Original Research Article

A study on ocular manifestations of neurofibromatosis type-1 in rural population of Chittoor district, Andhra Pradesh

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Abstract

Neurofibromatosis, an oculo--neurocutaneous syndrome is an autosomal dominant disorder involving multiple systems. It is of 2 types, Neurofibromatosis type-1 (NF-1) and Neurofibromatosis type-2 (NF-2) The syndrome is caused by genetic mutations on chromosome 17 in NF-1 and on chromosome 22 in NF-2. The disorder is characterized by considerable heterogeneity of clinical expression. **Materials and Methods:** The present study is an observational study conducted at Apollo institute of medical sciences and research, hospital, Chittoor district during the period of December 2018 to December 2019. The study included 36 patients with NF, presenting to Ophthalmology OPD with any complaints. Diagnosis of Neurofibromatosis was done based on the criteria proposed by the National Institutes of Health Consensus Development. **Results:** The most common ophthalmic manifestation in these patients was Lisch nodules (83.3%) and Neurofibromas of the upper and lower eyelid (83.3%). Plexiform neurofibroma was seen in 8 patients (22.2%) among which, 5 (62.5%) patients have upper lid involvement and 3 (37.5%) patients have both upper and lower lid involvement. Orbital neurofibroma was seen in 8 (22.2%) patients. Vision loss due to the disease was seen in 12 (33.3%) patients among which, 3 (25%) patients had vision loss due to Stimulus deprivation amblyopia due to plexiform neurofibroma, 3 (25%) had vision loss due to compressive optic neuropathy due to orbital neurofibroma, 5 (41.7%) had both plexiform and orbital neurofibromas,1 (8.3%) patient had coloboma choroid involving macular area. **Conclusion:** Lisch nodules in iris and neurofibromas of eyelids are the most common manifestation in Neurofibromatosis patients in our study. Visual impairment as a result of this disease was seen in 33% of patients in our study. So intervention at the earliest can avoid visual loss in Neurofibromatosis patients.

Key Words: Oculoneurocutaneous syndrome, Plexiform Neurofibroma, Orbital neurofibroma, Lisch nodules.

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INTRODUCTION

Neurofibromatosis, an oculo-neurocutaneous syndrome is characterized by multisystem involvement[1]. Neurofibromatosis type 1 (NF1) affects about 1 in 4000 individuals, and Neurofibromatosis type 2 (NF2) affects about 1 in 50,000[2]. Both forms are transmitted by an autosomal dominant mode of inheritance. Although the penetrance of both NF1 and NF2 is greater than 95%, the expressivity of the disease is highly variable[1,3,5]. Neurofibromatosis type 1, peripheral neurofibromatosis or von Recklinghausen's syndrome, is characterized by cutaneous neurofibromas, café-au-lait spots, Axillary and inguinal freckles, Lisch nodules of iris, Orbital neurofibromas, optic nerve glioma or solid tumors of central nervous system[4]. Neurofibromatosis type 2, central or bilateral acoustic neurofibromatosis, is characterized by central neural tumors. Its hallmark is bilateral acoustic neuroma[2]. In the present study, the most common ophthalmic findings in Neurofibromatosis and it's serious effects on the visual function of the patient were studied.

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MATERIALS AND METHODS

The present study is an observational study conducted at Apollo institute of medical sciences and research, hospital, Chittoor district during the period of December 2018 to December 2019. The study included 36 patients with NF, presenting to Ophthalmology OPD with any complaints. Diagnosis of Neurofibromatosis was done based on the criteria proposed by the National Institutes of Health Consensus Development[13]. A thorough clinical assessment of these patients was done by taking a brief history of presenting complaints, family history, and then thorough examination is done, which included Assessment of visual acuity through Snellen's chart, slit lamp examination, Fundus evaluation by direct and indirect ophthalmoscopy. Ultrasonography / Computed tomography / Magnetic resonance imaging of orbits were done wherever necessary.

