

Eye Disorders in Neurofibromatosis (NF1)

Rajko Kordić¹, Zlatko Sabol², Branimir Cerovski¹, Damir Katušić¹ and Tomislav Jukić

¹ University Department of Ophthalmology, Clinical Hospital Center »Rebro«, Zagreb, Croatia

² Policlinic Dr. Sabol, Zagreb, Croatia

ABSTRACT

Neurofibromatosis type 1 (NF 1) is an autosomal dominant disorder with high index of spontaneous mutations and extremely varied and unpredictable clinical manifestations. The aim of this work was to give an account of eye disorders in NF1. 132 patients of age 0–16 years with NF1 were followed up for 15 years. They were checked repeatedly for ophthalmologic disorders. Frequent eye disorders were: Lisch nodules (Iris hamartomas, IH) 78%, hyperthelormism 19.7%, bulbomotoric disorders 15.9%, disorders of the optic disc 16.7% and optic gliomas (18.9%). The highest incidence of eye disorders by NF1 patients showed Lisch nodules (IH). Its ease of clinical recognition and if present with other diagnostic signs (for instance café au lait patches) could be deemed as reliable diagnostic criterion of NF1 in childhood.

Key words: eye disorders, neurofibromatosis

Introduction

Neurofibromatosis type 1 (NF 1) is an autosomal dominant disorder with high index of spontaneous mutations and extremely varied and unpredictable clinical manifestations^{1–3}. Neurofibromatosis (now type 1 NF) came to be known as von Recklinghausen's disease following a classic description in which von Recklinghausen was the first to emphasize clinicopathological correlation and a common neural origin for various tumor types⁴. There may also be further forms of neurofibromatosis, including former central neurofibromatosis NF2 (VIII nerve masses), multiple meningeomatosis and spinal schwannomatosis NF3 and NF4, as well segmental neurofibromatosis (NF5)⁴. Neurofibromatosis type 1 is the commonest form of neurofibromatosis and has a frequency of about 1 in 3,000 to 1 in 3,500⁵. The gene for NF1 is located in the pericentromeric region of the long arm of chromosome 17:band q11.2. It contains an area coding for GAP-like protein, which may act as a »growth regulator«, interacting with the ras oncogen. Tumor formation in NF1 is a multistep process involving other growth regulator gene in addition to the NF1 gene⁵. Thus NF1 is a dominantly inherited condition associated with the formation of multiple tumor types, including neurofibromas, optic gliomas, neurofibrosarcomas, astrocytomas and phaeochromocytomas. The aim of this work was to give an account of eye disorders in neurofibromatosis type 1 (NF1).

Patients and Methods

A total of 132 patients of age 0–16 years with neurofibromatosis type 1 (NF1) were followed up for 15 years. They were checked repeatedly for ophthalmologic disorders. Examinations of visual acuity, ophthalmoscopy, tonometry, biomicroscopy, perimetry and bulbomotoric examinations were done. They all had to fulfil diagnostic criteria for neurofibromatosis type 1. The diagnostic criteria are met if a person has two or more of the following:

Six or more café au lait macules over 5 mm in greatest diameter in prepubertal persons and over 15 mm in greatest diameter in postpubertal persons; two or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; a distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis; a first-degree relative (parent, sibling or offspring) with neurofibromatosis type 1 by the above criteria. Radiological examination and pediatric follow up were done as well.

Results

A total of 132 patients with NF1 of age 0–16 years were followed up for 15 years. Incidence of eye disorders is given in Table 1. Frequent eye disorders were: Lisch

TABLE 1
INCIDENCE OF EYE DISORDERS IN 132 PATIENTS WITH NF1

Hypertheliorism	26	19.7%
Bulbomotorical disorders	21	15.9%
Exophthalmus	3	2.3%
Horner's syndrome	2	1.5%
Eyelid disorders	9	6.8%
Microphthalmus	3	2.3%
Glaucoma	2	1.5%
Aniridy	1	0.8%
Lisch nodules	103	78%

nodules (Iris hamartomas, IH) 78%, hypertheliorism 19.7%, bulbomotoric disorders 15.9%, disorders of the optic disc 16.7% and optic gliomas (18.9%).

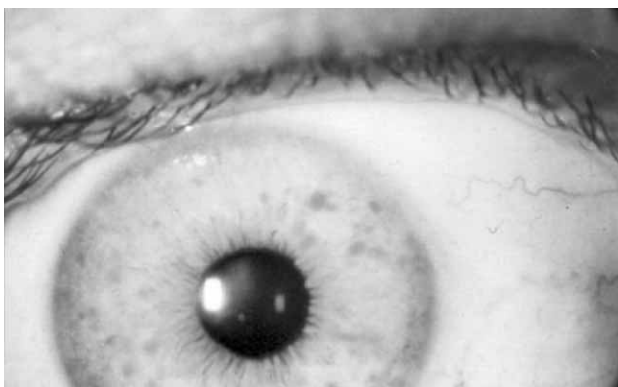


Fig. 1. Lisch nodules, iris hamartomas.

