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Neurofibromatosis and its varied manifestations in pregnancy: A case report

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Abstract
Neurofibromatosis is a specific autosomal dominant genetic disorder characterized by multiple cutaneous lesions along with widespread manifestations including all organ systems. Pregnancy in patients with Neurofibromatosis, less commonly seen earlier, is frequently seen now with more and more of those affected reaching reproductive age and finding partners, since fertility does not seem to be affected by the disease. However, pregnancy in women with neurofibromatosis may be high risk with the disease affecting various ectodermal and mesodermal tissues and can cause life threatening complications in some of them. It is imperative that these patients are treated at tertiary level centres with multidisciplinary management by obstetricians trained in managing high risk pregnancies.

Keywords: Neurofibromatosis type 1, Pregnancy, IUGR, Perinatal Complications

Introduction
Neurofibromatosis is an Autosomal dominant disease presenting with multiple cutaneous neurofibromas, café –au-lait macules, axillary freckling, Lisch nodules and optic gliomas. Pregnancy in individuals affected by neurofibromatosis is high risk and can pose multitude of challenges which need to be anticipated and managed preferably in a tertiary care facility. Since Neurofibromatosis effects all organ systems, effect on each of these has a possibility of making pregnancy in these patients hazardous. Here we present a case of an elderly Primi with Neurofibromatosis conceived after prolonged infertility successfully managed with good outcome.

Case report: 43year old female was referred to us from a peripheral centre as a Primi at 27weeks, a known case of Neurofibromatosis with complaints of difficulty in breathing and productive cough since 10 days. Patient had a spontaneous conception after 20 years of primary infertility.

On admission her BP was 160/100 mmHg and Mild pallor was present along with bilateral pitting pedal edema extending until knees. On respiratory system examination, air entry was decreased bilaterally with coarse crepitations all over. Pansystolic, high pitched murmur at left lower sternal border was heard on auscultation. On per abdomen inspection, several café-au-lait spots were present on trunk and extremities, multiple cutaneous soft rubbery lesions were present all over the body. A large cutaneous neurofibroma (15x12cm) were seen on lower right lateral aspect of flank. Breast examination showed evidence of lesions of neurofibromatosis on both breasts and involving the nipples. Neurological examination was within normal limits. MRI Brain revealed Buphthalamous but there was no evidence of optic nerve gliomas or schwannomas. Uterus was 24-26 weeks on palpation and liquor was clinically reduced. FHS was regular at 150 beats per min. On per speculum examination, internal os was closed, posterior and uneffaced.2-D Echo revealed mild to moderate mitral regurgitation with tricuspid regurgitation and Borderline Pulmonary arterial hypertension with normal ventricular systolic function, Left ventricular ejection fraction was 60%. Fundoscopy was suggestive of bilateral Hypertensive Retinopathy Grade –I, Cataract, Proptosis & Buphthalmos in both eyes. X Ray chest (with shield) revealed blunting of both costophrenic angles with non- homogenous opacities involving mid & lower zones and increased Bronchovascular markings s/o Pleural Effusion. Mild cardiomegaly was also seen. Ultrasound examination was suggestive of a single live fetus 25 weeks 3 days AFI-6cm with EFW-784gms and mild fetoplacental insufficiency with Cerebroplacental ratio of 1.7 on Doppler study.

Pregnancy was continued with conservative management in the form of anti-hypertensives, steroid cover and diuretics for pulmonary edema.

On third day of admission, patient complained of decreased fetal movements. Repeat ultrasound and Doppler showed reversal of Diastolic flow with CPR – 0.6. Decision of Emergency LSCS taken in view of Elderly Primigravida with infertility conception with preterm breech with Gestational HTN with IUGR with reversal of Diastolic flow. Patient was operated under epidural anesthesia. She delivered a live female baby of 686 grams who cried at birth.

There were many intraoperative obstetric challenges in this case like multiple Neurofibromatosis lesions over incision line, laxity and asymmetry of abdominal wall due to huge neurofibroma swelling in right lower quadrant, approx. 800cc ascitic fluid, arcuate uterus, increased vascularity and ill-formed lower uterine segment. Anticipating all these surgical challenges, the surgery was successfully completed.

