Subfoveal Serous Retinal Detachment in Patients With Uveitic Macular Edema

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Objective: To assess the clinical characteristics and effect on visual acuity (VA) of a subfoveal serous retinal detachment (SRD) associated with macular edema (ME) in patients with uveitis.

Methods: Clinical and optical coherence tomograph characteristics were retrospectively assessed in 37 patients with uveitic ME with a subfoveal SRD (case individuals) and 61 patients with uveitic ME without a subfoveal SRD (control individuals), matched for uveitis location, sex, and age. Scans of the case and control individuals took place between September 19, 2003, and July 21, 2008.

Results: Patients with a subfoveal SRD had a shorter history of uveitis ($P = .03$) and ME ($P = .03$) and a lower VA ($P = .003$). Mean total retinal thickness (TRT) in cases exceeded that of controls (449 vs 326 µm; $P < .001$). The median subfoveal SRD duration was 2 months, and 29 of 36 SRDs (81%) had disappeared at the 3-month follow-up examination. The improvement in VA and the decrease in TRT after 3 months were better in the subfoveal SRD group than in the control group ($P = .001$ for VA and $P = .001$ for TRT), resulting in similar VA and TRT after 3 months.

Conclusions: A subfoveal SRD was associated with lower VA and developed typically in the early stages of uveitis and ME. The subfoveal SRD and VA reacted favorably to treatment with periocular and systemic steroids and/or oral acetazolamide.


MACULAR EDEMA (ME) is a major cause of poor visual acuity (VA) in patients with uveitis.1-3 Frequently, ME also complicates the course of various other ocular disorders, such as diabetic retinopathy and retinal vein occlusions, and might develop after intraocular surgery.

After the introduction of optical coherence tomography (OCT) in 1995, it was observed that some patients with ME of diverse origins also have an associated subfoveal serous retinal detachment (SRD). The clinical effect of a subfoveal SRD in ME has not yet been extensively studied, and its consequences in uveitis have not yet been identified, to our knowledge. In patients with diabetic retinopathy, however, a subfoveal SRD was associated with poor visual outcome after grid laser photocoagulation and vitrectomy.4-5 Similarly, in branch retinal vein occlusions, the presence of a subfoveal SRD seemed to delay the absorption of ME and the recovery of VA after grid laser photocoagulation.6 The clinical relevance of a subfoveal SRD in uveitis patients remains unclear. In this study, we evaluate the effect on visual acuity of a subfoveal SRD in inflammatory ME.

METHODS

Ours was a retrospective case-control study at the Department of Ophthalmology of the University Medical Center Utrecht, Utrecht, the Netherlands. Approval was obtained from the institutional review board of the hospital. The evaluation of the clinical effect of a subfoveal SRD, we randomly selected 37 affected eyes of 37 uveitis patients with ME with a subfoveal SRD (case individuals) from our OCT database (numeric code). As control individuals we selected 61 eyes of 61 patients with ME without a subfoveal SRD (control individuals) from our OCT database, matched for anatomical location of uveitis, sex, and age. The OCT scans of the cases and controls took place between September 19, 2003, and July 21, 2008. There was no statistical difference in the time span of uveitis in which no OCTs were available (before September 19, 2003) between cases and controls (median of 4.3 years in the 21 cases vs 7.2 years in the 45 controls; Mann-Whitney $P = .55$). The time the first OCT with a subfoveal SRD present was diagnosed was considered to be the time of onset of the subfoveal SRD. For the cases, the start of analysis ($t = 0$) was the time of the diagnosis of the subfoveal SRD. After the matching for age, location of uveitis, and sex, we used the first OCT in that particular year in the controls. The date of this OCT was considered to be $t = 0$.

We reviewed the medical records of the cases and the controls and registered sex, age...
at onset of uveitis, age at onset of ME, age at diagnosis of subfoveal SRD, type of uveitis according to anatomical location and/or specific diagnoses, duration of uveitis and ME at \( t = 0 \), associated general and ocular diseases, total retinal thickness (TRT), the presence or absence of vitreomacular traction or an epiretinal membrane, and VA at \( t = 0 \), 3, and 6 months. In addition, we registered treatment regimens used before \( t = 0 \) and thereafter. Treatment regimens were registered as topical, periocular, and systemic, which was divided into a group of immunosuppressive agents (prednisone, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and infliximab) and a group composed of acetazolamide and octreotide acetate. Before \( t = 0 \), no differences in treatments with immunosuppressive agents or acetazolamide were identified (\( P = .33 \) and \( P = .78 \), respectively). No differences in the use of systemic or periocular steroids were observed between the subfoveal SRD cases and the controls (\( P = .70 \) and \( P = .12 \), respectively). All patients were classified using uveitis nomenclature according to the recommendations of the Standardization of Uveitis Nomenclature working group.\(^7\)

