A DECADE'S RETROSPECTIVE REVIEW OF NEUROFIBROMATOSIS IN A TERTIARY HOSPITAL IN SOUTH–SOUTH NIGERIA

AMADI E.S.[1], [1]ALTRAIDE D.D.[1], PEPPLE E.F.[2]

1.Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Alakahia

2. Department of Community Medicine, University of Port Harcourt Teaching Hospital, Alakahia

Correspondence:

E-mail: ekechiamadi@yahoo.com

ABSTRACT

Background:

Neurofibromatosis is a genodermatosis which is common worldwide without any age, gender or racial preference. Its effects are multi-systemic, requiring a multidisciplinary approach in management to reduce the morbidity and mortality associated with it.

Aim:

This study reviewed the epidemiology and management of patients with neurofibromatosis in the centre.

Method:

This study is a retrospective cross sectional study of neurofibromatosis cases seen over a ten year period within January 2006-December 2015 in the University of Port Harcourt Teaching Hospital Alakahia, in Rivers State, Nigeria

Results:

There were 32 patients with clinically diagnosed neurofibromatosis type 1 with an average incidence rate of 0.54%. There was slight female preponderance in the study. The highest incidence was seen in the second decade of life. The duration of the skin lesions before presentation to the dermatology clinic ranged from 1-31 years. Neurofibromas were seen in all patients of whom plexiform neurofibromas were seen in about 30% of the patients. The commonest site on the body which the lesions started from was the trunk (30%), followed by the face (10%). In terms of spread, the face (46.7%) was most affected, followed by the trunk (36.7%), the upper and lower limbs (33%) respectively. Axillary freckles and café au lait spots were the second commonest clinical features.

Conclusion:

Neurofibromatosis type 1(NF1) is of public health importance because it causes body distortion leading to social stigmatization. It can be mistaken for an infectious disease like leprosy or tuberculosis. It is more commonly seen than neurofibromatosis type 2 (NF2) in our region. Its diagnosis can be made clinically and by genetic testing.Complications are diverse and management is multidisciplinary.

INTRODUCTION

Neurofibromatosis in most cases presents as a disfiguring skin condition which is characterized by multiple widespread nodules on the skin. It is a genetic disorder of the nervous system. The name is gotten from the abnormal growth called neurofibroma. It is the commonest single genetic neurological disorder. It has no racial or sex predilection. The occurrence of neurofibromatosis is due to a gene mutation which is inherited usually in an autosomal dominant fashion or it could be sporadic.[1,2,3,4,5]

Neurofibromatosis is commonly divided into two major classifications Type 1 and type 2 which some medical scientists consider as peripheral and central respectively,[20] Recently, there are now known to be 5 classifications based on genetic science which are type 1 called von Recklingsen's disease, type 2 consisting mainly of bilateral vesicular schwannomas, segemental or mosaic neurofibromatosis, familial café au lait spots and the fifth being schwanomatosis.[1]

Type 1 is known to occur in a range of 1 in 2500-4000 births while Type 2 is rarer occurring once in

about 40000 births.[1,2, 3,4,5] The mode of inheritance for the two major types are 17q for type 1(NF1) and 22q for type 2(NF2). These both share a common gene loci at q11, which has become a subject of poetic description.[4,6,26] The NF1 encodes for the protein neurofibromin which is found in all cells they contain neural crests such as those found in the skin, bone, nerves and eyes. A mutation in this gene reduces the levels of neurofibromin which helps in suppressing tumor formation in the body. This is the basis for the development of the nodular lesions which most time is benign but poses a lot of physical discomfort due to the cosmetic disability and compression of vital organs.[1, 6] Type 2 is also known to encode a protein merlin or schwanominn which also acts as a tumour suppressor. NF2 or central neurofibromatosis is distinguished from NF1 by the scarce skin involvement but the presence of a significant numbers of menigiomas and acoustic neuromas [1,6]

According to the National Institute of Health after a conference that took place in 1987, criteria were set out to clinically diagnose neurofibromatosis type [1]. Any two out of the seven present qualifies as the diagnosis of neurofibromatosis. The criteria are six or more café au lait macules bigger than 0.5cm in the largest diameter in young children and 1.5cm in adolescence and adults; two or more neurofibromas of any type or one plexiform neurofibroma, axillary or inguinal freckling, optic glomas, two or more iris harmatomas or Lisch nodules, a bony lesion such as a sphenoid dysplasia or thinning of long bones with or without pseudoartrosis and a first degree relative(father, mother, sister, brother, son or daughter) with neurofibromatosis fulfilling the above criteria.[1,3,6]

