Refractive errors in neurofibromatosis type 1 and type 2

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Objective: To document the prevalence of refractive errors in patients with neurofibromatosis type 1 (NF1) and type 2 (NF2) and to compare it with that of age- and sex-matched controls.

Methods: 82 patients with NF1, 21 patients with NF2 and 103 age- and sex-matched controls were evaluated in this prospective observational case-control study. Cycloplegic autorefraction and dilated fundus examination were performed. Myopia was defined as the spherical equivalent refraction of at least -0.50 diopters (D), hyperopia as the spherical equivalent refraction of at least 2.0 D and astigmatism as the cylinder of at least 1.0 D. Main outcome measures were refractive error, IQ, years of education, height, weight and body mass index (BMI).

Results: The prevalence of myopia was 23.1% in patients with NF1, 23.8% in patients with NF2 and 16.5% in age- and sex-matched controls. These differences were significant ($p < 0.03$, $p < 0.03$), and adjusting for intelligence, education, height, weight and BMI increased the significance of this finding ($p < 0.001$, $p < 0.001$). The prevalences of astigmatism and hyperopia were similar in both groups.

Conclusion: A high prevalence of myopia seems to be an additional feature of NF1 and NF2.

The neurofibromatoses are genetic disorders of the nervous system. They have an autosomal dominant mode of transmission.¹ The gene for neurofibromatosis type 1 (NF1) is located on chromosome 17 and for neurofibromatosis type 2 (NF2) on chromosome 22.¹ NF1 is characterised by café-au-lait spots and neurofibromas of the skin, which may also involve the internal organs.² Iris hamartomas (Lisch nodules) are the main ocular finding.² NF2 is characterised by bilateral tumours on the eighth cranial nerve.³ There are various ocular findings of NF2, such as cataract, epiretinal membrane, retinal hamartoma, optic disc glioma and optic nerve sheath meningioma.³ Patients with NF1 or NF2 have no known predilection for refractive errors. The purpose of this study was to document the prevalence of refractive errors in patients with NF1 and NF2 and to compare it with that of age- and sex-matched controls.

MATERIALS AND METHODS

A total of 96 patients with NF1 and 27 patients with NF2 were examined. We reached all recorded patients with NF1 and NF2 of the Pediatric Neurology Department, Diskapi Children's Hospital, Ankara, Turkey, for this study. Exclusion criteria were any ocular or orbital pathology except Lisch nodules. In all, 14 patients with NF1 (2 with glaucoma, 2 with optic glioma and 10 with neurofibroma of the eyelid) and 6 patients with NF2 (2 with both cataract and optic glioma, 3 with optic glioma and 1 with epiretinal membrane) were excluded. In all, 82 patients with NF1 and 21 patients with NF2, with or without ocular complaints, were included in this prospective study. A total of 103 age- and sex-matched controls, with or without ocular complaints, were obtained by ophthalmological screening at the schools.

Visual acuity was tested by a Snellen chart at 6 m. Cycloplegic autorefraction (with cyclopentolate), slit-lamp biomicroscopy and dilated fundus examination were performed. Myopia was defined as the spherical equivalent refraction of at least -0.50 diopters (D), hyperopia as the spherical equivalent refraction of at least 2.0 D and astigmatism as the cylinder of at least 1.0 D. The prevalences of the refractive errors in patients with NF1 and NF2 were compared with the controls.

Myopia was classified into three groups as follows: mild, -0.50 to -3.0 D; moderate, -3.0 to -6.0 D; severe, > -6.0 D. Patients with bilateral myopia were classified according to the more myopic eye.

Data about the parameters reported to be associated with myopia such as IQ, years of education, height, weight and body mass index (BMI) were also noted. The patients with NF1 and NF2 were compared with the controls in terms of these parameters.

χ^2 and paired samples tests were used for statistical analysis. A value of $p < 0.05$ was considered significant. The Cochran-Mantel-Haenszel statistics were calculated to test the association between prevalence of NF1, NF2 and myopia adjusted for education, intelligence, height, weight and BMI.⁴

RESULTS

Male:female ratios were 42:40 in NF1, 11:10 in NF2 and 53:50 in the control group. Mean (SD) ages were 8.4 (2.6) years (range 4–12 years) in patients with NF1, 9.1 (2.8) years (range 5–14 years) in patients with NF2 and 8.6 (3.1) years (range 4–14 years) in the control group.

The prevalence of myopia was 23.1% in patients with NF1, 23.8% in patients with NF2 and 16.5% in controls. These differences were significant ($p < 0.03$, $p < 0.03$), and adjusting for intelligence, education, height, weight and BMI increased the significance of this finding ($p < 0.001$, $p < 0.001$).

The prevalence of mild and moderate myopia was significantly higher among the patients with NF1 and NF2 than among the controls, whereas that of severe myopia was similar in both groups. Table 1 summarises the distribution of individuals with myopia according to its severity.

