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Neurofibromatosis type I (von Recklinghausen's disease): A report of three cases

Kristina KOSTIĆ[1], Miroslav DINIĆ[1], Željko MIJUŠKOVIĆ[1], Lidija ZOLOTAREVSKI[2], Lidija KANDOLF-SEKULOVIĆ[1]*, Radoš ZEČEVIĆ[1]

[1]Department of Dermatovenereology, Center for Pathology and Forensic Medicine[2], Military Medical Academy Beograd
*Correspondence Lidija Kandolf-Sekulović, E mail: lkandolfsekulovic@gmail.com

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VERSITA

Abstract

Neurofibromatosis type I (NF1) is an autosomal dominant, multisystemic disease that usually affects the skin, nervous system and bones. Diagnosis is made by matching at least two of the following 7 diagnostic criteria: six or more café-au-lait macules over 15 mm in diameter, two or more neurofibromas, axillary and/or inguinal freckles, optic glioma, two or more Lisch's nodules (iris hamartoma), changes in the bones in the form of sphenoid dysplasia, thinning of the cortex of long bones and existence of neurofibromatosis in the first degree relatives. We report three patients, two men and a woman aged 18 to 33 years, in whom the first changes occurred at puberty, and there was no positive family history in any of them. All three patients had café-au-lait spots over 15 mm in diameter and numerous localized neurofibromas on the skin of the trunk and extremities that were histologically verified. In two patients, ophthalmic examinations recorded Lisch's nodules in the iris. In one of the patients, MRI of the head, revealed presence of oval lesions with diameters of 10-15 mm, which may correspond to neurofibromas, and in the other patient fibrous dysplasia of the femur and tibia were observed. Psychological testing in one patient revealed IQ at the lower limits of average (IQ 68). After the diagnosis of neurofibromatosis type I, the patients were given advice about the disease and a plan for the monitoring and control of possible symptoms, and also the possibility of genetic testing during pregnancy. A multidisciplinary approach is required for diagnosing and monitoring of patients with neurofibromatosis type 1.

Key words

Neurofibromatosis 1 + diagnosis + epidemiology + etiology + therapy; Genes, Neurofibromatosis 1; Signs and Symptoms;Disease Progression; Café-au-lait spots

Neurofibromatosis type I (NF1), von Recklinghausen's disease, is an autosomal dominant neurological and multisystem disease that usually affects the skin, nervous system and bones. The incidence of NF1 is 1 in 3000 live births. NF-1 is caused by changes (mutations) of a, relatively large gene on the long arm (q) of chromosome 17 (17q11.2). The gene regulates production of a protein known as neurofibromin, which is thought to function as a tumor suppressor. In about 50 percent of individuals with NF-1, the disorder results from spontaneous, sporadic mutations of the gene. In the other half, NF-1 is inherited as an autosomal dominant trait. First manifestations of disease usually appear in the early childhood.

Clinical diagnosis requires the presence of at least 2 of the following 7 diagnostic criteria:

1. Six or more café-au-lait spots or hyperpigmented macules larger than 5 mm in diameter in children under 10 years of age and to 15 mm in adults;
2. Two or more typical neurofibromas or one plexiform neurofibroma;
3. Axillary or inguinal freckles;
4. Optic nerve glioma;
5. Two or more Lisch nodules (iris hamartomas);
6. Sphenoid dysplasia or typical long-bone abnormalities;
7. A first-degree relative with NF1.

The earliest clinical findings are multiple *café-au-lait* spots. These may be present at birth, or may appear over time, frequently increasing in size and number throughout the lifetime. In adults, *café-au-lait* spots tend to fade and may be less obvious on clinical examination. Axillary or inguinal freckles are rarely present at birth, but appear during childhood through adolescence. Subcutaneous or cutaneous neurofibromas are rarely seen in young children, but appear over time in older children and adolescents. Deep-seated lesions can be detected only by palpation, whereas cutaneous lesions may appear initially as small papules on the trunk, extremities, scalp or face. Plexiform neurofibromas have more diffuse growth that can be locally invasive with bone erosion and pain. Lisch nodules occasionally can be seen with a direct or indirect ophthalmoscope, especially in individuals with light-colored iris.

Some of the more severe complications include visual loss secondary to optic nerve gliomas, spinal cord tumors, scoliosis, vascular lesions, and long bone abnormalities. Optic gliomas and both malignant and benign peripheral nerve sheet tumors are the most common malignancies arising in NF-1 patients (1). The treatment is symptomatic, such as surgical removal of neurofibromas if painful, or if they compromise a function due to the pressure.