Inclusion criteria:

1. All the patients who satisfy the criteria of Neurofibromatosis according to National Institutes of Health Consensus Development Conference13
2. Patients who are willing to participate in the study

Exclusion criteria:

1. Neurofibromatosis type-2 patients
2. Patients with atypical signs of Neurofibromatosis
3. Patients with any other genetic disorder apart from Neurofibromatosis

RESULTS

Out of 36 patients of neurofibromatosis, 21 (58.3%) were female and 15 (41.7%) were male. Most of the patients presenting to OPD were aged between 46-60 years (33.3%). The most common ophthalmic manifestation in these patients was Lisch nodules (83.3%) and Neurofibromas of the upper and lower eyelid (83.3%). Plexiform neurofibroma was seen in 8 patients (22.2%) among which, 5 (62.5%) patients have upper lid involvement and 3 (37.5%) patients have both upper and lower lid involvement. Orbital neurofibroma was seen in 8 (22.2%) patients. Among 36 cases normal visual acuity was observed in 24 cases (66.7%), visual impairment was seen in 12 cases (33.3%). Out of 12 (33.3%) patients with visual impairment, 3 (25%) patients had stimulus deprivation amblyopia due to plexiform neurofibroma, 3 (25%) had compressive optic neuropathy due to orbital neurofibroma, 5 (41.7%) had both plexiform and orbital neurofibromas, 1 (8.3%) patient had coloboma choroid involving macular area. Regarding the genetic pattern of inheritance, among 36 patients, single generation was affected in 18 (50%) patients, 2-generations were affected in 9 (25%) patients, 3-generations were affected in 3 (8.3%) patients, 4-generations were affected in 3 (8.3%) patients, 5-generations were affected in 3 (8.3%).

TABLE 1: GENDER DISTRIBUTION

Gender	Number of patients	Percentage %
Female	21	58.3%
Male	15	41.7%

TABLE 2: AGE OF PRESENTATION

Age of presentation	Number of patients	Percentage %
10-15 years	6	16.7%
16-30 years	3	8.3%
31-45 years	6	16.7%
46-60 years	12	33.3%
61-75 years	9	25%

TABLE3: OPHTHALMIC MANIFESTATIONS

Ophthalmic findings	Number of patients	Percentage %
Lisch nodules	30	83.3%
Neurofibromas on eyelids and eyebrows	30	83.3%
Plexiform neurofibroma of Eyelids	8 Upper and lower lid(3) Only Upper lid(5)	22.2% Upper and lower lid(37.5%) Only Upper lid (62.5%)
Orbital neurofibroma	8	22.2%
Coloboma of Choroid with macular involvement	1	2.8%

TABLE 4: VISUAL ACUITY OF PATIENTS

Visual acuity	Number of patients	Percentage
Normal	24	66.7%
Visual impairment (due to the disease proper)	12	33.3%

TABLE 5: CAUSE FOR AMBLYOPIA

Cause for Amblyopia	Number of Patients	Percentage %
Only Plexiform neurofibroma (Stimulus deprivation)	3	25%
Only Orbital neurofibroma (Compressive Optic neuropathy)	3	25%
Both Plexiform neurofibroma and Orbital neurofibroma	5	41.7%
Coloboma choroid	1	8.3%

TABLE 6: GENETIC PATTERN OF DISEASE TRANSMISSION

Generations affected	Single generation affected (denovo Mutation)	2 generations affected	3 generations affected	4 generations affected	5 generations affected
Number of Patients	18	9	3	3	3
Percentage %	50%	25%	8.3%	8.3%	8.3%

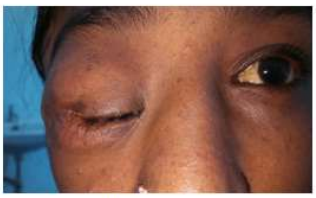

Figure 1:

Figure 2:

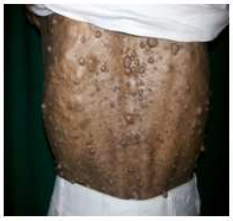

Figure 3:

Figure 1: Plexiform Neurofibroma of Upper eyelid; **Figure 2:** Plexiform Neurofibroma of Upper eyelid and Orbital neurofibroma; **Figure 3:** Cutaneous neurofibromas

