



Research paper

Optical coherence tomography findings in patients with bipolar disorder

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ABSTRACT

Background: Research in bipolar disorder suggests the presence of structural brain abnormalities. It is not clear whether these findings are trait markers or operate with the onset and progress with disease severity and duration. Optical coherence tomography (OCT) is a non-invasive technique that detects degenerative changes in the retina reflecting brain degeneration. This study aimed at detecting these changes and relating them to disease severity and clinical characteristics.

Methods: A case-control study conducted in Psychiatry and Addiction Medicine hospital, Faculty of Medicine at Cairo University. Forty inpatients with bipolar disorder -according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) - were compared to forty matched healthy controls. Patients were subjected to the Structured Clinical Interview of DSM-IV (SCID-I), Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS). Both patients and controls were subjected to OCT.

Results: Patients showed thinning of Retinal Nerve Fiber Layer (RNFL) relative to control subjects in most of the OCT parameters including Right average ($p < .001$ and 95% CI [14.39, 19.84]), Lt average ($p < .001$ and 95% CI [13.03, 19.42]). Patients also showed decreased Ganglionic Cell Complex (GCC) significantly in Rt average ($p = .002$ and 95% CI [2.33, 9.78]), Lt average ($p < .001$ and 95% CI [4.47, 11.63]). Age at onset, number of episodes, and severity did not significantly correlate with OCT parameters.

Limitations: The small sample and absence of follow-up.

Conclusions: Patients with bipolar disorder show degenerative changes detected by OCT in relation to healthy controls.

1. Background

Bipolar disorder is a chronic episodic psychiatric disorder that has a worldwide prevalence of 1% and causes severe deterioration of patients' quality of life and functions including social, occupational and cognitive (Cotrena et al., 2016; Merikangas et al., 2007).

Structural brain abnormalities are detected in patients with bipolar disorder starting from their first episode. Some changes are found to be progressive, such as reduction of brain gray matter in hippocampus, fusiform gyrus and temporal lobe. Severity of changes can be related to the severity of symptoms and the number of episodes (Moorhead et al., 2007; Vita et al., 2009). These progressive structural changes may support the neurodegenerative nature of the bipolar disorder, although systematic review of different studies examining bipolar patients using neuroimaging techniques failed to differentiate subtypes or dimensions in those patients (Hozer and Houenou, 2016; Kempton et al., 2008).

On the other hand, the neurodevelopmental theory of bipolar disorder was supported by previous research. There is an increased

risk of developing the disorder among first degree relatives of a bipolar patient. Family history of bipolar disorder affects the clinical characteristics of the disorder. Several neurodevelopmental factors related to bipolar disorder have been studied, including cell migration, extracellular matrix and calcium signaling (O'Shea and McInnis, 2016; Berutti et al., 2014).

The use of newer magnetic resonance imaging (MRI) techniques, such as magnetization transfer imaging, magnetic resonance spectroscopy and diffusion tensor imaging has led to only limited achievements in linking imaging data with clinical parameters of disease severity for most neurologic disease. Alternately, examining the retina has been incorporated as a novel technology that enables objective analysis of the processes of neurodegeneration through visualization of the retina (Galetta et al., 2011).

Retina is considered a part of the brain that contains several layers of neurons interconnected by synapses. Retinal nerve fiber layer thickness (RNFL) is made up of non-myelinated axons from the ganglion cells whereas, the ganglion cell complex (GCC) is the three

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Table 1
Comparison between patients and controls as regard demographics and Optical Coherence Tomography (OCT) measures.

	Patients N: 40		Controls N: 40		95% Confidence interval		p
	Mean	SD	Mean	SD	Lower	Upper	
Age (years)	30.90	9.31	32.85	8.77	– 2.08	5.98	.338
Sex	21 males (52.5%) / 19 females (47.5%)		23 males / 17 females				.653
Age of onset	23.77	7.57					
Number of manic episodes	3.00	2.87					
Number of depressive episodes	.20	.46					
Number of mixed episodes	.87	1.63					
Total number of previous episodes	4.07	3.58					
Number of episodes per year	.72	.31					
Rt average RNFL ^a	104.24	7.63	121.35	3.98	14.39	19.84	< .001
Lt average RNFL	104.42	9.35	120.65	3.70	13.03	19.42	< .001
Rt superior RNFL	104.07	9.06	116.82	21.80	5.25	20.23	.001
Lt superior RNFL	106.00	11.69	118.42	21.62	4.64	20.19	.002
Rt inferior RNFL	106.49	10.94	115.77	20.02	2.06	16.49	.013
Lt inferior RNFL	105.35	10.07	116.64	21.69	3.72	18.87	.004
Rt nasal RNFL	80.32	9.15	84.20	10.49	– .52	8.26	.082
Lt nasal RNFL	82.25	9.49	84.37	7.12	– 1.61	5.86	.262
Rt temporal RNFL	83.14	9.78	89.27	9.23	1.90	10.37	.005
Lt temporal RNFL	79.76	10.48	86.10	9.93	1.79	10.89	.007
Rt average GCC ^b	94.69	7.00	100.75	9.53	2.33	9.78	.002
Lt average GCC	93.71	6.68	101.76	9.17	4.47	11.63	< .001
Rt superior GCC	94.71	6.79	97.96	8.60	– .20	6.70	.064
Lt superior GCC	93.52	6.25	99.38	7.56	2.77	8.95	< .001
Rt inferior GCC	94.66	7.65	98.00	7.69	– .08	6.75	.055
Lt inferior GCC	94.32	7.59	98.42	6.79	.89	7.30	.013

