Diabetic Macular Edema With and Without Subfoveal Neuroretinal Detachment: Two Different Morphologic and Functional Entities

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• PURPOSE: To assess specific morphologic and functional characteristics in eyes with diabetic macular edema (DME) with subfoveal neuroretinal detachment (SND+) vs DME without SND (SND−).

• DESIGN: Cross-sectional, prospective, comparative case series.

• METHODS: Seventy-two patients (72 eyes: 22 eyes SND+ and 50 eyes SND−) with treatment-naïve, center-involving DME were evaluated. Data gathering included fundus color photographs, fluorescein angiography, spectral-domain optical coherence tomography (SD-OCT), best-corrected visual acuity (BCVA), and microperimetry. The following parameters were evaluated with SD-OCT: central macular thickness (CMT [including SND]); central retinal thickness (CRT [excluding SND]); choroidal thickness (CT); nasal and temporal retinal thickness (RT) at 500 μm and 1500 μm from the fovea; the number of hyperreflective retinal spots (HRS) in the central 3000 μm; and the presence of SND and integrity of the external limiting membrane (ELM). Retinal sensitivity (RS) was evaluated within 4 degrees and 12 degrees of the fovea. Correlation among CT, RS, and HRS in patients with and without SND was determined.

• RESULTS: CMT ($P = .032$), temporal RT at 1500 μm ($P = .03$), mean CT ($P = .009$), and mean number of HRS ($P = .0001$) were all higher in SND+ vs SND− eyes. CRT, BCVA, HbA1c, and prevalence of systemic arterial hypertension were not different between the 2 groups. RS within 4 degrees ($P = .002$) and 12 degrees ($P = .015$) was lower in SND+ vs SND− eyes. SND correlated significantly with disruption of the ELM (54.55% vs 24%, $P = .01$) and lower RS. A direct correlation was found between the number of HRS, presence of SND, CT, and RS within 12 degrees in SND− eyes, and an inverse correlation was found between CT and RS within 12degrees in SND+ eyes.

• CONCLUSIONS: These data may improve characterization of DME in eyes with SND. DME with SND correlates with greater CT, more HRS, disruption of the ELM, and significant macular functional impairment (RS decrease) vs SND−. (Am J Ophthalmol 2017;181:149–155. © 2017 Elsevier Inc. All rights reserved.)

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DIABETIC MACULAR EDEMA (DME) PRESENTS WITH different patterns on optical coherence tomography (OCT), including sponge-like swelling, cystoid macular edema, and subfoveal neuroretinal detachment (SND).[1] SND in DME is visible on OCT as a hypo-reflective area beneath the neuroretina and with a reported prevalence of approximately 15–30% in eyes with DME.[1–5] Recently, higher concentrations of inflammatory cytokines in the vitreous and aqueous humor have been reported in eyes with SND, thus suggesting the presence of a significant inflammatory component.[5–9] In particular, an increase in interleukin 6 (IL-6) has been associated with SND in DME.[5] Some authors have reported a poorer visual prognosis after treatment of eyes with SND.[10,11]

Different hypotheses regarding the pathophysiology of SND have been postulated for this specific pattern of DME.[1–4,12,13] Leakage from the retinal or choroidal circulation into the subretinal space that exceeds reabsorption capacity is thought to be the main mechanism.[14] Several authors have reported retinal pigment epithelium (RPE) dysfunction in experimental and human diabetes,[15–17] as RPE pumping capacity is decreased by hypoxia.[18] Moreover, an impairment of choroidal blood flow, which may cause tissue hypoxia and RPE dysfunction, was reported in patients with DME.[12] Also the integrity of the external limiting membrane (ELM) appears to contribute to the pathogenesis of SND. In fact, integrity of the ELM seems to be a key factor in preventing fluid from passing from the outer retina into subretinal space.[2]

The formation of SND is not associated with the duration or severity of DME.[2] Otani and associates postulated that transient SND may represent fluid movement from the retina to the subretinal space during the process of macular edema absorption.[10] Gaucher and associates reported

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that SND can occur very early in the genesis of DME, even before the accumulation of a large amount of fluid in the macula.[2] SND may disappear either before or after the reabsorption of intraretinal fluid, thereby suggesting that SND is not associated with severe DME.[2] Therefore, SND does not seem to be attributable to only the passive reabsorption of DME.[2]

Because little is known about the pathophysiology and the clinical characteristics of DME with SND, the main purpose of this study was to evaluate in detail morphologic and functional characteristics of patients with SND (SND+) and compare these to DME without SND (SND−).