In making diagnosis of neurofibromatosis type 2 the criteria commonly used is the 1997 Manchester Criteria which has to fulfill any 1 of the 3 conditions; bilateral vestibular schwanomatosis, 1 or more first degree relative (father, mother, brother or sister) with unilateral vestibular schwannoma at less than 30 years and 2 of any of the following glioma, juvenile posterior opacities, meningioma and schwannoma. [6, 7] This criteria had the drawback of diagnosing paediatric cases thus the Baser Criteria was developed in 2016.[7] Neurofibromatosis can be very devastating, counseling and psychotherapy are key in its management.

This study aims to look at the newly diagnosed cases of neurofibromatosis within this period at the University of Port Teaching Hospital and how they were managed and the outcome of management.

METHODOLOGY

The study is a retrospective cross sectional analysis of patients newly diagnosed with neurofibromatosis within the ten year period of January 2006- December 2015 who attended the Dermatology outpatient clinic of the University of Port Harcourt Teaching Hospital which is the premier tertiary institution in the state. Patients are referred from other medical units, surgery, pediatric and psychiatry departments. It also receives referral from neighbouring states within the South- South geo political zone as well as other parts of Nigeria. All patients were examined by dermatologists and diagnosis was mainly clinical. The hospital numbers, age and sex were gotten from the new patients clinical registrar which was used in extracting data from their folders using a semi structured questionnaire which was developed based on existing knowledge and management of neurofibromatosis available in the environment. 23 folders were retrieved out of the 32 new cases of neurofibromatosis seen within the decade out of 5961 new dermatological cases. The retrieved data were first entered into a computer based template and exported to Statistical Package for Social Sciences for Statistical analysis. Descriptive statistics using means, standard deviation, frequencies and proportions were employed as appropriate. Tables and charts were used in the presentation of data. Inferential statistics using chi square test was employed to determine significant differences in proportions of the age categories across the sex of the patients. Statistical significance was set at a level of 0.05.

RESULTS

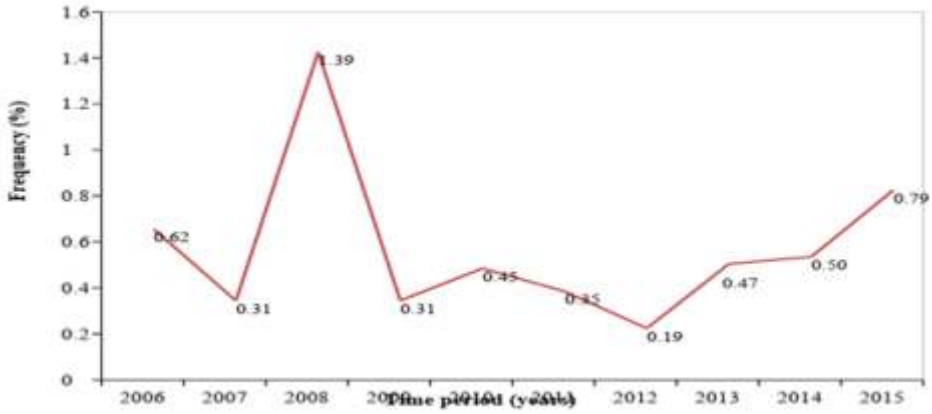


Figure 1…Ten year trend showing the incidence rates of Neurofibromatosis in 2006-2015

Table 1-Socio-demographic characteristics of patients with neurofibromatosis

Variables	n	%
Age in years (N = 30)		
≤10 years	2	6.7
11 – 20 years	10	33.3
21– 30 years	6	20.0
31 – 40 years	7	23.3
>40 years	5	16.7
Mean age = 27.00 ± 11.92 years		
Range = 2 – 51 years		
Sex (N = 32)		
Male	12	37.5
Female	20	62.5
Marital status (N = 16)		
Single	11	68.8
Married	5	31.2

Table 2-History of neurofibromas in patients with neurofibromatosis

Variables	N	%
Age at which lesion started (N = 18)		
≤15 years	10	55.6
>15 years	8	44.4
Mean age = 15.39 ± 8.85 years		
Range = 1 – 31 years		
Family history of similar lesion (N = 23)		
Yes	1	4.3
No	22	95.7
Duration of lesion before presentation (N = 20)		
≤25 years	18	90.0
>25 years	2	10.0
Mean age = 12.40 ± 11.19 years		
Range = 2 – 40 years		

