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CASE SERIES OF NEUROFIBROMATOSIS AND ITS VARIED MANIFESTATIONS IN PREGNANCY: AN OBSTETRICIAN'S PERSPECTIVE

Obstetrics & Gynaecology

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ABSTRACT

Neurofibromatosis (NF) type1 is a relatively common genetic neurocutaneous disorder with variable clinical expression. It has been linked with obstetric complications like preeclampsia in the mother and fetal growth restriction(FGR), preterm birth and stillbirth in the fetus. NF1 is frequently associated with bony dysplasia and neurological manifestations like seizure disorder, large disfiguring plexiform neurofibroma and malignant nerve sheath tumors.

Due to the above-mentioned concerns, pregnancy and childbirth can be challenging in women with NF1. Timely screening and regular monitoring are required for early diagnosis and treatment of these conditions, to ensure optimal obstetric care.

We present in our case series, the management, maternal and fetal outcomes of 7 pregnancies in five women with neurofibromatosis.

KEYWORDS

Neurofibromatosis, Plexiform neurofibroma, Preeclampsia, Pregnancy

BACKGROUND

Neurofibromatosis(NF) type1 or von Recklinghausen's disease, an autosomal dominant(AD) genetic disorder, has an incidence of 1 in 3000 live births. (Xiong et al., 2014) It is caused by mutations in NF1 gene in 17q11.2 and is characterised by diffuse cutaneous/mucosal nodules, large plexiform neurofibromas and Café-au-lait macules with increased risk of cancers like malignant peripheral nerve sheath tumour(MPNST).

Though fertility is unaffected, NF affects obstetric and anaesthetic aspects of pregnancy depending on the site and size of neurofibromas. Terry et al found a prevalence of 0.008% in pregnancy with higher odds of developing antenatal complications like preeclampsia. (Terry et al., 2013)

We report seven pregnancies in five patients with NF1 in whom there were obstetric or anaesthetic implications. These cases add to the existing literature of possible challenges in the management of pregnancy in patients with NF.

CASE REPORTS

Case 1.

A 23-year-old woman, with obstetric index of G3A2 was admitted at 8+4weeks of gestation with high blood pressure(BP) recordings. She has been hypertensive for 2years on regular anti-hypertensive medication(Amlodipine 5mg twice daily).

She was a known case of NF1 with positive family history. She presented with a large left sided neck swelling and multiple cutaneous nodules over the face and trunk. Prior to present pregnancy, contrast enhanced computed tomography(CECT) showed a plexiform neurofibroma in the neck extending from the floor of mouth to the mediastinum, involving the carotid space, submandibular, parapharyngeal and paraaortic spaces. Multiple scattered subcutaneous nodules were noted, largest 3.9x4.7cm in the gluteal region. She was evaluated for causes of secondary hypertension. On CECT, bilateral adrenal glands were normal and there were no vascular causes. Somatostatin receptor scintigraphy and urinary vanillylmandelic acid ruled out pheochromocytoma and paraganglioma. Cardiac and renal causes were excluded by echocardiogram, renal ultrasound and doppler.

After admission, anti-hypertensives were changed to Labetalol 100mg and Nifedipine 10mg thrice a day and low-dose Aspirin was started. She was worked up for the cause of previous two missed abortions. Normal levels of Anti-nuclear antibodies(ANA) and complement proteins C3, C4 excluded SLE and Antiphospholipid(APS) antibodies tested negative. Thyroid and cortisol levels were also normal. First trimester screening(FTS) was negative for chromosomal disorders.

At 24+2weeks she was readmitted for BP control. Serial monitoring of preeclampsia panel of investigations was normal. Proteinuria was not significant. Ophthalmological examination revealed Lisch nodules but there was no evidence of hypertensive retinopathy. Fetal growth monitoring and doppler measurements were normal. She was administered antenatal corticosteroids. As a result of worsening hypertension(170/110mmHg), pregnancy was terminated at 35+5 weeks by caesarean section(CS) due to cephalopelvic disproportion (CPD). But there were anaesthetic concerns like difficult airway(Mallampati grade IV) due to macroglossia and cervical plexiform neurofibroma(as shown in figure 1). Although spinal cord neurofibromas were not ruled out by MRI, we proceeded with CS under spinal anaesthesia as a safer option. A 2.87kg healthy male baby was delivered and intrauterine contraceptive device was placed. She had an uneventful post-operative course. Anti-hypertensive medications were titrated and she was discharged on regular follow-up.

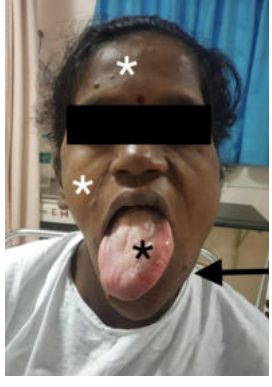

Figure1: Clinical photograph showing multiple cutaneous nodules (white asterix); macroglossia with Mallampati grade IV airway (black asterix); and plexiform neurofibroma in submandibular region and neck (black arrow)

Case 2
A 28-year-old primigravida presented to us in labour at 40+1weeks. Though she had an uneventful booked pregnancy thus far, her past history was significant. She was diagnosed with neurofibromatosis1 at 9years of age with multiple nodules all over her body which were slowly progressive. She had undergone right below-knee amputation 5years back for an ulcerated plexiform neurofibroma with suspected malignant change.

