RETINAL CHANGES ASSOCIATED WITH NEUROFIBROMATOSIS 2*

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STRUCTURED ABSTRACT

Introduction: Neurofibromatosis (NF) is now known to be more than one disease. NF2, formerly classified as central neurofibromatosis, is characterized by bilateral vestibular schwannomas, previously termed "acoustic neuromas", and is much less common than NF1. Lens opacities at an early age have been described in approximately 85% of NF2 patients.

Purpose: To determine the frequency of retinal abnormalities in NF2 patients.

Methods: We prospectively examined 15 consecutive patients who met the diagnostic criteria of NF2.

Results: We observed an epiretinal membrane in the macular or paramacular area in 12 of 15 patients, and a combined pigment epithelial and retinal hamartoma in the macula of one patient who also had an epiretinal membrane in the macula of the other eye. Additionally, 11 patients had central posterior cortical, subcapsular, or peripheral cortical lens opacities.

Conclusions: Children or young patients with epiretinal membranes, combined pigment epithelial retinal hamartoma, and lens opacities that are not the result of other ocular disorders should have a neurologic evaluation and a careful family history for NF2.

INTRODUCTION

Neurofibromatosis (NF), orginally described by von Recklinghausen in 1882, consists of at least two genetically distinct disorders: NF1 (von Recklinghausen's or peripheral neurofibromatosis) and NF2, formerly known as "central neurofibromatosis."[1-3] The prevalence of NF1 is approximately 1 in 4,000, and of NF2, 1 in 50,000.[2] Ocular manifestations of NF1, caused

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by genetic abnormalities on chromosome 17, include iris (Lisch) nodules, congenital glaucoma, optic nerve gliomas, plexiform neurofibromas of the eyelids, uveal hamartomas, and, rarely, retinal lesions.[4-7] NF2 is characterized by bilateral vestibular schwannomas (acoustic neuromas) and brain and spinal cord tumors, and it is transmitted in an autosomal dominant fashion by genetic abnormalities on chromosome 22.[2] Kaiser-Kupfer and colleagues described at an early age posterior subcapsular lens opacities, which are included in the diagnostic criteria of NF2, in 85% of patients with NF2.[8,9] Other reported ocular associations of NF2 include combined pigment epithelial and retinal hamartoma (CPERH), epiretinal membrane (ERM), optic nerve glioma, and, rarely, Lisch nodules.[9-17] The present study, which contains more data than our previous report,[14] describes the frequency and clinical appearance of retinal findings observed in a prospective study of 15 NF2 patients.

SUBJECTS AND METHODS

Between July 1990 and April 1995, we prospectively examined 15 consectutive patients who met the diagnostic criteria of NF2, which are (1) bilateral eighth nerve masses or (2) a first-degree relative with NF2 and either a unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lens opacity.[2]

All patients had an ocular examination, which included a dilated fundus examination. This was part of a thorough medical and neurologic evaluation of all NF2 patients seen by one of us (A.D.R.). We specifically evaluated the patients for iris, lens, and fundus abnormalities and performed fundus photography on those eyes with clear media. We performed fluorescein angiography on one patient; the findings were described in our prior report.[14]

RESULTS

We observed an ERM in 12 of 15 patients; 1 patient had an ERM in one eye and CPERH in the other eye (Table I). Representative fundus lesions are presented in Fig 1 through 4. Additionally, 11 of the 15 patients had lens opacities in the posterior subcapsular, posterior central cortical, and/or peripheral cortical part of the lens in one or both eyes; 7 of the 12 patients with an ERM and the patient with a CPERH (patient 12) had a lens opacity in the same eye (Table I). Two of the patients had mild to moderate corneal epithelial and anterior stromal changes secondary to a seventh nerve palsy.

