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Surgical removal of subfoveal choroidal neovascularization: visual outcome and prognostic value of fluorescein angiography and optical coherence tomography

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PURPOSE. *To study the functional results of macular surgery and determine pre-operative features associated with better final visual outcome.*

METHODS. *Forty-two consecutive patients underwent surgical removal of subfoveal choroidal neovascularization (CNV), related to age-related macular degeneration (AMD) in 8 eyes, degenerative myopia in 14 eyes, multifocal choroiditis (MFC) in 10 eyes, idiopathic CNV in 6 eyes and other etiologies in 4 eyes. Mean age was 49 years. Pre-operative visual acuity (VA) was 20/200 or less in 30 eyes (71.4%) and never better than 20/40. Fluorescein angiography was analyzed before and after surgery. Pre-operative optical coherence tomographs (OCT) were studied in a masked fashion. Mean follow-up was 12 months (range 4-48 months).*

RESULTS. *Final VA was 20/200 or less in 25 eyes (60%). According to the CNV etiology, the percentage were 87.5%, 80%, 57.1% and 20% respectively in eyes with AMD, MFC, high myopia, and idiopathic or other diseases. Post-operative VA improved in 21 eyes (50%) but subsequently declined in 7% by the final examination. Patients younger than 50 years had better functional results ($p=0.006$). Lack of retinal pigment epithelium (RPE) changes on pre-operative angiography was correlated with good visual outcome ($p<0.001$). The OCT study confirmed some features already described and showed some different CNV patterns: above and usually separated from the RPE, below and not separated from the RPE, and ungradable. Eyes with the first OCT pattern had the best visual outcome. Main complications included 4 (10%) retinal detachments and 9 (21%) recurrences. OCT was also useful to confirm CNV recurrences post-operatively.*

CONCLUSIONS. *CNV surgical excision results vary depending on the underlying disease, the RPE and choriocapillaris function, and the features observed on pre-operative OCT images. (Eur J Ophthalmol 2001; 11: 297-295)*

KEY WORDS. *Choroidal neovascularization, Macular surgery, Angiography, Optical coherence tomography, CNV recurrence*

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INTRODUCTION

Choroidal neovascularization (CNV) is one of the main causes of legal blindness in the western world. It is most commonly due to age-related macular degeneration (AMD) but other etiologies exist, especially in young adults: degenerative myopia, angioid streaks, multifocal choroiditis (MFC), presumed ocular histoplasmosis syndrome, traumatic choroidal rupture, and others. In 17% of patients, CNV cannot be related to

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any condition and is called "idiopathic" (1). CNV are mostly macular and already lie beneath the fovea in 26-50% of the affected eyes. The Macular Photocoagulation Study demonstrated a benefit of laser treatment for extrafoveal or juxtafoveal CNV in AMD (2), presumed ocular histoplasmosis syndrome (3) and idiopathic CNV (4). Subfoveal photocoagulation is more controversial, leading to an immediate marked loss of central vision (5); the benefit of laser treatment compared with observation can only be appreciated after two years. An alternative approach, perifoveal photocoagulation, gave similar long-term efficacy but without the sudden post-operative visual decrease (6).

Various alternatives, including pharmacotherapies, have been sought, to preserve central visual function. Recently, photodynamic therapy and surgical macular translocation have been advanced as vision-preserving therapies. Subfoveal CNV removal was the first alternative to thermal laser photocoagulation and thus has the longest follow-up.

Since 1988, many pilot studies (5, 7-21) have been published and the comparative results have allowed identification of favorable candidates for surgery. However, no data from multicenter randomized trials are available on the results of surgical removal of CNV, except in recurrent subfoveal neovascular lesions in AMD. The first report of a small pilot trial within the randomized Submacular Surgery Trials was recently published. Although the sample was too small to prove the efficacy or harm of subretinal surgery in these cases, no reason appeared to prefer submacular surgery over laser photocoagulation for treatment of recurrent subfoveal neovascular lesions (22).

The aim of this study was to identify prognostic angiographic signs, to evaluate the possible usefulness of optical coherence tomography (OCT) in selecting patients, and to report the results of vitreous surgery for subfoveal neovascular lesions of various etiologies.

PATIENTS AND METHODS

The patients selected for this study underwent surgical removal of subfoveal CNV in our department between April 1995 and December 1998. Inclusion criteria were clinical and angiographic evidence of subfoveal CNV of any etiology, with a significant deterioration of visual acuity (VA). Patients with previous macular laser treatment were not excluded.