She also gave history of breathlessness and hemoptysis for which she was evaluated and diagnosed with right fibrothorax with bronchiectasis. She received antibiotics and nebulisations as advised by pulmonologist.

She had no obstetric complications in the antenatal period and had a spontaneous vaginal delivery of a 2.54kg female baby. Postnatally, her respiratory symptoms decreased and she was discharged with oral antibiotics.

Her second pregnancy was 1.5years later which was booked and managed elsewhere. She had a term spontaneous vaginal delivery of a 2.40kg baby. There was fetal growth restriction(FGR) and respiratory infection due to which the baby expired 1month postnatally.

Her third pregnancy, 2years later, was complicated by APS and flare-up of bronchiectasis, which were managed appropriately. Due to fetal growth restriction, she was admitted and induced electively at 37+3weeks and delivered a healthy 2.43kg male baby vaginally.

Following year, she developed low grade MPNST in her amputated stump for which she underwent wide local excision. She was doing well on follow-up.

Case 3:
A 25-year-old primigravida was admitted at 39+4weeks with oligohydramnios. She was a diagnosed case of neurofibromatosis for past 10years with cutaneous nodules and Café-au-lait macules over her forearm and back.

She was a known case of seizure disorder with increased seizure frequency in the antenatal period, for which she required two anticonvulsants(Phenytoin and Levetiracetam). No intracranial lesion was found on evaluation.

Labour was induced at 39+5weeks due to oligohydramnios. Vacuum delivery was performed for fetal heart rate decelerations but the fetal outcome was good. An alive and vigorous 2.82kg male baby was delivered. Mother and baby were doing well and discharged after 2days.

Case 4:
A primigravida aged 25years presented with history of neurofibromatosis from 15years of age. She had thoracic kyphosis and plexiform neurofibroma over the right lumbar region. Multiple small cutaneous nodules were also noted over her abdomen and vulva.

She was referred to us at 41weeks with recently diagnosed severe preeclampsia(160/110mmHg) with proteinuria and grade 4 pedal edema. Intravenous Labetalol was administered for BP control. There were no other severe features and blood investigations were normal. There was no FGR and fetal heart rate was reassuring. Labour was induced in view of severe preeclampsia and a 3.3kg male baby was delivered vaginally. Care was taken while performing episiotomy to avoid the vulval neurofibroma.

Meconium-stained amniotic fluid was noted after delivery and the baby was non-vigorous and required resuscitation. Baby expired in neonatal intensive care unit(NICU) after 3 days due to perinatal asphyxia. Postnatally, the mother's BP recordings normalised and she was discharged for follow-up.

Case 5:
A 23year old primigravida was admitted at 40+6weeks in labour. She was a known case of neurofibromatosis diagnosed at a young age with positive family history in father and grandmother. She had an uncomplicated antenatal period with booked pregnancy and regular obstetric care. Obstetric examination revealed no abnormality.

However, she had multiple neurofibromatous nodules over her trunk, none of which seemed significant from obstetric point of view. Thus, she was allowed for vaginal delivery and she delivered an alive male baby of 2.73kg without any complications. Mother and baby were discharged in good health after 5days.

Table 1 compares the various clinical, obstetric and perinatal parameters of these above cases.

Table 1. Comparison of clinical, obstetric and perinatal parameters of our patients

S no.	Age (years)	Age at diagnosis of NF (years)	Obstetric Index	Gestational age at delivery (weeks)	Medical Complications	Obstetric complications	Mode of delivery	Perinatal outcome (Birth weight in kg)
1	23	5	G3A2	35+5	Chronic Hypertension Macroglossia Plexiform cervical neurofibroma	Cephalopelvic disproportion	CS*	2.87 Alive Preterm Healthy
2.A	28	9	G1	40+1	Fibrothorax Bronchiectasis Post Below-knee amputation	Nil	Vaginal	2.54 Alive Term Healthy
2.B	30		G2 P1 L1	Term		FGR+	Vaginal	2.40 Expired after 1month (respiratory infection)
2.C	31		G3 P2 L1	37+3		FGR APS++	Vaginal	2.43 Alive Term Healthy
3	25	15	G1	39+4	Epilepsy	Worsened Seizure activity	Vacuum instrumental delivery	2.82 Alive Term Healthy
4	25	15	G1	41	Nil	Severe Preeclampsia	Vaginal	3.30 MSAF# Expired after 3 days
5	23	12	G1	40+6	Nil	Nil	Vaginal	2.73 Alive Term Healthy