Case reports (Table 1)

We report three patients, two males and one female, aged 18 to 33 years, who were after a commission of examination at our Department, diagnosed with neurofibromatosis type I.

In all three cases, the first change in the form of light brown spots and small soft nodules on the skin, occurred during puberty. There were no family members suffering from neurofibromatosis or other genodermatoses. The patients were in good general condition and without health problems.

All three patients had *café-au-lait* macules over 15 mm in diameter (Figures 1, 2) and a number of neurofibromas present on the trunk and extremities (Figures 3, 4), while in the female patient nodular changes were localized also on the scalp (Figure 5).

All three patients underwent the following diagnostic procedures: basic laboratory tests (SE, blood tests, liver enzymes, immunoglobulins, urinalysis),

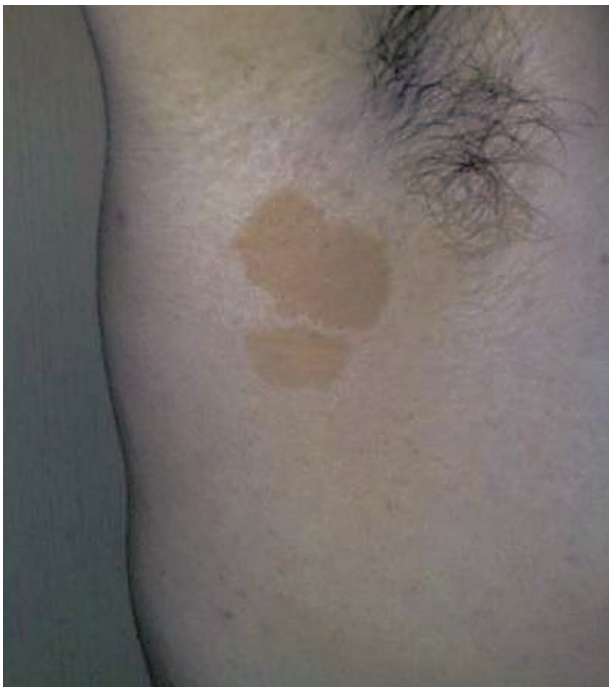

Figure 1. Patient No. 1. Two large *café-au-lait* macules on the trunk

biopsy of skin nodules with histopathological analysis, chest and long bones radiography, abdominal ultrasound, magnetic resonance imaging (MRI) of the head. Ophthalmological, neurological and orthopedic examinations were performed as well as psychological with testing IQ.

In all patients, neurofibromas were confirmed by histopathological examination (Figure 6). In two

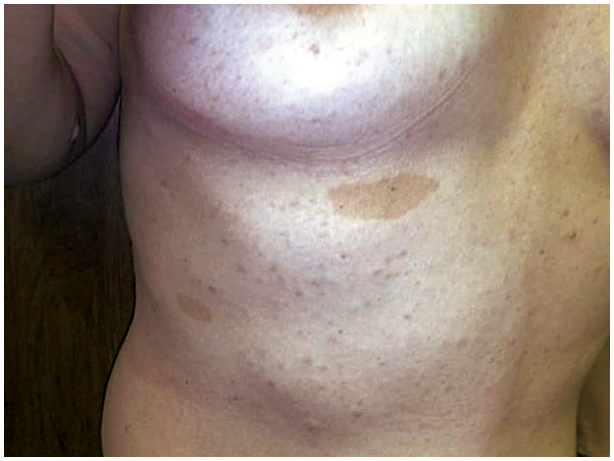

Figure 2. Patient No. 2. One large *café-au-lait* macula under the breasts, and a lot of small, brown neurofibromas