Post operative patient was managed with limited IV fluids, continuous moist oxygen, intravenous antibiotics & prophylaxis for venous thromboembolism. Patient was counseled regarding Neurofibromatosis being an Autosomal dominant disease and the possibility of it being inherited by the baby. Patient discharged after full recovery. Baby was discharged from Neonatal ICU at a weight of 1.5kg and is doing well.

Patient came for follow-up after 7 days of LSCS. From obstetric point of follow-up, she was recovering well.

Discussion

Neurofibromatosis 1 is a genetic neurocutaneus syndrome responsible for varied clinical manifestations, first described by German pathologist Fredrick Dan Von Recklinghausen in 1882 [1]. It is characterized by presence of café au lait spots, axillary freckling and neurofibromas. The gene for NF1 was first discovered by Wallace et al in 1990 [2]. It is 35 kilobase in size, located on chromosome 17q11.2. It encodes protein Neurofibromin that activates p21rasGTPase. P21rasGTPase inhibits the conversion of p21ras-GTP to p21-rasGDP and suppresses cell growth. Hence, NF1 gene acts as a tumor suppressor gene of the Ras family. Mutations or microdeletions in the NF1 gene causes what is known as rasopathies leading to cellular proliferation and tumerogenesis. These mutations are inherited in an autosomal dominant manner with almost 50% mutations being sporadic in nature. It has a very high spontaneous mutation rate – almost 100 fold higher than a typical mutation rate for a single locus. The gene shows complete penetrance, however the expressivity may vary [3]. Progression of the disease is always unidirectional to a higher grade.

The prevalence of neurofibromatosis 1 in the general population is 1 in 2500 [4] which makes it one of the most commonly encountered phakomatosis. The reported incidence of neurofibromatosis in pregnancy varies from 1:5000 to 1:18,500 [5]

The diagnosis of neurofibromatosis is based on 7 clinical criteria of which 2 are required for diagnosis- > 6 significant café-au-lait macules (CLM),> 2 neurofibromas of any type or 1 plexiform neurofibroma, freckling in the axillary or inguinal regions, optic glioma, >2 Lisch nodules, a distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis, a first-degree relative with NF1 [4].

Our patient was diagnosed as a case of Neurofibromatosis Type 1 due to extensive cutaneous neurofibromas, axillary freckling and a large plexiform neurofibroma causing cosmetic disfigurement in childhood. The diagnosis was primarily clinical based on pathognomonic clinical features. No documentation of any further childhood investigations was obtained. There was no family history of neurofibromatosis which points to the possibility of a de novo mutation causing the disease in the patient. The age of diagnosis of neurofibromatosis varies among patients. Patients with grossly visible disease during the childhood may be detected earlier. However, many patients may remain undiagnosed because of variable expressivity of the gene and some patients may even be detected for the first time during pregnancy when the lesions increase under the influence of pregnancy hormones. In the study by Abecassis et al the average age of diagnosis was found to be 13yrs [4].

Our patient was elderly, 43years of age and came with a history of prolonged Infertility of 20 years. The cause of this was never fully investigated. The present pregnancy was conceived spontaneously without any infertility treatment. Fertility in general does not seem to be affected by Neurofibromatosis Type I [6], though, a failure to find partners in severely affected individuals may be a reason why relative fertility may seem reduced. The autosomal dominant nature of the disease with a possibility of inheritance in the progeny with full penetrance may also be the reason why patients with neurofibromatosis may make the reproductive choice not to have children[7]. Besides these social aspects, the association of Infertility and neurofibromatosis needs to be more extensively explored. A recent study by Mbaekeni et al have reported the association of antiphospholipid syndrome and neurofibromatosis which can be an interesting reason for subfertility in neurofibromatosis patients[8]. However, since fertility in these patients is near normal and life expectancy exceeds the reproductive age, pregnancies in these patients will be encountered and the obstetrician should be adequately aware of potential complications in these subgroup of patients.