Table 3 Age by sex of patients with Neurofibromatosis

	Sex		
	Male	**Female**	**Total**
Age category	**n (%)**	**n (%)**	**n (%)**
≤10 years	2 (66.7)	1 (33.3)	3 (100.0)
11 – 20 years	3 (27.3)	8 (72.7)	11 (100.0)
21 – 30 years	3 (50.0)	3 (50.0)	6 (100.0)
31 – 40 years	1 (14.3)	6 (85.7)	7 (100.0)
>40 years	3 (60.0)	2 (40.0)	5 (100.0)

Fisher's exact test = 4.647; p-value = 0.336

Table 4 Range of sizes of the largest lesions in the affected persons

Variables	Ranges(cm)
Length	0.5-10.0
Width	0.25-5.0
Height	0.1-2.0

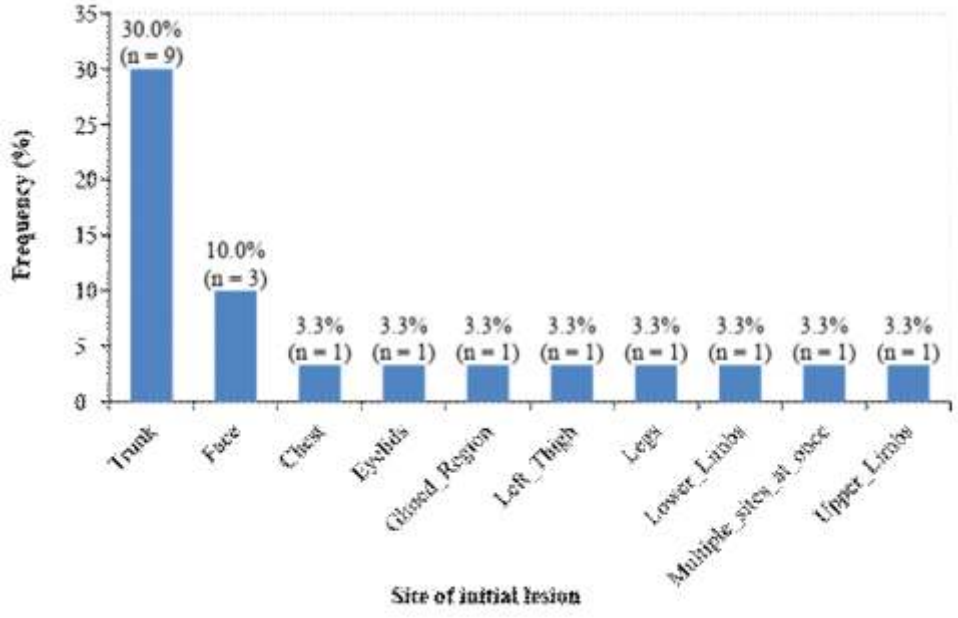


Figure 2….. Site of initial lesion in patients with neurofibromatosis

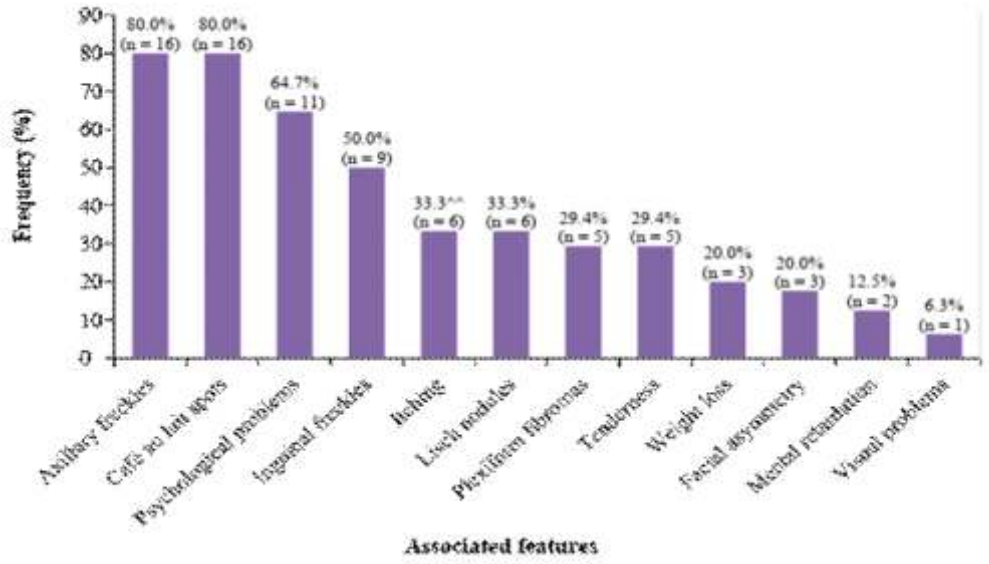


Figure 3… The associated clinical features of neurofibromatosis

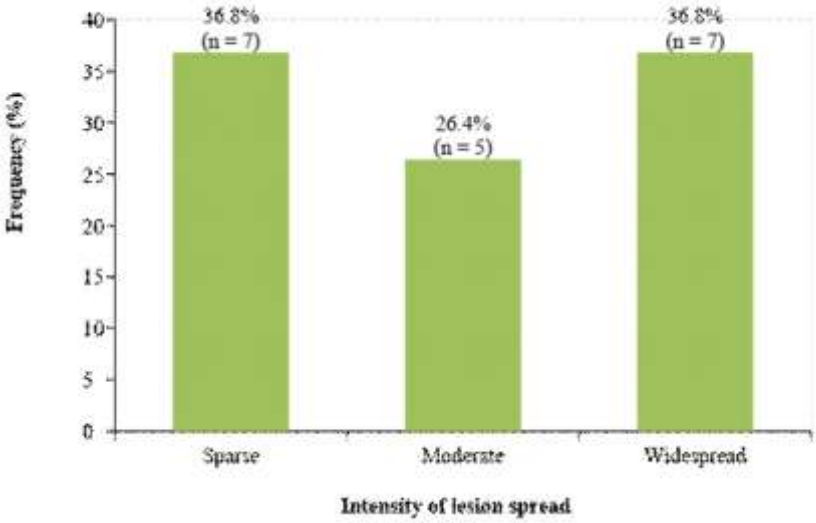


Figure 4… The severity of the lesions

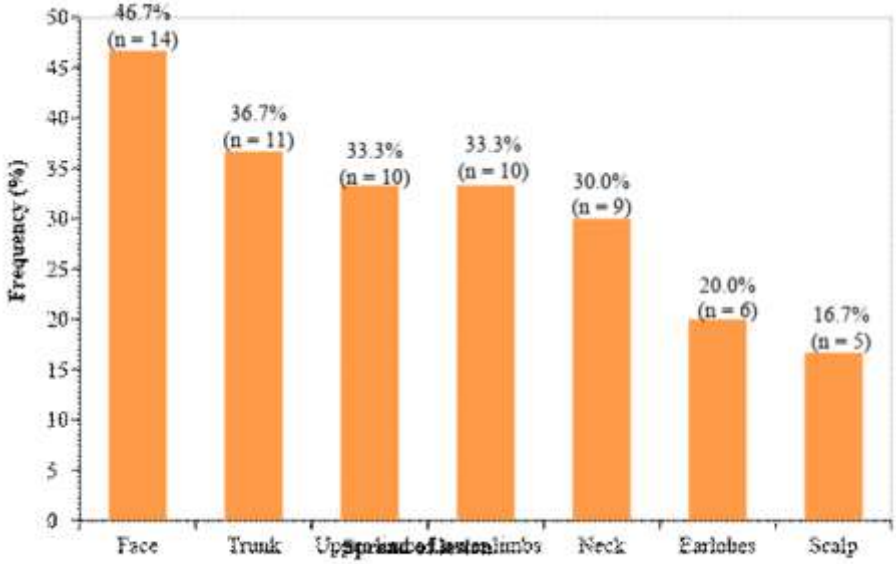


Figure 5….. Spread of lesion in patients with neurofibromatosis

Table 5- Medical history/problems of patients with neurofibromatosis

Variables*	**n**	**%**
HIV	1	4.3
Hypertension	1	4.3

*None of the respondents had any other medical history/problems

DISCUSSION

The average incidence of neurofibromatosis over the ten year period was 0.54% which is 5.4 persons per 1000 per year. Neurofibromatosis consisted of 1 in 186 new cases of dermatological diagnoses seen per year. In this study, type 1 was only type of neurofibromatosis that was diagnosed based on clinical grounds**.** There were no suspected cases of neurofibromatosis type 2 based on the fact there was history of hearing loss in patients or their relatives, genetic testing was not done for any of the patients to confirm the diagnosis. A hospital study within the same country but a different tertiary hospital also revealed similar incidence, 0.54% of new dermatological cases.[8] Population based studies in different age groups of patients such as the one done in Germany amongst 6 year old revealed the estimated incidence rate to be 30-38 cases per 100,000 live births and the crude prevalence to be 3.0x10, 000.[9]