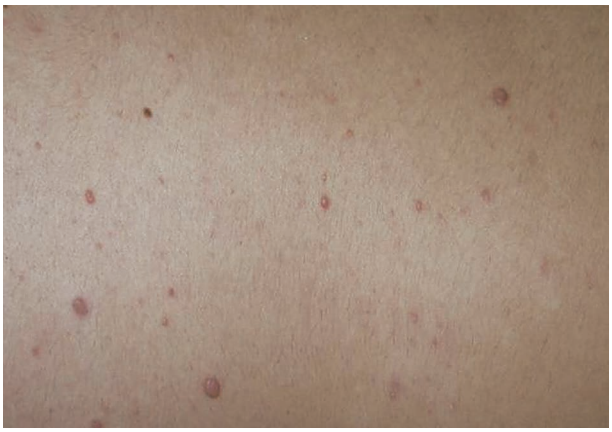

Figure 3. Patient No. 3. A lot of small neurofibromas on the trunk

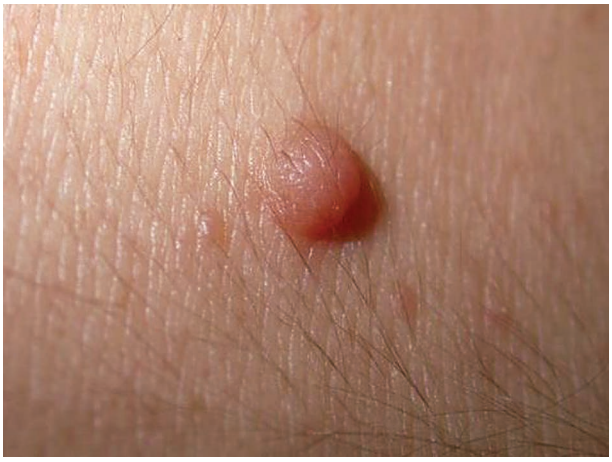

Figure 3a. Detail of fig. 3. One pink, soft neurofibroma on the back

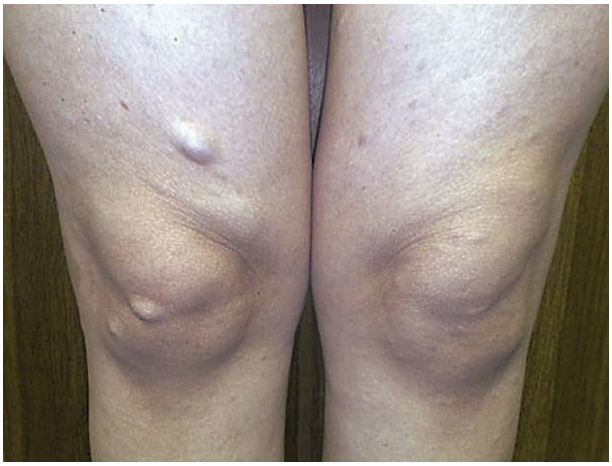

Figure 4. Patient No. 2. Deep neurofibromas on the legs

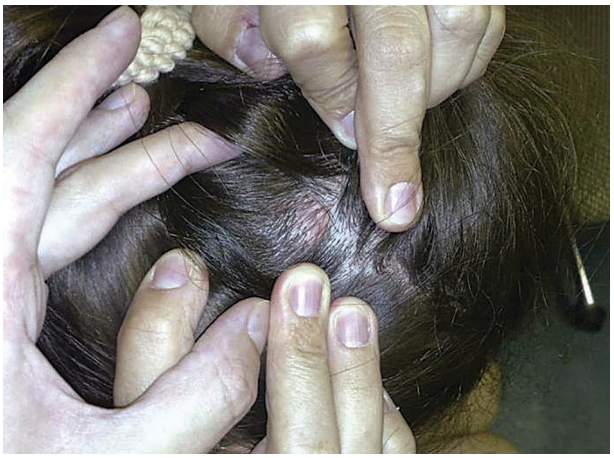

Figure 5. One big (> 2 cm in diameter) neurofibroma on the scalp of our female patient

patients, ophthalmologic examination revealed Lisch's nodules on the iris (Figure 7), while in one patient ophthalmological examination was normal. In one patient, brain MRI revealed intracranial presence of oval lesions 10-15 mm in diameter, which may correspond to neurofibromas. In other two patients brain MRI findings were normal.

In two patients there were no changes on the bones; in one patient in both the femur and the tibia fibrous dysplasia were observed. In two patients IQ (intelligence quotient) was average, 93 (IQ 80 -115) and in one under average, 68.

After examination the diagnosis of neurofibromatosis type I (Table 1), was made based

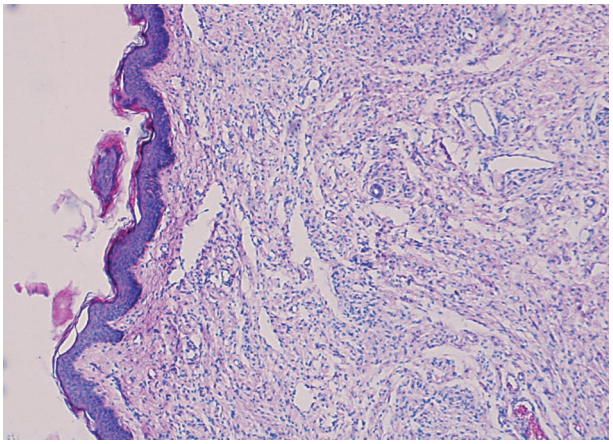

Figure 6. Histopathological analysis confirmed neurofibromas: well–differentiated tumors that contain elongated spindle-shaped cells as well as pleomorphic fibroblast-like cells (H&E x 100)

