

Reprinted from

International Journal
of
Health Research

Peer-reviewed Online Journal

<http://www.ijhr.org>

PORACOM
Academic Publishers

International Journal of Health Research

The *International Journal of Health Research* is an online international journal allowing free unlimited access to abstract and full-text of published articles. The journal is devoted to the promotion of health sciences and related disciplines (including medicine, pharmacy, nursing, biotechnology, cell and molecular biology, and related engineering fields). It seeks particularly (but not exclusively) to encourage multidisciplinary research and collaboration among scientists, the industry and the healthcare professionals. It will also provide an international forum for the communication and evaluation of data, methods and findings in health sciences and related disciplines. The journal welcomes original research papers, reviews, commentaries and case reports on current topics of special interest and relevance. All manuscripts will be subject to rapid peer review. Those of high quality (not previously published and not under consideration for publication) will be published without delay. The maximum length of manuscripts should normally be 10,000 words (20 single-spaced typewritten pages) for review, 6,000 words for research articles, 3,000 for technical notes, case reports, commentaries and short communications.

Submission of Manuscript: The *International Journal of Health Research* uses a journal management software to allow authors track the changes to their submissions. All manuscripts must be in MS Word or RTF format and in English, and should be submitted online at <http://www.ijhr.org/jmanager/>. Authors who do not want to submit online or cannot submit online should send their manuscript by e-mail attachment (in single file) to the editorial office below. Submission of a manuscript is an indication that the content has not been published or under consideration for publication elsewhere. Authors may submit the names of expert reviewers or those they do not want to review their papers.

Enquiries:

The Editorial Office
International Journal of Health Research
Dean's Office, College of Medicine
Madonna University, Elele Campus, Rivers State, Nigeria
E-mail: editor@ijhr.org or poracom@gmail.com

PORACOM
Academic Publishers

Facial Plexiform Neurofibromatosis in a 16 Year-Old Female from Eastern Nigeria: A Rare Presentation

Received: 30-Jul-08

Revision received: 13-Aug-08

Accepted for publication: 14-Aug-08

Abstract

Plexiform neurofibromatosis or von Pleckingshausen's disease is an uncommon variety of neurofibromatosis type I, usually associated with trigeminal nerve. We report a rare case of the disease on the face of a 16 year-old female patient. The patient presented with overhanging mass of skin folds on the face, completely covering one eye and partially covering the second eye, as well as occasional pain and itching. Physical examination revealed the presence of café au lait macules, freckling in the axillary, optic glioma and iris hamartomas. Family history was not contributory. An interventional reconstructive surgical procedure with excision of surplus skin folds on the face and lip margin was performed on the patient. Doloneurobion[®] (paracetamol and vitamins B1, B6 and B12 combination) as well as Vecuten[®] (neomycin sulphate, clotrimazole and dexamethosone combination) cream were used to successfully manage the occasional pain and itching. There was evidence of re-growth of the tumours over a one year follow-up period.

Keywords: Facial plexiform neurofibromatosis, von Pleckingshausen's disease, neurofibromatosis type I, Eastern Nigeria.

John E Arute¹

Paul JC Nwosu²

Patrick O Erah^{3*}

¹Department of Clinical Pharmacy, Faculty of Pharmacy, Madonna University, Elele Campus, Rivers State, Nigeria. E-mail: arute4john@yahoo.com

²Department of Surgery, Faculty of Medicine, College of Medicine, Madonna University, Elele Campus, Rivers State, Nigeria.

³Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

***For Correspondence:**

E-mail: p_erah@yahoo.com
Tel: +234-805-526-3622

Introduction

Plexiform neurofibromas (PNF) are benign tumors which originate from nerve sheath cells, subcutaneous, or visceral peripheral nerves that can involve multiple fascicles¹. At least eight forms of neurofibromatosis are recognized, the most common form being neurofibromatosis type I (NF-I), or von Recklinghausen's disease. NF-I is estimated to occur in one of every 3000 births with no sex predilection. PNF usually occur in as much as 30% of patients with neurofibromatosis type I (NF-I) – an autosomal dominant disorder caused by defect of one allele of the tumor suppressor gene, *NF1* on 17q²⁻⁶. The gene encodes a protein termed neurofibromin, which has a guanosine triphosphatase (GTPase) region that binds to Ras and positively modulates conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). *NF1* gene has at least 59 exons and encodes the 327-d protein known as neurofibromin.

PNF present at birth and often progress during early childhood at a growth rate and pattern which vary significantly and unpredictably. The condition can cause disfigurement by entwining important supportive structures⁷⁻⁸. Because of the

involvement of multiple fascicles of nerves and tissues and the spread of PNF, there is high risk of neurological and functional destruction when surgical resection is carried out. The surgical interventions are frequently postponed as long as possible from the early childhood. Most cases require repeat surgery since they are limited to debulking as PNF often re-grow later⁸.

