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Original Research Article

A Retrospective Study Evaluating the Ocular Symptoms of Neurofibromatosis Type-1 in a Rural Community

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Abstract

Aim: To determine the ocular symptoms of neurofibromatosis type-1 in a rural community.

Materials and Methods: The present study is an observational study was conducted in the Department of Ophthalmology, Patna medical college and hospital, Patna, Bihar, India for six Months. 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. 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. All the patients who satisfy the criteria of Neurofibromatosis according to National Institutes of Health Consensus Development Conference and Patients who are willing to participate in the study.

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 neuro fibroma 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 neuro fibroma 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 neuro fibroma, 3 (25%) had compressive optic neuropathy due to orbital neuro fibroma, 5 (41.7%) had both plexiform and orbital neuro fibromas, 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%).

Conclusion: In conclusion, Lisch nodules in iris and neuro fibromas 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.

Keywords: Ocular symptoms, Neurofibromatosis type-1, Rural community

Introduction

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by a wide array of clinical manifestations, affecting various organ systems, including the ocular system. This autosomal dominant condition, caused by mutations in the NF1 gene located on chromosome 17, is one of the most common genetic disorders, with an incidence of approximately 1 in 3,000 individuals worldwide . [1-4] NF1 is primarily known for its cutaneous features, such as café-aulait spots and neurofibromas, but it also has significant ocular manifestations that can impact vision and quality of life. One of the hallmark

ocular symptoms of NF1 is the presence of Lisch nodules, which are benign melanocytic hamartomas of the iris. These nodules are often detectable on slit-lamp examination and can be used as a diagnostic criterion for NF1. Although Lisch nodules typically do not affect vision, their identification is crucial for the diagnosis and monitoring of the disease. [5-7] Optic pathway gliomas (OPGs) represent another critical ocular manifestation of NF1. These low-grade gliomas can affect the optic nerve, chiasm, and tract, potentially leading to visual impairment. OPGs are found in approximately 15-20% of individuals with NF1, with the majority developing during early childhood. While many OPGs remain asymptomatic, some can cause progressive vision loss, necessitating regular ophthalmologic surveillance and intervention when necessary. Additionally, NF1 patients may exhibit various other ocular abnormalities, including plexiform neurofibromas involving the eyelids, which can lead to ptosis and mechanical ocular surface issues. These neurofibromas, while benign, can cause significant cosmetic and functional concerns, often requiring surgical management. Retinal abnormalities, such as retinal astrocytic hamartomas, have also been reported in individuals with NF1. [8-10] These lesions, although typically asymptomatic, can occasionally lead to visual disturbances depending on their size and location. Regular retinal examinations are therefore recommended as part of the comprehensive ocular assessment in NF1 patients. Moreover, individuals with NF1 are at an increased risk for developing glaucoma. The exact prevalence of glaucoma in NF1 patients is not well established, but it is thought to be higher than in the general population. The mechanisms underlying glaucoma in NF1 are multifactorial and may include secondary causes such as angle anomalies and neurofibromatosis infiltration of the trabecular meshwork. The management of ocular symptoms in NF1 requires a multidisciplinary approach, involving ophthalmologists, neurologists, and geneticists. Early diagnosis and regular monitoring are essential to prevent and mitigate visual impairment. Advances in imaging techniques, such as optical coherence tomography (OCT), have enhanced the ability to detect and monitor ocular abnormalities in NF1, facilitating timely intervention . [11,12]

Materials and Methods

The present study is a retrospective study was conducted in the Department of Ophthalmology, Patna medical college and hospital, Patna, Bihar, India for six months. 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:

- All the patients who satisfy the criteria of Neurofibromatosis according to National Institutes of Health Consensus Development Conference [13]
- Patients who are willing to participate in the study

Exclusion Criteria:

- Neurofibromatosis type-2 patients
- Patients with atypical signs of Neurofibromatosis
- 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: Demographic Characteristics of Neurofibromatosis Patients

Characteristic	Number of Patients (n=36)	Percentage (%)
Gender		
Female	21	58.3
Male	15	41.7
Age Group		
0-15 years	6	16.7
16-30 years	8	22.2
31-45 years	10	27.8
46-60 years	12	33.3

Table 2: Ophthalmic Manifestations in Neurofibromatosis Patients

Ophthalmic Manifestation	Number of Patients (n=36)	Percentage (%)
Lisch nodules	30	83.3
Neurofibromas of eyelids	30	83.3
Plexiform neurofibroma	8	22.2
Upper lid involvement	5	62.5 (of those with plexiform)
Both upper and lower lid	3	37.5 (of those with plexiform)
Orbital neurofibroma	8	22.2

Table 3: Visual Acuity in Neurofibromatosis Patients

Visual Acuity	Number of Patients (n=36)	Percentage (%)
Normal	24	66.7
Impaired	12	33.3

Table 4: Causes of Visual Impairment in Neurofibromatosis Patients

Cause of Visual Impairment	Number of Patients (n=12)	Percentage (%)
Stimulus deprivation amblyopia	3	25.0
Compressive optic neuropathy	3	25.0
Both plexiform and orbital neurofibromas	5	41.7
Coloboma choroid involving macular area	1	8.3

Table 5: Genetic Pattern of Inheritance in Neurofibromatosis Patients

Generations Affected	Number of Patients (n=36)	Percentage (%)
Single generation	18	50.0
2 generations	9	25.0
3 generations	3	8.3
4 generations	3	8.3
5 generations	3	8.3

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 1990. [9,10,11] The hallmark of the NF 1 gene is its high mutation rate with up to 50% of cases being caused by de novo mutations.[12] 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, neurofibr osarcoma. [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 reconstruction. [22]

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.

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