The ERMs ranged from 0.5 to 4 disc diameters in size; were translucent, semitranslucent, or whitish grey; and, in some cases, caused tractional changes of the retina without exudation. Most of the ERMs in the macula

TABLE I: OCULAR FINDINGS IN NF2

PATIENT AGE/SEX	BEST CORRECTED VISUAL ACUITY	ERM LOCATION	CPERH LOCATION	LENS OPACITY°	COMMENTS
1 38 M	OD - 20/25 OS - 20/30	OS macula	--	OD	--
2 22 F	OD - 20/25 OS - 20/20	OS macula	--	--	--
3 33 F	OD - Enucleated OS - 20/30	OS macula	--	OS	Right sphenoid ridge supraorbital meningioma
4 24 F	OD - Enucleated OS-20/400	OS superior to macula	--	OU	OD, retinal glioma, retinal detachment, phthisis; OS, amblyopia
5 23 F	OD - 20/30 OS - 20/200	OS macula	--	OU	Left optic nerve meningioma
6 19 F	OD - 20/50 OS - 20/30	OD macula OS superior to macula	--	OS	Cataract Surgery OS at age 5
7 22 F	OD - 20/200 OS - 20/20	OD macula	--	--	--
8 20 M	OD - 20/20 OS - 20/20	--	--	OU	--
9 32 F	OD - 20/20 OS - 20/25	--	--	OU	--
10 39 M	OD - 20/50 OS - 20/40	--	--	--	Corneal changes OU
11 16 M	OD - 20/25 OS - 20/400	OD supero-temporal to macula	--	OU	OS, amblyopia
12 19 F	OD - LP OS - LP	OD macula	OS macula juxtapapillary	OU OU	Optic atrophy† OU
13 29 M	OD - 20/20 OS - 20/20	OS - macula	--	--	--
14 35 M	OD - 20/30 OS - 20/400	OS - macula	--	OU	Amblyopia, optic atrophy† OS; corneal changes OU
15 32 M	OD - 20/20 OS - 20/20	OS - inferior to macula	--	OS	--

CPERH, combined pigment epithelial retinal hamartoma; ERM, epiretinal membrane.
°Lens opacity in posterior capsular or peripheral cortical area of lens.
†Optic atrophy was secondary to optic nerve glioma or increased intracranial pressure because of NF2 lesions.

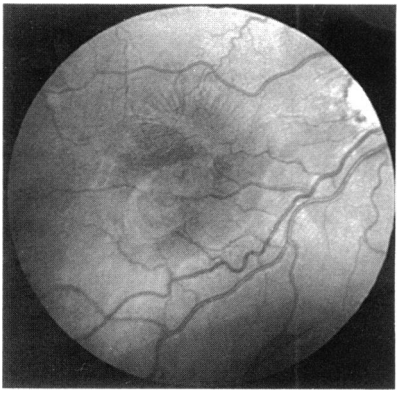

FIGURE 1
Fundus photograph of patient 6 showing ERM with underlying mild retinal striae in macula of right eye.

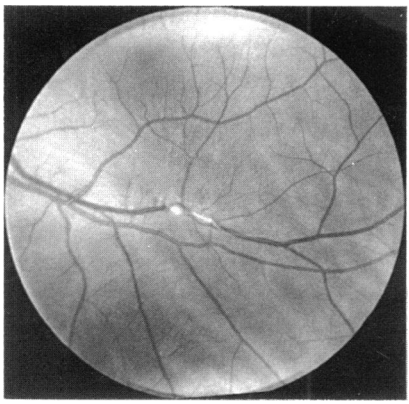

FIGURE 2
Fundus photograph of patient 15 showing ERM along inferior arcade in left eye.

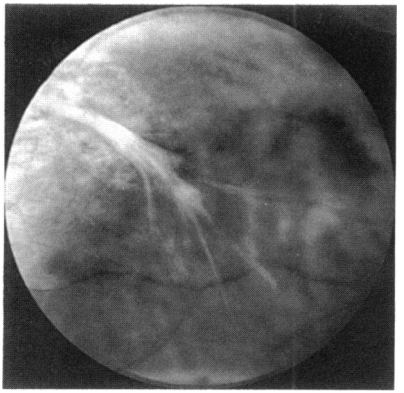

FIGURE 3
Fundus photograph of patient 11 showing ERM with underlying retinal depigmentation superotemporal to macula in right eye.