The age range of patients was 2-51 years with the highest number of cases within the age range of 11-20years consisting of more than one-third of the new cases seen within the period with the mean age to be 27.00 ±11.92. This is different from other studies done in Nigeria where most of the cases seen where in the third decade.[8,10,11] It is known that neurofibromatosis is an autosomal condition and is it fully penetrant but the expressivity is variable. It is known to manifest in childhood fully by the age of 8 years, but in this environment where knowledge is lacking about the disorder, presentation may be delayed.

The female: male ratio was approximately 1.6:1. This is slightly higher than other studies done within the same country that showed a slight male preponderance.[8,10,11,12] In a study done in India there was a higher proportion of females.[14] The slight female preponderance might be related to the higher cosmetic value a female attaches to her appearance. Parents and caregivers are more likely to seek help for their daughters or female wards believing that an early intervention to remove the tumours would secure their chances for marriage. However with regards to this study there was no statistical significant relationship between age categories and sex.

This study revealed that there were more single persons with neurofibromatosis. This is likely to be reflection of the socio dynamics of the age group with highest incidence of neurofibromatosis in this study. In current times there is delay in marriage in pursuit of western education compared to years prior to western education. Other studies done within the country showed similar findings but even with a higher percentage of unmarried persons. Neurofibromatosis is known to cause cosmetic disabilities and affect social life of patients.[1,2,3]

Majority of the patients fell within the group,' ≤15 years' which the first manifestations of neurofibromas started. The reason is as earlier explained neurofibromatosis is fully penetrant at a young age and there is an increased awareness amongst people about the availability of dermatologists in the area. The age range at which the patient had lived with the lesions before presenting to the clinic was 2-40 years, on the average of 12.40± 11.59 years. This is a reflection of the various ages at which the patient or parents/guardians may decide to seek medical care.

The site at which the initial lesions started was at the trunk in majority of cases followed by the face, however in terms of spread of lesions the face was noted to be the most involved in a majority of patients followed by the trunk. A hypothesis which was proposed that the trunk having a higher temperature than the other parts of the body is more likely to develop neurofibromas.[16] Other studies done in Nigeria also showed the trunk as the most common site of presentation.[10,18]There was no significant difference in the grade of severity of lesions amongst different individuals.

Only 4.3% (1) of the patients were noted to have a positive family history. The patient was a female patient with her two brothers having similar lesions but they were not as severe as hers. This finding is similar to other studies within health centres in Nigeria.[8,10] Higher values were seen in a studies and Northern Nigeria and in North West England. [13] Sporadic mutations are also common amongst people living with neurofibromatosis. [5,13]

Among the clinical presentation, neurofibromas were seen in all patients, followed by axillary freckles and café au lait (more than 6 of them) with four fifths of the patients with these features. This finding is in keeping with other studies.[8, 9, 10, 13] Café

au lait spots have been observed to show a poor contrast in Nigerian children thus was recommended to be called café sans lait spots or black brownish spots in Africans.[12] Café au lait spots are usually visible in 95% of children by the age of 6.[9] About 13.7% of children who were screened in a study had only café au lait spots; based on the recent classification of neurofibromatosis , these children would be said to have neurofibromatosis if they have a positive family history of café au lait macules.[1,9] Plexiform neurofibromas were seen in less than a third of the patients while the rest were subcutaneous and cutaneous. Similar values have also been documented in other studies and case reports.[10, 13,18, 25] Neurofibromas can vary in size as reflected in the range of sizes above. Lisch nodules were seen in about one third of patients, this value is less when compared to other studies.[10, 13, 20] Itching and tenderness were seen in about one third of patients. These are not unusual in patients with neurofibromatosis and have been documented in studies in medical literature.[1, 3, 4] Mental retardation was documented in one tenth of patients. This is similar to finding in other studies.[10, 20]. Weight loss was as common as mental retardation in this study and may be linked to several factors such as neurofibromas compressing the stomach causing easy satiety, anorexia following depression due to the social stigmatization, gut dysmotility, associated tumours like carcinoid, sarcoma or ganglioneuroma.[25] The presence of weight loss and the skin lesions in one of the patients made the patient to be initially referred to the tuberculosis clinic however was proved be free from tuberculosis after some investigations. Facial asymmetry and visual problems were also found to be complications of neurofibroamatosis in this study and have also been documented in other studies as a result of compression of the tumours on nerves that supply this parts.[1,3,11,20]

