

Research Article

Macular Anatomy and Abnormalities in Neurofibromatosis Type 2

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Abstract

Purpose: To describe macular anatomy and abnormalities on Spectral-Domain Optical Coherence Tomography (SD-OCT) in a large series of patients with Neurofibromatosis Type 2 (NF2).

Methods: Retrospective review of all consecutive patients with NF2.

Results: A total of 166 eyes in 83 patients with NF2 were identified from February 2014 to May 2015. Macular SD-OCT was available for 124 eyes (75%). Isolated epiretinal membrane (ERM) was diagnosed in 52% of patients (n=43) with bilateral ERM in 15 cases. ERM was commonly fine (64%), non-retractile (90%), extra-foveolar (90%), discontinuous (78%) and without posterior vitreous detachment (93%). Combined Hamartoma of the Retina and Retinal Pigmented Epithelium (CHRRPE) was seen in 12% of patients (n=10); three of which were bilateral. Additional OCT anomalies identified include Congenital Hypertrophy of Retinal Pigment Epithelium (CHRPE), internal limiting membrane irregularities, inner retinal tufts, serpentine-like extensions into the vitreoretinal interface, focal alterations of inner retinal lamination and infiltration of the posterior vitreous cortex. All retinal anomalies identified suggest pathological involvement of Müller cells.

Conclusion: Our series underscores the utility of macular SD-OCT in patients with NF2. While ERM and vitreoretinal interface abnormalities are the most common macular pathology identified in NF2, all SD-OCT pathology suggests Muller cell involvement.

Keywords: Combined Hamartomas of the Retina; Retinal Pigmented Epithelium; Epiretinal Membrane; Neurofibromatosis Type 2; Spectral-Domain Optical Coherence Tomography

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant condition, although approximately half of all cases arise sporadically. Epigenetic determination in NF2 occurs on the long arm of chromosome 22 [1]. NF2 is characterized by the development of multiple nerve tissue tumors [2]. In practice, 20-30% of patients afflicted with NF2 exhibit a mosaic expression [3]. This genetic heterogeneity occurs largely at the phenotypic level and severity varies from case to case [4]. Severe forms of NF2 - involving multiple tumors of the central nervous system, rapid progression and considerable reduction in life expectancy - correlate with mutation type and early onset of disease (less than 20 years of age) [5,6]. The Manchester criteria allows NF2 to be diagnosed clinically, even in the absence of identifiable genetic anomalies [7,8].

NF2 is dominated by the occurrence of Vestibular Schwannomas (VS) that are often bilateral and result in auditory and balance impairment. Other tumors of the central nervous system can also be present such as meningioma, schwannomas, neurofibromas

and low-grade glial tumors [2,4,9]. The first symptoms usually appear in young adults, even though pediatric and late-occurring forms have also been reported. Pediatric forms pose considerable diagnostic challenges because presentation is often atypical compared to the adult forms, with a general absence of VS as well as of prominent ophthalmological anomalies [10].

Ophthalmological findings are common and comprise NF2-type cataracts, Epiretinal Membranes (ERM), Combined Hamartomas of the Retina and Retinal Pigmented Epithelium (CHRRPEs), exposure keratitis, oculomotor impairments, tumors of the optic nerve sheath and melanocytosis of the optic nerve [11-14]. Similar to NF2-type cataracts, retinal abnormalities are key ophthalmological markers which can contribute to early diagnosis of NF2 and are usually linked with severe disease phenotype [4,11,15,18]. Recent literature has underlined the use of macular spectral-domain optical coherence tomography (SD-OCT) in NF2 to aid description of ERM and CHRRPEs [19,20]. However, a significant knowledge gap remains when describing macular abnormalities in patients with NF2 [12,13,16,17]. Here, we describe the macular anatomy and abnormalities on SD-OCT in a large series of patients with NF2.

Material and Methods

Ours is a retrospective observational case series involving consecutive patients with NF2 referred to the Pitié Salpêtrière Hospital (Paris, France) department of ophthalmology. All research conducted follows the tenets of the Declaration of Helsinki.