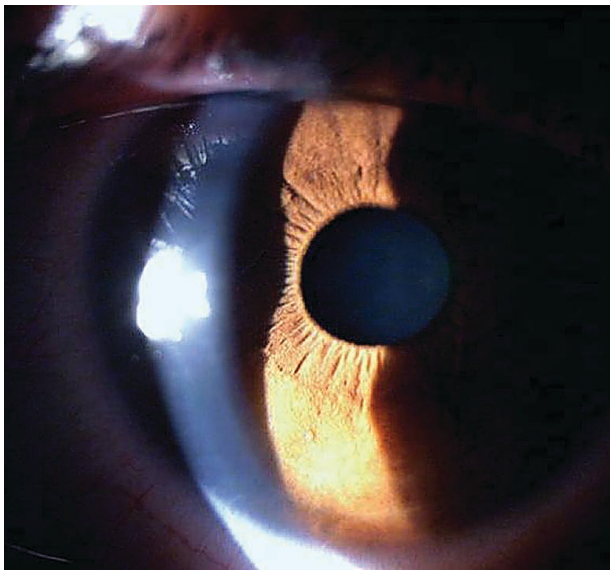

Figure 7. Lisch nodules of the iris

on diagnostic criteria. It was concluded that, for the time being, there were no indications for surgery. Patients were given advice about the disease and a plan for monitoring and control of possible symptoms.

Discussion

The estimated incidence of NF1 is 1 in 3000, and both sexes are affected equally with this autosomal dominant desease. The actual incidence of the disease may be higher, due to possible underdiagnosis of patients without family history of the disease, that represents cases with a new genetic event, i.e. mutation (2). None of our patients had positive family history of neurofibromatosis. The first manifestations of the disease usually occur in early childhood, but clinical manifestations may appear slowly over many years (3). In our patients first manifestations of the disease appeared during puberty, and the first manifestations of the disease were *café-au-lait* spots. Most ofen, the first manifestations of the disease appear before 10 years of age, but in about 30% of patients disease appears later.

Learning disabilities, with or without so called attention deficit hyperactivity disorder (ADHD), are found in approximately 40% of NF1 affected individuals (4). A much smaller percentage experiences more significant cognitive difficulties, such as mild or moderate mental retardation (4). One

Table 1. Diagnostic examination of three patients affected with NF1

	Patient 1	**Patient 2**	**Patient 3**
Age	23 years	33	18
Gender	male	female	male
Basic laboratory tests	Normal	Normal	Normal
Lisch nodules	+	-	+
Radiography of long bones	-	-	Femoral and tibial fibrous dysplasia
Brain MRI	3 intracranial neurofibromas	-	-
Psychology test	IQ 113	IQ 68	IQ 93

MRI, magnetic resonance imaging; IQ, intelligence quotient

of our patients with IQ near the lower average limits, also presented with speech disabilities. The occurrence of Lisch nodules appears to be age dependent; more than 95% of NF1–affected individuals older than 10 years have this iris finding (5). Two of our patients were diagnosed with Lisch nodules of the iris.

Histopathological analysis confirmed neurofibromas in all three of our patients. Neurofibromas were described as well–differentiated tumors that contained elongated spindle-shaped cells as well as pleomorphic fibroblast-like cells (Figure 7).

Clinical diagnosis requires presence of at least 2 of 7 criteria to confirm the presence of NF1. Two of our patients had 4 criteria (*café-au-lait* spots over 15 mm in diametar, neurofibromas, axillary freckles, Lisch nodules) and one patient had 5 criteria (*café-au-lait* spots over 15 mm in diametar, neurofibromas, axillary freckles, Lisch nodules and fibrosis of long bones). In one of our patients radiography of the long bones showed fibrosis of both femur and tibia bones, without any clinical symptoms.

Lifetime risks for ocurrence of benign and malignant tumors are increased in NF-1 affected individuals (6). Optic gliomas and both malignant and benign peripheral nerve sheet tumors are the most common malignancies arising in NF-1 patients (1).

No known medical therapies are beneficial to patients with NF1. Several clinical trials have been initiated, looking for medications that slow or stop growth of neurofibromas (farnesyl-transferases in combination with lovastatin, sorafenil, rapamycin complex 1 inhibitor, hyaluronan oligomers). So far, none of these medications has demonstrated significant benefit (4).

Treatment is symptomatic and most often it is surgical removal of neurofibromas for cosmetic reasons or if they cause complications. Some of the more severe complications are visual loss secondary to optic nerve gliomas, spinal cord tumors, scoliosis, vascular lesions, and long bone abnormalities.