Hypertension has been associated with neurofibromatosis which may be due to association with phaechromocytoma, compression of the kidney or heart and their vessels by neurofibromas such as renal artery stenosis or coarctation of the aorta or it could be a co –morbidity. Unexplained vascular changes have also noted to occur with neurofibromatosis.[24], [25] Only one patient had hypertension in this study who happened to be a male in his 5th decade of life may have been most likely due to age related changes. HIV co-existing with neurofibromatosis has been documented in a case report within the same country. There was no associated worsening of symptoms of neurofibromatosis as also seen in this study. There was no significant correlation of neurofibromatosis to any particular medical illnesses. Majority of the patients had no associated chronic medical illness. Other notable complications such as skeletal disorders, endocrine disorders and malignant transformation documented in studies conducted within the same country was not seen amongst patients with neurofibromatosis in this centre.[10.11,15]

Management of all patients was multidisciplinary involving the dermatologists, radiographers, ophthalmologists, optometrists, counselors, psychotherapists, surgeons, nurses and other medical workers. They were all counseled about the disease condition and prognosis, 100 %(23) were placed on ketotifen which is a mast cell stabilizer and anti-allergic drug which has proven useful in treatment of patients with neurofibromatosis. It has been shown to reduce tumour growth, pruritus and pain.[2, 23, 24] A side effect of the drug which is weight gain can also be of benefit to those with weight loss. They were appropriately managed for co morbidities and referred to various departments according to their health peculiarities and were placed on regular follow ups. There was improvement of symptoms such as pruritus and pain. Unfortunately 99.5 %(22) were lost to follow up after two to three visits and 0.5 %(1) was referred to surgical clinic for excisional biopsy.

CONCLUSION

Neurofibromatosis type 1(NF1) is a disease of public health importance because it causes physical distortion of the body and can be a source of social stigmatization. It can also be mistaken for an infectious disease such as leprosy or tuberculosis. It is not uncommon in our environment and is more commonly seen than neurofibromatosis type 2 (NF2).The diagnosis of NF1 can be made clinically although genetic testing is a more reliable method in distinguishing it from NF2. Complications are

diverse in different individuals and management is multidisciplinary.

RECOMMENDATIONS

1 .The public should be enlightened about the clinical features of neurofibromatosis, its management and prognosis in order to encourage persons with the disease and their caregivers to seek care early.

2. Health workers at all levels should also be enlightened about this condition.

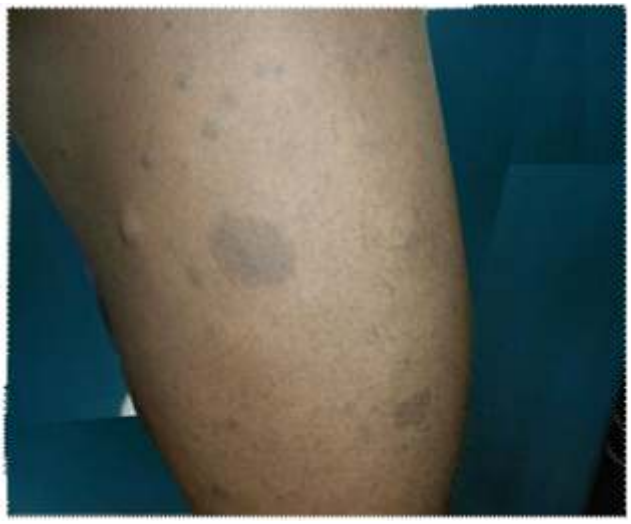
3. Neurofibromatosis support groups should be formed to provide supportive care and prevent social stigmatization.