NF2 diagnosis was based on the Manchester criteria. All the patients received a full ophthalmological examination including Best-Corrected Visual Acuity (BCVA), oculomotor screening, slit-lamp anterior segment examination and dilated fundus examination. All patients had macular OCT imaging (CIRRUS HD-OCT 5000, Carl Zeiss Meditec, Dublin, CA, USA) with horizontal HD 5 line-raster and vertical and macular cube (512 by 128). Whenever possible, an additional 49-line horizontal raster scan with was performed (Heidelberg Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany).

OCTs were analyzed by two readers; in case of discordance, a third reader was used to adjudicate queries. A diagnosis of CHRRPE was based on the presence of a pigmented mass at the posterior pole with associated retinal thickening [21]. On OCT, CHRRPE were diagnosed based on thickening and disorganization of the inner retina, loss of laminar structure and decrease in the reflectivity of the outer retina and the retinal pigment epithelium [22].

For statistical analysis, chi2 test was used to compare categorical data. A p-value of less than 0.05 was considered significant. Statistical analyzes were carried out using SPSS for Windows version 16.0 (SPSS, Inc., Chicago, IL).

Results

A total of 166 eyes in 83 patients with NF2 were reviewed (33 males, 50 female) from February 2014 to May 2015. Median age was 34 years (SD $\pm$ 13.9, range 15 to 71). The age of disease onset was early (<20years) for 35 patients (42%), late (>20 years) for 18 patients (22%) and unknown for 30 patients (36%). Eight out of 83 patients had a family history of NF2. All patients were symptomatic except for one 48-year-old patient who was diagnosed by the detection of NF2 mutation. Sixty-one percent of the patients had bilateral VS and 16% unilateral involvement. The average BCVA (log MAR) was 0.34 ± 0.61 (Snellen equivalent of approximately 20/40).

Macular SD-OCT was obtained for 124 eyes (75%) with CIRRUS-HD and an additional 38 eyes (28%) also had macular imaging with Heidelberg Spectralis. Forty-two eyes did not have acceptable macular OCT imaging, either due to media opacity or inability maintain adequate fixation and were excluded from analysis. Isolated ERM (not associated with CHRRPE) was diagnosed in 43 patients (52%) with bilateral ERM in 15 cases. In most cases, ERMs were fine (64%), non-retractile (90%), extra-foveolar (90%), discontinuous (78%), without total posterior vitreous detachment (93%), without cystoid macular edema (0%) or alteration of the ellipsoid line (0%) (Fig. 1, Table 1).

Furthermore, other OCT anomalies identified include (Table 2): irregularities of the Internal Limiting Membrane (ILM) (32/124) (Fig. 2), serpentine-like extension of the vitreoretinal interface (22/124) (Fig. 3), infiltration of the posterior vitreous cortex (20/124) (Fig. 3), focal alterations of inner retinal lamination (15/124) (Fig. 3) and tufts of the inner retina (6/124) (Fig. 2). We prefer this

term to “tufts of a nerve fiber layer” 20 because the contents of the tuft are not limited to the nerve fiber layer. We encountered CHRRPEs in 10 patients (12%) with bilateral condition in 3 cases.

Macular abnormalities on macular SD-OCT were seen in 65% (54/83) of cases. Most commonly, macular pathology was found in early-onset disease (80%, 28 of 35) versus 44% (8/18) in the late-onset and 60% (18/30) in the unknown groups ($p=0.009$). For the 10 patients with CHRRPE, age of disease onset was early in 7 cases and unspecified for 3 cases. Other ophthalmologic findings related to NF2 identified in our review include: NF2-type cataract (44/83), oculomotor disorders (35/83), alteration of the optic nerve (atrophy or edema) (27/83) and exposure keratopathy (20/83).