The OCT was performed with a STRATUS OCT (model 3000; Carl Zeiss Meditec, Jena, Germany), and analysis was based on 6-mm 6-radial scan lines of each eye, centered on the patient’s fixation point. The OCTs of the cases and controls were reviewed and coded in a masked fashion for the various types and features of ME.\(^8\) Patients were included if their TRT was greater than 210 \( \mu \)m in the 1-mm region and/or greater than 300 \( \mu \)m in the 3-mm region. Diffuse ME was characterized by increased retinal thickness, disturbance of the layered retinal structure, or spongiform low reflective areas. Cystoid ME was characterized by the formation of clearly defined intraretinal cystoid spaces.\(^8\) A subfoveal SRD was defined as fluid separating the neurosensory retina from the RPE, which was visible on OCT as an optically clear space between the retina and RPE. The subfoveal SRD height was measured at the fixation point manually at its thickest point using calipers and was defined as the average distance between the RPE and the outer neurosensory retinal surface on vertical and horizontal scans (Figure). The neuroretinal thickness (NRT) was defined as the distance between the inner and outer neuroretinal layers at the fixation point (Figure). The TRT was measured automatically with OCT retinal mapping software in the central 1-mm region and was defined as the sum of the NRT and the subfoveal SRD. Good reproducibility of these measurements using OCT mapping software has been demonstrated.\(^9\) For simplicity, in the “Results” section of the text, the TRT in controls is called the NRT when compared with the NRT of the cases.

Fluorescein angiograms were available for 32 patients within 3 months of the date of the OCT and available in 13 patients on the same day. The angiograms were examined for signs of central serous chorioretinopathy.

For statistical analyses the \( t \), Pearson \( \chi^2 \), and Fisher exact tests were used whenever appropriate (SPSS statistical software version 15.0 for Windows; SPSS Inc, Chicago, Illinois). The \( \chi^2 \) or Fisher exact test was used to compare categorical data. To compare means of nonnormally distributed variables, we used the Mann-Whitney or Kruskal-Wallis test, and \( P < .05 \) was considered statistically significant. We transformed Snellen VA to the logarithm of the minimal angle of resolution (logMAR) to perform statistical analysis and afterward converted the results back to Snellen equivalents. Values in the text and Table are converted from logMAR to Snellen VA. Results are represented according to the distribution of the calculated variables, which means the mean is given if the variables have a normal distribution (Kolmogorov-Smirnov \( P > .05 \)) and the median if the distribution is nonnormal. Using univariate linear regression analysis, the correlation of the variables duration of uveitis, duration of ME, type of ME, height of the subfoveal SRD, TRT, NRT, and presence or absence of cataract with logMAR VA (all at \( t = 0 \)) were analyzed. These variables were also included in a multivariate regression analysis.

RESULTS

General characteristics and demographic data of the cases and the controls are summarized in the Table. Because of the matching, no significant differences in sex, age, and anatomical location of the uveitis were found. Furthermore, no differences in uveitis origin were observed between the cases and the controls. Diabetes mellitus was not present in any of the cases but was present in 8 controls, all of whom were without diabetic retinopathy (\( P = .02 \)); systemic hypertension was present in 7 cases and 9 controls.

The uveitis was bilateral in 28 of the 37 cases (76%) and in 49 of the 61 controls (80%; \( P = .60 \)). Macular edema was present in 19 of the 35 fellow eyes (54%) of the subfoveal SRD cases (OCTs were not available for 2 fellow eyes). In 8 of these 19 eyes, a subfoveal SRD was also noted (in 5 simultaneously).

At \( t = 0 \), subfoveal SRD-positive cases exhibited a shorter median duration of uveitis (33 months for cases vs 62 months; \( P = .03 \)) and a shorter median duration of ME (2 months for cases and 17 months for controls; \( P = .03 \)). In contrast, median VA at \( t = 0 \) was worse in the subfoveal SRD group: 0.30 in cases and 0.50 in controls (\( P = .003 \)).