REFERENCES

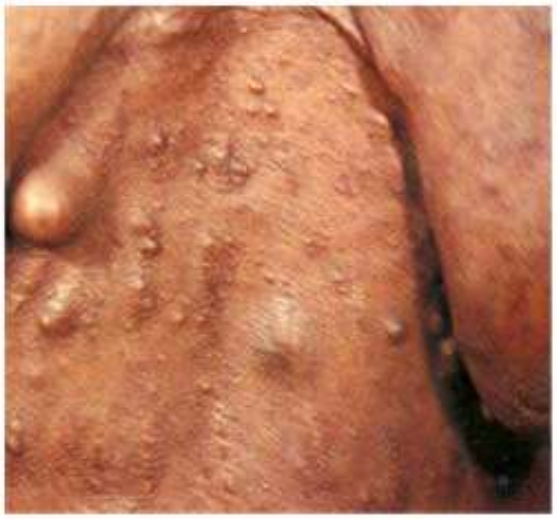
1. Listenick R, Charrow J, *Neurofibromatosis* Fitzpatrick Dermatology in General Medicine7th ed. In Wolff K et al ed. New York, McGraw- Hill, pp 1331-1336
2. Thakker RV- Chapter 408 *Multiple Endocrine Neoplasia*; In: Longo D et al ed. Harrison's Principles of Medicine, 19th edition, 2016, United States of America, The McGraw-Hill companies pp2343
3. Yusuf S *Genodermatosis* African Dermatology, 2014,Ibadan, Ibadan University Press pp341-343
4. Longmore M et al Neurofibromatosis, Oxford Handbook of Clinical Medicine 9th ed. 2014 Oxford, Oxford University Press pp518-519
5. Kongkham P, James TR; *Neurocutaneous syndromes*, Available at ekinygos. Ismum/springer/…/327-343pdf… (Accessed 25th May 2018)
6. Baliga R (2012) *Neurofibromatosis* 250 Cases in Clinical Medicine, 4th ed. Edinburgh, Saunders Elsevier pp. 377-78
7. NF2 Information and services, https://www.nf2is.org/diagnosis.php (Accessed 21st May 2018)
8. Onunu AN, Lawal NA, Neurofibromatosis1: A clinical study of the Nigerian African. *Annals of Biomedical Sciences 2002*, 1(2) Available at www.ajol.info/index.php/abs/article/view/40631 (Accessed on 19th April 2018)
9. Lanmert M, Friedman JM, Kluwe L, Mautner VF, Prevalence of Neurofibromatosis type 1 at an elementary school enrollment, *Arch Dermatol 2005* Jun :141(1): 71-74 Available at www.ncbi.nim.nih.gov/pubmed/15655144 (Accessed on20th April 2018)
10. Odebode TO, Afolayan EO, Adigun IA, Daramola OM, Clinicopathological Study of Neurofibromatosis in Type1 , *International Journal of Dermatology* 2005; 44(2):116-120, Doi 10 : 11114:1365-4632.2005.020386 Available at https://www.ncbi.nim.nih.gov/pubmed/15689208 (Accessed on 20th April 2018)
11. Nyandaiti YW, Tahir C, Nggada, HA, Ndahi AA Clinico-pathologic presentation and management of neurofibromatosis 1(von Recklinghausen's) disease among eastern Nigerians. A six year review, *Niger Med.J[serial online] 2009*[cited 2018 May 20]:50:80-3. Available http://www.nigeriamedj.com/text.asp?2009/50/4/80/71964
12. Ademiluyi SA, Ijaduola GTA, Neurofibromatosis in Nigerian Children ,Annals of Tropical Paediatrics- *International Child Health, 1987*[online 2016], 7(2):145-148, Available at https://www.ncbi.nim.nih.gov/pubmed/2441653 (Accessed 20th May 2018)
13. McGaughran JM et al: A Clinical Study of Type 1 Neurofibromatosis in North West England., *Journal of Medical Genetics, 2005* 36(3) Available at http//jmg.bmj.com/content/36/3/197 (Accessed 15th May 2018)
14. Lakshmanan A et al, A Clinical Study of Neurobibromatosis-1 at a Tertiary Health Care Centre in South India , *Pigment International 2016*, 3(2):102-107 Available at http://www.pigmentinternational.com/article.asp?issn=2349-5847; year=2016; volume=3;issue=2;spage=102;epage=107;aulast=Lakshmanan
15. Ofondu E, Achigbu E, Achigbu K, Ekweigwe N, Osuagwu C, Adimorah(2016), Unilateral Gynaecomastia and Neurofibromatosis: A case report, Book of Abstracts of the 1st scientific Meeting of The African Society of Dermatology &Venerology and the 10th Annual Scientific &Annual General Meeting of the Nigerian Association of Dermatologist held in Abuja from 12th-16th July 2016
16. Isa SE, Akindele S, Daniyam C, Iroezindu M,