METHODS

• **POPULATION:** This is a cross-sectional, prospective, comparative, consecutive case series of 72 eyes (72 patients) with treatment-naïve, center-involving DME. All patients underwent a complete ophthalmologic examination with best-corrected visual acuity determination (BCVA), color fundus photographs, spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography, and microperimetry. Exclusion criteria were any previous macular/retinal treatment (laser, intravitreal injections, and surgery), presence of macular traction on SD-OCT, history of uncontrolled glaucoma or ocular hypertension, and ischemic maculopathy. Informed consent was obtained from each patient and the research was carried out in accordance with the Declaration of Helsinki. Local Ethics Committee approval for the study was obtained.

• **VISUAL ACUITY:** BCVA was measured by a certified examiner using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocol at a distance of 4 meters with a modified transilluminated ETDRS distance chart (Precision Vision, Bloomington, Illinois, USA). Visual acuity was scored as the total number of letters read correctly, calculated according to the ETDRS score method, and annotated in the clinical chart.

• **SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY:** SD-OCT was performed with the Spectralis (Heidelberg Engineering, Heidelberg, Germany; Software 5.3.0.15), with the following scan patterns: 1 linear scan of 8.8 mm at 0 degrees centered on the fovea in High Speed mode and in Enhanced Depth Imaging (EDI) mode with a resolution of 100 automatic real time (ART), and a 6 × 6-mm macular map with resolution of 50 ART, centered on the fovea. Measurements made with the Heidelberg Eye Explorer software (EYEX) included the presence and height of SND, central macular thickness (CMT) (automatically measured within central 1 mm including also the SND), central retinal thickness (CRT; obtained excluding the SND, by measuring the SND height), and nasal and temporal thickness of the inner retina (IRT) and the outer retina (ORT) at 500 μm and 1500 μm from the fovea (IRT was measured from the inner limiting membrane to the outer plexiform layer).

The following parameters were also measured: ORT from the outer nuclear layer to the RPE; the total number of retinal hyperreflective spots (HRS) (calculated in the area of 3000 μm centered on the fovea); integrity of the external limiting membrane (ELM) within the central 3 mm; choroidal thickness measured at the fovea (foveal CT) and at 500 μm and 1500 μm from the fovea on the nasal and temporal side; and mean CT (mean value of 5 measured values: foveal CT, nasal and temporal CT at 500 μm and 1500 μm) on linear B-scans obtained with EDI mode passing through the center of the fovea at 0 degrees (Figures 1 and 2).

• **MICROPERIMETRY:** Microperimetry was performed on all subjects using the MP1 Microperimeter (Nidek, Gamagori, Japan). The following standard parameters were used for DME patients: a fixation target consisting of a red ring, 1 degree in diameter; white, monochromatic background at 4 asb; stimulus size of Goldman III, with 200 ms projection time; customized radial grid of 45 stimuli covering the central 12 degrees (centered onto the fovea), 1 degree apart (inner stimuli) and 2 degrees apart (outer stimuli).[19]

The starting stimulus light attenuation was set at 10 dB. A 4-2 double staircase strategy was used with an automatic eye tracker that compensates for eye movements. Pretest training was performed and 5-minute mesopic visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupils. Mean retinal sensitivity (RS) was evaluated within the central 4 degrees and 12 degrees, approximately covering 1 mm and 3 mm of the central retina area on OCT mapping.[19] Fixation stability and location were evaluated by the classification of Fujii and associates (stable, relatively unstable, and unstable; central, relatively eccentric, and eccentric fixation).[20]

• **FLUORESCEIN ANGIOGRAPHY:** Fluorescein angiography was performed with the Heidelberg Retinal Angiograph 2 (HRA 2; Heidelberg Engineering, Heidelberg, Germany). Angiography images were evaluated for the presence of significant retinal capillary dropout in the macula. All measurements were evaluated independently by 2 masked graders. In case of disagreement, a final adjudication was made by the senior retina specialist.

• **STATISTICS:** Fisher exact test was used to compare the prevalences of hypertension in SND+ and SND− patients. Mean HbA1c values were compared by Student *t* test for independent samples. Mean values of CMT, CRT, retinal thickness (RT), CT, RS, and number of HRS were compared between groups by Student *t* test for independent samples. The location and stability of fixation were