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Research paper

Retinal changes in patients with major depressive disorder – A controlled optical coherence tomography study

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ABSTRACT

Background: Recent studies on the pathophysiology of major depression (MD) indicate that degenerative and inflammatory processes may play a role. This finding is supported by magnetic resonance imaging (MRI)-based meta-analysis that show volume reductions in circumscribed areas of the brain in patients with MD. Using optical coherence tomography (OCT), retinal changes have been demonstrated in neurodegenerative disorders. In light of this inflammatory/degenerative hypothesis, we tested whether patients with MD exhibit retinal alterations that might correlate with the severity and duration of the disease.

Methods: Patients with MD and age- and gender-matched healthy controls were recruited for the measurement of the total volume and thickness of their retina as well as the thicknesses and volumes of five different retinal layers using single-layer-analysis provided by the spectral-domain-OCT.

Results: OCT data from 28 patients with MD and 20 healthy controls were available for evaluation. The exploratory intra-individual group comparison of the two eyes showed a small but significant difference in the retinal total volume (right = 8.69 mm^3; left = 8.72 mm^3; p = 0.03) only in patients with MD. There were no other significant differences between the patients with MD and the healthy controls with respect to the OCT measurements.

Limitations: The small group size as well as the absence of correction for multiple testing due to the exploratory design should be considered as limitations of our study.

Conclusion: While retinal total volume differs between the eyes of patients with MD, the comparison of retinal parameters between these patients and age- and gender-matched healthy volunteers did not show any differences.

1. Introduction

1.1. Degenerative aspects of major depression (MD) and the visual system

Recent studies on the pathophysiology of major depressive disorder (MD) show that degenerative and inflammatory processes may play a role (Wuwongse et al., 2010). This statement is based principally on magnetic resonance imaging (MRI)-based meta-analytical studies, which support a reduction in volume in frontal and hippocampal structures in patients with MD (Arnone et al., 2012; Bora et al., 2012; Kempton, 2011). In addition, postmortem studies have reported a loss of synapses and decreased expression of genes associated with synaptic functions. Furthermore, several studies have elicited a link between dementia and depression. Patients who had a depressive episode in their past showed an increased life-time risk of developing Alzheimer's dementia (AD) (Ownby et al., 2006); patients with AD who had depressive episodes in their medical history also had an increased accumulation of Alzheimer-plaques and neurofibrillary bundles in the hippocampus (Rapp et al., 2006). In both entities (MD and AD), the decline in neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) and the increase in pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNFα) play an etiological role (Wuwongse et al., 2010).

MD is very manifold from a symptomatic perspective, and although

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visual symptoms are not primarily associated with its classical clinical presentation, disturbances in the visual system or visual perception seem to be more frequent in these patients. Healthy subjects with a subjective impairment of vision exhibit a twofold higher prevalence of depressive symptoms compared with subjects without visual impairment (Zhang et al., 2013). Recent studies have reported abnormalities in the visual system and the processing of visual information in patients with MD. A significant reduction of pattern electroretinogram (PERG) amplitudes has also been found in patients with MD, which also correlates directly with the severity of depressive symptoms (Bubl et al., 2010). The reduced PERG response is associated with a reduced activity of retinal ganglion cells (Bubl et al., 2012). A reduced amplitude of the visually evoked potentials (VEP) has also been shown in patients with MD compared with healthy controls (Bubl et al., 2015; Normann et al., 2007).

1.2. Optical coherence tomography

In vivo visualization of the retina by means of optical coherence tomography (OCT) provides a promising methodological approach for investigating abnormalities in the visual system possibly related to degenerative changes in neural structures. Based on interferometric measurements of reflected light beams, the OCT technique creates three-dimensional images non-invasively and rapidly (within a few minutes) without known side effects. The spatial resolution of OCT is in the range of 3–4 µm and is comparable to that of histological examinations (Kim et al., 2009; Blumenthal et al., 2009) (Fig. 1; a detailed description of the method has been presented elsewhere (Schönfeldt-Lecuona et al., 2015)).

Several OCT studies showed a direct correlation between retinal nerve fiber layer thickness (RNFLT) and electrophysiological measurements (e.g., amplitude reduction in the PERG in patients in the early stages of glaucoma disease and in patients with multiple sclerosis) (Parisi et al., 2001, 1999; Ventura et al., 2006). Furthermore, certain OCT parameters appear to be related to MRI characteristics that are a measure of volume loss of the brain tissue (Gordon-Lipkin et al., 2007; Grazioli et al., 2008; Ong et al., 2015). Additionally, in psychiatric cohorts, especially in patients with schizophrenia, changes in the retinal layer thicknesses have been demonstrated in various investigations (Ascaso et al., 2010; Lee et al., 2013). On the other hand, the retina is considered to be the "window to the brain," since, from an embryological point of view, it arises (together with the optical nerve) from ectodermal germ cells of the diencephalon (London et al., 2012; Schönfeldt-Lecuona et al., 2015). In some degenerative diseases, such as dementia of the Alzheimer's type and in Parkinson's disease, a reduction of the retinal nerve fiber layer has been demonstrated by means of OCT (Petzold et al., 2010; Yu et al., 2014).