Agaba A, Agbaji O, An HIV-1 Infected Patient with Neurofibromatosis Type 1: A Case Report, *Nigerian Health Journal, 2012* :12(2):52-54

17. Kieseme BE, Dongo AE, Prisadov G, Okonta K, Imoloamen C, Giant Intrathoracic Neurofibroma with significant Mediastinal Shift: A case report and Review of Literature, *case Reports of Pulmonology* 2013 article ID 619729 https://doi/10/115/2013/619729/ Available at www.hindawi.com/journals/cripu/2013/619729 (Accessed 26th May 2018)
18. Abubakar U et al- Excision of a giant anterior chest wall nurofibroma and chest wall reconstruction with methylmethacrylate and rectus abdominis flap; case report, *Niger J Med 2014*;23(4):344-350
19. Kaufman D., Tinschert S., Algermissen B. Is the distribution of dermal neurofibromatosis type 1 NF l related to the pattern of the skin surface temperature? *Eur J Dermatolol* 2001; **11:** 521525.
20- Ropper AH, Brown RH; Adams and Victor's Principles of Neurology,8th ed. New York McGraw-Hill 2005; pp 869-871
21. Riccardi VM, Mast- cell stabilization to decrease neurofibroma growth. Preliminary experience with ketotifen, *Arch Dermatol, 1987* Aug; 123(8):1011-6 Available at https://www.ncbi.nim.nih/m/pubmed/3115189/?i=2&from=/2511044/related (Accessed 1st June 2018)
22. Haustein UF, Ketotifen inhibits urticarial and tumour progression in neurofibromatosis, *Dermatol Monatsschr*:1989;175(9):581-4, Available at https://www.ncbi.nim. nih.gov/pubmed/2511044/?i=4&from/2452604/related (Accessed 1st June 2018)
23. Riccardi VM, Ketotifen suppression of NF1 neurofibroma groeth over 30years,*Am J Med Genet A, 2015*; 167(7) Available at https/online library.wiley.com/doi/abs/10.1002/ajmg.a37045 (Accessed 1st June 2018)
24. Gaurang M et al Neurofibromatosis type 1-associated hypertension secondary to coarctation of the aorta, *Clin Kidney J*; 2014 Aug;7(4):394-395
25. Hirsch NP, Murphy A, Radcliffe JJ, Neurofibromatosis: Clinical Presentations and Anaesthetic Complications, *British Journal of Anaesthesia,2001*, April 86(4)pp555-564 Available at https://academic.oup.com/bja/article/86/4/555/293778 (Accessed 2nd June 2018)
26. Amadi E; Psalms of Infirmity, Abuja, Best Choice Global Network Limited, 2017 pp 351,359



A- café au lait spots on the thigh



B cutaneous neurofibromas on the trunk

PROFORMA FOR A DECADE'S RETROSPECTIVE REVIEW OF NEUROFIBROMATOSIS IN A TERTIARY INSTITUTION IN SOUTH-SOUTH NIGERIA

Hospital number----------

BIODATA

1) Age---------- 2) Sex: Male Female 3) Marital status ----------

4) Tribe---------- 5) State----------

6) Home address----------

HISTORY OF NEUROFIBROMATOSIS

Age at which lesion started----------

Family history of similar lesions----------

Duration before presentation----------

Site of initial lesion----------

Estimated size of largest lesions----------

Intensity of lesions: Sparse ☐ Moderate ☐ Widespread ☐

Spread

Scalp ☐ Face ☐ Ear lobes ☐ Neck ☐ Upper limbs ☐ Trunk ☐ Lower limbs ☐

Associated Features

Axillary freckles ☐ Café au lait spots ☐ Facial Asymmetry ☐ Hearing loss ☐ Inguinal ☐ Freckles ☐

Itching ☐ Lisch Nodules ☐ Mental retardation ☐ plexiform fibromas ☐ Psych. problems ☐

Seizures ☐ Stature abnormalities ☐ Tenderness ☐ Visual Problems ☐ Weight loss ☐

Chronic Medical Problems

Asthma ☐ Epilepsy ☐ DM ☐ HBsAg ☐ HCV ☐ HTN ☐ HIV ☐ Malignancy PUD ☐

Histological Diagnosis: Yes ☐ No ☐ **MRI Diagnosis:** Yes ☐ No ☐

Treatment

Previous before hospital visitation Yes ☐ No ☐ State----------

Hospital: ketotifen 2mg Yes ☐ No ☐ Others ----------

Improvement after treatment Yes ☐ No ☐