Vascular involvement is a hallmark of neurofibromatosis type I. It is postulated that arterioles involved by the disease fail to expand due to atrophy of the media and elastic layers and are hence, unable to accommodate the changes of pregnancy. There is also increased association of renovascular hypertension, renal artery stenosis and oligophrenia with neurofibromatosis [9]. Also, Pheochromocytoma which is associated with many neurocutaneous syndrome may contribute to hypertension not responding to conventional treatment. High index of suspicion in these patients should be kept as neurofibromatosis is present is almost 5 % of patients with pheochromocytoma [10]. This hypertension arising due to vasculopathies may get superimposed with pregnancy induced hypertension and proteinuria as seen in our patient, and managing this hypertension may prove to be challenging. In cases with fluctuating or refractory hypertension specially in the first two trimesters of pregnancy should be evaluated for pheochromocytoma and care should be taken to not dismiss these symptoms as pregnancy induced hypertension as untreated, sudden hypertensive crisis may prove catastrophic for mother and baby. Also, many other endocrine diseases such as Addison's disease, Acromegaly and hyperparathyroid are found to be associated with neurofibromatosis.

Cardiovascular involvement in neurofibromatosis is well documented. This is primarily due to the absence of neurofibromin protein which causes overabundance of endocardial cushions due to hyperproliferation secondary to lack of apoptosis. Patients with NF1 are at risk of many cardiovascular abnormalities such as valvular heart disease, most importantly pulmonary stenosis, atrial and ventricular

septal defects, coarctation of aorta and hypertrophic obstructive cardiomyopathy as NF1 gene is expressed in vessels as well as myocardial cells. [11] This predisposition coupled with hemodynamic changes of pregnancy can lead to patients presenting with features of cardiac failure. There are even reports of cardiac valvular neurofibromas being found in neurofibromatosis patients [12]. The possibility of hypertrophic cardiomyopathy should also be kept in mind in these patients. Hence, Blood pressure recordings in all four limbs, Fundoscopic examination for hypertensive retinopathy, bupthalmos and a baseline 2-D Echo should always be performed in all pregnant patients of neurofibromatosis to avoid catastrophic cardiac decompensation specially in the postpartum period. Our patient presented with feature of right sided failure and was detected to be Mitral regurgitation with Pulmonary arterial hypertension which was managed conservatively with diuretics. Vascular anomalies can also include cerebral aneurysms, ectatic or stenosed vessels which can give rise to cerebral haemorrhage [6].

Pregnant patients with neurofibromatosis may show increase in cutaneous lesions and hyperpigmentation under the growth stimulus provided by pregnancy hormones, androgens, epidermal growth factor, fibroblast growth factor and transforming growth factor alpha [13]. New neurofibromas may grow and sudden rapid increase in size of large neurofibromas may cause haemorrhage within tumors causing anaemia and pain. If rapid growth of a neurofibroma is observed then imaging should be done to rule out malignant transformation [14]. In one study as many as 52.4 % women felt that their lesions increased during pregnancy [15]. This was seen in our patient as well who reported a subjective increase in lesion compared to pre-pregnancy.

The sudden increase in cutaneous vascular neurofibromas in pregnancy may also raise concern over the increase in size of internal neurofibromas which can cause mass effects and obstruction. USG is of limited value here as it can only dileanate large neurofibromas and small lesions may be missed. Since CT scan cannot be used due to the fear of irradiation, MRI scan can serve as the investigation of choice to look for internal neurofibroma and their location. This can help plan the mode of delivery in presence of pelvic neurofibromas and also assist while planning for anaesthesia during cesarean section.

Pregnancies in patients with neurofibromatosis are predisposed to obstetric complications due to multisystemic nature of the disease. These patients have a higher incidence of miscarriages, stillbirths, pre-eclampsia, IUGR, oligohydramnios, preterm labor and cerebrovascular complications [6]. Pre- eclampsia and IUGR can be attributed to vasculopathy leading to placental hypoxic changes. A large growing neurofibroma compromising the uterine blood flow may also cause IUGR in the baby. In view of these complications, it may be wise to manage these patients at a tertiary centre with a multidisciplinary team.

