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Case report

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Neurofibromatosis-1 and Pregnancy: Case report

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Abstract

Introduction: Neurofibromatosis type-1 (NF-1) is one of the most common genetic diseases following an autosomal dominant inheritance pattern. Maternal and fetal complications have been reported. **Purpose:** To present a very interesting and rare case report regarding neurofibromatosis – 1 (NF-1) in pregnancy and to create a complete review concerning this genetic disease. **Materials and Methods:** Articles were identified through electronic databases; no date or language restrictions were placed; relevant citations were hand searched. The search was conducted using the following terms: neurofibromatosis, neurofibromatosis type-1, pregnancy. **Case presentation:** We present a case of a 36-year-old nulliparous pregnant woman affected by NF-1. She presented with café-au-lait spots and cutaneous/subcutaneous neurofibromas, progressively increasing in size and number. The unique obstetric complication was placenta previa, diagnosed in the second trimester. A caesarean section was performed on the 36th week. A healthy male neonate unaffected by NF-1 was born. Both post-operative period and puerperium were uneventful. **Conclusions:** This case report highlights the fact that a normal pregnancy outcome can occur in pregnant women with NF-1 and proper counselling should be in place so that informed decisions can be made by future parents.

Key words: neurofibromatosis, neurofibromatosis type-1, pregnancy

Introduction

Neurofibromatosis type-1 (NF-1) is an autosomal dominant disorder with variable clinical manifestations, such as café-an-lait spots, axillary freckling, cutaneous neurofibromas and iris hamartomas (Lisch nodules), occuring in most patients. It is characterized by different types of mutations of the NF-1 gene[1, 2]. Approximately 50% of the NF-1 gene mutations result from de novo mutations[3-5]. The reported incidence of neurofibromatosis (NF) in pregnancy varies from 1:5000 to 1:18.500[6].

The management in cases of NF-1 complicating pregnancy is crucial since there is limited information available on pregnant women with NF-1. Current obstetrical bibliography reports that this group of women has an increased risk of complications. NF-1 is associated with fetal complications, such as spontaneous miscarriage, preterm delivery, in-

trauterine growth retardation, and stillbirths, as well as maternal disease aggravation (hypertensive and cerebrovascular complications)[7,8] We present a case of NF-1 complicating pregnancy and a short review of the literature. (Table 1)

Table 1. Review of literature concerning all NF-1 cases reported.[6, 8-14].

Review of literature					
Study	**Study purpose**	**Sample Size**	**Maternal Manifestations**	**Maternal Complications**	**Fetal Complications**
Weissman A, Jakobi P, Zaidise I, Drugan A. 1993. Neurofibromatosis and pregnancy. An update. J Reprod Med. 1993 Nov;38(11):890-6.	To present their experience with 34 pregnancies in 9 NF patients who delivered at their medical center.	9 cases	café-au-lait spots multiple fibromas all over the body	none	- spontaneous abortions of first-trimester (20.7%) - stillbirths (8.7%) -intrauterine growth retardation (13.0%) - high rate of cesarean section (26%)
Terry AR, Barker FG, Leffert L, Bateman BT, Souter I, Plotkin SR. 2013. Neurofibromatosis type 1 and pregnancy complications a population-based study. Am J Obstet Gynecol. 2013 Jul;209(1):46.e1-8.	To determine whether vascular and other complications are more common in pregnant with NF-1	1553 cases (identified among 19 million pregnancy-related admissions . between 1988 and 2009)	- café-au-lait spots - multiple fibromas all over the body	- gestational hypertension - preeclampsia - cerebrovascular disease	- intrauterine growth-restriction - preterm labor by cesarean delivery
Posma E, Aalbers R, Kurniawan YS, van Essen AJ, Peeters PMJG, van Loon AJ. 2003. Neurofibromatosis type I and pregnancy: a fatal attraction? BJOG: An International Journal of Obstetrics and Gynaecology May 2003, Vol. 110, pp. 530 – 532	To present the development of malignant schwannoma during pregnancy in a patient with NF-1 .	1 case	- typical neuro-cutaneous signs, such as multiple neurofibromas - café-au-lait spots a 3-cm mass near the aortic arch (interpreted as a benign neurofibroma)	- thoracic pain - a 5-cm mass in the upper mediastinum (a large infiltrating mass in the-foramina of the 3rd and 4th thoracic vertebrae without infiltration of the spinal cord) - a malignant nerve sheath tumour grade III (not radically resected) - photon radiotherapy- - tumour-free for 3 years - 2nd pregnancy after ovulation induction - a short episode of sudden-onset thoracic and abdominal pain (subsided spontaneously)	- termination of the 1st pregnancy at 20 weeks of gestation - delivery of the second child at 40 weeks of gestation