We report a case of facial plexiform neurofibromatosis. To the best of our knowledge, this condition has not been reported previously in Nigeria even though anecdotal evidence indicates rare cases of neurofibromatosis occurring in different parts of the body in some tertiary health facilities.

Case Report

A 16-year-old female patient presented to us with a history of growth on the face, especially the right side, left orbital, and both sides of the chin and jaws (Figure 1). The patient reported that the face disfiguring growth started at birth and continuously increased in size since then. She could not see with the right eye and was spoke with difficulty. She complained of occasional pain and itching on the face. There was no history of any similar swelling, pain, trauma,



Figure 1: Anterior (left) and left lateral (right) views of a 16-year old Nigerian female with plexiform neurofibromatosis prior to surgery

constitutional symptoms and tingling numbness elsewhere over the body, or any distal neurological deficit. The patient is the third child of her parents of four children (3 females and 1 male). Though both parents are from the Eastern part of the country, she was first abandoned in a motherless baby home in Lagos early in life and later brought into a religious community by her father who then abandoned her. There was no known evidence of hereditary disease in the family and none of the other relatives had a known history of the disease.

On physical examination, she was pale and anecteric, and the face was disfigured with growth completely overhanging the right eye and partially covering the left eye and mouth. Vision on the right eye was completely obscured. *Café-au-lait* macules (with some measuring over 5.5 mm) as well as several freckles were observed in the axillary, back and chest regions including the breast. Superficial Lisch nodules were seen around the eyes on slit lamp examination. There were also skin folds on the upper lip margin. The patient was admitted and the laboratory results of malaria parasite, Widal test, skull X-ray, full blood count and retroviral screening were uneventful. Histopathological examination of sections of five pieces of the affected facial tissue, each measuring approximately 4.5 x 3.0 cm and 15 gm in weight with hemorrhagic pale white and brownish cut surfaces, revealed bundle masses with spindle-shaped cells and waxy cytoplasm (figure 2). A comprehensive patient interview conducted by two clinical pharmacists (first and third authors) to detect any relevant history of drug use and adverse drug reactions did not reveal any previous adverse reactions to any drug by either the patient or any other family member. Further investigations to rule out other features of neurofibromatosis type I and the possibility of any systemic involvement was then carried out. A final diagnosis of facial plexiform neurofibromatosis was thereafter made.

Reconstructive surgical procedure with excision of surplus skin folds on the face and lip margin was then performed under general anesthesia. Occasional pain and itching were managed with Doloneurobion® (a combination of paracetamol, Vitamins B1, B6 and B12 administered as one tablet thrice daily for two weeks, as necessary) and Vecuten® (dexamethasone 6 mg, clotrimoxazole 150 mg and neomycin sulphate 96.8 mg per 15 g) cream (as necessary). Also, malaria parasites, and urinary tract infections detected while the patient was being managed were successfully treated with antimalarials, analgesic and antibiotics. The patient received adequate psychotherapy and genetic counseling as often as necessary. As part of the management procedure, it was decided that she should be kept under observation and reviewed once in every 3 months for as long as possible. Unfortunately, the possible date of her return to her family could not be ascertained because of family rejection. However, she was doing well even though the face was still disfigured and a 12 months follow-up had shown clear evidence of re-growth of the tumours.

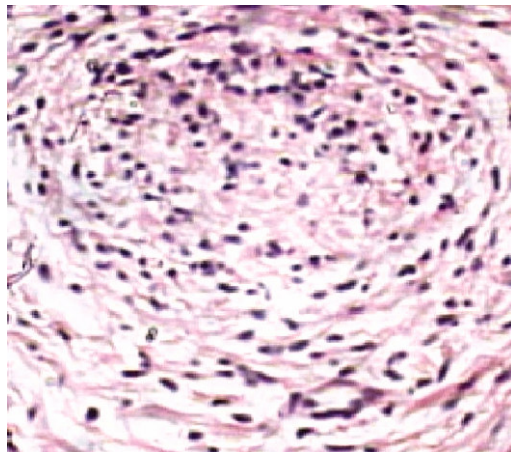


Figure 2: Histological features of the section of the facial tissues of a 16-year old Nigerian female with plexiform neurofibromatosis

Discussion

Plexiform neurofibroma is a rare type of generalised neurofibromatosis, which occurs due to overgrowth of neural tissue in the subcutaneous fat or deeper in the body. It is usually considered to be a hamartoma rather than a typical tumour⁹⁻¹⁰. They originate from nerve sheath cells, subcutaneous or visceral peripheral nerves, and can involve multiple fascicles. The term plexus refers to a combination of interlaced parts or a network. PNF are uncommon and occur almost exclusively in about 5-15% patients with neurofibromatosis type I¹⁰. Malignant changes in 2.4-29% of patients with neurofibromatosis have been reported¹¹. The condition is autosomally dominant, with variable penetration, and presents as multiple nodules of various sizes, which are firm and non-tender, often associated with *café au lait* spots and spindle deformities. Two types of PNF that have been recognized are (i) diffuse type/elephantiasis neurofibromatosis and (ii) nodular neurofibromatosis⁷.

