

# Neurofibromatosis Type 1 in Pregnancy

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## ABSTRACT

*The report presents two cases of neurofibromatosis type 1 one previously known and one detected during pregnancy. It describes how the disease was detected and diagnosed, and what was the outcome of pregnancies. This is the first case of prenatal neurofibromatosis type 1 diagnosed in our clinic.*

**Key words:** pregnancy, neurofibromatosis, NF1, prenatal diagnosis

## Introduction

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders with an incidence of 1 in 3,500 live births. It is an autosomal dominant condition with a wide range of clinical manifestations. There are at least 250 unique NF1 mutations reported so far. Specific prenatal diagnosis is only possible through an indirect linkage analysis in families with a previously identified mutation. To date, only limited information is available on pregnancy in women with NF1, but current obstetrical literature indicates that this group of women has increased complications associated with pregnancy.

## Case Reports

The patient was a nulliparous, 32-year-old woman who was referred to our Prenatal Care Unit to confirm intrauterine growth restriction. Clinical history and physical examination did not reveal any relevant information. The first ultrasound was made in our Outpatient Sonography Unit at 25 weeks of gestation, when the diagnosis of NF1 was made.

She was admitted to our Clinic at 33 weeks of gestation, after a physical examination that showed inappropriate distance from uterine fundus to symphysis. Ultrasound examination confirmed intrauterine growth retardation (IUGR) diagnosis. NF1 was suspected when the obstetrician saw café-au-lait spots and multiple fibromas all over her body. From her family history it is important to mention that her mother passed away from brain tumor, arising suspicion of brain malignancy as a form of genetic disease. She was a single child, and could not provide any

information on other family members that we could link with clinical symptoms and signs of a disease.

The patient herself was never seriously ill, save for allergic reaction to penicillin. Her intellectual capabilities were below average, what can be interpreted as a sign of a disease. She underwent dermatological, ophthalmologic, head and neck examinations, as well as a CT scan of the brain. Dermatological examination showed multiple café-au-lait spots and all over her body, with the biggest one on the back of her neck. Multiple fibromas were also spread all over the body, with the most visible change on the left side of her abdomen. Other examination results were normal.

In addition to IUGR the ultrasound of the fetus, showed oligohydramnios. It is the case when the volume of amniotic fluid is far below the normal limits and it can occasionally be reduced to only a few mL of viscid fluid. Oligohydramnios is usually associated with adverse conditions of the fetus, mother, or placenta.

Color Doppler showed increased resistance index (RI) of umbilical cord artery and medial cerebral artery (ACM).

After administering 1x12 mg of dexamethason for two days, the pregnancy was terminated by cesarean section in the gestational age of 34 weeks. A 1400/41 neonate was born, Apgar score 6 / 6 / 7. A neonate was immediately admitted in the Neonate Intensive Care Unit.

Other patient was a 24-year-old nulliparous woman affected by NF1 and with a known familial history of a disease. Her younger sister and father had heavy clinical symptoms of NF1. The older sister, two sons and her mother, who died of breast cancer had no signs of the dis-

ease. The whole family underwent genetically testing, which showed that beside her younger sister and the father, our patient was also affected by NF1. She had but a few café-au-lait spots on her body, but had ophthalmologic lesions and a change on the optical nerve which is likely to be optic glioma. She underwent genetic counseling and opted for prenatal testing, although prenatal diagnosis can only identify whether a fetus will develop NF1, and not whether serious complications will occur. Amniocentesis was performed at 16 weeks of gestation and total DNA was directly extracted from the sample. Blood samples of all family members and the husband were collected and linkage analysis was carried out. Karyotypic analysis of all blood samples and fetal origin (cell culture from amniotic fluid) was performed via polymorphic markers of gene NF1 (exon 5 RsaI polymorphism, IVS38GT53.0, IVS27AC28.4 and Alu polymorphism of intron 27). Genomic analysis has identified the same haplotype from four samples (father, two sisters and fetus), which is enough to make the diagnosis of NF1. After finding out about the results, our patient decided to have an abortion, which was induced by prostaglandins at 20 weeks of gestation.

