Aus der Augenklinik der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Optical Coherence Tomography Based Observation of the Natural History of Drusenoid Lesion in Eyes with Dry Age-Related Macular Degeneration

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
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ABSTRACT (English)

Title: Optical coherence tomography based observation of the natural history of Drusenoid lesion in eyes with dry age-related macular degeneration.

Purpose: To use spectral domain optical coherence tomography (SD-OCT) to investigate risk factors predictive for the development of atrophy of drusenoid lesions (DLs) (drusen and drusenoid pigment epithelium detachment) in eyes with non-neovascular age-related macular degeneration (NNVAMD).

Design: Cohort study.

Participants: Forty-one eyes from 29 patients with NNVAMD.

Methods: Patients with NNVAMD who underwent registered SD-OCT imaging over a minimum period of 6 months were reviewed. Drusenoid lesions that were accompanied by new atrophy onset at 6 months or last follow-up (FUL) were further analyzed. Detailed lesion change was described throughout the study period. Odds ratios (ORs) and risk for new local atrophy onset were calculated.

Main Outcome Measures: Drusenoid lesion features and longitudinal changes in features, including maximum lesion height, lesion diameter, lesion internal reflectivity, and presence and extent of overlying intra- retinal hyperreflective foci (HRF). Subfoveal choroidal thickness (SFCT) and choroidal thickness (CT) were measured below each lesion.

Results: A total of 543 individual DLs were identified at baseline, and 28 lesions developed during follow-up. The mean follow-up time was 21.3 ± 8.6 months (range, 6-44 months). Some 3.2%of DLs (18/571) progressed to atrophy within 18.3 ± 9.5 months (range, 5-28 months) of the initial visit. Drusenoid lesions with heterogeneous internal reflectivity were significantly associated with new atrophy onset at 6 months (OR, 5.614; 95% confidence interval [CI], 1.277-24.673) and new atrophy onset at FUL (OR, 7.005; 95% CI, 2.300-21.337). Lesions with the presence of HRF were significant predictors of new atrophy onset at 6 months (OR, 30.161; 95% CI, 4.766-190.860) and FUL (OR, 11.211; 95% CI, 2.513-50.019). Lesions with a baseline maximum height >80 µm or CT ≤ 135 µm showed a positive association with the new atrophy onset at FUL (OR, 7.886; 95% CI, 2.105-29.538 and OR, 3.796; 95% CI, 1.154-12.481, respectively).

Conclusions: The presence of HRF overlying DLs, a heterogeneous internal reflectivity of these lesions, was found consistently to be predictive of local atrophy onset in the ensuing months. These findings provide further insight into the natural history of anatomic change occurring in patients with NNVAMD.

ABSTRAKT (Deutsch)

Titel: SD-OCT basierte Beschreibung des natürlichen Verlaufes von Drusen bei trockener altersbedingter Makuladegeneration.

Hintergrund: Ziel war es, die SD-OCT dazu zu verwenden, prädiktive Risikofaktoren für den Übergang von Drusen zu Atrophiezonen bei Augen mit trockener altersbedingter Makuladegeneration (AMD) zu untersuchen.

Design: Kohortenstudie.

Probanden: Einundvierzig Augen von 29 Patienten mit trockener AMD.

Methoden: Wir untersuchten retrospektiv Patienten mit trockener AMD, die über mindestens 6 Monate mittels registrierter SD-OCT-Scans beobachtet wurden. Drusen im OCT, die sich nach 6 oder mehr Monaten zu Atrophiezonen entwickelten, wurden eingehend untersucht. Hierfür wurden Parameter wie maximale Höhe, Drusendurchmesser, interne Reflektivität, Dicke der Chorioidea und intraretinale hyperreflektive Foci (HRF) ausgewertet. Odds ratios (OR) und Konfidenzintervalle (KI) für das Risiko einer Atrophieentwicklung wurden errechnet

Hauptuntersuchungsmerkmale: Merkmale drusenoider Pigmentepithelabhebungen(DPE) und longitudinale Veränderungen dieser Merkmale, eingeschlossen maximaler DPE-Höhe, DPE-Durchmesser, interne DPE-Reflektivität und das Vorhandensein bzw. das Ausmaß über der DPE liegender hyperreflektiver Foci (HRF). Die subfoveale Chorioideadicke (SFCT) sowie die choroidale Dicke unterhalb der DPE (CT) wurden ebenfalls gemessen.