				- in the postpartum period, severe abdominal pain recurred and became progressive (recurrent malignant schwannoma) - the patient passed away 3 months after delivery.	
Kosec V and Márton I. 2006. Neurofibromatosis Type 1 in Pregnancy. Coll. Antropol. 30 (2006) 1: 247–249	To present two cases of neurofibromatosis type 1, one previously known and one detected . during pregnancy	2 cases	- café-au-lait spots - multiple fibromas all over the body - ophthalmologic lesions	optic glioma	- intrauterine growth retardation - preterm delivery by cesarean section (1st case) - termination of the pregnancy at 20 weeks of gestation (2nd case)
Jain K, Sharma M, Mangal H 2015. Neurofibromatosis in pregnancy: study of 2 cases. Jain K et al. Int J Reprod Contracept Obstet Gynecol. 2015 Apr; 4 (2): 483-485	To present two cases of NF, to illustrate how women with NF have increased complications associated with pregnancy and to describe the diagnostic possibilities, management of pregnancies and dilemmas in everyday clinical practice of a gynecologist	2 cases	- pallor - icterus - multiple big and small fibromas all over the body - numerous large and small neurofibromas all over the body with a big plexiform mass hanging out from right eye	- generalized tonic -clonic seizure on 4th postop day due to a meningioma - cholelithiasis	- placenta praevia grade III - severe oligohydramnios (AFI 3cm) - preterm delivery by cesarean section
Dahiya S, Mukherjee S, Premi HK. 2016. Neurofibromatosis in Pregnancy. International Journal of Advanced & Integrated Medical Sciences, April-June 2016;1(2):91-92	To present a rare case report with NF in pregnancy, in which transmission to the baby has also occurred.	1 case	skin lesions all over the body	vaginal bleeding	- placenta praevia - delivery by cesarean section - neurofibromatosis lesions on the newborn on the 3rd day of delivery
Xiong M, Gilchrest BA, Obayan OK. 2015. Eruptive neurofibromas in pregnancy. JAAD, Volume 1, Issue 1, Pages 23–24	To report a patient who had multiple neurofibromas beginning in the 3rd month of her 1st pregnancy leading to a diagnosis of NF1.	1 case	- dozens of new papules and nodules, progressively increasing in size and number - 3- to 10-mm dark brown hyperpigmented papules and soft nodules located primarily on the back, chest, abdomen, and arms - numerous 1- to 2-mm hyperpigmented freckles on the trunk, face, and axillae	none	none

			- more than 6 café-au-lait macules larger than 1.5 cm on the trunk - a dark brown hyperpigmented plaque on her right thigh (plexiform neurofibroma) mild scoliosis		
Harshini V, Vidyashree JB, Renuka R. 2014. A pregnant woman with NF-1. ejbps, 2015, Volume 2, Issue 1,170-173	To report a case of woman with NF-1, who had conceived spontaneously and her pregnancy outcome	1 case	- neurofibromas all over the body café-au-lait spots all over the body	none	none

Case presentation

A 36-year-old nulliparous pregnant woman affected by NF1 presented in the outpatient department of "Alexandra" Maternity Hospital, Athens. She had no previous family history of this disorder. On clinical examination, she had café-au-lait spots and multiple lesions of NF of variable sizes (cutaneous and subcutaneous), which – according to the patient – had been increasing in size and number (Figure 1). The latest magnetic resonance imaging exam (MRI) of the brain and spine was performed two months prior to current pregnancy and revealed demyelination lesions of the brain and arteriovenous malformation (AVM) of subarachnoid space of the cervical spine. On admission, the cardiovascular assessment did not reveal hypertension or any other cardiovascular disease and neither did the neurosurgical assessment. The patient underwent typical prenatal screening examinations. Genetic counselling was also offered to the couple regarding prenatal invasive procedures (chorionic villus sampling or amniocentesis). During pregnancy, no obstetric complications occurred apart from the diagnosis of placenta previa during the 18-23 weeks' ultrasound scan. The pregnancy was uncomplicated until the 36th week of gestation when a caesarean section was performed due to spontaneous onset of labor and the presence of placenta previa. It was performed under general anesthesia because of the presence of spinal AVM. A healthy male neonate was born weighing 2650gr. The neonate was admitted in the Neonate Intensive Care Unit for 3 days. Both the post-operative period and the puerperium were uncomplicated. The neonate was not affected by NF I.