Pre-operative evaluation included VA measured on a Snellen chart, biomicroscopic fundus examination and fluorescein angiography. Indocyanine green angiography was performed when occult neovascularization was suspected. Since September 1997, every patient has been examined by OCT.

All patients signed an informed consent form and were operated on by two of us (A.G-B. and G.M.). The surgical procedure, previously described (20), consisted of regular three-port pars plana vitrectomy with detachment and removal of the posterior hyaloid. The retinotomy site varied depending on the location of the neovascular membrane but was most commonly superior-temporal to the fovea. Generally, after BSS injection beneath the neurosensory retina, the CNV was liberated with a spatula to break adherence between the membrane and the overlying retina and the underlying retinal pigment epithelium (RPE). CNV was then grasped and removed with forceps. A fluid/air exchange was performed at the end of the surgical procedure, without endophotocoagulation around the retinotomy site.

Post-operatively, patients were examined at 1 week, 1 month, 2 months and then every 3 months to detect recurrent CNV. Visual acuity, biomicroscopic exa-mination, fluorescein angiography and OCT were systematically performed.

Pre-operative fluorescein angiography allowed determination of the exact location, size (measured in optic disc dia-meters: DD), the type of the CNV (well and/or ill defined), RPE changes, choriocapillaris vascular dye-filling patterns (homogeneous or not), the presence of drusen, of lacquer cracks and of myopic staphyloma. The size of the post-operative RPE atrophy was compared to the initial size of CNV.

Optical coherence tomography (Humphrey instrument, Zeiss) produces retinal cross-sectional images of the retina after pupillary dilatation. All OCT images were reviewed in a masked fashion by one of us (F.C.). The following aspects were specifically analyzed (23): fusiform thickening and disruption of the RPE, choriocapillaris reflection, back-scattering, serous retinal detachment, intraretinal thickening consistent with intraretinal fluid accumulation, intraretinal optically empty spaces corresponding to cysts of cystoid macular edema, and RPE detachment. The normal minimally reflective band of the retinal photoreceptor lay-

er was considered an indicator of the quality of the image.

Classification was based on the description by Gass (24): type 1 CNV lying beneath the RPE and resulting in diffuse thickening of the RPE/choriocapillaris layer, and type 2 CNV extending beneath the neurosensory retina and usually with a cleavage plane between the CNV and RPE.

Post-operatively, additional features were analyzed on the OCT images: increased optical reflectivity of a well-defined area with back-scattering due to a fibrous scar, the recovery of the foveal depression, or signs of recurrent CNV (persistence of intraretinal or subretinal fluid, intraretinal cysts, thickening of the RPE/choriocapillaris layer).

Chi-square analysis (modified by Yates for small samples) and Student's t-test were used to compare qualitative and quantitative variables in the different groups.

RESULTS

Between April 1995 and December 1998, 42 eyes of 18 (43%) men and 24 (57%) women underwent surgical removal of subfoveal CNV. Ages ranged from 15 to 78 years (mean 49). Degenerative myopia was the most frequent etiology (14 eyes, 33.3%), with a mean refraction of -14 D (range from -9.25 D to -23 D), followed by MFC (10 eyes, 23.8%) and AMD (8 eyes, 19%). Four eyes with various other etiologies were included: angioid streaks, multifocal placoid pigment epitheliopathy, osteoma and iatrogenic CNV. Idiopathic CNV were diagnosed in 6 eyes (14%). Mean time between the onset of visual symptoms and surgery was 5 months (range 1-45). Mean follow-up was 12 months (range 4-48).

Pre-operatively, VA was 20/200 or less in 30 eyes (71.4%) and from 20/125 to 20/50 in 12 (28.6%). Post-operatively, VA was 20/200 or less in 50% of the eyes and in almost 60% at the last follow-up (Fig. 1). Nevertheless six eyes (14.3%) had post-operative VA of 20/40 or more, including five eyes which kept it until the end of follow-up. In the AMD and myopic groups, post-operative VA never exceeded 20/50 (Fig. 4). In the MFC group, post-operative VA improved in all eyes after surgery (VA was 20/200 or more in 50% of these eyes), but only 2 out of l0 eyes retained best post-operative VA, due to recurrent CNV (Fig. 3). In the other etiologies, including a majority of idiopathic CNV, 8 patients out of 10 achieved a final VA of 20/125 or more. No relation was found between the final post-operative VA and sex, duration of symptoms, pre-operative VA, post-operative complications or CNV size, though post-operative VA was significantly better in patients under 50 years of age (p=0.006).