While mode of delivery in neurofibromatosis is decided primarily by obstetric indications, rate of cesarean section is relatively increased in these patients. This is due to an increased rate of pregnancy complications necessitating a decision for induction increasing the possibility of cesarean or a decision for primary cesarean may be made in view of unavoidable medical or obstetric reason. Presence of pelvic neurofibromas can cause labour dystocia and cesarean may be prudent in such cases[15].

Cesarean section in cases of neurofibromatosis can be challenging. Site of incision may contain multiple cutaneous neurofibromas. Presence of kyphoscoliosis can make administration of regional anesthesia difficult. Also, spinal anesthesia in neurofibromatosis patients may present with increased instances of bleeding, epidural haematoma formation, patchy block due to foraminal neurofibromas and raised intracranial pressure [16]. It has also been reported that patients with neurofibromatosis also have increased sensitivity to succinylcholine as well as non depolarizing neuromuscular blocking agents. Difficult airway may be encountered due to the presence of neurofibroma in tongue, oral cavity etc. Chest wall deformities can cause suboptimal respiratory compliance and the presence of co-morbidities such as hypertension, pheochromocytoma and renal disease can further complicate the administration of anaesthesia [17]. An MRI Brain and spine may need to be performed antenatally to rule out peripheral nerve sheath tumors or neurofibromas in the spine. Short stature and pelvic deformities may necessitate cesarean due to pelvic inadequacy.

Preconceptional counselling in patients with neurofibromatosis desirous of a pregnancy is also critical. If patient presents in preconceptional period, timely genetic counselling can be done and informed reproductive choices made by the couple in view of autosomal dominant inheritance of the disease. However, since the disease has variable expressivity, it may be difficult to know exactly how effected the baby may be. Preconceptional genetic diagnosis can be used to selectively transfer embryos that are not affected by the mutation. Since Neurofibromatosis is an autosomal dominant monogenic condition with full penetrance, it is the sixth most common monogenic disorder detected by PGD. Comprehensive genetic analysis of the NF1 gene is available since 2000 and current testing can identify causative gene in > 95% cases [18]. The couple can also choose to take a donor gamete (egg/ sperm) depending on which partner is carrying the mutation so that progeny can be free of disease.

If the couple chooses conceive the pregnancy, then proper preconceptional advice should be given. Antihypertensive therapy may need to be re-evaluated and baseline imaging such as CT/ MRI for any occult neurofibromas may be performed.

After conception, patients should be given the option of prenatal testing for neurofibromatosis in the baby. Fetal cell free DNA testing can be used to detect the presence of the mutation in the baby if the familial mutation is known [19]. Chorionic villus sampling or amniocentesis can also be used but these have an increased risk of miscarriage. But this can be carried out if the parental mutation is known or if multiple family members are affected then if linkage has been established. The risk of congenital anomalies should be explained to the parents and detailed anomaly scan should be done between 18-20 weeks to rule out other structural anomalies and accomplish early diagnosis. However, despite genetic diagnosis, it is difficult to predict the severity of disease in the baby and so the decision for termination or continuation of pregnancy on the basis of mere presence of mutation may be a difficult one to make.

Increased surveillance and prompt management will be required during antenatal period to pre-empt any complications such pre-eclampsia, IUGR, preterm labour which are seen with increasing frequency in patients of neurofibromatosis.

Certain neoplasms such as gliomas, malignant peripheral nerve sheath tumors and benign tumors of the peripheral and central nervous system are commonly seen in neurofibromatosis. These can very possibly undergo malignant change specially in the setting on increased hormones of pregnancy. A sudden and significant change in the size of the neurofibroma should be investigated to rule out haemorrhage within the lesion and or a more sinister malignant transformation. If such a change is detected, prompt management should be instituted and surgery or excision be planned. Postoperative chemoradiotherapy may

also be needed in these cases and that can raise the pertinent question of its effects on the pregnancy and whether it can be continued or needs to be terminated prioritizing the health of the mother.

