Factors Associated with Early Detection of Choroidal Neovascularization in Age-Related Macular Degeneration in the Clinic Setting

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ABSTRACT: **Background:** Delayed diagnosis of choroidal neovascularization (CNV) in age-related macular degeneration (AMD) adversely affects visual outcome.

Objectives: To identify factors associated with early detection of CNV in the clinic setting.

Methods: Demographic and clinical data and lesion characteristics were retrospectively collected from 76 consecutive AMD patients who had a history of CNV in one eye and presented with CNV in the second eye. These data were evaluated for association with visual acuity (VA) at the time of presentation.

Results: Better VA was associated with a history of CNV in the fellow eye ($P < 0.0001$), adherence to follow-up every 4 months ($P = 0.015$), younger age ($P = 0.03$), smaller lesion ($P < 0.0001$), and non-subfoveal location ($P = 0.048$). VA of the fellow eye did not correlate with VA at presentation with CNV.

Conclusions: These data suggest that patients' experience of CNV, regardless of VA, facilitates early diagnosis in the fellow eye. Adherence to follow-up in the routine clinic setting also facilitates early detection of CNV.

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KEY WORDS: age-related macular degeneration (AMD), choroidal neovascularization (CNV), visual acuity (VA), follow-up, clinic setting

Age-related macular degeneration is a common cause of blindness in the developed world including Israel [1]. Intravitreal administration of anti-vascular endothelial growth factor compounds markedly improves visual outcome in patients with neovascular AMD [2-6]. While such compounds are effective in treating patients with variable degrees of visual loss, eyes with preserved visual acuity at the time treatment is begun are likely to have a better outcome [7,8]. This fact underscores the importance of early detection of choroidal neovascularization before substantial visual loss occurs.

However, it has been reported that in the clinic setting eyes diagnosed with CNV commonly present with substantial visual loss and subfoveal lesions [9-11]. On the other hand, data from three clinical trials – the Submacular Surgery Trials (SST), the Complications of Age-related Macular Degeneration Prevention Trial (CAPT), and the Choroidal Neovascularization Prevention Trial (CNVPT) – suggest that monitoring with periodic follow-up examinations and fluorescein angiography facilitate early detection of CNV in patients with NVAMD [12-14]. Combined, these studies suggest that the treatment algorithm for eyes with non-neovascular AMD should be improved to bridge the gap between the rate of early detection of CNV reported from clinical trials and the rate reported in the clinic setting. As an initial step towards this goal, we evaluated data from patients diagnosed with CNV in the clinic to identify factors associated with early detection of CNV.

PATIENTS AND METHODS

We conducted a retrospective study of patients with newly diagnosed CNV secondary to AMD. AMD was diagnosed following the AREDS grading system [15]. The study group consisted of 76 patients with bilateral CNV. These patients were identified from a group of 219 consecutive eyes treated with photodynamic therapy for NVAMD between November 2004 and January 2006 and a group of 78 consecutive treatment-naïve eyes treated with intravitreal injections of bevacizumab between January and June 2006. All patients were treated at the Retina Service of the Hadassah-Hebrew University Medical Center in Jerusalem, Israel. The study was approved by the Institutional Ethics Committee.

Only cases with bilateral CNV were included in the analysis to control for the effect of development of CNV in the first vs. second eye, and because these patients were routinely recommended periodic follow-up examinations every 3–4 months following diagnosis of CNV in the first eye. Factors included in the analysis were age, gender, history of smoking, initial best

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AMD = age-related macular degeneration

CNV = choroidal neovascularization

NVAMD = neovascular AMD

AREDS = Age-Related Eye Disease Study

corrected ETDRS visual acuity in the eye with incident CNV and in the fellow eye (visual acuity is routinely recorded with an ETDRS chart in our retina clinic), initial visual acuity at the time of presentation with CNV in the first eye, and adherence to follow-up examinations in the retina clinic every 4 months or less. Patients who were examined in the retina clinic during the 4 months prior to the diagnosis of an incident CNV were defined as adhering to follow-up.

Lesion characteristics according to fluorescein angiogram were evaluated for the purpose of the study by an observer who was masked with respect to other clinical and demographic parameters (e.g., visual acuity, adherence to follow-up). Minimally classic and occult lesions were classified as occult, while predominantly classic and classic lesions were considered classic. Lesions were measured using the OIS WinStation XP 5000 software (MeidVision, Yokneam, Israel). As previously reported with regard to this dataset [16], the masked observer's lesion classification of the entire dataset was compared with the classification made by the treating retina specialist at the clinic. There was agreement in 83.4% of cases between the investigator and the treating retina specialist's classification (kappa measurement of agreement 0.68, $P < 0.0001$).