Discussion

Neurofibromatosis type 1 is one of the most common genetic disorders, caused by mutations of the NF-1 gene on chromosome 17. This condition can either be inherited, or occur de novo as a result of spontaneous mutations[7] The clinical manifestations of NF-1 range from mild cutaneous lesions and axillary freckling to plexiform neurofibromas, optic gliomas, bony abnormalities, pseudoarthosis and malignancies[9, 15]. About two thirds of the affected population with NF-1 have parents with NF-1 and inherit the disease from one of them. The risk for each child is estimated to be about 50%. The remaining third of the population develops this condition due to spontaneous mutations. It seems that most of the NF-1 mutations reported so far are unique[10].

Many authors have suggested that pregnancy complications are more common in women with NF-1. So far, only limited information is available on

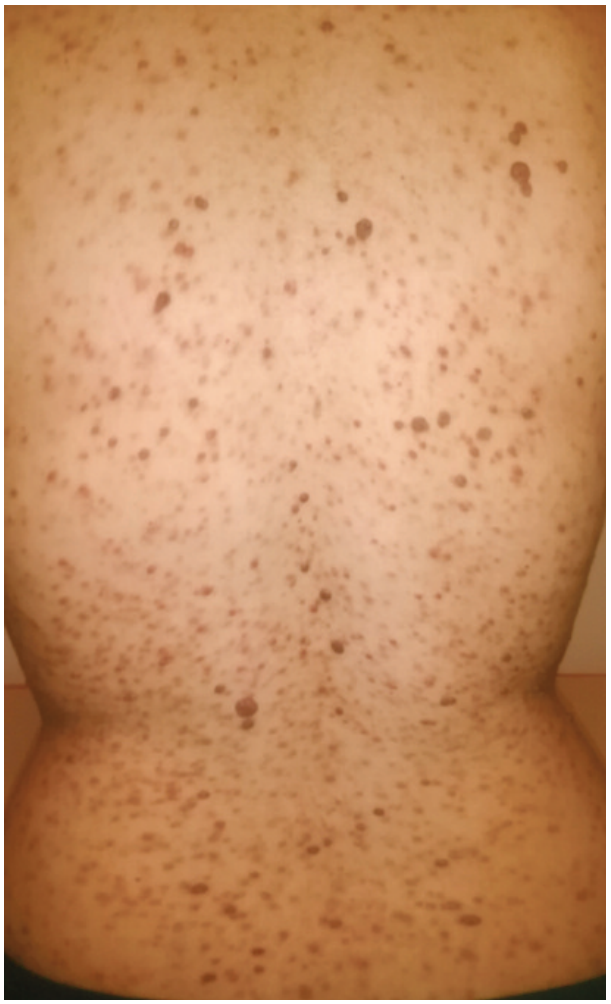

Figure 1. Café-au-lait spots and multiple lesions of neurofibromatosis of variable size.

pregnancy in women with NF-1. Published case reports demonstrate the association with intrauterine growth restriction, eclampsia, oligohydramnios, stillbirth, pregnancy-induced hypertension and preterm labor[6-8, 10]. Furthermore, pregnancy tends to increase the number and size of cutaneous neurofibromas in women through pregnancy, with an apparent decrease in size subsequent to delivery[16]. Some neurofibromas contain oestrogen receptors, suggesting the existence of a correlation between the increase in number and size of neurofibromas and the increase in serum oestrogen levels during pregnancy[17]. An increased rate of cesarean section is also reported. This could be attributed to fetal distress, malpresentations and cephalopelvic disproportion due to undiagnosed pelvic neurofibromas and pelvic contractures, including cases of kyphoscoliosis affecting the lower spine (sequelae of NF-1)[16]. Many authors suggest to proceed to early termination of pregnancy and sterilization of women because of the adverse effect of pregnancy on the course of the disease, poor pregnancy outcome and the possibility of transmission to the fetus. This decision can only be made by pregnant women [10, 18].

The case report that we present is the fourth study in literature suggesting that NF-1 may not be associated with significant obstetric complications and may have normal pregnancy outcome[6, 16, 19]. The present case shows that a normal obstetric outcome could be expected in pregnant women with NF-1.

Clinicians have to make an accurate prenatal diagnosis, if possible. The extreme variability of the phenotypic expression of the NF-1 gene makes it very difficult for NF-1 families to decide whether to have children or not, as molecular diagnosis cannot predict clinical expression of the disease[20]. The psychological management of parents should therefore be very sensitive. Clinicians must discuss with parents the diagnostic possibilities and dilemmas during counseling and should keep in mind that a normal obstetric outcome could also occur in pregnant women with NF-1.

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