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Exacerbation of neurofibromatosis and adverse pregnancy outcome. A case report and review of the literature

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Summary

Neurofibromatosis type 1 (NF-1) is a condition which has markedly variable clinical expressions. During pregnancy the manifestations of the disorder are exacerbated, and as a result, mild to severe maternal and fetal complications may appear. A case of neurofibromatosis affected by pregnancy is presented. The mother presented with high arterial blood pressure, renal insufficiency, and visual impairment. At the same time the baby was born with growth restriction and cerebellar haemorrhage. Altogether, NF1 is associated with increased maternal and fetal morbidity in pregnancy but not with increased maternal mortality.

Key words: Neurofibromatosis; Obstetric complication; Visual impairment.

Introduction

Neurofibromatosis type 1 (NF1) is a common genetic disorder of the neural crest tissue with an incidence of one in 3,500 live births. Half of the cases are due to an autosomal dominant mutation of the NF-I gene on chromosome 17q codes for neurofibromin protein, the other half are new mutations arising in patients with unaffected parents. Neurofibromatosis type 2 is an autosomal dominant condition that is rarely associated with severe pregnancy complications. Specific prenatal diagnosis is only possible through an indirect linkage analysis in families with a known identified mutation.

In current literature only a few studies suggest that NF1 may not be associated with significant obstetric complications and may have normal pregnancy outcome [1-3]. In the present authors' unit, out of 2,800 deliveries in the last three years, one case of NF1 was reported.

Case Report

A white nulliparous pregnant woman 41 years of age, was referred to the authors' Unit at 27 weeks of gestational age due to increased arterial blood pressure (180/90 b/m) and indication of intrauterine growth restriction after a physical examination that revealed inappropriate distance from uterine fundus to symphysis. She was diagnosed with NF1 (Von Recklinghausen) disease at the age of 18 months, due to spontaneous mutation. All family members were healthy and unaffected from this condition. At the age of 20 because of unexplained headaches, she had an MRI where glioma was diagnosed on the optic chiasm with involvement of the left optic nerve. In 2011 she became pregnant for the first time, but due to severe renal insufficiency the pregnancy was terminated by C-section at 25 weeks. After the first pregnancy the patient underwent several operations due to formation of new neurofibromas on the left upper extremity. In 2015 she had a spontaneous pregnancy. The pregnancy was dated according to the CRL. The nuchal scan (11-13 weeks) indicated a low risk for trisomies. At 20 weeks she had a routine anomaly scan where the fetus appeared anatomically normal but smaller for given gestational age by two weeks. Aside from this, the hyperechogenic bowel was prominent. Moreover, uterine arterial Doppler was significantly increased (right uterine artery PI 1.82, left uterine artery PI 2.18). TORCH was negative. The couple decided to have amniocentesis to exclude trisomies. The procedure showed a normal karyotype of male fetus.

In the present authors' Unit, on admission, cutaneous manifestations of neurofibromatosis on the entire surface of the body where observed: café au lait spots and neurofibromas. The cardiological examination and respiratory system were normal. The mother reported increased blood pressure and swelling in the lower extremities by the end of the first trimester. Additionally she complained of decreased visual acuity on the left side.

As far as the fetus was concerned, ultrasound confirmed growth restriction (< 5th centile). Amniotic fluid volume and Doppler studies were within the normal range.

During the inpatient stay, she was diagnosed with high arterial blood pressures (mean 156/87 b/m), severe edema in the extremities, and increased protein in the urine (7,700 mg/24 hours). A combined follow up and treatment by several specialties was necessary.

The nephrologist recommended daily electrolytes measurement in the blood and 24-hour protein urine collection. Arterial blood pressured was maintained (130/70 b/m) with the combination of methyldopa 250 mg 2-1-2-1 daily and nifedipine 20 mg 1x1 daily.