PNF can occur anywhere along a nerve and may appear on the face^{10,12-13}, orbit and globe¹⁴, legs¹⁰, scalp, neck, chest, pelvis, abdomen^{11,15} or spinal cord and frequently involve the cranial and upper cervical nerves¹². The fifth, ninth and tenth cranial nerves are most commonly involved¹⁶. The condition can be quite disfiguring, as in the case being presented, and hemifacial hypertrophy can occur secondary to a plexiform tumor involvement¹⁷. Symptoms ranging from minor discomfort to extreme pain^{7,16,18} may occur. Complications include bleeding from trauma, neurological deficits, limited limb, and psychological disturbance because of abnormal anatomy¹⁰. There is evidence that only 50% of PNF patients have a positive family history of the disease and the remaining represent spontaneous mutations^{10, 16-18}. This evidence is consistent with the case being reported.

Neurofibromas are characterized by wavy and spindle-shaped nuclei as in the case with our patient. Although most individuals

who develop neurofibromatosis are not born with *café au lait* macules, these skin lesions develop during the first 3 years of life²⁰ and were observed in our patient. Lisch nodules, hamartomas of the iris that appear dome shaped found superficially around the eyes on slit lamp examination, help to confirm the disease. Axillary freckling (observed in our patient) and inguinal freckling often develop during puberty⁷. Various neurologic abnormalities, acoustic nerve involvement and deafness as well as gliomas of the optic nerve may occur. Several tumors, such as astrocytoma, meningioma, intramedullary glioma, and ependymoma, occur at high rate in some patients. The tumors may cause increased intracranial pressure, seizure, ataxia, or cranial nerve abnormalities. Many patients with NF-1 (25-40%) often have below average intelligence while 5-10% may have mental retardation^{7,19,20} which were not observed in our patient.

As proposed by the National Institutes of Health Consensus Development Conference in 1988, the criteria for neurofibromatosis type I are met if a patient has two or more of the following features²⁰:

- a) Six or more *café au lait* macules over 5 mm in greatest diameter in prepubertal persons and over 15 mm in greatest diameter in post-pubertal persons;
- b) Two or more neurofibromas of any type or one plexiform neurofibroma;
- c) Freckling in the axillary or inguinal regions;
- d) Optic glioma;
- e) Two or more Lisch nodules (iris hamartomas);
- f) A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis; and
- g) A first-degree relative (parent, sibling or offspring) with neurofibromatosis type I, based on the above criteria.

Central nervous system (CNS) tumors, macrocephaly, mental deficiency, seizures, short stature and sclerosis are some of the other possible abnormalities that can occur. Sexual precocity is seen in 3-5% of affected children^{7,19,20}. The patient in our case fulfilled many of the above criteria; she had more than six *café au lait* macules, plexiform neurofibroma, fleckles in the axillary, optic glioma as well as iris hamartomas but no evidence of CNS tumors, macrocephaly, mental deficiency, seizures, short stature or sclerosis.

Imaging is frequently employed in the confirmation of diagnosis of PNF. Superficial ultrasonography may show homogeneous hypoechogenicity or slight echogenicity. Contrast enhanced computed tomography is useful in predicting resectability, detecting metastasis, and evaluating response of the treatment. Magnetic resonance imaging often reveals peripheral hyperintensity and central hypointensity on T2-weighted sequences and marked contrast enhancement after gadolinium^{11,16}. Histopathologic distinction of the lesion may not be always easy but provides a confirmatory diagnosis. The application of ⁶⁷Ga citrate scintigraphy as primary investigation in patients with neurofibromatosis and suspected malignant change has been reported²¹.

Although there is no specific therapy for PNF, treatment is often directed towards prevention or management of the disease. Though surgery is the mainstay of treatment for solitary neurofibromas, it does not cure PNF because they are entwined with normal tissues and the invasive nature and location of the tumors prevent complete resection¹⁰. Retinoic acid therapy, angiogenesis inhibitors (such as interferon and thalidomide) are alternative therapies to surgery that have been tried. Oral farnesyl protein transferase inhibitors and cytokine modulators are also under investigation¹⁹. Vecuten[®] cream contains antibiotics (neomycin sulphate), antifungal (clotrima-

zole) and a steroid (dexamethasone) and has been effective in managing the itching occasionally experienced by our patients. A combination of an analgesic (paracetamol) and vitamins (B1, B2 and B12), Doloreubion[®], often recommended as 1-2 tablets thrice daily for neuritis and neuralgia, especially cervical syndrome, shoulder-arm syndrome, lumbalgia, ischialgia, herpes zoster, post-operative pain, intercostal and trigeminal neuralgia (as in the case of our patient) has also been effective in controlling the occasional pain experienced by our patient.