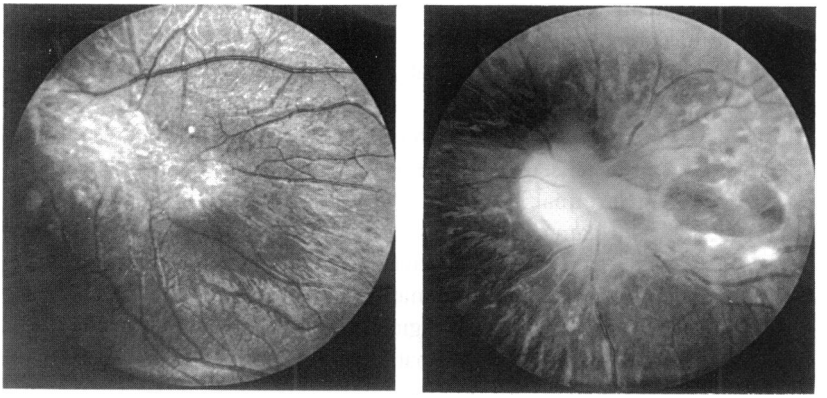

FIGURE 4
Fundus photographs of patient 12 showing ERM with underlying retinal pigmentary changes in temporal perifoveal area of right eye (A) and CPERH involving disc and macula of left eye (B).

did not affect vision. In patient 6, the macular ERM in the right eye (Fig 1) decreased vision moderately and caused some distortion on the Amsler grid test. The macular ERM in the right eye (Fig 4A) of patient 12 may have affected vision before the onset of optic atrophy, but we could not document this; there was a CPERH in the left macula (Fig 4B).

DISCUSSION

In our prospective series of 15 young NF2 patients, we observed ERMs in 12 patients (80%) and a CPERH in 1 patient. The high proportion of NF2 patients with ERMs in this study and in a recent report[16] (4 of 6 patients), as well as the several reported cases of CPERH in NF2 patients, suggest that these retinal lesions are ocular manifestations of NF2 and not merely chance associations.[9-11,13,15,17,18] In two case reports of NF2 patients, one eye had a CPERH involving the disc and macula and the other eye had an ERM similar to those observed in our patients.[10,17] Thus, in addition to lens opacities at an early age, ERMs and CPERH in young patients should also be considered part of the diagnostic criteria of NF2.[2] Epiretinal membranes unassociated with CPERH have not been reported in NF1.

Epiretinal membranes are commonly associated with other ocular conditions, such as posterior vitreous detachment, retinal detachment or breaks, ocular inflammation, retinal vascular disorders, and trauma.[19,20] In children or young adults, epiretinal membranes that are not the result of other ocular disorders are unusual and presumed to be congenital in origin.[21,22] CPERH, initially described in children and young adults without neurofibromatosis by Gass, has been reported in patients with NF1 or NF2.[5,7,9-11,13,15,17,18,23] Epiretinal membranes are nearly always associated with CPERHs. Some investigators have proposed that CPERH is part of a spectrum of lesions from vascular malformations at one end to ERMs at the other, and others have postulated that ERMs in NF2 patients are a form fruste of CPERH.[16,24]

In our previous study,[14] we reported that the histopathologic examination of one eye of a deceased patient revealed an epiretinal membrane overlying an area of intraretinal astrocytic proliferation, which may have represented an early glial hamartoma. Thus, it is possible that some of our patients with ERMs may have an underlying retinal glial hamartoma that we could not detect on our clinical examinations or that they later may develop one. Alternatively, the histophathologic findings in this eye may not have been representative of ERMs in NF2 patients. Further histopathologic studies are needed to elucidate the relationship between ERMs, CPERH, and glial hamartoma in patients with NF2.