Note: *CS- caesarean section; +FGR- Fetal Growth Restriction; ++APS- antiphospholipid syndrome; #MSAF- Meconium-stained amniotic fluid

DISCUSSION

Neurofibromatosis is a neurocutaneous disorder with variable clinical expression characterized by tumors in the nervous system and skin. NF1 constitutes 90-95% of cases of neurofibromatosis (Santoro et al., 2018) and it is diagnosed in the presence of any two of the following criteria. (Le & Bedocs, 2021)

Table 2. Diagnostic criteria for Nf1

S. no	Diagnostic criteria for NF1 (any two of the following)
1.	6 or more café-au-lait macules more than 15mm in diameter
2.	2 or more cutaneous or 1 plexiform neurofibroma
3.	Axillary or inguinal freckling

4.	Optic glioma
5.	2 or more Lisch nodules (iris hamartoma)
6.	Bony dysplasia (sphenoid dysplasia, bowing of long bones, pseudoarthrosis)
7.	Family history (first degree relative)

Our first case presented with 5 of these criteria whereas others had at least 2 criteria including family history. Gravid women with Neurofibromatosis-1 have a varied peripartum course depending on number and site of tumors and associated complications.

These patients have higher risk of pheochromocytoma and hypertension. Via mechanisms not fully understood, NF accelerates cardiovascular disease and increases cardiac mortality. (Terry et al., 2013)

Sharma et al reported high incidence of preterm labour with FGR, stillbirths and preeclampsia. (Sharma et al., 1991) Swapp et al also reported similar results in their respective case series. (Swapp & Main, 1973) However, both these results were based on small case series of around 10patients and 20pregnancies and thus could be anecdotal evidence at best. Dugoff et al in a larger series reported no increase of hypertensive disorders of pregnancy but noticed higher rates of preterm labour and need for caesarean section, though not all were attributable directly to NF. (Dugoff & Sujansky, 1996) In our series, the first patient had uncontrolled chronic hypertension and iatrogenic preterm birth due to the same. The fourth patient had severe preeclampsia and her baby expired postnatally after 3 days due to perinatal asphyxia. One of the pregnancies of the second patient resulted in infant mortality after 1 month of birth due to respiratory infection. Fortunately, all others had term deliveries and successful neonatal outcomes. Maternal outcome was good in all five of our patients.

In our series, third patient had seizure disorder which worsened in pregnancy, requiring anticonvulsant polytherapy. NF1 has been reported to have an association with epilepsy with a prevalence of 4-10%. These could be due to various brain lesions, tumors or perinatal asphyxia and hydrocephalus. However, in some patients, no organic cause may be identified. (Santoro et al., 2018)

Though vaginal delivery is not necessarily contraindicated in all patients with NF, this has to be decided on case-to-case basis. Tumors in the spinal foramina can enlarge during pregnancy and cause neurological deficits like paraparesis, necessitating caesarean section. Pelvic neurofibromas and kyphoscoliosis may pose significant challenge during vaginal delivery as well as CS. (Dugoff & Sujansky, 1996) NF is associated with short stature in 8% of the patients and contracted pelvis in such women may mandate caesarean section as was the case in our first patient. (Soucy et al., 2013) All other cases were allowed to deliver vaginally.

These patients may have multiple neurological manifestations due to cranial nerve tumors, vertebral or spinal nerve tumors and skeletal deformities. The first and fourth patient in our series had inadequate pelvis and kyphosis respectively.

There is an increased predilection for malignant transformation/ de novo MPNST. (Leppävirta et al., 2017) Patients with NF1 need regular follow-up and prompt presentation if increase in size of pre-existing neurofibromas or appearance of new swellings anywhere in the body is noted, for early diagnosis and radical management. In our series, the second patient developed de novo MPNST and was treated with wide local excision.

There are mixed opinions about the effects of pregnancy on NF lesions. Some reports noted increase in size and number of lesions during pregnancy which regressed postnatally. The reason for such flaring-up of NF in pregnancy, if any, is unknown. (Jarvis & Crompton, 1978; Swapp & Main, 1973) None of our patients had any documented increase in size of the existing nodules or new onset lesions. Contraception and genetic counselling are essential to prevent the AD transmission of this disease

CONCLUSION

Many women with NF may complete their pregnancy with no hurdles. However, multiple complications can occur making it a high-risk pregnancy. Appropriate screening and extensive evaluation can recognise these complications early. Good antenatal and peripartum care with multi-disciplinary team is crucial for optimal maternal and fetal outcomes in these women. Also, the need for regular follow-up for NF-associated tumors is essential to be impressed upon the patient.

ABBREVIATIONS

AD- autosomal dominant
ANA- Anti-nuclear antibodies
APS- Antiphospholipid antibody syndrome
CECT- Contrast enhanced computed tomography
CPD- Cephalopelvic disproportion
FTS- First trimester screening
MPNST- Malignant peripheral nerve sheath tumor
NF, NF1- Neurofibromatosis type 1
NICU- Neonatal intensive care unit

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