Conclusion

The disfiguring nature of facial PNF can be psychologically traumatic for most patients and often require good counseling. The patient being reported has not only be abandoned by her family but has also dropped out of school at her secondary education level, making things even worse for her. Nevertheless, we have been able to rehabilitate her temporarily in a hospital environment and the patient is currently able to relate well with University medical students and hospital staff.

Acknowledgement

We would like to thank the management of Madonna University Teaching Hospital, Elele, Rivers State, Nigeria for the permission to publish this report.

References

1. Kleinhues P, Cavenee WK. Tumours of the nervous system. In *World Health Classification of Tumours*. IARC Press, Lyon, 2000.
2. Huson SM, Hughes RAC. *The Neurofibromatosis: A Pathogenetic and Clinical Overview*. Chapman and Hall Medical, London, 1994.
3. Cawthon RM, Weiss R, Xu GF, Viskochil D, Culver M, Stevens J, Robertson M, Dunn D, Gesteland R, O'Connell P, et al. A major segment of the neurofibromatosis type I gene: cDNA sequence, genomic structure, and point mutations. *Cell*. 1990,

- 62:193-201. Erratum in: Cell 1990; 62: following 608.
4. Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolf RK, Culver M, Carey JC, Copeland NG, Jenkins NA, et al. Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type I locus. Cell. 1990; 62:187-192.
 5. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, Fountain JW, Brereton A, Nicholson J, Mitchell AL, et al. Type I neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. Science. 1990; 249:181-186. Erratum in: Science. 1990; 250:1749.
 6. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997; 278:51-57.
 7. Kam JR and Helm TN. Neurofibromatosis (von Recklinghausen's disease). eMedicine. Available at <http://www.emedicine.com/DERM/topic287.htm>. Accessed July 28, 2008.
 8. Friedrich RE, Schmelzle R, Hartmann M, Fünsterer C, Mautner V. Resection of small plexiform neurofibromas in neurofibromatosis type I children. World J Surg Oncol. 2005; 3:6-11.
 9. Sengupta SP. Tumours and cysts. In: Long and Short cases in Surgery. 1st ed. New Centre Book Agency Publications, Calcutta, 1996; 39-75.
 10. Patil K, Mahima VG, Lahari K. Facial plexiform neurofibroma in a child with neurofibromatosis type I: A case report. J Indian Soc Pedodontics Prevent Den. 2007; 25(1):30-35.
 11. Pui MH, Yang ZY, Li ZP. Computed tomography of abdominal neurogenic tumours. Australas Radiol 1998; 42:183-187.
 12. Wheeler JM. Plexiform neurofibromatosis (von Recklinghausen's disease) involving the choroid, ciliary body, and other structures. Trans Am Ophthalmol Soc. 1936; 34:151-162.
 13. Sienkiewicz H, Wójtowicz PM. A case of plexiform neurofibroma of the face. Otolaryngol Pol. 1985; 39(3):253-256
 14. Davis FA. Plexiform Neurofibromatosis (von Recklinghausen's Disease) of the Orbit and Globe, with Associated Glioma of the Optic Nerve and Brain: Report of a Case. Trans Am Ophthalmol Soc. 1939; 37:250-271.
 15. Ferrozzi F, Zuccoli G, Bacchini E, Piazza P, Sigorini M, Virdis R. Extracerebral neoplastic manifestations in neurofibromatosis 1: integrated diagnostic imaging. Radiol Med (Torino) 1998; 96:562-569.
 16. Cunha KS, Barboza EP, Dias EP, Oliveria FM. Neurofibromatosis type I with periodontal manifestation. A case report and literature review. Br Dent J. 2004; 196:457-460.
 17. D'Ambrosio JA, Langlais RP, Young RS. Jaw and skull changes in neurofibromatosis. Oral Surg Oral Med Oral Pathol. 1988; 66:391-396
 18. Neville BW, Damm DD, Allen CM, Bouquet JE. Oral and maxillofacial pathology. 2nd ed. Elsevier, Philadelphia, 2002; 457-461.
 19. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000; 105(3 Pt 1):608-614.
 20. National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference statement. Arch Neurol. 1988; 45(5): 575-578.
 21. Levine E, Huntrakoon M, Wetzel LH. Malignant nerve sheath neoplasms in neurofibromatosis: Distinction from Benign tumours by using imaging techniques. Am J Roentgenol. 1987; 149:1059-1064.