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Neurofibromatosis in pregnancy: The pitfalls

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Abstract
Introduction: Neurofibromatosis is an Autosomal dominant disease characterized by different types of mutations of the NF-1 gene1, 2. approximately 50% of the NF-1 gene mutations result from de novo mutations. The reported incidence of neurofibromatosis (NF) in pregnancy varies from 1:2500-1:3500.
Case Report: A 31-year-old G3P1L1A1,31+5 weeks of gestation, Prev caesarean, hypothyroidism, breech, known case of neurofibromatosis 1 presented with complaints of headache to the emergency with a BP of 160/98 mm of Hg. USG showed fetoplacental insufficiency with doppler changes showing a cerebroplacental ratio <1. Blood pressure was not controlled on IV antihypertensives and MgSO4.
Decision of emergency caesarean section was taken in view of uncontrolled hypertension, IUGR, doppler changes.
Conclusion: These patients are at higher incidence of miscarriages, stillbirths, pre-eclampsia, IUGR, oligohydramnios, preterm labour, pulmonary stenosis, valvular disease septal defects, coarctation of aorta, cardiomyopathy due to neurocutaneous changes. Associated phaeochromocytoma contribute to hypertension not responding to treatment Patients with neurofibromatosis are advised to undergo genetic, prenatal, and antenatal counselling.

Keywords: Genetic, hypertension, rasopathies

Introduction
Von Recklinghausen's disease, also known as neurofibromatosis type-1 (NF1), is a very prevalent multisystem hereditary autosomal dominant ailment that is brought by a mutation in the (NF1) gene on chromosome 17. Multiple neurofibromas, café-au-lait spots, Lisch nodules (Iris hamartomas), freckling of the axillar or inguinal regions, and optic gliomas are the major symptoms seen. The worldwide incidence of Neurofibromatosis varies between 1:2500-1:3500 [1]. Pregnancy-related hormonal alterations may result in the development of new neurofibromas and an enlargement of pre-existing ones. Neurofibromin protein, which functions as a negative regulator of Ras cellular pathways, is produced by the NF-1 gene and functions as a tumor suppressor. Preterm delivery, intrauterine growth retardation, spontaneous miscarriage, and stillbirth are among the fetal morbidities in affected women, whereas hypertension and cerebrovascular disease are the most common maternal complications. Although most NF1 women have safe pregnancies, but require close observation for early detection and treatment of complications [2].

Case report
A 31 year old G3P1L1A1 at 31+5 weeks of gestation, previous caeserian section, hypothyroidism, breech, known case of neurofibromatosis 1 presented with complaints of headache to the emergency. On admission, her BP was 160/98 mm of Hg, pulse rate of 72 bpm.On chest auscultation normal vesicular breath sounds were heard and ECG was within normal limits. An admission USG was performed which suggested a single live fetus, breech presentation, EFW: 1.5 Kg, AFI:8.6 cm, 30+5 weeks of gestation and fetoplacental insufficiency with doppler changes showing a cerebroplacental ratio <1.
Antihypertensive (Intravenous Labetalol) were given to control the blood pressure. Injection MgSo4 was started for neuroprotection and injection dexamethasone was given for steroid coverage.
In view of uncontrolled hypertension and alteration of cerebroplacental ratio, a decision for emergency caesarean section was taken. She delivered a live female baby of 1.52 kg, cried at birth.

Post operatively, patient was managed conservatively with IV fluids, antibiotics and tapering of antihypertensives. Patient was discharged after full recovery on post-operative day 3 on oral nifedipine. Baby was discharged from Neonatal ICU, is doing well.

Patient was counselled regarding genetic testing of Neurofibromatosis in the baby as it is an autosomal dominant disease.

Patient came for follow-up after 14 days of LSCS. From obstetric point of follow-up, she recovered well.

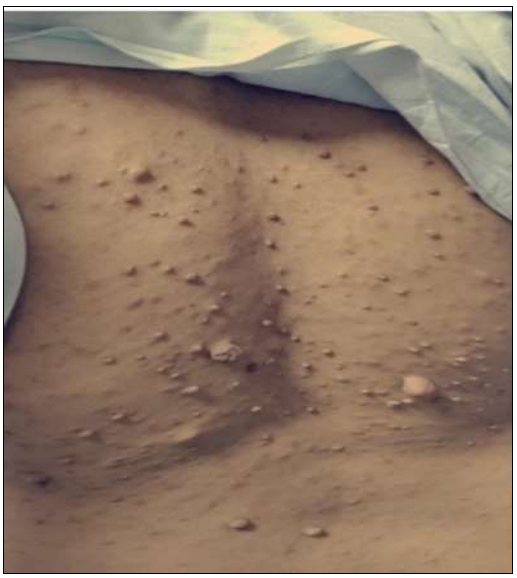

Fig 1: Neurocutaneous lesion in neurofibromatosis.