Progressive MRI-volumetric changes in frontal and hippocampal brain regions as well as abnormalities in the visual system suggest that the retinal structures are altered in patients with MD. To review this hypothesis, two OCT studies were performed in patients with depressive disorders (Kalenderoglu et al., 2016a; Yildiz et al., 2016). However, the findings of these studies are heterogeneous and partially inconsistent, which may be partly due to methodological differences. We present a study in which a cross-sectional OCT retinal examination (using retinal single-layer measurement for the first time in a psychiatric cohort) was performed in patients with MD. The measurements were then compared with a control group adjusted for age and gender. In addition, the influence of certain disease parameters, such as the duration of the disease or the severity of the symptoms, was examined for the OCT values.

2. Methods and materials

2.1. Patients and controls

We investigated patients with unipolar depression who were in inpatient treatment at the Department of Psychiatry and Psychotherapy III of the Ulm University Clinic, as well as age-matched healthy controls from the clinic staff and from the environment of the investigators. Inclusion criteria for patients were a diagnosis from the spectrum ICD-10 F32.x or F33.x and age between 18 and 65 years. All participants gave their written informed consent after a detailed explanation of the study. The study was approved by the Ethics Committee of the University of Ulm (No. 59/14 - CL / se) and was carried out between June 1, 2014 and November 30, 2015.

Exclusion criteria were ophthalmological diseases or systemic diseases that could affect the optic nerve, the retina or the choroid (e.g., diabetes mellitus, refractory arterial hypertension, oncological disorders), neurological brain diseases, clinically relevant cognitive impairment (Mini-Mental-State-Examination/MMSE) $\leq$ 25, a history of alcohol or drug dependence or current alcohol/drug abuse, treatment with corticosteroids and autoimmune diseases. Patients with optical media opacities that might affect a good quality imaging acquisition were also excluded. Comorbid mental disorders were assessed by means of a structured clinical interview. These comorbidities may not have been the focus of the clinical symptoms nor the reason for the present inpatient treatment. All patients received antidepressants as mono- or combination therapy. None of the controls received psychopharmacological medication. In the healthy controls, a current relevant somatic disorder was excluded by means of a detailed medical history and clinical exploration; a psychiatric disorder (axis I or II) was excluded by using the short version of the Diagnostic Interview for Mental Disorders (Mini-DIPS). To rule out an ophthalmologic disease, all subjects underwent a complete ophthalmological examination (tonometry, slit lamp, indirect ophthalmoscopy, determination of contrast sensitivity, visual acuity and refraction). Participants with ophthalmological abnormalities were excluded.

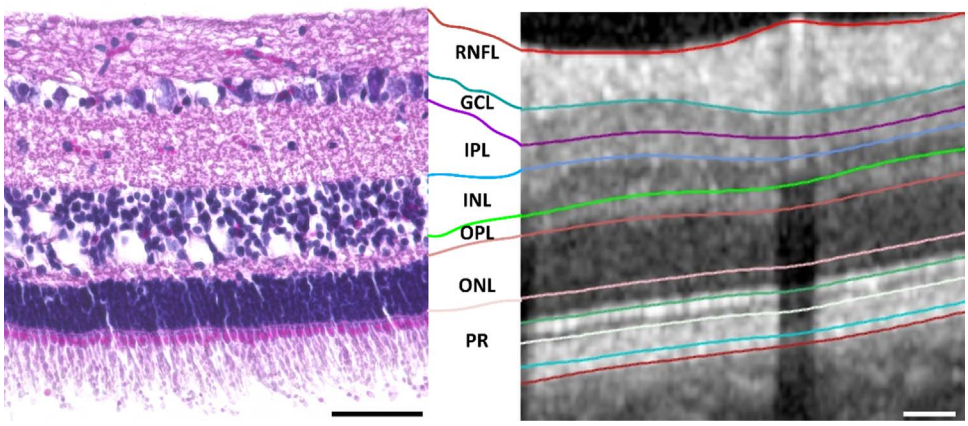

Fig. 1. ***Comparison of a histological section of the retina and an OCT image.*** The histological section of a porcine retina is shown in comparison with an OCT-B scan, which is automatically segmented by the Heidelberg Eye Explorer. The OCT is able to display the histological layers in detail. RNFL = retinal nerve fiber layer, GCL = ganglion cell layer, IPL = inner plexiform layer, INL = inner nuclear layer, OPL = outer plexiform layer, ONL = outer nuclear layer. The layers segmented in the lower sections of the image do not have a direct anatomical correlate; those are indicated with "PR" = photoreceptor layers.