Out of the 42 eyes, VA improved in 21 (50%), worsened in 9 (21.5%) and was unchanged in 12 (28.5%). These results worsened with time (Fig. 2) and at last follow-up the groups were respectively 18 (42.9%), 14 (33.3%) and 10 (23.8%). VA was more likely to improve in patients under 50 years of age and those with worse initial VA (20/200 or less) than in older patients (p=0.02) or those with VA more than 20/200 (p=0.01).

On pre-operative fluorescein angiographies, all CNV were well-defined and subfoveal, extending inside the foveal avascular zone; 90% reached the geometric center of the fovea. Mean size was 0.74 + 0.36 DD. Mean size was not statistically a factor of good functional result, but only four neovascular membranes were larger than 1 DD. We noted that a gray homogeneous vascular filling of the choriocapillaris and absence of associated lesions (drusen, RPE hyper- or hypopigmentation, lacquer cracks) were important parts of the prognosis. Of the 17 eyes with no associated lesions on angiography, 15 (88%) experienced an improvement in VA by more than 3 lines. In contrast, among the 23 eyes with RPE lesions or choriocapillaris vascular defects VA improved in only 5 (22%) (p<0.001).

Post-operative size of the RPE atrophy was 1.25 DD, 1.9 times larger than the original CNV. This ratio was 2.5 in the AMD group and 1.8 for other etiologies; this difference was significant (p=0.03).

Pre-operative OCT was obtained in 21 eyes (50%). A fusiform hyperreflective thickening of the RPE/choriocapillaris layer, described in the literature as corresponding to the extent of CNV, was always observed. In 62% of cases, its edges were clear-cut. The type of CNV, as previously defined, could be determined in 15 (71%) eyes examined with OCT. Type 1 CNV was identified in 6 cases (1 AMD, 1 MFC, 1 idiopathic and 3 myopic CNV). Type 2 CNV was assessed in 9 eyes (6 MFC, I AMD, 2 "other etiologies") including 5 with a cleavage plane between the thickened area and the under-

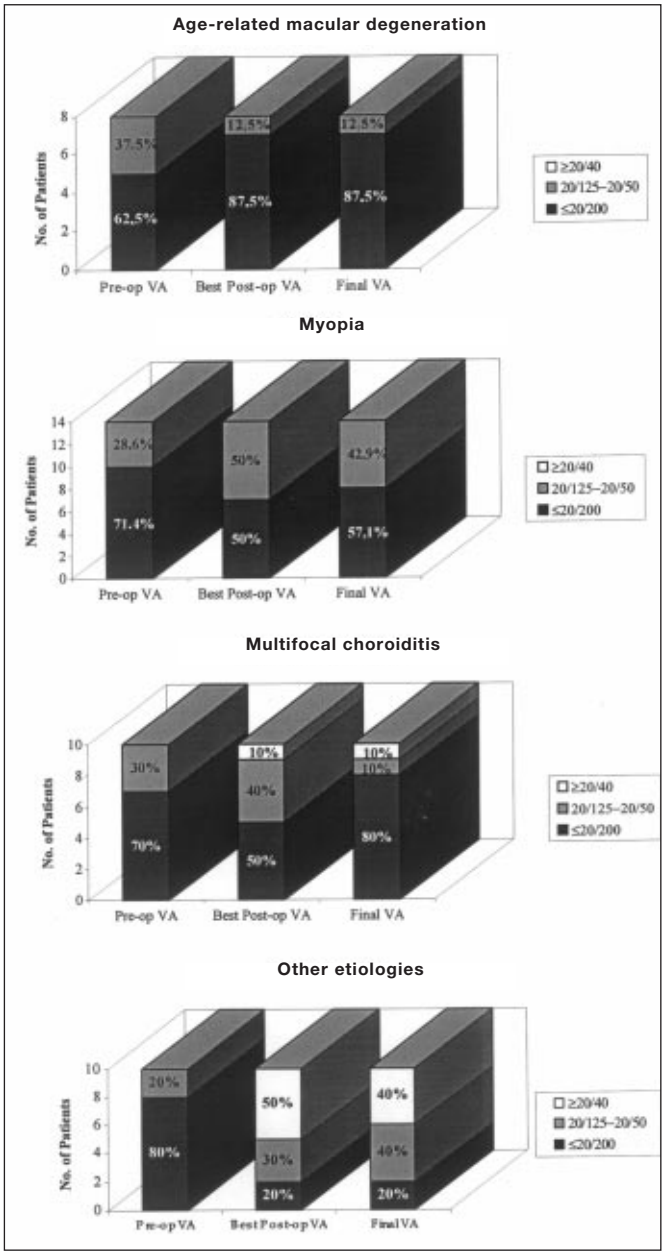

Fig. 1 - *Distribution of pre-operative visual acuity (VA), best post-operative VA and visual acuity at last follow-up according to the CNV etiology.*