P less than .05 is considered significant.

^a RNFL: Retinal Nerve Fiber Layer.

^b GCC: Ganglion Cell Complex.

innermost retinal layers: the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer (Khalil et al., 2016).

Peripapillary RNFL decreased thickness is related to neurons loss and axonal loss. Being non-myelinated, it is valued as a more sensitive and also non-invasive parameter for evaluating degeneration in neurological and psychiatric disorders like multiple sclerosis and schizophrenia (Bock et al., 2013).

Optical coherence tomography (OCT) is a noninvasive imaging technique that provides high-resolution, cross-sectional images of the retina, and automatic measurement of RNFL (Frohman et al., 2008). Abnormal findings in OCT -namely RNFL thinning- have been reported in multiple neurological disorders with degenerative changes including Parkinson Disease, Alzheimer Disease, and Multiple Sclerosis (MS) (Lu et al., 2010; Petzold et al., 2010).

In psychiatric disorders, OCT as a diagnostic tool for degenerative changes is gaining an increasing interest. Patients with schizophrenia have shown abnormal OCT findings in the form of decrease in the overall RNFL (Lee et al., 2013), the superior quadrant (Cabezón et al., 2012), right nasal quadrant (Chu et al., 2012). Similarly, ganglion cell layer (GCL) -which is a part of the ganglion cell complex- and internal plexiform layer (IPL) were decreased in patients with schizophrenia and both were found to be correlated with the severity of the disease (Celik et al., 2016).

Yildiz et al. have found that depressed patients were not different from the healthy controls as regard OCT parameters. Ganglion cell inner plexiform layer (GCIPL) and nasal RNFL were correlated with the duration of the latest depressive episode. Some measures of OCT were negatively associated with clinical variables like a family history of psychiatric diagnosis and the duration of the latest episode (Yildiz et al., 2016a, 2016b).

Bipolar disorder patients were also studied using OCT. 60 eyes of 30 patients with bipolar disorder and 60 eyes of 30 age-matched healthy control subjects were examined using OCT. Mean RNFLT, the inferior,

superior, and nasal quadrants were significantly lower than the control group; however, the temporal quadrant was not reduced significantly. The duration of illness was correlated to RNFLT (Mehraban et al., 2016).

Another study that included 40 patients with bipolar disorder also found that RNFL thickness was significantly lower in patients in comparison to controls at all measured regions. The GCL volume was also significantly lower in the patient group. There was a significant negative correlation between GCL volume and disease duration, severity of illness measured by Young Mania Rating Scale (YMRS) score, Clinical Global Impression (CGI) score, and number of hospitalizations (Kalenderoglu et al., 2016).

Moreover, Glutamate is the main excitatory neurotransmitter in the brain and also has an important role in vision. Other neurotransmitters, such as serotonin, dopamine, GABA, glycine, acetylcholine, and taurine, have been hypothesized to have a role (Ivleva et al., 2013). Dopamine is known to play a role in both retinal function and in bipolar disorder, and it has other roles in psychotic symptoms and cognitive impairment (Zhao et al., 2015).

According to the available data, we hypothesized that retinal nerve fiber layer (RNFL) thickness is reduced in patients with bipolar disorder in comparison to the control healthy group. We also looked for associations between OCT findings and clinical characteristics of the disease.

2. Methods

2.1. Design and subjects

This was a case-control observational study that compared two groups. The first group enrolled 40 patients - ranged from 18 to 55 years old and of both sexes - who have bipolar I disorder according to the criteria of the 4th edition of the Diagnostic and Statistical Manual of

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