The median TRT (including the subfoveal SRD) was higher in the cases than in the controls (449 vs 326 \( \mu \)m;
controls), but this finding was much more prominent in the subfoveal SRD group (P = .001, Table). An improvement in VA of at least 2 Snellen lines after 3 months was identified in 18 of the 36 cases (data for 1 case missing at 3-month follow-up) and 12 of the 53 controls (data for 8 controls missing at 3-month follow-up) (P = .007).

At the 3-month follow-up, the median TRT decreased from 449 to 275 μm (P < .001) in the subfoveal SRD group and from 326 to 289 μm (P < .001) in the control group. The decrease in the TRT after 3 months was more prominent in the subfoveal SRD group than in the controls (P = .001). The median NRT after 3 months was 261 μm in the subfoveal SRD group and 289 μm in the controls (P = .18). After 3 months the NRT had decreased significantly in both groups: 87 μm in the cases (range, −239 to 426 μm; P = .002) and 44 μm in the controls (range, −22 to 357 μm; P < .001); however, there was no significant difference between both groups (P = .28).

The median subfoveal SRD duration was 2 months, and 29 of the 36 subfoveal SRDs (81%; data for 1 subfoveal SRD missing) had disappeared at the 3-month follow-up OCT examination. The OCT examination results were not available in 7 patients with a subfoveal SRD.
at 3-month follow-up, but in 5 of them, OCTs within the first 3 months had already shown that the subfoveal SRD had disappeared. The range of the subfoveal SRD duration was 6 days (resolution after periculbar betamethasone injection) to longer than 19 months (in the individual in question, the subfoveal SRD was still present on the last OCT).

Using univariate linear regression analysis, only the TRT was significantly associated with logMAR VA ($R=0.25, P=0.02$). In the subfoveal SRD group, the height of the subfoveal SRD did not correlate with the NRT ($R=-0.13, P=0.50$). Using the NRT and the height of the subfoveal SRD (which was 0 in the controls) as the variables in a linear regression analysis, only the height of the subfoveal SRD was significantly associated with logMAR VA ($\beta=0.23, P=0.03$). In a stepwise linear regression analysis using the variables duration of uveitis, duration of ME, NRT, height of the subfoveal SRD, type of ME, and presence or absence of cataract, again, only the height of the subfoveal SRD was significantly associated with logMAR VA ($\beta=0.22, P=0.04$).

Treatment of the cases and controls during follow-up did not differ. No differences in the start of acetazolamide (or octreotide) therapy, periculbar injections, systemic steroid therapy, or all immunosuppressive therapy were found ($P=0.37, P=0.79, P=0.37$, and $P=0.15$, respectively) after OCT at $t=0$.

We documented that a subfoveal SRD developed typically in the early stages of uveitis and ME and reacted well to the recommended treatment given for inflammatory ME (periculbar or systemic steroids and/or acetazolamide). Despite the presence of a subfoveal SRD and lower VA at onset, VA at 6-month follow-up was similar for patients with and without a subfoveal SRD.

Our findings on subfoveal SRD–positive ME in uveitis are distinct from some of the studies on ME of other origins. Diabetic subfoveal SRD–positive ME was associated with a poor visual outcome 6 months after a grid photocoagulation was performed and with a poor visual outcome after vitrectomy. Recovery of VA after grid laser photocoagulation in branch retinal vein occlusion was also slower if a subfoveal SRD was present. Our findings are, however, consistent with those of Gaucher et al., who reported that a subfoveal SRD was associated with early-stage ME. Previously, Markomichelakis et al. found a subfoveal SRD to be associated with decreased VA in patients with uveitis. In contrast, Catier et al., and more recently Tran et al., could not identify a significant association between a subfoveal SRD and VA in uveitic patients. Our results indicate that VA of subfoveal SRD–positive eyes is worse during the presence of a subfoveal SRD; however, follow-up VA (at 3 and 6 months) was similar for both groups.

We hypothesize that in the early stage, VA is negatively influenced by the presence of a subfoveal SRD and its disappearance during follow-up might explain the larger visual gain but similar follow-up VA as the controls. One might argue that the controls had a longer duration of uveitis and ME and their improvement would be therefore limited. However, the decrease of the NRT in the cases was not significantly different from that in the controls ($P=0.28$).

Our series included 8 patients with diabetes mellitus, all in the control group. Although none of the diabetic patients had documented retinopathy, we cannot entirely exclude the possibility that changes in retinal vascular permeability might negatively influence the visual gain in the controls.