Ergebnisse: Insgesamt konnten 543 individuelle DPE zum Startzeitpunkt idenitifiziert werden, 28 neue DPE entwickelten sich im Verlauf der Studie. Die mittlere Beobachtungszeit war 21.3 ± 8.6 Monate (Bereich, 6-44 Monate). Bei 3.2 Prozent der DPE (18/571) bildete sich eine Atrophiezone innerhalb von 18.3 ± 9.5 Monaten (Bereich, 5-28 Monate) nach Beginn der Beobachtung aus. DPE mit heterogener interner Reflektivität waren signifikant häufiger mit neuer Atrophie nach 6 Monaten (OR, 5.614; 95% Konfidenzintervall [CI], 1.277-24.673) und neuer Atrophie zum letzten Beobachtungszeitpunkt (FUL) (OR, 7.005; 95% CI, 2.300-21.337) assoziiert. DPE mit HRF waren signifikante Prädiktoren für neue Atrophie nach 6 Monaten (OR, 30.161; 95% CI, 4.766-190.860) und zum FUL (OR, 11.211; 95% CI, 2.513-50.019). Läsionen mit einer maximalen Höhe > 80 µm oder CT ≤ 135 µm zu Beginn der Beobachtung waren ebenfalls positiv mit dem Auftreten neuer Atrophie assoziiert (OR, 7.886; 95% CI, 2.105-29.538 und OR, 3.796; 95% CI, 1.154-12.481).

Zusammenfassung: Das Vorhandensein von HRF über einer DPE, sowie eine heterogene interne Reflektivität der DPE waren signifikant mit der lokalen Entwicklung von Atrophie innerhalb der folgenden Monate assoziiert. Diese Ergebnisse erweitern unser Verständis der morphologischen Veränderungen im natürlichen Verlauf der trockenen AMD.

Optical Coherence Tomography Based Observation of the Natural History of Drusenoid Lesion in Eyes with Dry Age-Related Macular Degeneration

Affidavit

I, Yanling, Ouyang certify under penalty of perjury by my own signature that I have submitted the thesis on the topic "Optical Coherence Tomography Based Observation of the Natural History of Drusenoid Lesion in Eyes with Dry Age-Related Macular Degeneration". I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The section on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) corresponds to the URM (s.o) and are answered by me. My contribution in the selected publication for this dissertation corresponds to those that are specified in the following joint declaration with the responsible person and supervisor.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

_____

Date 16. Aug. 2014 Signature

Detailed Declaration of Contribution

Publication: Yanling Ouyang, Florian M. Heussen, Amirhossein Hariri, Pearse A. Keane, Srinivas R. Sadda. **Optical coherence tomography based observation of the natural history of drusenoid lesion in eyes with dry age-related macular degeneration.** (Ophthalmology). 2013 Dec;120(12):2656-65. Epub 2013 Jul 4.

Contribution in detail:
Yanling Ouyang has conducted the experiment, collected and analysed/interpreted the data, wrote the article and proofed/revised the article. Amirhossein Hariri has provided part of the materials. Pearse A. Keane has revised the article. Florian M. Heussen and Srinivas R. Sadda have together designed the experiment, supervised the experiment, and proofed/revised the article.