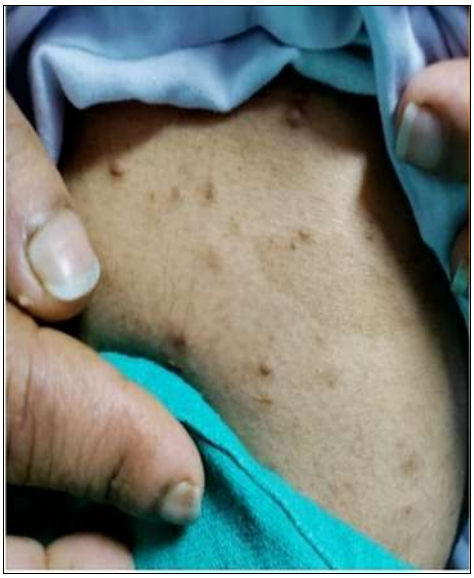

Fig 2: Characteristic Cafe-au lait spot

Discussion

Rasopathies which result in cellular proliferation and tumerogenesis, are caused by mutations or microdeletions in the NF1 gene. Seven clinical criteria are used to diagnose neurofibromatosis, and two of these are essential: > 6 substantial café-au-lait macules, > 2 neurofibromas of any kind, or > 1 plexiform neurofibroma, ocular glioma, >2 Lisch nodules, freckling in the axillary or inguinal regions, a characteristic osseous lesion like sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis, or a first-degree relative with NF1 [3].

One characteristic of neurofibromatosis type I is vascular involvement. It is hypothesized that atrophy of the media and elastic layers prevents the disease-related arterioles from expanding and are therefore unable to adapt to pregnancy's changes. Additionally, there is a stronger correlation between neurofibromatosis and oligophrenia, renal artery stenosis, and renovascular hypertension. Additionally, phenochromocytoma, which is linked to numerous neurocutaneous syndromes, may be a factor in hypertension that does not improve with regular medication [4].

Patients with NF1 are susceptible to a variety of cardiovascular disorders, including hypertrophic obstructive cardiomyopathy, atrial and ventricular septal defects, pulmonary stenosis, valvular heart disease, and coarctation of the aorta. This is because the NF1 gene is expressed in both myocardial cells and vessels. The main cause is the lack of neurofibromin protein which regulates apoptosis leading to hyperproliferation of endocardium.

Pregnancy-related rapid increase in size of cutaneous vascular neurofibromas may also prompt concerns about the growth of internal neurofibromas, which can have mass consequences including obstruction. In this case, USG is not very useful because it can only detect giant neurofibromas and may miss smaller lesions. Due to radiation apprehension CT scan cannot be used. Therefore, MRI scans are the preferred method of examination for locating internal neurofibromas. This can support the planning of anesthesia for a cesarean section as well as the mode of delivery in the presence of pelvic neurofibromas.

These patients are more likely to experience premature labor, oligohydramnios, IUGR, pre-eclampsia, stillbirths, miscarriages, and cerebrovascular problems. Both IUGR and pre-eclampsia could be explained by vasculopathy causing variations in placental hypoxia. Additionally, IUGR in the infant may result from a big, developing neurofibroma that impairs uterine blood flow. It is therefore advisable to treat these patients with a multidisciplinary approach at a tertiary facility. Patients with neurofibromatosis have a significantly higher rate of cesarean sections [5].

Preconceptional counselling is necessary in patients with neurofibromatosis. To ensure that their offspring are disease-free, the couple may also decide to use a donor gamete (Egg or sperm) based on which partner has the mutation.

The couple should receive appropriate pre-conceptional counseling if they decide to become pregnant. Re-evaluating antihypertensive medication and doing baseline imaging, such as CT/MRI, to check for any hidden neurofibromas, may be necessary.

Prenatal testing for neurofibromatosis in the fetus should be offered to patients after conception. The diagnosis can be made by amniocentesis, chorionic villus sample, or fetal cell free DNA [6].

Conclusion

Neurofibromatosis can be diagnosed based on the evaluation of clinical symptoms, pedigree analysis, and radiological assessment. Pregnant women with NF2 can experience clinical deterioration due to rapid tumor growth during pregnancy. Patients with neurofibromatosis are advised to undergo genetic, prenatal, and antenatal counseling to better plan pregnancy and prevent lower the risk of inherited disease. NF tumor genetic and molecular testing should be performed to confirm the diagnosis. Multidisciplinary management in tertiary hospitals should be carried out in pregnant women with neurofibromatosis to fetal and maternal morbidity and mortality.

Conflict of Interest
Not available.

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Not available.

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