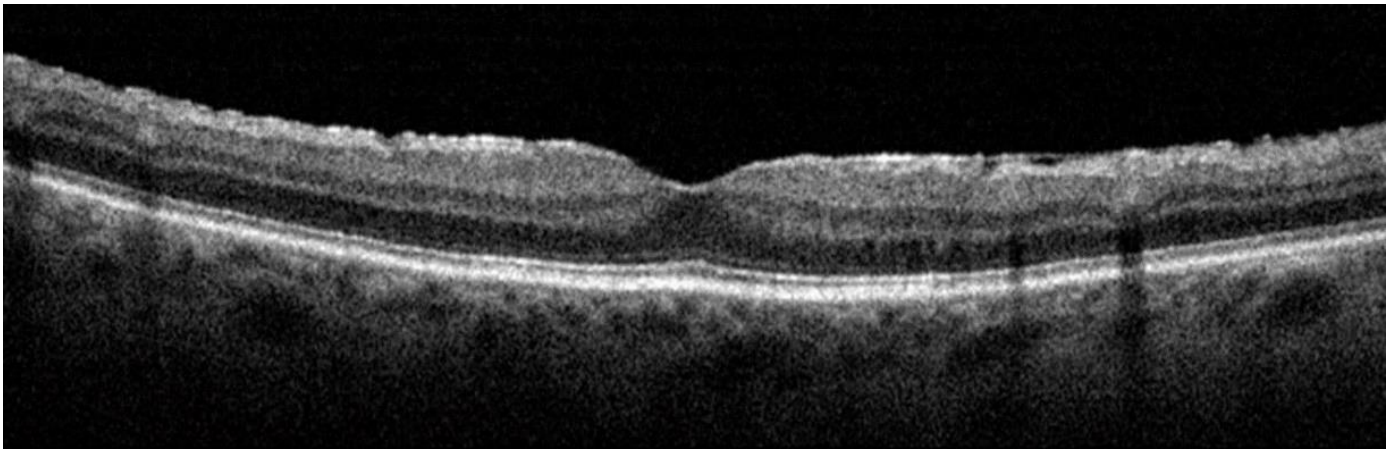


Figure 1: Extrafoveal, thin and non-retractile ERM.