Statistical analysis was performed using the SPSS software (SPSS, Chicago, IL, USA) and the Instat software (GraphPad, San Diego, CA). The *t*-test, Mann-Whitney test, Fisher's exact test, and Pearson correlation test were applied.

RESULTS

FACTORS ASSOCIATED WITH INITIAL VA

Univariate analysis was performed to identify factors associated with initial visual acuity in newly diagnosed CNV. This analysis was performed on data from 76 patients who had bilateral CNV. First eyes that developed CNV had a mean VA of 1.1 logMAR (0.08 ETDRS acuity, 20/250) at the time of diagnosis of CNV, while second eyes had a mean VA of 0.52 logMAR (approximately 0.32 ETDRS equivalent, 20/63, $P < 0.0001$) [Table 1]. This difference between the initial VA at the time of diagnosis of CNV in the first and second eyes equals approximately 6 ETDRS lines. There was no correlation or inverse correlation between VA in the first eye and second eye of the same patient at the time of diagnosis of CNV in second eyes [Table 2].

Adherence to follow-up examination 4 months or less before the diagnosis of CNV in the second eye was also associated with initial visual acuity. Patients who adhered to follow-up had a mean initial VA of 0.38 logMAR (approximately 0.4 ETDRS equivalent, 20/50), whereas those who did not adhere had a mean initial VA of 0.58 logMAR (approximately 0.25 ETDRS equivalent, 20/80, $P = 0.015$) [Table 1]. Thus, patients who adhered to follow-up recommendations had a mean initial visual acuity that was approximately 2 ETDRS lines better compared with those who did not adhere.

Additional factors associated with better initial VA included smaller lesion size, non-subfoveal location of CNV, and younger patient age [Table 2]. Gender, lesion classification according to fluorescein angiography, and history of smoking were not associated with initial visual acuity [Table 1].

VA = visual acuity

Table 1. Association of factors with initial visual acuity in patients with neovascular AMD

	No. of patients	Visual acuity (logMAR)		*P*
First eye/second eye initial visual acuity	76	1.1 ± 0.85	0.52 ± 0.57	< 0.0001
Gender				
Female	35			
Male	41	0.53 ± 0.43	0.60 ± 0.73	0.53
Smoking history*				
Yes	27			
No	38	0.55 ± 0.59	0.61 ± 0.56	0.6
Adherence to follow-up				
Yes	46			
No	30	0.38 ± 0.27	0.58 ± 0.39	0.015
Lesion type				
Classic	17			
Occult	59	0.88 ± 0.61	0.61 ± 0.57	0.12
Lesion location				
Subfoveal	44			
Non-subfoveal	32	0.61 ± 0.37	0.41 ± 0.23	0.048

*Smoking history was missing for 11 individuals

Table 2. Correlation of factors with initial visual acuity in patients with neovascular AMD

	Correlation with initial VA (r^2)	*P*
Age	0.2	0.03
Lesion size (GLD)	0.48	< 0.0001
Fellow eye visual acuity (LogMAR)	0.13	0.2

*Smoking history was missing for 11 individuals

FACTORS ASSOCIATED WITH ADHERENCE TO FOLLOW-UP

We analyzed the association of factors (in addition to initial visual acuity reported above) with adherence to follow-up. Gender, age, smoking history, and lesion type were not associated with adherence to follow-up. However, non-subfoveal lesion location at the time of diagnosis was associated with adherence to follow-up ($P = 0.034$). There was also a non-significant trend towards smaller lesion size in patients who were followed [Table 3].

DISCUSSION

Beginning treatment for CNV after substantial visual loss results in poor visual outcome compared with initiation of

Table 3. Association of factors with adherence to follow-up examinations in patients with neovascular AMD

	Adherence to follow-up		
	Yes (n=46)	No (n=30)	*P*
Gender			
Female	24	11	
Male	22	19	0.13
Age (yrs)	80 ± 7.4	78 ± 8.9	0.13
Smoking history*			
Smoking	24 (63%)	14 (52%)	
Not smoking	14 (37%)	13 (48%)	0.44
Lesion type			
Classic	12 (26%)	5 (17%)	
Occult (%)	34 (74%)	25 (83%)	0.4
Lesion location			
Subfoveal	22 (48%)	22 (73%)	
Non-subfoveal	24 (52%)	8 (27%)	0.034
Lesion size (GLD ± SD, μ)	2552 ± 970	3148 ± 1268	0.16

*Smoking history was missing for 11 individuals
GLD = greatest linear dimension

therapy when the visual acuity is still preserved [7,8]. This fact underscores the importance of early detection of CNV in order to obtain maximum benefit from novel anti-VEGF therapies. Yet, NVAMD patients who are diagnosed with CNV in the setting of a clinic commonly present with substantial visual loss and large and subfoveal lesions [9,10,17,18].