lying layer. CNV type was undetermined on 6 OCT because of the poor quality of the images or inadequate OCT discrimination. Back-scattering was observed in 81% of eyes. When the foveal depression could initially be identified (25% of the cases), the thickening was located strictly underneath, confirming the subfoveal location of CNV. Other features were: RPE detachments in 2 eyes, serous retinal detachments in 15 (71%), intraretinal cysts in 4 (19%) and intraretinal thickening in 4 (19%), reflecting possible retinal edema.

Visual acuity improved in 6 out of 9 eyes (66%) in which OCT showed type 2 CNV, and only 1 of the 12 (8%) type 1 or unclassified CNV ($p<0.05$). The distribution of final VA, however, was not correlated to the type of CNV on OCT, possibly because of the small sample size. Post-operative VA was 20/200 or more in 9 eyes with sharp edges (70%) and in 2 eyes (25%) with diffuse ill-defined thickening. Post-operative visual outcome was better when the CNV edges were well-defined on OCT but the difference was not statistically significant. VA improved more than 2 lines after surgery in 61% of cases with well defined edges.

During follow-up, cataract developed in some eyes causing a secondary decrease in VA: one eye was operated on by phacoemulsification 18 months after macular surgery. Four retinal detachments (9.5%) occurred in three myopic eyes and in one MFC eye, and were all successfully repaired surgically. Nine persistent or recurrent CNV (21.4%) were observed (1 AMD, 4 MFC, 2 myopic, 1 angioid streaks and 1 idiopathic CNV) 10 days to 10 months after surgery (mean 3 months). When the CNV excision zone presented blurred borders with hyperfluorescent zones, OCT was useful to differentiate between RPE atrophy and CNV recurrence. The persistence of serous retinal detachment, of cystoid macular edema, of RPE thickening and the absence of the foveal depression were commonly observed in cases of CNV recurrence or persistence. Five of the nine recurrent CNV were subfoveal and were surgically removed, but with no VA improvement. Four juxta- or extrafoveal recurrences were laser-treated.

DISCUSSION

The first reports on surgical excision of subfoveal CNV were encouraging, reporting VA improvement in 50% of eyes, but CNV recurrence in 13-30% of the eyes. With longer follow-up results appear to depend on the etiology.

Though AMD remains the principal cause of CNV, the visual results after surgical excision are disappointing. In the Ormerod study (18), pre-operative VA was 20/400 or less in 10 AMD eyes, including only two with VA of 20/200 at best. In Thomas' series of

