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Neurofibromatosis type 1 and pregnancy outcome: A case report

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Abstract

Background: Neurofibromatosis is a genetic disorder with high variability of clinical expression. Cutaneous manifestations such as café-au-lait spots, freckling patterns, and dermal neurofibromas, are the most distinguishable and common signs appearing in the vast majority of individuals with NF-1. Instances where a patient is both pregnant and affected with neurofibromatosis are less common and the information about the maternal-fetal outcomes are mainly from case reports in the literature.

Case presentation: A 33-year-old multiparous pregnant patient affected by NF-1 presented to the Obstetrics and Gynecology Clinic in Prishtina in Kosovo in the 36th week of pregnancy. The patient displayed signs of NF-1 exemplified by the growth of existing neurofibromas and the development of new ones. In addition, the patient experienced a placental abruption which is a life-threatening obstetrical complication rarely reported in the literature as a complication associated with maternal NF-1. An emergent cesarean section was performed and a healthy neonate unaffected by NF-1 was born.

Conclusions: Pregnant patients with NF-1 are prone to the worsening of NF-1 symptoms and obstetrical complications. Increased antenatal care for these patients is recommended to ensure the well-being of the mother and fetus.

Key words: Neurofibromatosis, pregnancy, outcome

Introduction

Neurofibromatosis type 1 (NF-1) – also known as von Recklinghausen disease – is a genetic disease caused by mutations of the NF-1 gene located in the 17th chromosome. The NF-1 gene regulates the production of the neurofibromin protein which acts

as a tumor suppressor. Individuals with NF-1 lack the tumor suppressor function of neurofibromin and they develop multiple benign tumors of the nerves and skin (neurofibromas). Approximately 50% of individuals with NF-1 inherit the mutation from

their parents as an autosomal dominant trait and the other approximately 50% develop the disorder from spontaneous (de novo) mutations of the gene with no known reason.

The reported incidence of NF-1 is about 1 in 2,600 to 3,000 individuals.¹ Although NF-1 is a multisystem disorder the most common clinical manifestations are multiple abnormal skin pigmentations (café-au-lait spots), freckling in the armpits or groin area, and multiple tumoral growths on or under the skin called neurofibromas.²

Pregnancy in individuals with NF-1 may worsen symptoms and signs of the disease, however, the correlation of NF-1 and obstetrical complications is still a matter of dispute.³ In this case report we present a pregnancy with NF-1 which is complicated with placental abruption. The following case report conforms to the Care – Guidelines.

Case Presentation

A 33-year-old multigravida, para 3 at 36 weeks and 5 days gestation, affected by NF-1, was admitted at the Obstetrics and Gynecology Clinic in Prishtina due to complaints of a sudden onset of abdominal pain. Patient family history was positive for NF-1 in two previous generations including her Grandmother and her Aunt. The patient's siblings, two brothers and two sisters, were not affected. The patient was diagnosed with NF-1 in early adolescence when abnormal skin pigmentation (café-au-lait spots) and tumoral growths on the skin appeared. The skin condition caused aesthetic changes and per self-report negatively affected the patient's social life. The patient did have two previous pregnancies that were unremarkable and with vaginal deliveries without complications.

During the second and third trimester of the third and current pregnancy, the patient noticed development of more neurofibromas and gradual growth of existing ones. Two neurofibromas approximately

3-4 centimeters in size located in the inner side of the left thigh continued growing during pregnancy to approximately 13x10 centimeters. These tumor masses caused discomfort and pain.

On examination the patient had a large number of abnormal skin pigmentations (café-au-lait spots) and multiple skin neurofibromas on the face, chest, abdomen, back and extremities (Figure 1).

On the skin on the inner side of the left thigh there were two prominent tumor masses each with dimensions about 13x10 centimeters (Figure 2). These tumors, on palpation, were soft, mobile, and slightly painful.