It is necessary to inform patients with NF1 in reproductive period, that this genetic disease can be diagnosed during the prenatal period with specialized cytogenic tests (6). Only two clear correlations have been observed between particular mutant *NF1* alleles and consistent clinical phenotypes. The first is a whole *NF1* gene deletion associated with large numbers and early appearance of cutaneous neurofibromas, more frequent and more severe than average cognitive abnormalities, and sometimes somatic overgrowth, large hands and feet, and dysmorphic facial features. The second is a 3-bp in-frame deletion of Exon 17 (c.2970–2972 delAAT) associated with typical pigmentary features of NF1, but no cutaneous or surface plexiform neurofibromas (7).

Genetic testing is necessary to provide prenatal diagnosis and may be used as an adjunct to clinical diagnosis in cases with atypical presentation or in which the child is too young to have developed most characteristic features. A multi-step mutation detection protocol that identifies 95% of pathogenic *NF1* mutations in individuals fulfilling the NIH diagnostic criteria is available (8). This protocol, which involves analysis of both mRNA and genomic DNA, includes real-time polymerase chain reaction, direct sequencing, microsatellite marker analysis, multiplex ligation-dependent probe amplification, and interphase fluorescence in situ hybridization. Because of the frequency of splicing mutations and the variety and rarity of individual mutations found in people with NF1, methods based solely on analysis of genomic DNA have lower detection rates. Testing by fluorescence in situ hybridization, multiplex ligation dependent probe amplification, or analysis of multiple single nucleotide polymorphisms (SNPs) or other polymorphic genetic markers in the *NF1* genomic region is sometimes performed to look just for whole *NF1* gene deletions when the "large deletion phenotype" is clinically suspected. Whole *NF1* gene deletions occur in 4% to 5% of individuals with NF1 (9).

Conclusion

In conclusion, neurofibromatosis 1 is a relatively rare autosomal dominant disease. For individuals diagnosed with NF1 routine examinations should focus on the potential complications. Annual examinations permit early detection of complications, decreasing morbidity and improving quality of life. Annual eye examinations are important in early detection of optic nerve lesions. Removal of neurofibromas for medical or cosmetic reasons is one of the most common procedures in individuals with NF1. In most cases, symptoms of NF1 are mild, and patients live normal and productive lives.

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Neurofibromatoza tip I (von Recklinghausenova bolest): prikaz tri slučaja

Sažetak

Uvod: Neurofibromatoza tip I (NF1) je autozomno dominantno, nasledno neurogeno, multisistemsko oboljenje koje najčešće zahvata kožu, nervni sistem i kosti. Dijagnoza ovog oboljenja se postavlja ukoliko su ispunjena najmanje dva od sledećih 7 dijagnostičkih kriterijuma: šest ili više *café au lait* makula promera preko 15 mm, dva ili više neurofibroma, aksilarne i/ili ingvinalne makule, optički gliom, dva ili više Lisch-ovih nodula (hamartromi dužice), promene na kostima u vidu sfenoidne displazije, istanjenje korteksa dugih kostiju sa ili bez pseudoartroze i postojanje neurofibromatoze kod rođaka prvog stepena.
Prikaz bolesnika: Prikazujemo tri bolesnika, dva muškarca i ženu starosti od 18 do 33 godine kod kojih je, nakon učinjenog kliničkog ispitivanja postavljena dijagnoza neurofibromatoze tipa I. Kod sva tri bolesnika prve promene u vidu svetlosmeđih mrlja i sitnih mekih čvorića na koži javili su se u dobu puberteta. Sva tri pacijenta imala su *café-au-lait* makule promera preko 15 mm i brojne neurofibrome lokalizovane na koži trupa i ekstremiteta koji su patohistološki verifikovani. Kod dva pacijenta oftalmološkim pregledom evidentirani su Lischovi noduli na dužici, dok je kod jednog pacijenta pregled pomoću nuklearne magnetne rezonancije glave ukazao na endokranijalno prisustvo ovalnih lezija dijametara od 10-15 mm koji mogu odgovarati neurofibromima, a rendrengrafijom na oba femura i obe tibije uočena fibrozna displazija.
Lečenje: Terapija neurofibromatoze tipa I je simptomatska i predominantno hirurška uz adekvatno praćenje i multidisciplinarni pristup bolesniku i odgovarajuće genetsko savetovanje.

Ključne reči

Neurofibromatoza tip 1 + dijagnoza + epidemiologija + etiologija + terapija; Geni neurofibromatoze tipa 1; Znaci i simptomi; Tok bolesti; Pigmentne fleke boje bele kafe