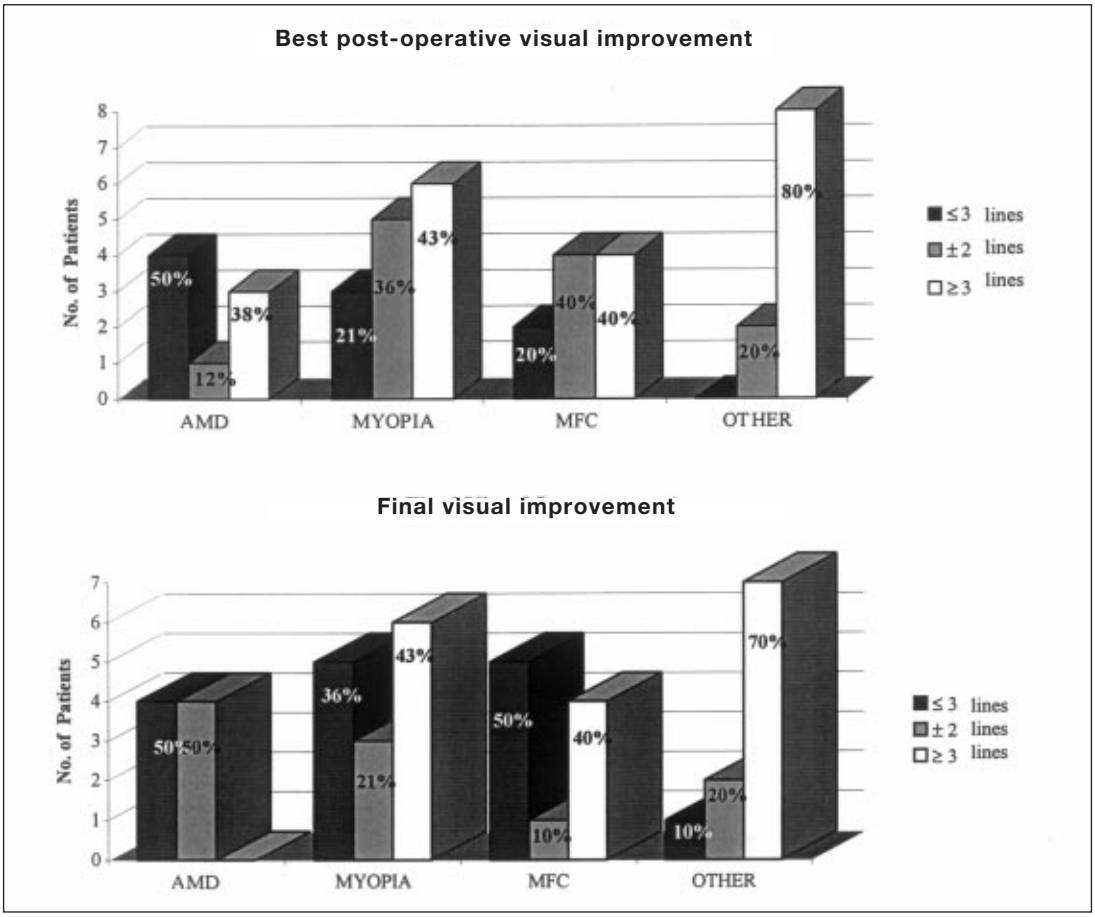

Fig. 2 - *Changes in visual acuity in EDTRS lines according to the CNV etiology, after surgery and at last follow-up.*

41 eyes final VA was better than 20/200 in 13% and improved by more than two lines in l2% (20). In a later study of 64 eyes, these rates were respectively 17% and 30% with 19 months' follow-up (17). In our eight AMD eyes, mean final VA was similar to published series (12.5% better than 20/200). VA remained at best stable (50%), never improved, and decreased by three lines or more in 50% of eyes, which is consistent with the first report of the randomized Submacular Surgery Trials that showed no reason to prefer submacular surgery over laser photocoagulation for recurrent subfoveal neovascular lesions (22).

Patients with degenerative myopia are younger, so subfoveal CNV is a dramatic event. In five myopic eyes, Adelberg noted a significant improvement in two, but only one VA over 20/200 (7). Benson did not observe any improvement in 43 operated eyes (8). Out of the 23 eyes with high myopia studied by Uemura (19) VA improved by two Snellen lines or more in 39%, and final acuity was 20/40 or better in 35% of eyes, with a mean follow-up of 24 months. In Bottoni's series of 21 eyes with 12-month follow-up, VA improved in 48%, 62% having 20/200 or more. Our results on 14 myopic eyes are similar: 43% visual improvement with VA better than 20/200 in 43%. The rate of recurrence (14%) was low, as in other series: three retinal detachments occurred, 21.4% in myopic eyes vs. 9.5% in the total group.

MFC is an inflammatory choroidopathy and shares clinical symptoms with the presumed ocular histoplasmosis syndrome, which in a U.S. series led to the best visual results after surgical excision. Final VA was 20/50 or more in 17% of eyes and improved in 35% after a follow-up of two years (9). In another series (13), 85% of eyes had stable or improved VA, with an improvement by at least three lines in 40% of them. Unfortunately, the recurrence rate was about 40% in a one-year follow-up (9, 19, 25). Published reports of surgical excision of subfoveal CNV in MFC found 30-50% improvement by three lines or more (7, 12) but