Postpartum contraception in these patients with progesterone only pills should be treated with caution as presence of progesterone receptors in the neurofibroma can cause escalation of disease. Use of barrier contraception in these patients should be encouraged. Tubal sterilization can be offered to patients in appropriately selected cases after adequate counselling.

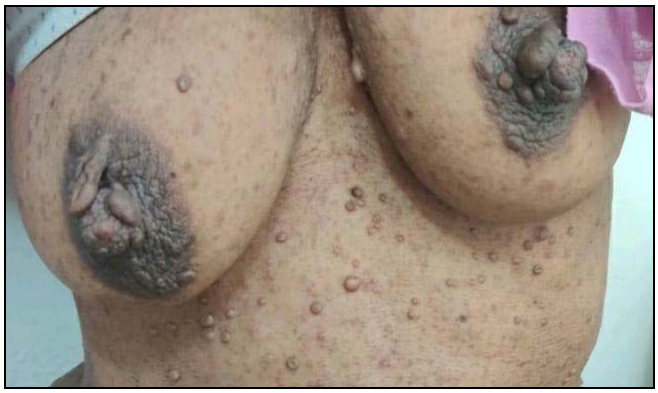

Fig 1: Extensive Neurofibromatosis on the breast

Fig 2: Café –au-lait spots which are pathognomonic to NF 1

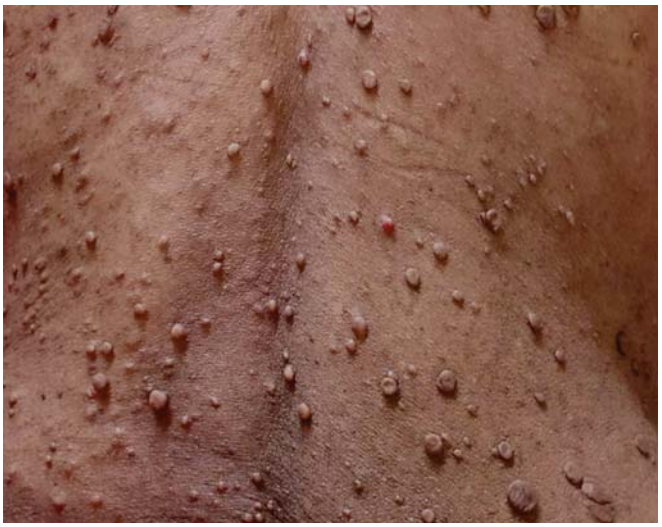

Fig 3: Extensive neurofibromatosis over the back

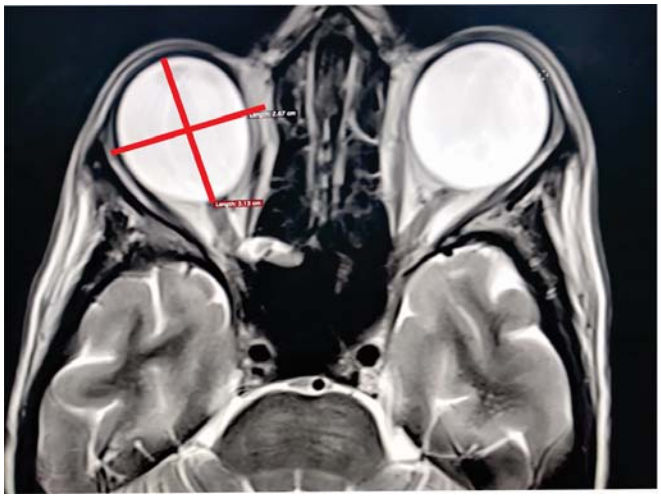

Fig 4: CT suggestive of Bupthalmos in both eyes

Conclusion

With more and more patients with neurofibromatosis achieving pregnancies, it is imperative that Obstetricians be familiar with the issues unique to these pregnancies and aware of the potential complications that these pregnancies can present with. A multidisciplinary approach, thorough pre-partum planning and appropriate counselling can help these patients reach successful pregnancy outcomes.