We also demonstrated a positive correlation between the TRT and logMAR VA ($P=0.02$) in uveitis patients, independent of the presence of a subfoveal SRD. This association was also reported by Tran et al. The Diabetic Retinopathy Clinical Research Network found a modest correlation between TRT and VA in diabetic ME. In addition, an increased TRT in patients with a subfoveal SRD was strongly correlated with lower VA compared with their nonsubfoveal SRD counterparts (Table). The prevalence of subfoveal SRD–positive ME was reported in approximately 20% of uveitic eyes with OCT-proven ME. The exact occurrence of a subfoveal SRD in uveitic ME is difficult to examine because it is temporary. Ideally, the incidence and prevalence of a subfoveal SRD should be determined in a long-term follow-up study of all patients with newly developed inflammatory ME by frequent OCT examinations.

A possible hypothesis explaining the pathogenesis of subfoveal SRD could be the high resistance of the retinal tissue layers to the influx of fluid in the early phase of fluid accumulation (and inflammation). Therefore, the excess of fluid may first accumulate under the retina, resulting in a subfoveal SRD. Later, when more inflammatory damage develops and/or fluid volume increases, the retinal resistance may become insufficient, and as a consequence the fluid may enter the neuroretinal tissue and form cysts. After this extracellular cyst formation, the fluid finally would enter the intracellular environment. The transient aspect of a subfoveal SRD in uveitis and favorable response to treatment also support this hypothesis and the observation by Tran et al and Gaucher et al. that a subfoveal SRD might also be documented in patients with normal NRT and without edema. In our study, 8 of the 35 cases (23%; data missing for 2 cases) had an NRT of less than 212 μm. In addition, Gaucher et al. reported that 20% of the patients with subfoveal SRD–positive ME and diabetes had a normal NRT. Of interest, they observed that the subfoveal SRD could resolve itself despite worsening of the diabetic ME.

Also, using multivariate linear regression analysis, the height of the subfoveal SRD was associated with VA. The NRT in patients with a subfoveal SRD was not different from that in controls. This observation suggests that the presence of a subfoveal SRD itself has a negative influence on VA in patients with inflammatory ME. Possible explanations might include the impaired renewing of the photoreceptor cells or their inadequate nutrition in the presence of a subfoveal SRD. Another possible explanation for decreased VA in subfoveal SRD might include the diminished directional sensitivity (ie, optical Stiles-Crawford effect) and disorientation of the foveal cone photoreceptors.
Macular edema develops in disorders accompanied by a compromised inner and/or outer blood retinal barrier (BRB). To our knowledge, the exact mechanism that determines the distribution of excess fluid in retinal layers, formation of cysts, and intracellular edema has not yet been identified. Intraretinal fluid distribution is restricted by 2 diffusion barriers, the inner and outer plexiform layers. In cases with a compromised outer BRB, the accumulation of fluid in the subretinal space, especially in the early stages, may be expected. In contrast, the accumulation of fluid in cases with a compromised inner BRB is not easily explained. Subfoveal SRD also develops in patients with (branch) retinal vein occlusions, in whom the primary lesion lies in the inner BRB. Kang et al. postulated that in broken inner BRB, fluid and albumin might reach the subretinal space through the permeable external limiting membrane. However, the pathogenesis of subfoveal SRD in patients with a broken inner BRB deserves further investigation.

Obviously, our study has several shortcomings related to the character of the case-control study. We have chosen to match for age, sex, and anatomical location of uveitis. The matching for various additional factors involved in uveitis (eg, etiologic diagnosis, onset of uveitis, and onset of ME) was not feasible. Our study was not designed to evaluate various treatment strategies for ME and subfoveal SRD. Overall, the systemic treatment modalities in the cases and controls did not differ. An important issue is the occurrence of an SRD after the use of steroids in various administrative strategies for ME and subfoveal SRD. Overall, the systemic treatment modalities in the cases and controls did not differ. Our results suggest that an important issue is the occurrence of an SRD in early stages of uveitis and ME and was at the time of diagnosis associated with lower VA compared with the nonaffected group. A subfoveal SRD in ME reacted favorably to systemic or periocular steroids or acetazolamide.

In conclusion, a subfoveal SRD developed typically in the early stages of uveitis and ME and was at the time of diagnosis associated with lower VA compared with the nonsubfoveal SRD group. A subfoveal SRD and VA of affected patients with uveitis reacted favorably to treatment with periocular and systemic steroids or acetazolamide.

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