Discussion and Conclusion

In this study, the highest incidence of eye disorders showed Lisch nodules (78%). Iris hamartomas (IH), also known as Lisch nodules are melancytic iris naevi, and occur in almost all adults with NF1 (Figure 1). If present with other diagnostic signs of NF1 (for instance café au lait patches (Figure 2.)), IH confirm the diagnosis⁶. Although IH are not easily detectable at birth, their

prevalence increases to about 50% of 5-year-olds, 75% of 15-year-olds, and 95–100% of adults over 25 years⁷. We found in our patients up to 16 year-olds 78% IH.



Fig. 2. Café au lait patches.

Wolters⁸ found high incidence of hypertheliorism (24%) by our patients that was almost 20%. Moreover, hypertheliorism was found exclusively in neurofibromatosis patients with brain involvement and therefore seems to herald a severe expression of M.von Recklinghausen. The bones of the face and the base of the skull are mesenchymal structures of neural crest origin and skull dysplasia – e.g. hypertheliorism – fit well into neurocristopathy concept of neurofibromatosis. Its ease of clinical recognition and its presence at birth makes the hypertheliorism an early diagnostic criterion.

Gliomas of the anterior visual pathway are well recognized in NF1⁹. Although the frequency of this varies from 10–70% depending on the study, two prospective studies have shown the incidence of anterior pathway gliomas to be about 15% of NF1 patients^{10,11}. Our patients showed almost 19% of optic gliomas.

The highest incidence of eye disorders by NF1 patients showed Lisch nodules (IH). Its ease of clinical recognition and if present with other diagnostic signs (for instance café au lait patches) could be deemed as reliable diagnostic criterion of NF1 in childhood.

REFERENCES

1. LOPEZ-PISON, J., M. CUADRADO-MARTIN, M. C.BOLDOVA-AGUAR, A. MUNOZ-MELLADO, R. CABRERIZO DE DIAGO, J. L. PENNA-SEGURA, Rev. Neurol., 9 (2003) 820. — 2. HUSON, S., D. JONES, L. BECK, Br. J. Ophthalmol., 71 (1987) 235. — 3. KOSA, E., V. CSAKVARY, Orv. Hetil., 29 (2004) 473. — 4. RAGGE, N. K., Br J. Ophthalmol., 77 (1993) 662. — 5. RICCARDI, V. M., N. Engl. J. Med., 305 (1981) 1617. — 6. ZEHAVI, C., A. ROMANO, R. M. GOODMAN, Clin. Genet., 29 (1986) 51. — 7. RAGGE, N. K., R. E. FALK, W. E. COHEN, A. L.

MURPHREE, Eye, 7 (1993) 95. — 8. WOLTERS, E. Ch., W. WESTERHOF, J. W. DELLEMAN, P. DIJKSTRA, Neuropediatrics, 17 (1986) 175. — 9. IMES, R. K., W. F. HOYT, Am. J. Ophthalmol., 111 (1991) 729. — 10. LEWIS, R. A., L. P. GERSON, K. A. AXELSON, V. M. RICCARDI, R. P. WHITFORD, Ophthalmology, 91 (1984) 929. — 11. HOCHSTRASSER, H., E. BOLTSHAUSER, A. VALAVANIS, Neurofibromatosis, 1 (1988) 233.

R. Kordić

University Department of Ophthalmology, Clinical Hospital Center »Rebro«, Kišpatićeva 12, 10000 Zagreb, Croatia

OČNE PROMJENE KOD NEUROFIBROMATOZE (NF1)

S A Ž E T A K

Neurofibromatoza tip 1 (NF1) je autosomno dominantan poremećaj s visokim indeksom spontanijh mutacija i izrazitom varijabilnosti. Cilj ovog rada je prikazati očne poremećaje kod NF1. 132 pacijenta s NF1 u dobi 0–16 godina, praćena su 15 godina. Opetovano su pregledavani zbog očnih promjena. Najčešće očne promjene su bile: Lischovi noduli (hamartomi irisa, HI) 78%, hipertelorizam 19,7%, poremećaji bulbomotorike 15,9%, promjene na papili optičkog živca 16,7% i gliomi optikusa 18,9%. Najveću incidenciju od očnih promjena su imali Lischovi noduli (HI). Zbog njihove lagane kliničke uočljivosti, te ako su prisutni s drugim znakovima NF1 (npr. Café au lait pjegama), mogu se smatrati pouzdanim dijagnostičkim kriterijem NF1 u djetinjstvu.