## Discussion

Neurofibromatosis type 1 (NF1, peripheral neurofibromatosis, von Recklinghausen disease) is one of the most common genetic disorders occurring once in every 4,000 births. It is an autosomal dominant condition which has markedly variable clinical expressions, with manifestations ranging from mild cutaneous lesions like café-au-lait spots and axillary freckling to plexiform neurofibromas, optic gliomas, bony abnormalities, pseudoarthrosis and malignancies<sup>1</sup>. Some people with NF1 also have other manifestations, such as learning disability and macrocephaly. About two thirds of the people who have NF1 type inherit the disease from one of the parents and the risk for each child is estimated to about 50%. The remaining third of the population develops this condition due to spontaneous mutation. It seems that most of the NF1 mutations reported so far (at least 250) are unique.

Neurofibromatosis type 2 (NF2, central neurofibromatosis) is characterized by bilateral vestibular schwannomas. NF2 is also an autosomal dominant disorder with an incidence of 1 in 40,000 persons. As their very different clinical manifestations suggest, NF1 and NF2 are caused by two entirely different genes<sup>2</sup>. The NF1 gene on chromosome 17 codes for a huge protein named neurofibromin, and was first cloned in 1990. Its function remains unclear, although it does contain a single domain

with GTPase activating activity. The NF2 gene on chromosome 22 was first cloned in 1993 and given the snazzy name merlin. The exact function of merlin is also unknown, but it is highly homologous to a family of cytoskeleton – associated proteins including moesin, ezrin, radix and talin.

Many authors have suggested that pregnancy complications were more common in women with NF1<sup>3</sup>. To date, only limited information is available on pregnancy in women with NF1. Published case reports point to an association with intrauterine growth restriction, eclampsia, oligohydramnios, stillbirth, pregnancy-induced hypertension, preterm labor, spontaneous labor and growth of neurofibromas with regression in size after delivery<sup>4</sup>. With respect to NF1 changes during pregnancy, the majority of women report the development of new neurofibromas, the growth of existing neurofibromas or both, indicating that pregnancy may promote neurofibroma growth. However, the reported initial appearance of neurofibromas during pregnancy, regression of some neurofibromas immediately after termination of pregnancy and the presence of estrogen receptors in selected neurofibromas in some women support the belief that this growth is not purely coincidental<sup>4</sup>.

On the other hand, some authors suggest that the only obstetrical complication they observed was somewhat more frequent cesarean section delivery.

Some recommend early termination of pregnancy and sterilization of women because of the adverse effect of the pregnancy on the course of the disease, poor pregnancy outcome and the possibility of transmission to the fetus. This decision, however can only be made by the patient.

Whether she is either willing to continue or terminate pregnancy, it is our obligation, as an obstetrical team to help her in the best way possible. On the other hand, we are also obliged to make as accurate prenatal diagnosis as possible. Since the disease is causing mutations that are dispersed throughout the gene, prenatal diagnosis usually relies on linkage analysis of family members and rarely on direct characterization of the mutation. The extreme variability of the phenotypic expression of the NF1 gene makes it very difficult for NF1 families to decide whether to have children or not, as molecular diagnosis cannot predict clinical expression of the disease<sup>5</sup>. The psychological management of would-be parents is therefore very sensitive.

With these case reports, we wanted to describe the diagnostic possibilities, management of pregnancies and dilemmas in every-day clinical practice of a gynecologist.

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## **NEUROFIBROMATOZA TIP 1 U TRUDNOĆI**

### **S A Ž E T A K**

Izložili smo dva slučaja neurofibromatoze tip 1 (NF1) u trudnoći, jedan je slučaj neurofibromatoze poznat od ranije, a drugi dijagnosticiran u trudnoći. Opisujemo dijagnostiku neurofibromatoze, način izvođenja i mogućnosti prenatalne dijagnostike, kao i ishode ovih trudnoća. Ovo je prvi slučaj prenatalno dijagnosticirane NF1 u našoj Klinici.