The ophalmological examination indicated decreased visual acuity in both eyes (OD: 7/10 cc, OS: 5/10 cc), significant visual field loss (bitemporal hemianopia with further visual field loss on the left eye), impaired colour vision in both eyes (using Ishihara's

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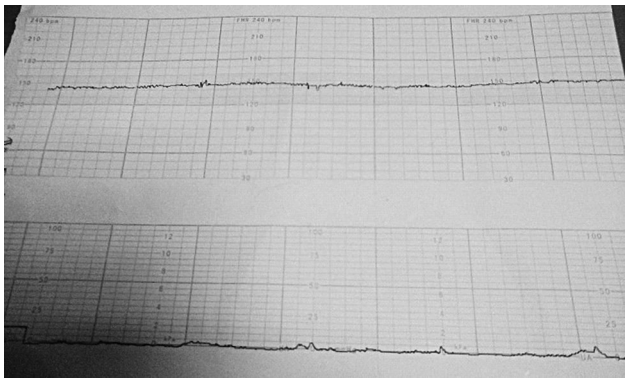

Figure 1. — Pathologic NST.

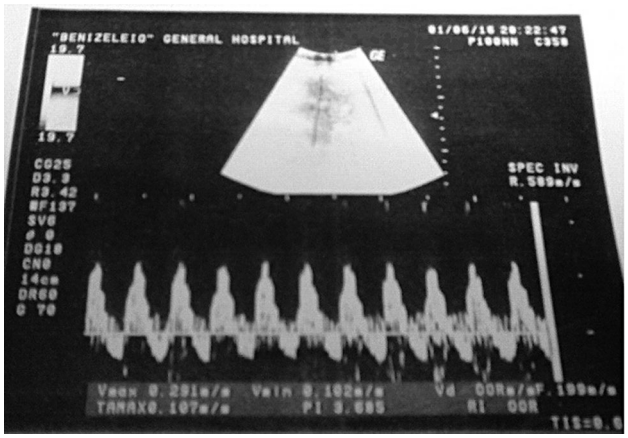

Figure 2. — Reversed end diastolic flow in umbilical artery.

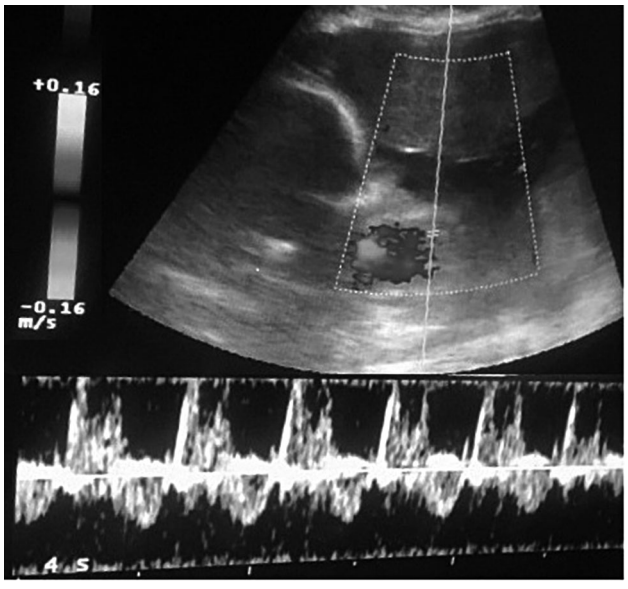

Figure 3. — Reversed DV.

test), and relative afferent pupillary defect (RAPD) on the left eye. Upon slit lamp examination, Lisch nodules in the iris were observed in both eyes. Intraocular pressure (IOP) was normal in both eyes. Upon fundus examination, optic disk edema was observed in the left eye. No chorioid hamartomas were observed.