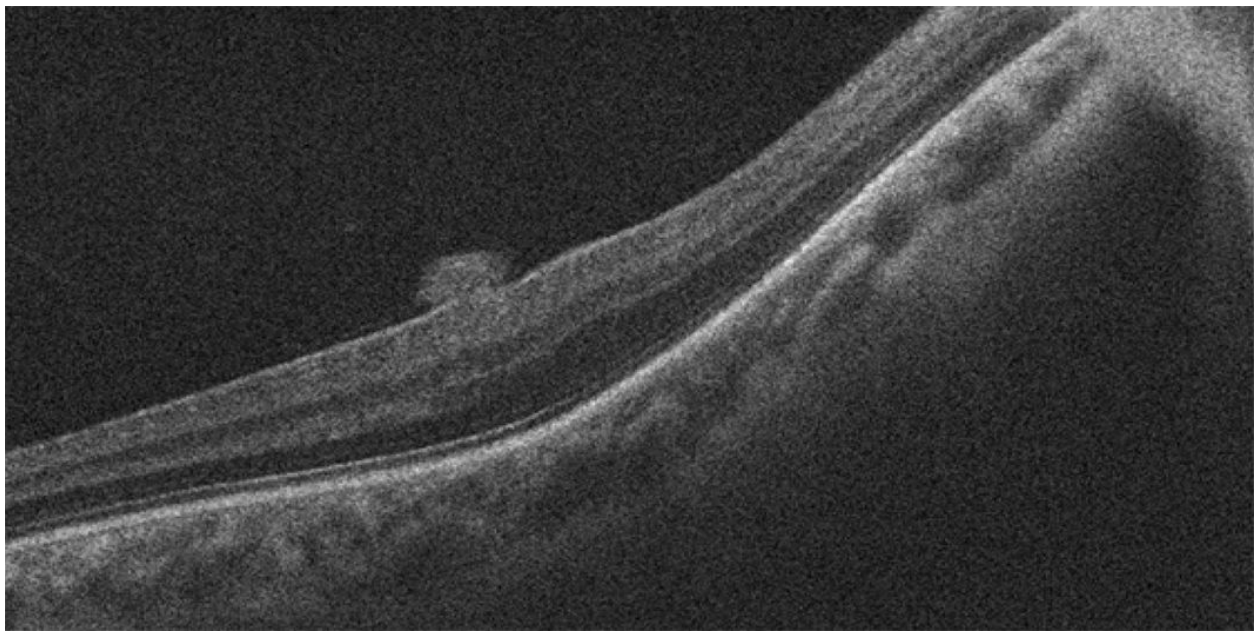


Figure 2: Defect of the ILM with tufts of the inner retina in the vitreous cavity.

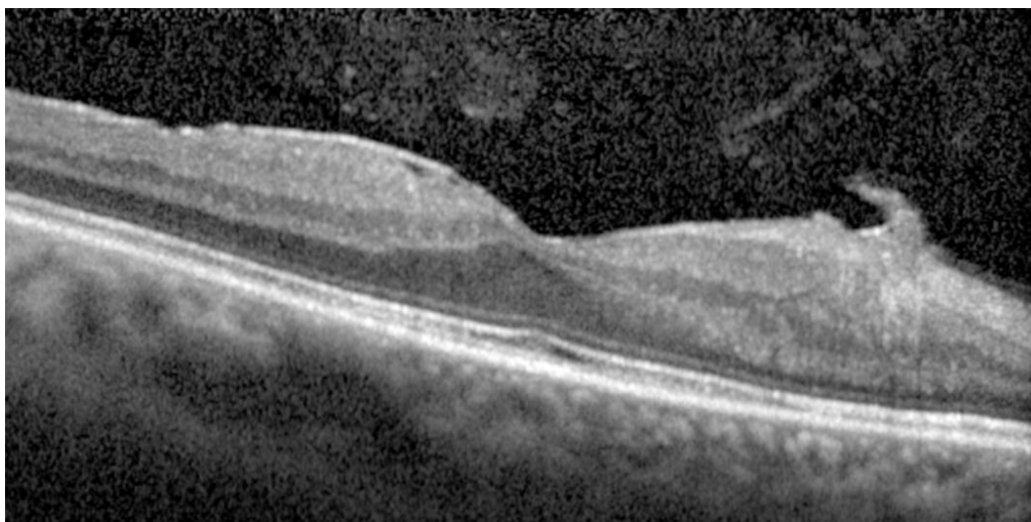


Figure 3: Thick and retractile ERM with a nasal serpentine like extension in the vitreous-retinal interface and focal alteration of the inner retinal layers that remain individualizable, albeit with a thickened and irregular appearance. Diffuse infiltration of the posterior vitreous cortex. Preservation of the reflectivity of the ellipsoid line and the retinal pigment epithelium.