We found that patients' previous experience of CNV in the fellow eye and adherence to follow-up every 4 months or less are strongly associated with visual acuity at the time of presentation with CNV. The mean difference in the visual acuity between the first and second eyes was 6 ETDRS lines. Such difference in visual acuity is larger than that detected between the treatment and control groups in the MARINA and ANCHOR trials [2,3].

Interestingly, patients' experience of CNV in one eye was associated with early detection of CNV in the fellow eye, regardless of the visual outcome of the first eye. A similar lack of association between visual acuity in the fellow eye and early detection of CNV was recently described by Acharya and colleagues [9]. Thus, decreased vision in the fellow eye is not the major factor affecting early detection of CNV. Other potential factors underlying early detection of CNV in second eyes affected are patients' experience with the symptoms of CNV, understanding the urgency for obtaining appropriate care, and familiarity with the referral system in those who experienced CNV in the first eye.

In our study, adherence to follow-up examinations was associated with early detection of CNV in terms of better initial visual acuity and higher frequency of non-subfoveal lesions. Eyes that were followed in the clinic had approximately two ETDRS lines better initial visual acuity compared with eyes that were not followed, and lesions were subfoveal in less than half the eyes that were followed. CNV that developed in eyes that were carefully monitored in clinical trials were reported to have similar characteristics. For example, in the Submacular Surgery Trials (SST) most of the incident CNV lesions in fellow eyes were occult, smaller than 3 disk areas, and associated with VA of 20/40 or better. In addition, lesions were non-subfoveal in 39% of cases [14].

In accordance with the SST findings, in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT), most (68%) of the CNV lesions were occult only, almost half were (54%) subfoveal, and in the majority (56%) the size was ≤ 2 disk areas. Visual acuity was 20/40 or better in most eyes (69%) when measured at the time of diagnosis of CNV [13]. Finally, in the Choroidal Neovascularization Prevention Trial (CNVPT) 17 of 18 eyes that developed CNV during the trial showed occult CNV, size ranged between 2 and 3.5 disk areas, and only half of the 14 treated eyes showed subfoveal involvement. At the time of diagnosis only 9 of 18 eyes showed > 2-line loss of vision from baseline [12].

Our data emphasize the importance of routine follow-up examinations for early detection of CNV. Our findings suggest that the benefit from follow-up in the setting of a clinic is similar to that obtained in clinical trials in terms of facilitating early detection of CNV. They also suggest that patients with NNV-AMD should be informed about the symptoms of CNV and of the urgency of examination and initiation of treatment once symptoms occur.

Conceivably, shorter time intervals between follow-up visits in patients with NNV-AMD would lead to an improved rate of early diagnosis of CNV. Determination of the optimal time interval between follow-up visits should take into account factors such as inconvenience for patients associated with frequent follow-up visits as well as cost-effectiveness of multiple visits. Additional methods such as optical coherence tomography and preferential hyperacuity perimeter may be combined in a treatment algorithm to improve the rate of early detection and reduce costs associated with multiple visits [19-22]. The prevalence of NNV-AMD, its potential devastating consequences for vision, and the fact that in the clinic setting routine follow-up is effective, mandate additional research aimed at optimizing the NNV-AMD treatment protocol.

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VEGF = vascular endothelial growth factor

NNV-AMD = non-neovascular-AMD

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Capsule

Clonally dominant cardiomyocytes direct heart morphogenesis

As vertebrate embryos develop to adulthood, their organs undergo marked changes in size and tissue architecture. The heart acquires muscle mass and matures structurally to fulfill increasing circulatory needs, a process that is incompletely understood. Gupta and collaborators used multicolor clonal analysis to define the contributions of individual cardiomyocytes as the zebrafish heart undergoes morphogenesis from a primitive embryonic structure into its complex adult form. The authors found that the single-cardiomyocyte-thick wall of the juvenile ventricle forms by lateral expansion of several dozen cardiomyocytes into muscle patches of variable sizes and shapes. As juvenile zebrafish mature into adults, this structure becomes fully enveloped by a new lineage of cortical muscle. Adult cortical muscle originates from a small number of cardiomyocytes – an average of approximately eight per animal – that display clonal dominance reminiscent of stem cell populations. Cortical cardiomyocytes initially emerge from internal myofibers that in rare events breach the juvenile ventricular wall, and then expand over the surface. Our results illuminate the dynamic proliferative behaviors that generate adult cardiac structure, revealing clonal dominance as a key mechanism that shapes a vertebrate organ.