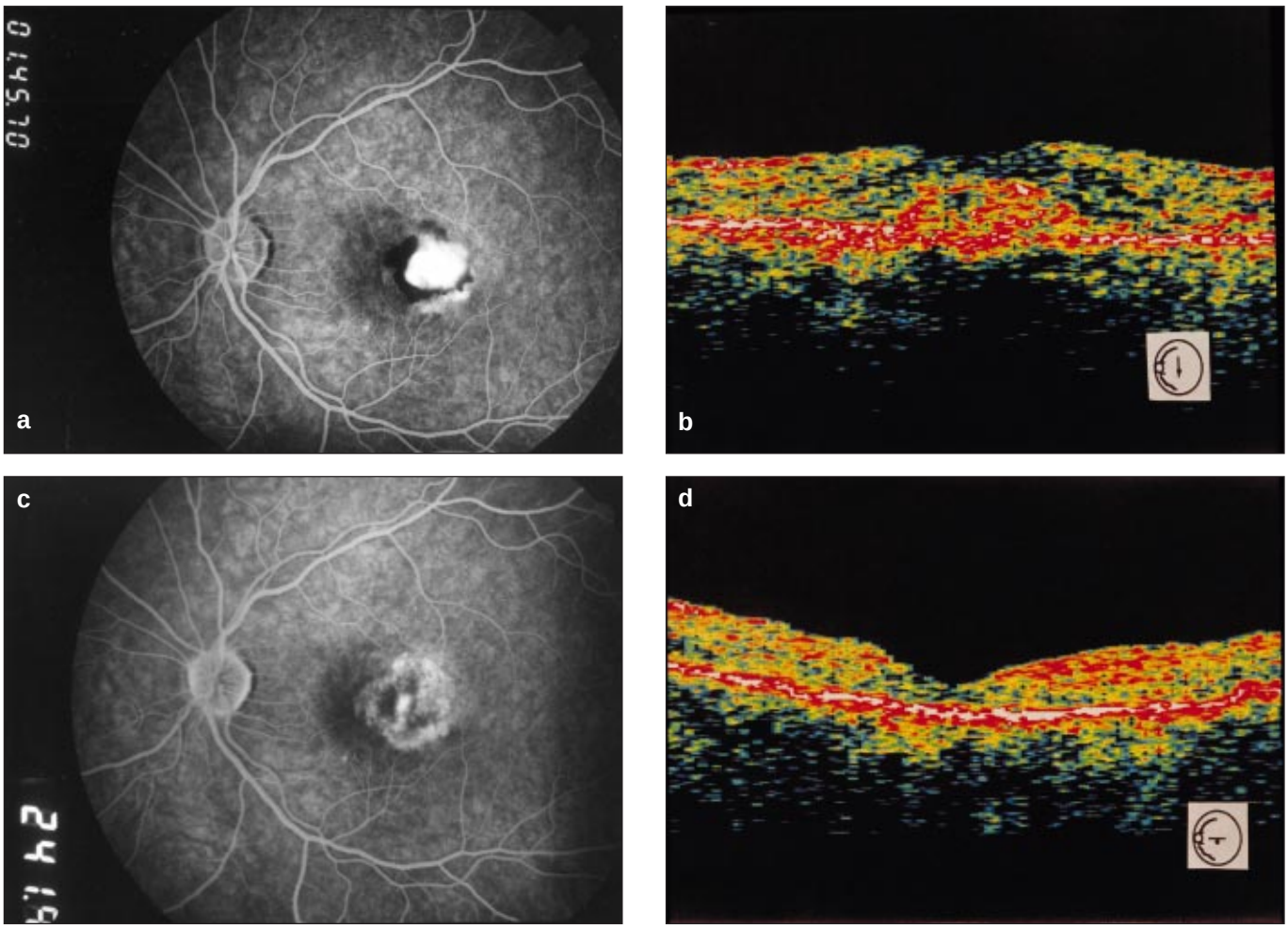

Fig. 3- ***a)*** *The pre-operative fluorescein angiogram showed subfoveal CNV in a 36-year-old woman with obvious multifocal choroiditis in the other eye. Pre-operative VA was 20/200.* ***b)*** *The pre-operative OCT showed clearly limited thickening of the RPE/choriocapillaris layer under the foveal contours, corresponding to the CNV. The hyperreflective area was above the RPE layer with no cleavage plane.* ***c)*** *The post-operative angiogram showed the atrophic scar of CNV removal. Post-operative VA was 20/32, with no recurrence.* ***d)*** *Post-operative OCT recovered nearly to normal, with evidence of foveal depression, disappearance of the thickened hyperrefective zone and a regular RPE band.*

10-20% of eyes developed recurrences, mostly within six months of surgery. In our series, five out of ten cases had post-operative VA of 20/125 or better, with improvement or stabilization in 80%. Within the follow-up period, four CNV recurred. By the end of follow-up, only two eyes (20%) retained a VA of 20/125 or more and five (50%) lost at least three lines.