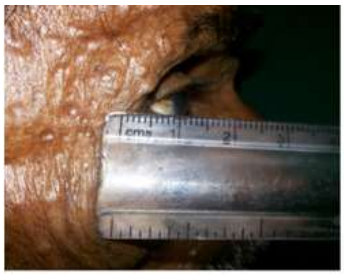

Figure 4: Orbital Neurofibroma of Left eye

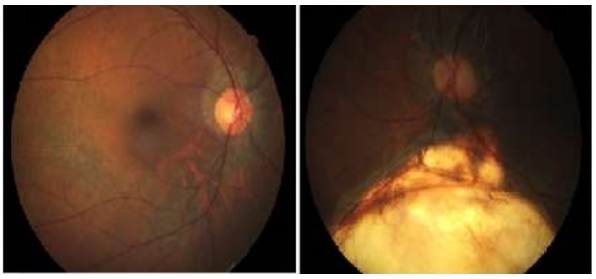

Figure 5: Coloboma choroid of Left eye in a patient with Neurofibromatosis

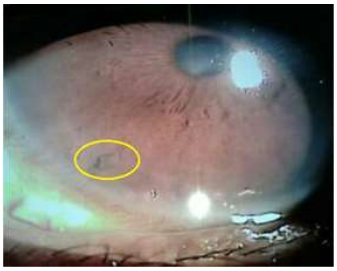

Figure 6: Lisch nodules over the Iris

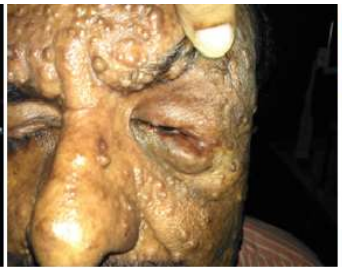

Figure 7: Plexiform neurofibroma of upper and lower eyelid

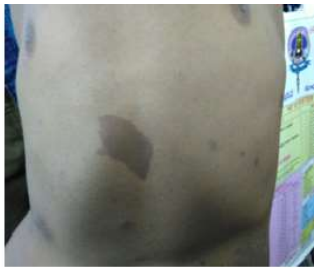

Figure 8: Café-au-lait spots

DISCUSSION

Neurofibromatosis is a group of autosomal-dominant disorders, characterized by genetically distinct neurocristopathies (multiple hamartomas of neural crest origin) in which individuals develop both benign and malignant tumors at an increased frequency[6,7,8]. The NF 1 gene is on the long arm of chromosome [17]. It has been cloned and its protein product, neurofibromin, was identified in 19909,[10,11]. The hallmark of the NF 1 gene is its high mutation rate with up to 50% of cases being caused by de novo mutations12. The diagnosis of NF 1 is based primarily on clinical criteria. The diagnostic criteria for NF1 as originally established by the NIH Consensus Development Conference specified that two or more of the following be present: [1] six or more cafe-au-lait macules more than 5mm in greatest diameter in prepubertal individuals and more than 15mm in greatest diameter after puberty, [2] two or more neurofibromas of any type or one plexiform neurofibroma, [3] freckling in the axillary or inguinal regions, [4] optic nerve glioma, [5] two or more Lisch nodules (iris hamartomas), [6] an osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of the long bones(with or without pseudarthrosis), and [7] a first-degree relative with NF 1 by the above criteria[13] Approximately 25% of patients with Neurofibromatosis develop complications, which include plexiform neurofibroma, malignancies like orbital neurofibroma, optic nerve glioma, neurofibrosarcoma[7]. Orbital Neurofibroma is the most common cause for the development of amblyopia in neurofibromatosis patients. It is probably the most frequent peripheral nerve tumor of the orbit, accounting for 0.8 to 3.0% of all histopathologically proven orbital lesions [14–16]. It is classified into three subsets: Plexiform, Diffuse, and Localized. The localized type is only seldom associated with neurofibromatosis[17,5]. It behaves like many other solitary well-circumscribed soft tissue tumors in the orbit and presents at a later age than the plexiform type. The typical patient is a young or middle-aged adult[18,19]. The diagnosis of neurofibromatosis is clinical. Linkage analysis using polymorphic DNA markers can be performed, allowing prenatal diagnosis or presymptomatic diagnosis. Additionally, a commercial assay for NF1 gene mutations is available that is based upon a protein truncation test[20], with limited sensitivity (60%-70%), however, and is not yet recommended as the single diagnostic tool for NF1; rather, it can be used in conjunction with the clinical findings. Early diagnosis and early treatment of plexiform neurofibroma, orbital neurofibromas, and optic nerve glioma decrease the chances of development of amblyopia and compressive optic neuropathy respectively, which affects 5 % of patients suffering from neurofibromatosis [21]. The management of localized orbital neurofibroma consists of total excision. Postoperatively, a sensory skin deficit was present in 72% of the patients with an isolated orbital neurofibroma. 46% of tumors can usually be dissected completely from the surrounding orbital contents. Plexiform neurofibroma can be managed by excision of the neurofibroma followed by eyelid reconstruction22.