Pathogenetically, NF2 is considered to be one of the neurocristopathies that are systemic syndromes of multifocal proliferations of neural crest–derived cells.[25] Embryologically, the ocular associations of NF2 (ERMs,

CPERH, and lens opacities) reflect involvement of the surface ectoderm and neuroectoderm. By 24 days' gestation, neural crest cells are between the surface ectoderm, which gives rise to the lens, and the adjacent neuroectoderm, which differentiates into the retinal pigment epithelium, the inner layer of the optic stalk, and retinal glial cells.[26-28] Neural crest cells have been identified in the avian vitreous near the retina in elegant experiments that grafted quail neural crest cells, which have a heterochromatin nuclear marker, into host chick embryos.[29] We speculate that in NF2, in response to pathophysiologic factors that cause proliferation of neural crest and other cells elsewhere in the nervous system, cells of neural crest or neuroectodermal origin at the vitreoretinal juncture or in the retina and lens ectodermal cells proliferate or develop abnormally, resulting in ERMs, CPERH, lens opacities, or some combinations of these conditions at an early age.

The early diagnosis of NF2 may allow preservation of auditory and facial nerve function. Surgical resection of the vestibular branch of the eighth nerve when the tumor is small results in the best prognosis.[3,30,31] Thus, children or young patients with ERMs, CPERH, and lens opacities that are not the result of other ocular disorders should have a neurologic evaluation and a thorough family history for NF2; genetic counseling should be provided if NF2 is diagnosed.

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DISCUSSION

DR. MURIEL I. KAISER-KUPFER. I was very pleased in having the opportunity to open the discussion of this very fine paper on Retinal Changes Associated with Neurofibromatosis 2 presented by Dr Sanford Meyers and his colleagues from the Cleveland Clinic. The authors expand their previously reported experience of 9 patients by including 6 additional patients, bringing the total number of cases to 15. Once again, it may be seen how important the ophthalmologists' role is in establishing or confirming the diagnosis of a systemic disease associated with significant morbidity, as is the case with NF2, by the recognition of ophthalmic manifestations.

Dr Meyers and colleagues confirm our original observation of an 81% frequency of posterior capsular or peripheral cortical opacities with their

report of a 73% incidence in their patients. However, their major contribution focuses upon the finding of epiretinal membranes (ERMs) in 12 of 15 patients and a combined pigment epithelial and retinal hamartomas (CPERHs) in 1 eye of 1 patient.

As the authors note, CPERHs, first described by Gass, have been recognized increasingly in patients with NF2. The consensus is that the cause is probably a developmental defect. In our experience, this is supported by the report of macula CPERH in 4 persons of a three-generation family. The affected NF2 individuals in this family included 2 young children, aged 5 years and 8 months. Epiretinal membranes frequently are associated with CPERH, as in Dr Meyers' case 12. We agree that although the mechanism for these entities is unknown, it is likely they are probably developmental in origin and represent a spectrum of vascular lesions from ERM at one end to CPERH at the other end.

One would like to speculate as to why there was such a high frequency of ERM observed in the authors' series. Several possibilities come to mind. First, it may attest to Dr Meyers' skills as an excellent retinal examiner. Other studies may have more patients with hazy media due to the presence of cataract or corneal changes secondary to postoperative neurosurgical procedures. This would result in more difficulty for the ophthalmoscopic examination of these NF2 patients. A third possibility remains. Dr Parry and our group at the National Institutes of Health published the experience with 63 affected individuals from 32 families, including sporadic cases, describing the clinical characteristics. Usually the clinical manifestations and course were similar within families but differed among families. The severest cases were associated with a young age at onset, presence of central nervous system tumors other than vestibular schwannomas, and presence of CPERH. Thus, patients with the severest type of NF2, sporadic or familial, have an increased frequency of ERM and CPERH. The high frequency of ERM in the authors' series and in Landau's series is a noteworthy and interesting observation. It appears that ERM and CPERH are present primarily, if not solely, in patients with severe NF2. Thus, the present authors' findings may reflect the selective referral pattern of patients with severe NF2 to their clinic.

It would appear from details of the clinical findings of the first 9 cases previously reported that they were indeed young patients with severe NF2. It would be interesting to have this information about the additional 6 patients. Clarification as to subtype may aid in counseling with regard to long-term prognosis and in formulating individualized guidelines for medical surveillance. With the gene for NF2 cloned, it will soon be possible to determine if the phenotype can be identified from the genotype. This brings us to the point of new developments that have resulted from molecular genetic studies.