Our last group of 10 eyes with a majority of idiopathic CNV had the best visual outcome. In the current study, 80% had VA of 20/125 or more and 40% had 20/40 or more at last follow-up. As in other reports (5, 19), VA was either unchanged or improved after surgery, but the recurrence rate was lower in our palients: two recurrent CNV were noted (20%) whereas this rate may reach 50% in other series (7, 19).

Clearly therefore, NVC etiology has an influence on visual outcome, though other prognostic factors have been studied. For Merill and coworkers, visual recovery was significantly better when CNV measured more than 2 DD, with small hemorrhages (17). Conversely, for Bottoni, in AMD, the smaller the neovascular membrane, the better the functional improvement (5). In the current study, 90% of CNV measured less than 1 DD. When the CNV ingrowth site was extrafoveal, VA

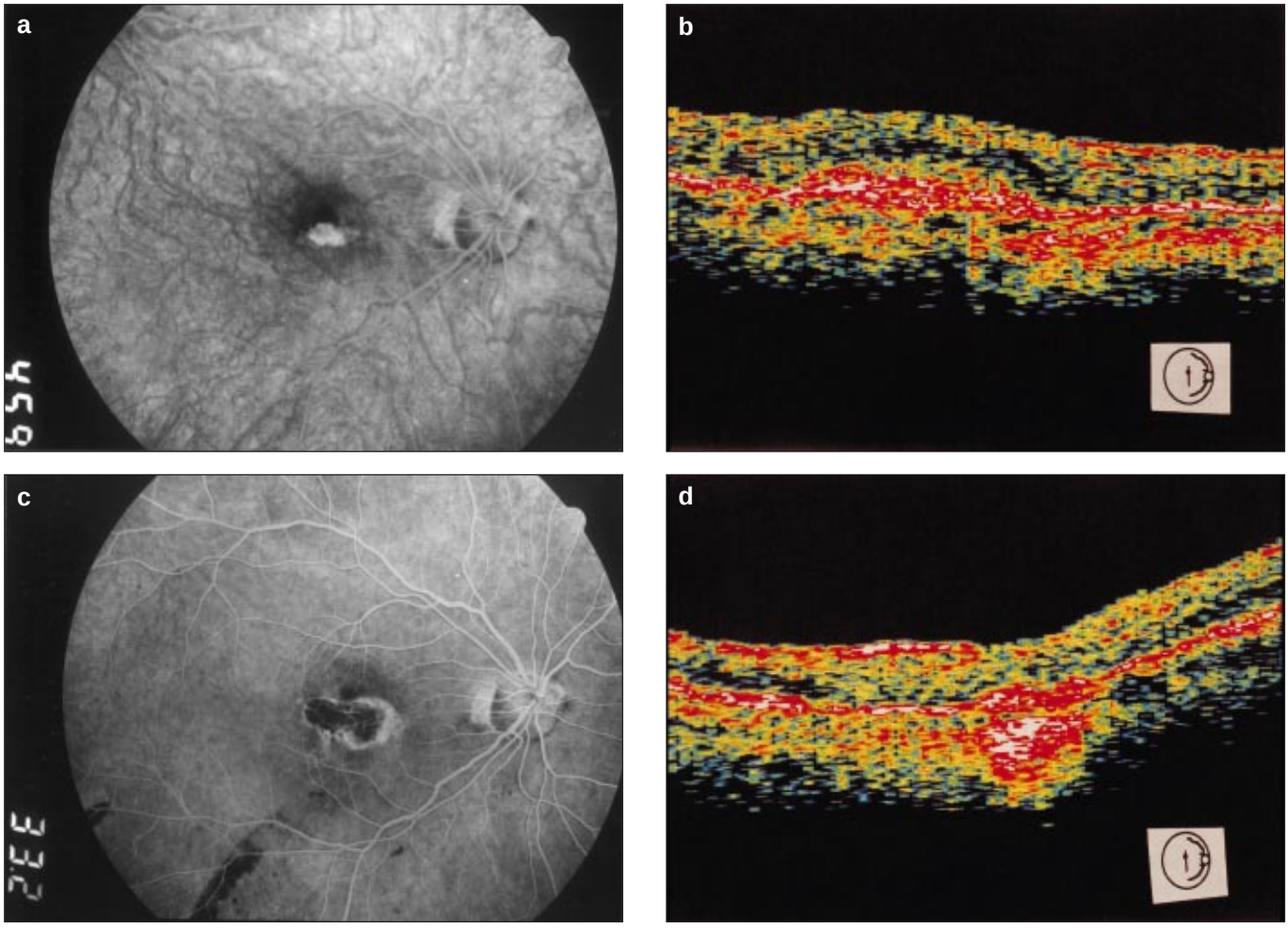

Fig. 4 - ***a)*** *Pre-operative angiogram in a myopic 42-year-old woman with well defined subfoveal CNV. Pre-operative VA was 10/200.* ***b)*** *The pre-operative OCT showed diffuse thickening of the RPE hyperreflective layer. Foveal contours are not evident.* ***c)*** *On the post-operative angiogram, the RPE atrophy was larger than the pre-operative CNV. Post-operative VA was 20/200 without recurrence after a follow-up of 18 months. A retinal detachment was successfully treated one month after the CNV excision.* ***d)*** *Post-operative OCT showed almost complete recovery of the foveal contours. Retinal thickening decreased. Localized hyperreflectivity under the RPE corresponded to an atrophic scar.*

was 20/40 or more in 60% of those eyes (26), but determination of this site on the earliest frames of the fluorescein angiogram is often questionable. In addition, in our series, the vascular filling of the choriocapillaris by the dye, the presence of lacquer cracks, RPE changes and pigment clumping all appeared to have significant value in predicting final visual outcome. In 88% of the eyes in which fluorescein angiography showed normal vascular filling of the choriocapillaris and none of the above lesions, VA improved by at least three lines and 76.4% retained thc same level of VA at the last visit. The difference was highly significant ($p<0.001$). According to Melberg, RPE integrity near the CNV excision area explains the functional recovery when the ingrowth site was extrafoveal. The healing of disrupted RPE areas by adjacent RPE cell proliferation has already been observed (27).

The conditions for a favorable visual outcome seem to be minimal RPE changes, normal vascular filling of the choriocapillaris, and presence of metabolically active RPE cells. This would explain the poor visual outcome in cases of AMD or myopic choroidopathy. Indocyanine green angiography should provide important additional data.