During a four-week period, the authors attempted to stabilize the arterial blood pressure and minimize the edema and proteinuria (< 3,000mg/24 hours).At 30 weeks of the gestational age the mother reported decrease fetal movements. The Non Stress Test (NST) showed normal fetal heart rate (FHR) of 145 b/m, but significantly reduced variability (Figure 1). Ultrasound examination confirmed the evidence of fetal distress. IUGR fetus (< 3 centile) with reversed end diastolic flow in the umbilical artery and significantly increased PI (Figure 2). Furthermore, reversed ductus venosus (DV) and decreased fetal movements were obvious during the scan (Figure 3). Reversed end diastolic flow in the umbilical artery and reversed DV are markers for an urgent C-section (< 48 hours).

Emergency C-section was performed under general anaesthesia. Ascites in the abdominal cavity were diagnosed in the operating theater, due to severe proteinuria and hyponatremia of the mother. A 870-gram male baby was born. Intubation was not necessary as the APGAR score was good. Furthermore, according to the neonatologist, the infant developed periventricular leukomalacia due to prematurity. All maternal complications were minimized five days after the delivery except for the ophthalmic manifestations.

Discussion

Women with NF1 have an increased risk of maternal and fetal complications. Pre-eclampsia, hypertension, renal artery stenosis, and intrarenal parenchymal abnormalities can lead to chronic ischemia, fibrosis, spontaneous miscarriage, preterm delivery or fetal growth restriction. Neurofibromatosis has markedly variable clinical expressions, ranging from mild cutaneous lesions like café-au-lait spots, cutaneous and plexiform neurofibromas, and bony abnormalities. Ophthalmic manifestations appear in over 95% of adult patients and include Lisch nodules in the iris, congenital glaucoma, chorioid hamartomas, retinal tumors, and visual pathway gliomas involving the optic nerve, chiasm, or optic tract, that can lead in visual impairment and learning disability in 50% of cases [3-5].

Neurofibromas, the hallmark of NF1, are benign masses that can result in several maternal and fetal complications. Pregnancy promotes neurofibroma growth. This could be either due to haemorrhage within the mass or lysophosphatidic acid mediated promotion of actin polymerization with increase migration and survival of Schwann cells or due to hormonal changes during pregnancy, such as estrogen, progesterone, epidermal growth factor, and fibroblast growth factor .Moreover, the literature reports that in half of women with NF1, pregnancy leads to growth in size and number of neurofibromas, but eruptive forms as the first presenting sign of neurofibromatosis in pregnancy are minor [6-8].

Neurofibromas formation can lead to secondary hypertension that can mimic pre-eclampsia. Renal artery stenosis is seven times more likely in the younger age group (<

18 years) and phechromocytoma in older ages. The arterial lesions are classified into two main categories: adventitial neurofibromas or ganglioneuromatous tissue which involve the aorta and major branches, and small vessel lesions which include proliferation of intimal spindle cells. Renal angiography is essential in the investigation of women with NF. In the presence of renovascular lesions, medical therapy to control the hypertension is usually less successful.

As far as fetal complications are concerned, growth restriction and Doppler are useful prenatal sonographic markers. The data of the present case report support that reversed end diastolic flow in the umbilical artery, reversed DV, and decrease fetal activity indicated emergency C-section. According to the literature, additional scans should be taken every two weeks during the third trimester to evaluate the growth, Doppler, and amniotic fluid. Furthermore, in these conditions, an increased rate of C-section is reported which could be due to fetal distress, cephalopelvic disproportion due to undiagnosed pelvic neurofibromas, and pelvic contractures [9-15].

Conclusion

With this case report the authors described the main complications, diagnostic possibilities, and management of pregnancies associated with NF1. In early pregnancy it is recommended to make an accurate prenatal diagnosis through linkage analysis of family members. Additionally, it is important to mention that the evaluation of the fetal well-being requires experienced doctors and therefore, cases of suspected growth restriction should be referred to a maternal unit with knowledge in the prenatal and postnatal management. Moreover, all the new-borns require at least yearly review until the disease status is clarified.

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