15 (2)	2+0+6	Abdomen	3+0+4	None		None
2	F	67	Many	2+0+many	Plantar, trunk	2 - 5	None	Hypertrichosis	None
3	M	61	9 (10) ; 3 (2)	5+0+6	Trunk, face and foot	1,5 – 3	Yes		None
4	M	40	Many (11x7)	3+0+5	Extremities, face	3+0+6	Yes	17q11.2 gene	None
5	M	46	Many (6)	4+0+many	Abdomen, thigh	3+0+3-6	Some		None
6	F	54	Many (3)	6+5+10	Trunk, extremities	5+4+6-7	Some		None
7	F	31	Many (7x4)	4+ 0+10	Trunk	5+0+4	Three		None

Table continued

Patient				Systemic findings				Diagnosis
No	Sex	Age (yrs)	Café au lait spots (diameter in cm)	Lisch nodules	Bone lesions	Affected first-degree relative	Other findings	
1	F	33	15 (2)	Yes	None	Father, sister		NF1
2	F	67	Many	None	None	Daughter	Diff. dysrhythmic irritative brain changes	NF1
3	M	61	9 (10); 3 (2)	None	None	Daughter, grandmother	Peritronchantritis l. sin.; Kidney cysts	NF1
4	M	40	Many (11x7)	None	None	None		NF1
5	M	46	Many (6)	None	None	Grandmother		NF1
6	F	54	Many (3)	Yes	None	Daughter, son	Dysrhythmic brain lesions	NF1
7	F	31	Many (7x4)	Yes	None	Mother	Tm. n. optici dex.	NF1

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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.

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