The prevalence of astigmatism was 19.5% in patients with NF1, 19.0% in patients with NF2 and 19.4% in age- and sex-matched controls. These differences were not significant ($p > 0.05$, $p > 0.05$).

The prevalence of hyperopia was 9.7% in patients with NF1, 9.5% in patients with NF2 and 10.6% in controls. These differences were also not significant ($p > 0.05$, $p > 0.05$). Table 2 summarises the data on the refractive errors.

Table 3 summarises the data on the parameters reported to be associated with myopia such as refractive error, IQ, years of education, height, weight and BMI.

Abbreviations: BMI, body mass index; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2

Table 1 Distribution of individuals with myopia according to its severity

Severity of myopia	Number of patients								
	Controls			NF1			NF2		
	Male	Female	All	Male	Female	All	Male	Female	All
Mild (−0.5 to −3.0 D)	3	4	7	3	5	8	1	1	2
Moderate (−0.3 to −6.0 D)	3	3	6	4	4	8	1	1	2
Severe (>6.0 D)	2	2	4	2	1	3	1	—	1
Overall myopia	8	9	17 16.5%	9	10	19 23.1%	3	2	5 22.8%

NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2.

Table 2 Comparison of the percentages of refractive errors between patients with neurofibromatosis type 1, neurofibromatosis type 2 and the controls

Refractive errors	Number of patients								
	Controls			NF1			NF2		
	Male	Female	All	Male	Female	All	Male	Female	All
Myopia	8	9	17 16.5%	9	10	19 23.1%	3	2	5 23.8%
Astigmatism	11	9	20 19.4%	10	8	16 19.5%	2	2	4 19.0%
Hyperopia	6	5	11 10.6%	4	4	8 9.7%	1	1	2 9.5%

NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2.

Table 3 Comparison between patients with neurofibromatosis type 1 and neurofibromatosis type 2, and controls, regarding IQ, years of education, height, weight and BMI

Parameters	Males		Females		Overall significance
	Controls	NF1 and NF2	Controls	NF1 and NF2	
IQ	104.3 (5.3)	98.2 (7.4)	109.3 (6.2)	101.3 (8.2)	p<0.05
Age (years)	12.4 (3.2)	12.3 (3.1)	11.6 (2.8)	11.5 (2.9)	NS
Height (cm)	153 (10.2)	148 (9.4)	143 (8.3)	138 (7.6)	p<0.05
Weight (kg)	49.4 (7.4)	46.2 (6.3)	45.3 (5.7)	41.6 (5.2)	p<0.05
BMI (kg/m ²)	21.1 (2.3)	20.9 (2.1)	20.7 (1.8)	20.6 (1.7)	P>0.05
Years of education	7.4 (1.1)	5.6 (1.2)	6.2 (1.3)	4.8 (1.0)	p<0.05

BMI, body mass index; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2.
The results are given as mean (SD).

DISCUSSION

Neurofibromatosis is an autosomal dominant disorder that affects the bone, nervous system, soft tissues and skin. Two major subtypes exist: NF1, which is referred to as peripheral NF; and NF2, which is referred to as central NF.

The diagnostic criteria for NF1 are met if two or more of the following features are present:

- ≥6 café-au-lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals;
- ≥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; and

- a first-degree relative with NF1 according to the above criteria.

The diagnostic criteria for NF2 are met if either of the following is present:

- bilateral masses of the eighth cranial nerve; and
- a first-degree relative with NF2 and either (a) a unilateral mass of the eighth cranial nerve or (b) two of the following: neurofibroma, meningioma, glioma, schwannoma or juvenile posterior subcapsular lens opacities.

This study documented that myopia is more common in patients with NF1 and NF2 than in controls, whereas the prevalences of astigmatism and hyperopia are similar. As far as the severity of myopia is concerned, mild (−0.25 to −3.0 D) and moderate (−3.0 to −6.0 D) myopia were more common among patients with NF1 and NF2 than among controls. The

prevalence of myopia varies in different populations—17.4% in 18-year olds in Denmark⁵ and 17.7–25% in the US.⁶ Our study showed an overall myopia in the same order of magnitude (16.5%) in the control group.

In a single previous study evaluating the prevalence of myopia in patients with NF1 aged 17 years, it was reported that myopia is significantly more common among patients with NF1 than among controls.⁷ In that study, myopia among patients with NF1 was also of mild (−0.25 to −3.0 D) and moderate (−3.0 to −6.0 D) types. There was no difference in the prevalence of severe myopia between the study and the control groups.⁷ However, there are no data on the refractive state of patients with NF2 in the literature.

In conclusion, a high prevalence of myopia seems to be an additional feature of patients with NF1 and NF2. In these patients, mild and moderate myopia are more common than in controls.

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