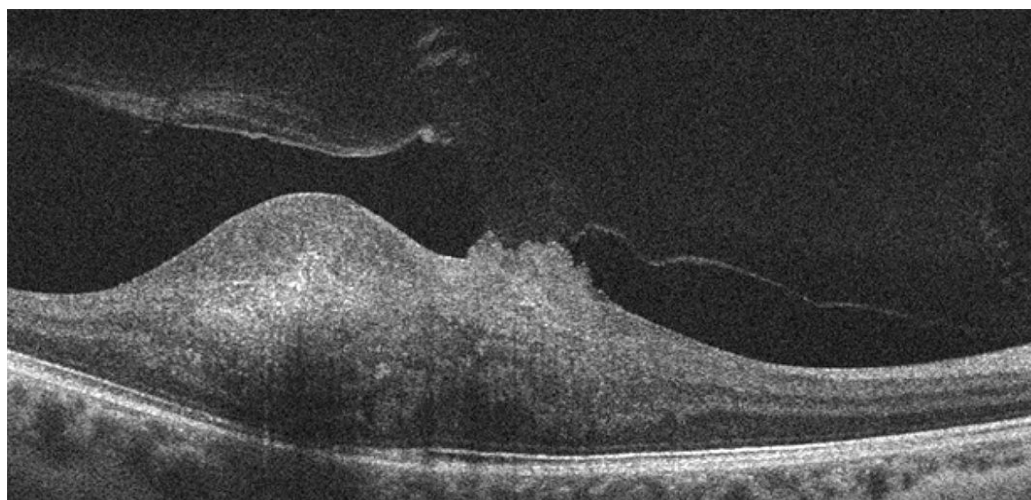


Figure 4: CHRRPE: Hyper-reflective mass of the inner retina with total loss of its laminar architecture. Interruption of the ellipsoidal line and hypo-reflectivity of the retinal pigment epithelium. Partial detachment of the vitreous with irregularity of the ILM at the level of the vitreo-retinal adherence. Infiltration of the posterior vitreous in front of the posterior hyaloid away from this adherence.

Epiretinal Membrane	58 (47%)
• Thin/Thick	64%/36%
• Non retractile/retractile	90%/10%
• Extra-foveal/ Foveal	90%/10%
• Discontinuous/ Continuous	78%/22%
• Posterior Vitreous Detachment	7%
• Alteration of Ellipsoid Line	0%
• Cystoid Macular Edema	0%
^a Not associated with Combined hamartomas of the retina and retinal pigmented epithelium	

Table 1: Aspect of epiretinal membranes on 124 NF2 eyes.

Irregularity of Internal Limiting Membrane	32 (26%)
Serpentine Like Extension into the Vitreoretinal Interface	22 (18%)
Infiltrate of Posterior Cortex Vitreous	20 (16%)
Focal Alteration of Inner Retina Lamination	15 (12%)
Tufts of Inner Retina	6 (5%)
^a not associated with combined hamartomas of the retina and retinal pigmented epithelium	

Table 2: Others macular OCT findings on 124 NF2 eyes.

Discussion

Ophthalmological signs are an integral part of the clinical presentation of NF2 and vitreoretinal findings are predominantly ERM and CHRRPE. The prevalence of ERM in NF2 reported in the literature varies from 11 to 80% [11,16,18,23]. We found ERM occurrence comparable to those previously reported in the literature. The dominant aspects of ERM in NF2 -fine and non-retractile - explain why they are often missed with only dilated fundus examinations, hence underscoring the relevance of OCT with these patients. In our series, 18 patients had “normal” dilated fundus evaluations; 50% of these were later diagnosed with ERM based on macular SD-OCT. Scheffler, et al., first described ERM with “serpentine and curled edges stretching into the vitreoretinal interface” [19]. Later, Waisberg, et al., described “fine undulations of the retina surface and retinal tufts of a nerve fiber layer” [20]. Here, we provide clear OCT evidence of these features.

The pathogenesis of ERM in NF2 remain poorly understood, particularly because they appear early in life despite and tend to occur in the absence of Posterior Vitreous Detachment (PVD). The common etiologies of ERM comprise PVD, retinal detachment, retinal breaks, retinal vascular disease, intraocular inflammation and trauma. In NF2, the elevated frequency of ERM, as well as NF2 cataracts and CHRRPEs, underline the pathological implication of neural crest cells [23].

Histological arguments for the formation of ERM in NF2 implicate glial cells distinct from the ILM that proliferate into plaques on the ILM [23,24]. Müller cells are the likely histological origin of NF2 ERMs. These glial cells derived from the neural crest undergo excessive proliferation due to alteration of contact inhibition; consequently, this perturbs the ILM (which acts as a barrier between the vitreous and the inner retina) and alters the laminar architecture of the inner retina [25]. The OCT anomalies we describe here support this histological hypothesis because ILM defects allow colonization of the surface of the retina (forming ERM) as well as the fibers of the vitreous cortex to be oriented perpendicular to the retina (forming serpentine-like extension into the vitreous) (Fig. 3) [25].