Signature, date and stamp of the supervising University teacher

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☐	15	ACTA OPHTHALMOL	1755-375X	4978	2.345	2.428	0.425	212	8.2	0.01099	0.762
☐	16	OPHTHAL EPIDEMIOL	0928-6586	1175	2.182	2.296	0.373	59	5.9	0.00378	0.851
☐	17	VISION RES	0042-6989	15840	2.137	2.345	0.363	223	>10.0	0.02491	1.003
☐	18	MOL VIS	1090-0535	5160	1.987	2.311	0.175	314	4.5	0.01679	0.624
☐	19	CLIN EXP OPHTHALMOL	1442-6404	2110	1.964	2.047	0.581	129	5.1	0.00735	0.734

4. Copy of the publication:

Ouyang Y, Heussen FM, Hariri A, Keane PA, Sadda SR.

Optical coherence tomography based observation of the natural history of drusenoid lesion in eyes with dry age-related macular degeneration. Ophthalmology. 2013 Dec;120(12):2656-65. http://dx.doi.org/10.1016/j.ophtha.2013.05.029. Epub 2013 Jul 4.

5. Curriculum vitae:

For data protection reasons, my resume is not published in the electronic version of my thesis.

LIST of PUBLICATIONS

Original Publications

1. **Ouyang Y,** Shao Q, Scharf D, Joussen AM, Heussen FM. Retinal Vessel Diameter Measurements by Spectral Domain Optical Coherence Tomography. **Graefe's archive for clinical and experimental ophthalmology**. Accepted.
2. McDonnell EC, Heussen FM, Ruiz-Garcia H, **Ouyang Y**, Narala R, Walsh AC, Sadda SR. Effect of anti-VEGF treatment on choroidal thickness over time in patients with neovascular age-related macular degeneration. Eur J Ophthalmol. [Epub ahead of print]
3. **Ouyang Y**, Shao Q, Scharf D, Joussen AM, Heussen FM. Easy Method to Differentiate Retinal Arteries from Veins by Spectral Domain Optical Coherence Tomography: Retrospective, Observational Case Series. **BMC Ophthalmology**. 2014 May 15;14:66.
4. **Ouyang Y**, Pleyer U, Shao Q, Keane PA, Stübiger N, Joussen AM, Sadda SR, Heussen FM, Evaluation of Cystoid Change Phenotypes in Ocular Toxoplasmosis using Optical Coherence Tomography. **PLOS One**. 2014 Feb 5;9(2):e86626.
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6. **Ouyang Y**, Heussen FM, Keane PA, Sadda SR, Walsh AC. Comparison of Non-Mydriatic Fundus Photography and Three Dimensional Optical Coherence Tomography for Detection of Retinal Irregularities. **Investigative ophthalmology & visual science.** 2013 Aug 21; 54(8): 5694-700.
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16. Pappuru RR, Briceno C, **Ouyang Y**, et al. Clinical significance of B-scan averaging with SD-OCT. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2012;43:63–8.
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27. **Ouyang Y**, Zhang Y, Xu G, et al. Clinical features of Best vitelliform macular dystrophy. Zhonghua yan ke za zhi. **Chinese journal of ophthalmology.** 2007;43:1089–92. (Chinese)

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1. Heußen FM, **Ouyang Y**, Joussen AM. Retinal angiomatous proliferations. Klinische Monatsblätter für Augenheilkunde. 2012;229:877–81 (review). (German)
2. **Ouyang Y**, Zhang Y. Best vitelliform macular dystrophy. International Review of Ophthalmology. 2007;31:110–113. (review) (Chinese)

3. **Ouyang Y**, Zhang Y, Wang W. Application of Bevacizumab (avastin) in Ophthalmology. Chinese Journal of Ophthalmology and Otorhinolaryngology. 2007;7:126–128. (review) (Chinese)
4. **Ouyang Y**, Zhang Y, Zhang C. Ocular cicatricial pemphigoid. International Review of Ophthalmology. 2007; 31: 322–325. (review) (Chinese)

Case report

1. **Ouyang Y**, Zhang Y. A case report of syphilitic optic neuritis. Chinese Journal of Ocular Fundus Diseases. 2007; 23: 371–372. (case report) (Chinese)

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