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Eitan Israeli

Too often we underestimate the power of a touch, a smile, a kind word, a listening ear, an honest compliment, or the smallest act of caring, all of which have the potential to turn a life around

Leo Buscaglia (1924-1998), American author and motivational speaker, and professor in the Department of Special Education at the University of Southern California; also known as "Dr. Love"

Large Hemorrhagic Pericardial Effusion

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ABSTRACT: **Background:** Establishing the etiology of a large pericardial effusion is of crucial importance since it is likely the result of a serious underlying disease. However, there is a paucity of literature on the diagnostic management of patients with large hemorrhagic effusions.

Objectives: To analyze the management of patients with large hemorrhagic pericardial effusion.

Methods: We reviewed seven cases of large hemorrhagic pericardial effusions hospitalized in Soroka University Medical Center in 2010.

Results: All seven patients underwent a comprehensive evaluation followed by pericardiocentesis. Six of the seven cases demonstrated echocardiographic signs of tamponade. Large amounts of hemorrhagic pericardial effusion (› 600 ml) were aspirated from each patient. A pericardial window was performed in two of the seven patients. The causes for the hemorrhagic effusions were malignancy, streptococcal infection, familial Mediterranean fever exacerbation, and idiopathic. Four patients completely recovered. The condition of one patient improved after initiation of chemotherapy for lung cancer, and two patients with progressive malignancies passed away shortly after discharge. Two cases of massive pulmonary embolism were diagnosed and resolved spontaneously without anticoagulation therapy after the effusion was treated.

Conclusions: All cases of pericardial effusion resolved after rapid diagnosis and initiation of specific treatment. Pulmonary embolism in situ may be a complication of large pericardial effusions that does not require anticoagulation treatment after the effusion resolves.

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KEY WORDS: large hemorrhagic pericardial effusion, pericardiocentesis, pericardial window

Pericardial disease and a variety of systemic disorders may lead to the development of pericardial effusion. Establishing the etiology of pericardial effusion is important for prognosis (e.g., malignancy), treatment (e.g., acute pericarditis, autoimmune disease, tuberculosis), or both (dissection of the ascending aorta, iatrogenic causes). The etiology of pericardial effusion varies in published reports, depending in part on geographic location, patient population, and the indications for pericardiocentesis [1-4]. The cause of pericardial effusion is often recognized by the clinical context in which it occurs [1], and the likelihood of establishing a specific diagnosis appears to increase with larger effusions (90% of cases) [2].

Establishing the etiology of a large pericardial effusion is of crucial importance because it can be life-threatening; it is more likely the result of a serious illness, and the diagnosis can be made relatively easily and safely [3]. Most cases of "acute idiopathic pericarditis" with small effusions are of short duration and have a low mortality rate [3,5]. Therefore, pericardiocentesis of small effusions is of less diagnostic importance. The most common causes of moderate to large pericardial effusions are iatrogenic, infection, malignancy, chronic idiopathic effusion, post-acute myocardial infarction, autoimmune disease, radiation, renal failure with uremia, and hypothyroidism [1,3,4,6]. A comprehensive systemic evaluation in combination with fluid and tissue analysis following subxiphoid pericardiotomy yields a diagnosis in the majority of patients with large pericardial effusions [2]. Rapid diagnosis of these diseases may lead to earlier therapy and improved survival.

Patients with hemorrhagic pericardial effusions have a somewhat different distribution of etiologies, although the overlap with serous effusions is significant. The most frequent causes of bloody pericardial effusions are: malignancy, post-procedural (transcatheter interventions and pacemaker insertion), post-pericardiotomy syndrome, complications of myocardial infarction, idiopathic, uremic, aortic dissection, and trauma [6,7]. In addition, tuberculosis is a frequent cause of hemorrhagic effusion in endemic areas [7-10].

Pericardial fluid can be sampled or drained either by closed needle pericardiocentesis or via surgical incision. The 2004 European Society of Cardiology guidelines on the diagnosis and management of pericardial diseases recommended percutaneous pericardiocentesis in patients with tamponade. Surgical intervention was recommended only in patients with very large chronic effusions in whom repeated pericardiocentesis was not effective. An open surgical procedure is required for pericardial biopsy [11].

Pericardial effusions may persist for extended periods and can also recur. The management in these settings is based on the treatment of the underlying disorder. Percutaneous drainage of the effusion is reserved for hemodynamically significant or persistently symptomatic effusions [12].