Family studies and tumor analysis have indicated that the tumors in

NF2, both familial and sporadic, are caused by inactivation of a tumor suppressor gene located on 22q12. Recently the gene encoding merlin, a novel member of a family of cytoskeletal-associated proteins, was identified as the NF2 tumor suppressor gene. Inactivation of merlin is a common feature underlying inherited and sporadic forms of schwannomas. The inactivation of the merlin protein may explain or contribute to our understanding of the frequent occurrence of cataract, CPERH, and ERM. In the case of cataract, abnormalities may occur in cell-to-cell adhesion, and in the case of ERM and CPERH, it may be due to lack of the effect of the suppressor gene. Current practice requires screening of all "at risk" family members for NF2 with repeated magnetic resonance imaging. As in many other genetic diseases, the identification of DNA mutations in the NF2 gene will permit molecular testing to diagnose more precisely affected individuals.

DR. J. BROOKS CRAWFORD. Last year, in discussing a paper by Dr. Klein on the Epidemiology of Epiretinal Membranes, I mentioned that Bill Hoyt and I had had the opportunity to examine the histopathology of the eyes from two patients with neurofibromatosis II. Let me share with you the photomicrographs. The first case was a patient who came from Caracas; Ralph Eagle kindly provided us with the material from which these pictures were prepared. This patient was deaf and had bilateral optic nerve meningiomas. Notice the perineural cyst (Fig. 1) which could be seen on the CT scan and is characteristic of some meningiomas of the optic nerve. Here is a posterior subcapsular cataract (Fig. 2), another feature of NF II. The cortex is liquefied just in front of the posterior capsule. In the retina there were numerous defects in the internal limiting membrane. Extending through many of these, glial proliferations formed plaques on the internal limiting membrane (Fig. 3).

The other case was reported in a paper by Saran and Winter in the American Journal of Ophthalmology, September 1967. This patient was blind and deaf, and had bilateral optic nerve gliomas and multiple spinal cord

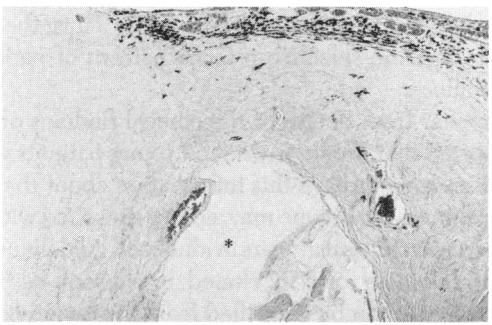

FIGURE 1
Perineural cyst in patient with NF II. Peripapillary choroid on top; optic nerve on left; dural sheath of optic nerve on right.

meningiomas. Here again we have throughout the retina unusual epiretinal membranes composed of proliferating glia. Here we can see an area where there are two of them (Fig. 4). We think these atypical epiretinal membranes correlate very well with the retinal lesions seen in the excellent clinical photographs that have just been presented by Dr. Meyers.

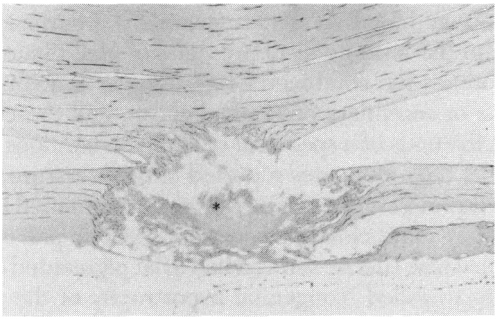

FIGURE 2
Posterior subcapsular cataract in patient with NF II.