In order to explain the different outcomes after CNV excision, Gass described two histological types of CNV (24): type 1 CNV extending under the RPE within Bruch's membrane, most frequently observed in AMD, and type 2 CNV located above the RPE and limited by monolayered RPE cells, creating a cleavage plane with the underlying RPE. Surgery would be easier in type 2 eyes, with minimal loss of RPE cells. A correlation was made between the presumed pre-operative CNV type and the histopathologic diagnosis, in nine eyes (28).

Stereoscopic angiography allowed spatial localization of CNV in relation to the neurosensory retina and RPE. OCT examination with cross-sectional imaging of ocular tissues appears appropriate and easy to carry out, but its interpretation is still controversial because the 10-micron longitudinal theoretical resolution does not allow a clear differentiation between the various retinal layers. Moreover, the optical reflectivity of the CNV and the RPE/choriocapillaris layer is similar.

Though type 2 CNV are the most common in MFC or idiopathic CNV, type 1 CNV was noted in our series in one eye with MFC, and type 2 in one eye with AMD. Surprisingly, there were no type 2 CNV in myopic eyes. There was no statistically significant association between visual outcome and CNV type on OCT, possibly due to the small sample size. Nevertheless VA improved most in type 2 CNV: 66% of type 2 CNV eyes gained three lines or more, versus 16% of type 1 CNV. More than the exact NVC spatial localization, the importance of well-defined edges of the CNV on the OCT section could be of interest for final VA. Giovannini, in a recent series of nine eyes, illustrated the possible use of OCT for selection for surgery (29): five out of 23 AMD (21.7%) and four out of 10 idiopathic or inflammatory CNV (40%) were selected for surgery as the neovascular membrane was overlying the RPE on OCT. Post-operative VA of four AMD eyes improved by at least two lines, the fifth VA remaining unchanged. Unfortunately, the authors do not specify the initial VA or the duration of follow-up.

CONCLUSIONS

Visual results in our series are consistent with other reports and confirm that idiopathic CNV in young patients have the best prognosis. Some pre-operative data in the current study seem to lead to a favorable prognosis, such as normal vascular filling of the chorio-capillaris and absence of RPE changes or lacquer cracks on fluorescein angiography. Our study also confirms that type 2 CNV, and well-delined edges of the CNV observed pre-operatively on OCT, seem to lead to a better visual outcome. The correlation remains to be established between histologic CNV types and their OCT imaging.

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