CONCLUSION

In conclusion, Lisch nodules in iris and neurofibromas of eyelids are the most common manifestation in Neurofibromatosis patients in our study. Visual impairment as a result of the disease can occur in 33% of patients either due to stimulus deprivation amblyopia or due to compressive optic neuropathy, which can be intervened by early diagnosis. Denovo mutations are more common accounting for 50% of cases in this study.

REFERENCES

1. Sippel KC. Ocular findings in neurofibromatosis type 1. Int Ophthalmol Clin 2001; 41:25–40.
2. The National Institutes of Health Consensus Development Conference. Neurofibromatosis. Arch Neurol 1988; 45:575–578.
3. Rettele GA, Brodsky MC, Merin LM, *et al*. Blindness, deafness, quadriparesis and a retinal malformation: The ravages of neurofibromatosis 2. Surv Ophthalmol 1996; 41:135–141.
4. Riccardi V M.Neurofibromatosis:Past, present and future.N Engl J Med. 1991;324:283-5.
5. Zia Chaudhuri,MVanathi: Post graduate Ophthalmology.1st edition. 2012. vol.2:1891-2.
6. Huson SM, Compston DAS, Clark P, *et al*: A genetic study of von Recklinghausen neurofibromatosis in south east Wales. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. JMed Genet 26:704-711, 1989
7. Riccardi VM: Neurofibromatosis: Past, present, and future. N Engl J Med 324:1283-1285, 1991
8. Riccardi VM, Eichner JE: Neurofibromatosis: Phenotype, natural history, and pathogenesis, ed 2. Baltimore, Johns Hopkins University Press, 1992
9. Cawthon RM, Weiss M, Xu G, *et al*: A major segment of the neurofibromatosis Type I gene: cDNA sequence, genomic structure, and point mutations. Cell 62193-201, 1990
10. Van der Hoeven J: Les phacomatoses de Burnsville, de Recklinghausen et de von Hippel-Lindau. Journal of Belgian Neurology and Psychiatry 33:752-762, 1933
11. Weiss DI: Dial origin of glaucoma in encephalotrigeminal haemangiomatosis: A pathogenetic concept based upon histopathologic and hemodynamic considerations.Trans Am Ophthalmol SOC 93:477-493,1973
12. Huson SM, Hughes RAC: The Neurofibromatoses: A Pathogenetic and Clinical Overview. London, Chapman and Hall, 1994.

13. Neurofibromatosis conference statement. National Institutes of Health Consensus Development Conference.Arch Neurol.1988;45(5):575-78.
14. Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit. Arch Ophthalmol 1984; 102:1606–1611.
15. Henderson JW, Campbell RJ, Farrow GM, Garrity JA. Orbital Tumors. New York: Raven Press; 1994:43–52.
16. Sen DK. An aetiological pattern of orbital tumors in India and their clinical presentations. A 20-year retrospective study. Orbit.1990;9:299–302
17. Shields JA. Diagnosis and Management of Orbital Tumors.Philadelphia: WB Saunders; 1989:149–169
18. Krohel GB, Rosenberg PN, Wright JE, Smith RS. Localized orbital neurofibromas. Am J Ophthalmol 1985; 100:458–464.
19. Rocca RCD, Roen J, Labay GR, Bedrossian E. Isolated neurofibroma of the orbit. Ophthalmic Surg 1985; 16:634–638.
20. Heim RA, Silverman LM, Farger RA, *et al*: Screening for truncated NFL proteins. Nat Genet 8:218-219,1994
21. Samuelsson B. Neurofibromatosis. A clinical and genetic study of 96 cases in Gothenberg, Sweden. Acta Derm Veneered (stock) 1981;95 (suppl):67-71.
22. Rose GE, Wright JE. Isolated peripheral nerve sheath tumors of the orbit. Eye 1991;5:668–673.

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