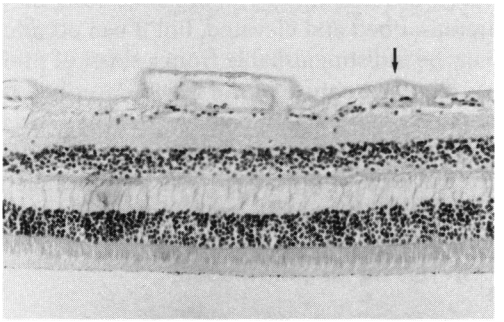

FIGURE 3
Glial plaque (arrow) protruding through defect in internal limiting membrane in patient with NF II.

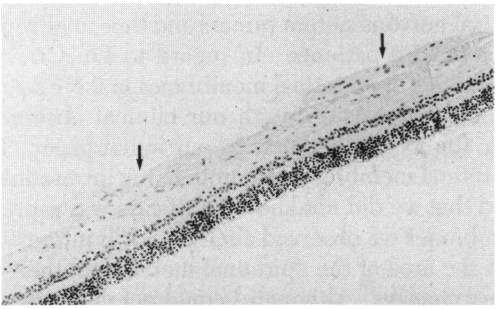

FIGURE 4
Two glial pre-retinal membranes (arrows) in another patient with NF II.

JERRY A. SHIELDS, MD. Dr. Meyers has presented cases of peculiar fundus lesions in patients with neurofibromatosis type 2. Although these lesions have been called "combined hamartomas" in the recent literature, some of them do not have the classic features originally attributed to combined hamartomas. The classic combined hamartoma is a mossy gray lesion that is usually found in a juxtapapillary location, but occasionally in the peripheral fundus. The retinal blood vessels are generally abnormal and sometimes are dragged into the lesion due to presence of glial tissue on or near the surface. Sometimes the combined hamartoma is difficult to differentiate from idiopathic or secondary pre-retinal gliosis, and these two conditions may represent the ends of a spectrum of similar conditions.

Like some of the other cases reported in the literature, those reported by Dr. Meyers do not have the classic features of combined hamartoma and, in some ways they more closely resemble idiopathic preretinal gliosis. In addition, the final case that he showed had a flat pigmented component that was identical to so called "congenital hypertrophy of the retinal pigment epithelium".

There is also a possibility that some of the lesions seen in neurofibromatosis type 2 are actually sessile glial hamartomas similar to those associated with tuberous sclerosis. In tuberous sclerosis, the glial hamartoma is often well circumscribed and elevated, but it can occasionally be diffuse or sessile and may be indistinguishable from a sheet of preretinal gliosis.

In summary, the exact nature of the lesion described by Dr. Meyers is not clearly understood. Although it could represent a variant of combined hamartoma, it seems prudent to avoid that term when we describe these lesions. Perhaps the term preretinal fibrosis or preretinal gliosis might be safer until we obtain more histopathologic information on the true nature of these lesions.

I thank Dr. Meyers for his contribution.

SANFORD M. MEYERS. I appreciate the kind, generous comments by Dr. Kaiser-Kupfer and the other disscussants. I agree with Dr. Kaiser-Kupfer that these neurofibromatosis type 2 (NF2) patients may represent a biased sample because of the severity of the NF2. All of the 15 cases had multiple spinal and central nervous system tumors and thus, may represent the most severely affected NF2 patients. In regard to Dr. Crawford's excellent histopathologic slides of epiretinal membranes in 2 NF2 patients, I believe that they are more consistent with our clinical observations than the histopathologic findings of one case in our initial paper. In that case, we showed an epiretinal membrane with underlying intraretinal glial proliferation, but stated that we did not know if this case was representative of the epiretinal membranes we observed clinically. It is interesting that in some of our cases in the area of the epiretinal membrane, there are very subtle hypopigmentary changes. Although I could not clinically detect thickness to the retina underlying the epiretinal membrane in our cases, some of the cases may have subclinical intraretinal glial proliferation or a glial hamartoma

underlying the epiretinal membrane. As for Dr. Shields' comments, I agree that in my experience, our case of a presumed combined pigment epithelial retinal hamartoma (CPERH) is not a typical looking CPERH as described in an article by Dr. Shields and colleagues. However, our case appears similar to the cases of CPERH in NF2 patients reported by other investigators as referenced in our manuscript.