References

1. Schönebeck J, Ljungberg O. Recklinghausen's disease: a multifacetted syndrome. Acta Pathologica Microbiologica Scandinavica Section A Pathology 1970;78(4):437-42**.**
2. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulina AM et al. Type 1 Neurofibromatosis gene: Identification of a large transcript disrupted in three NF1 patients. Science 1990;249:181.
3. Viskochil DH. The structure and function of the NF1 gene: molecular pathophysiology. In: Friedman JM, Gutmann DH, MacCollin M, Riccardi VM, eds. Neurofibromatosis phenotype, natural history, and pathogenesis, 3rd ed. Baltimore: The Johns Hopkins University Press 1999, 119-141.
4. Abecassis S, Bastuji-Garin S, Khosrotehrani K, Zeller J, Revuz J, Wolkenstein P. Age at diagnosis of neurofibromatosis 1: an audit of practice. Dermatology. 2008;216(4):347.
5. Posma E, Aalbers R, Kurniawan YS, Van Essen AJ, Peeters PM, Van Loon AJ. Neurofibromatosis type I and pregnancy: a fatal attraction? Development of malignant schwannoma during pregnancy in a patient with neurofibromatosis type I. BJOG: An International Journal of Obstetrics & Gynaecology. 2003;110(5):530-2.
6. Terry AR, Barker II FG, Leffert L, Bateman BT, Souter I, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications: a population-based study. American journal of obstetrics and gynecology 2013;209(1):46-e1.
7. Ponder M, Murton F, Hallowell N, Statham H, Green J, Richards M. Genetic counseling, reproductive behavior and future reproductive intentions of people with neurofibromatosis type 1 (NF1). Journal of genetic counseling 1998;7(4):331-44.
8. Mbekeani JN, Galvez-Ruis A, Nezzar H, Conca W, Ahmed M. Antiphospholipid syndrome and neurofibromatosis type

I: a coincidence or new association?. Arquivos brasileiros de oftalmologia 2019;82(2):155-7.
9. Swapp Gh, Main RA. Neurofibromatosis in pregnancy. British Journal of Dermatology 1973;88(5):431-5.
10. Healey Jr FH, Mekelatos CJ. Pheochromocytoma and Neurofibromatosis: Report of a Case. New England Journal of Medicine 1958;258(11):540-3.
11. İncecik F, Hergüner ÖM, Erdem SA, Altunbaşak Ş. Neurofibromatosis type 1 and cardiac manifestations. Turk Kardiyol Dern Ars. 2015;43(8):714-6.
12. Akyüz AR, Korkmaz L, Turan T, Akşan B. Mitral Valve Neurofibroma in A Patient with Neurofibromatosis Type 1: A Rare. Koşuyolu Heart Journal 19(3):211-2.
13. Xiong M, Gilchrest BA, Obayan OK. Eruptive neurofibromas in pregnancy. JAAD Case Reports 2015;1(1):23-4.
14. Blickstein I, Lancet M, Shoham Z. The obstetric perspective of neurofibromatosis. American journal of obstetrics and gynecology 1988;158(2):385-8.
15. Dugoff L, Sujansky E. Neurofibromatosis type 1 and pregnancy. American journal of medical genetics 1996;66(1):7-10.
16. Sakai T, Vallejo MC, Shannon KT. A parturient with neurofibromatosis type 2: anesthetic and obstetric considerations for delivery. International journal of obstetric anesthesia 2005;14(4):332-5.
17. Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: clinical presentations and naesthetic implications. Br J Anaesth 2001;86:555-564.
18. Merker VL, Murphy TP, Hughes JB, Muzikansky A, Hughes MR, Souter I et al. Outcomes of preimplantation genetic diagnosis in neurofibromatosis type 1. Fertility and Sterility 2015;103(3):761-8.
19. Gruber A, Pacault M, El Khattabi LA, Vaucouleur N, Orhant L, Bienvenu T et al. Non-invasive prenatal diagnosis of paternally inherited disorders from maternal plasma: detection of NF1 and CFTR mutations using droplet digital PCR. Clinical Chemistry and Laboratory Medicine (CCLM) 2018;56(5):728-38.