An ultrasound examination was performed and normal sonographic findings were confirmed. These were consistent of a singleton near term pregnancy with a live fetus, amniotic fluid index at the 60th percentile, and posterior placenta without retroplacental hematoma. For further evaluation of the



Figure 1. Multiple cutaneous neurofibromas and café-au-lait macules.



Figure 2. Large tumor masses in the extremities.

fetus' wellbeing the patient was placed in cardiocotographic monitoring.

While on CTG monitoring the patient complained of intense abdominal pain followed by profuse genital bleeding. FHR abnormality and uterine tenderness led to clinical confirmation of placental abruption. The patient underwent emergent cesarean section and a healthy newborn male weighing 2760 grams with an Apgar Score of 5/6 was born. The post cesarean and postpartum period was without complications for both mother and newborn.

Discussion

Neurofibromatosis type 1 is a genetic disorder caused by the mutations of the NF-1 gene and this disorder can be caused by de novo spontaneous mutations or it could be inherited.⁴ De novo mutations account for about 50% of cases of NF-1 while the other 50% of cases are inherited by the autosomal dominant trait.⁵ The case presented here represents an inherited disorder based on positive family history in two previous generations.

The most characteristic clinical manifestations of the NF-1 are abnormal skin pigmentation (café-

au-lait discoloration), development of multiple benign tumors of nerves and skin (neurofibromas), and freckling in the armpits and groin area. Other manifestations of NF-1 may include visual, skeletal, and mental abnormalities.⁶ The existing literature indicates aggravation of the clinical manifestations of NF-1 during pregnancy which was experienced by the patient in this case study. Additionally, a study conducted by Dugoff et al. (1996) reported that 60% of the 105 pregnant subjects affected by NF-1 reported the growth of new neurofibromas and 52% reported enlargement of existing neurofibromas.⁷ These findings also align with the experience of the patient in this case study where both enlargement and development of new neurofibromas occurred.

Conflicting data exists regarding the possibility of obstetrical complication in pregnant patients with NF-1. Nevertheless, in the case being presented complication did occur. In the 36 + 5 week of pregnancy placental abruption occurred, due to which patient underwent emergent cesarean section. This evidence contributes to the existing data that suggests the risk of obstetrical complication in pregnant women with NF-1 and the increase in likelihood for cesarean delivery.^{8,9,10}

Given the rarity of association between pregnancy with NF-1 and placental abruption, the underlying mechanism that may explain this correlation warrants further research. A number of studies, however, have shown that an increased level of specific micro RNA-s in pregnancy plays a functional role in the enlargement and progression of neurofibromas and also the development of numerous obstetrical complications related to the placenta including placental abruption.^{11,12,13} A method of possibly using the aforementioned micro RNA-s as a biomarker to follow up on pregnancies at risk such as cases with NF-1 and for early detection of complications in such cases is still in development. While this research is underway, close follow up on pregnancies at risk is

suggested as it could significantly improve maternal and fetal outcomes.¹⁴

Conclusions

Existing literature and data in this case report corroborate the conclusion that pregnant patients with NF-1 are prone to the worsening of NF-1 symptoms such as the growth of new neurofibromas and the enlargement of existing ones. Furthermore, obstetrical complications are likelier in patients with NF-1 which may require subsequent emergent cesarean section. In summary, due to these findings, increased antenatal care and ongoing research is recommended in order to ensure the well-being of the mother and fetus.

Authors contribution

V.A.I.: conceptualization, study design, data collection, analysis, literature search, writing the manuscript. H.L.: study design, analysis, writing the manuscript. L.I.: literature search, analysis, writing. : A.E.M.: writing-review& editing

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Study registration

N/A.

Disclosure of Interests

The authors declare that there are no conflicts of interest related to this article.

Ethical Approval

This study was approved by the Ethics Committee of the Medical Faculty, University of Prishtina "Hasan Prishtina" (approval number 10801).

Informed consent

An informed written consent was obtained from the patient before describing the case-report.

Data sharing

Data are available under reasonable request to the corresponding author.

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