Terms non-exudative and non-neovascular: awaiting entry at the doors of AMD reclassification

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Key messages

- Type 1, 2 and 3 MNV terms are well accepted and clinically used on the basis of recommendations by the Consensus on Neovascular Age-Related Macular Degeneration Nomenclature (CONAN) Study Group in the recent past.
- Emerging evidences with the help of multimodal imaging have thrown light on the terms non-exudative and non-neovascular that may need attention during the further revision of nAMD classification and the term “non-exudative” may be considered to be ready for inclusion in the repertoire of terms.

The nomenclature of age-related macular degeneration (AMD) has undergone several changes in the recent past. These changes have evolved over time to help clinicians understand the disease better. Initially, the term wet macular degeneration was used [1]. Subsequently wet was replaced with neovascular which clearly linked the physical signs to the underlying pathology. The neovascular component in nAMD was referred to as choroidal neovascularization (CNV) as the new vessels were observed to originate from the choroid. CNV was then classified into classic, occult,

and mixed based on the leakage patterns that were observed on fluorescein angiography (FA) [2]. With the introduction of spectral-domain optical coherence tomography (SD-OCT) into routine clinical practice, the appreciation from 3-dimensional imaging of the relationships between the different retinal layers and the neovascular complexes began to allow more precise localization of the nAMD lesions. Combined with FA, the use of OCT led to an improved understanding of the different subtypes of nAMD which has been formally adapted into a consensus document [3]. A more scientifically rigorous nomenclature for the nAMD subtype has been proposed and includes type 1 macular neovascularization (MNV) to replace occult CNV, type 2 MNV for classic CNV, and type 3 MNV for retinal angiomatous proliferation (RAP). The term MNV instead of CNV is also more appropriate as type 3 MNV does not originate from the choroid. Furthermore, CNV is not restricted to the macular area alone. The other variant of nAMD, namely idiopathic polypoidal choroidal vasculopathy (IPCV) is also a misnomer as polyps are solid outgrowths of tissue. The polyps in IPCV are vascular structures and exhibit pulsative blood flow and hence do not fit the physical characteristics of a polyp which ordinarily refers to solid growth of tissue from a mucous membrane. Therefore, the current view is that IPCV should be termed aneurysmal type 1 neovascularization though consensus remains lacking. The Consensus

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on Neovascular Age-Related Macular Degeneration Nomenclature (CONAN) Study Group has highlighted the fact that given the rapid rate of change in AMD knowledge, any nomenclature system is likely to be a work in need of periodic revision [3]. With the development of OCT angiography (OCTA) and swept-source technology, finer details of AMD-related lesions are becoming apparent and with other newer terminologies at the threshold, it is likely that nomenclature will continue to evolve as morphological details that were previously undetectable become visible *in vivo*. The aim of the present editorial is to highlight two additional findings that might find their way into AMD nomenclature.

The first is non-exudative nAMD. Non-exudative nAMD refers to new vessels in the macular tissues without signs of exudation such as intraretinal fluid (IRF), subretinal fluid (SRF), and subretinal pigment epithelial (sub-RPE) fluid. Although non-exudative nAMD lesions were described based on findings seen on indocyanine green angiography (ICGA) [4] and clinicopathological studies [5], it was not established as a separate entity partly due to a lack of knowledge on its natural history. This would have necessitated frequent assessments using ICGA as an invasive procedure in asymptomatic patients. When OCT and subsequently OCT angiography (OCTA) entered routine clinical care, these imaging modalities allowed retinal structure and blood flow to be evaluated repeatedly with little or no discomfort to the patient and in an entirely noninvasive manner. This allowed clinicians to visualize the depth-resolved images of the retina, RPE, and Bruch's membrane, at regular intervals in persons with very high risk of development of nAMD. It was observed that blood vessel complexes were present in a small proportion of eyes within the sub-RPE space but without signs of exudation into the macular tissues, resulting in a resurgence of interest in non-exudative AMD.

Studies in the recent past have shown that the prevalence of subclinical, non-exudative nAMD in the fellow eyes of patients with unilateral exudative AMD ranged from 6.25 to 27% [6]. Non-exudative lesions were also described in cases of geographic atrophy (GA) [7]. Most of the authors have described that these lesions do not cause any subjective or objective disturbances in visual acuity. If non-exudative AMD is detected, it is now considered to be a predictor of conversion to exudative AMD and it has been shown that the incidence of clinically evident exudation ranges between 20 and 80% during the 6 months to 2 years of follow-up [6]. However, randomized trials have revealed no benefit from treatment prior to the onset of exudation leading most experts to suggest that these indolent non-exudative AMD should be observed. Non-exudative MNV may have a protective effect in slowing the progression of geographic atrophy (GA) by providing nutrition to the RPE. Optical coherence tomography can show non-exudative MNV as a double layer sign but OCTA has better sensitivity as it directly shows the complex.

Non-exudative MNV is typically a type 1 neovascular lesion without evidence of IRF or SRF. However, a few authors have described cases mimicking type 3 MNV.

Second is non-neovascular AMD. Non-neovascular AMD was commonly considered to be dry AMD. However, many groups have described the presence of fluid on OCT which may be seen in the subretinal space even in the absence of neovascularization. Recently, Hilely et al. [8] described three patterns of non-neovascular fluid detected on SD-OCT. First, a crest of fluid over the drusenoid pigment epithelial detachment (PED); second, a pocket of fluid at the angle of a large druse or within the crypts of confluent drusen; and third, the draping of low lying fluid over confluent drusen. A crest of fluid over the PED was the most common pattern observed followed by a fluid at the angle and the least common was the draping of low lying fluid. Furthermore, the crest pattern was most commonly associated with retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA). Hilely et al. hypothesized that due to the separation of RPE from Bruch's membrane, there is an increased distance between choriocapillaris and RPE which leads to impairment of oxygen supply to the RPE. This results in an impaired ability of the RPE to clear debris which accumulates as vitelliform material. Furthermore, chronic hypoxia causes vascular endothelial-derived growth factor (VEGF) production which might cause transudation in the subretinal space. However, Sikorski et al. have attributed this type of fluid collection to mechanical strain or tensile strain of the drusenoid PED over the outer retinal layers that locally pulls the sensory retina away from its normal position [9].

Both non-exudative AMD and non-neovascular AMD are not yet part of a widely accepted parlance that is applicable to the wide constellation of signs that are encountered in AMD. The prevalence of non-exudative nAMD is described to be in the range of 6.25 to 27% AMD in the fellow eyes of patients with unilateral exudative AMD. The prevalence of non-neovascular AMD (SRF without neovascularization) is not known as current knowledge has been based only on case reports [8–10]. Because most of the published data on this entity come from studies using SD-OCT, it is likely that as more information on this variant of AMD will become available from swept-source OCT and OCTA that our understanding of this condition may change and lead to a different terminology.

To summarize, the term “non-exudative” would appear to be ready for inclusion in the repertoire of terms used in describing the various manifestations of AMD classification. It is possible that some reclassification of nAMD into exudative and non-exudative may be required; however, more structural data are needed before this entity becomes accepted as a manifestation of AMD. The improved understanding of AMD pathophysiology and the evolution of AMD lesions has resulted in better characterization of phenotypic variants and

thus the introduction of new terms to describe such variants is likely to be of help in ensuring appropriate management and personalized medicine. Furthermore, if both these entities are correctly defined, thus aiding their inclusion in prospective clinical trials and cohort studies, it might pave the way for an improved new era of understanding AMD.

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Declarations

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