This colonization of the vitreous humor likely occurs due to loss of contact inhibition of the Müller cells in the presence of hyaluronic acid and CD44, which are both present in the vitreous cortex [26]. The focal alterations of the inner retinal lamination could correspond to an alteration of the framework support function of the Müller cells. Histological reports [24] noted that the retina underlying the ERM had a specific appearance, with light distortions mainly at the level of the internal layers. Irregularities of the ILM may be secondary to alteration of the role of Müller cells in the homeostasis of the ILM, thereby allowing defects (Fig. 2), undulations, or loss of its anatomical architecture to appear.

Tufts of the inner retina are like serpentine-like extensions of ERM. Infiltration of the posterior vitreous cortex (Figure 3) may represent a more diffuse form of the colonization of the vitreous by Müller cells. These retinal anomalies could, therefore, be different aspects of the same pathophysiological process, firstly due to the instability and dysfunction of the Müller cells and hence the inner retina. Therefore, the point of departure of ERM linked with NF2 is the inner retina and not the vitreoretinal interface as in idiopathic ERM. Indeed, all the retinal anomalies described here in NF2 involve the inner retina and the vitreoretinal interface, with a well-preserved outer retina (latter exception is CHRRPE). The fact that most ERMs described present a discontinuous appearance provides an additional argument for the dysfunction of Müller cells and inner retina.

CHRRPE are rare benign tumors in the general population, usually unilateral, with appearance of an elevated mass associated with pigment and vascular tortuosity [21]. Their prevalence in NF2 varies from 3-22% with bilateral involvement that is pathognomonic for NF2 [4,11,13,23]. Despite the numerous differences, several reports hypothesize ERM and CHRRPE are derived

from a common pathophysiological process based on histological similarities of a common glial cell origin; this is supported by the evidence that 80% of CHRRPE exhibit ERM on their surface [21,24,25,28]. These two lesions are overrepresented in NF2 relative to the general population. Furthermore, atypical OCT anomalies described here can be associated with each of these such as infiltrations of the posterior vitreous cortex, irregularities of the ILM, or serpentine-like extensions in the vitreoretinal interface (Fig. 4). Lastly, it should be noted that what we describe as focal alterations of the inner retinal lamination may correspond to very small CHRRPE-like changes. Evidence to the latter is found in reports of CHRRPE in NF2 with mild alterations of the reflectivity of the ellipsoid zone [22].

The vitreoretinal alterations in NF2 and particularly CHRRPE, are a marker of severe disease phenotype and associated with severe mutations and early-onset disease [4,11,16,18,20,25]. Contrastingly, mosaic NF2 phenotypes have milder vitreoretinal and macular anomalies [17]. Our series is consistent with these previous observations given that the early onset group had a clear increase in frequency of macular abnormalities and CHRRPE compared to the late-onset group.

Our study comprises several limitations which need to be presented. Our retrospective design and lack of follow preclude temporal analysis of the findings we present here. Nonetheless, given the large size of our series and extensive macular imaging, the macular abnormalities in NF2 underscores the utility of macular SD-OCT in identifying relevant pathology that will aid diagnostic and prognostic considerations for clinical care.

Conclusion

In conclusion, to date, retinal disorders are not part of the Manchester criteria for NF2 diagnosis. However, macular SD-OCT imaging in current practice could greatly aid diagnosis and facilitate counseling on disease severity for patient with diagnosis made on genetic testing rather than age of disease onset. Macular pathology in NF2 centers on alterations of the ILM and proliferation of Müller cells that results in ERM, tufts of the inner retina, serpentine-like extension into the vitreoretinal interface and infiltration of the posterior vitreous cortex. Longitudinal studies with serial macular imaging will be needed to explore progression of macular pathology in patients with NF2.

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Conflict of Interest

The authors have no conflict of interest to declare.

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