Peripapillary Retinal Nerve Fiber Layer Thickness in Bipolar Disorder

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OCT (Optical Coherence Tomography) presently is used in neurological disorders, multiple sclerosis [1,2] and also others including Alzheimer [3] and Parkinson [4]. In multiple sclerosis, cognitive and physical disability was correlated with degree of RNFL atrophy [5].

Between psychiatric disorders, decreasing RNFLT (Retinal Nerve Fiber Layer Thickness) was reported in Schizophrenia with possible relations to neurodegeneration process [6,7]. Duration of schizophrenia was correlated to RNFL thinning, macular thinning, and reduction of macular volume [8] and severity of symptoms to smaller macular volume [9].

Between psychiatric disorders, decreasing RNFLT was reported in Schizophrenia with possible relations to neurodegeneration process [10,11]. Duration of schizophrenia was correlated to RNFL thinning, macular thinning, and reduction of macular volume [12] and severity of symptoms to smaller macular volume [13].

In a prospective comparative case series, we compared 60 eyes of thirty patients with bipolar disorder to 60 eyes of thirty age-matched healthy control subjects.

The patients underwent a complete psychiatric examination including semistructured clinical interview following the verified persian translation SCID outline for bipolar disorder diagnosis and fulfilled the inclusion and exclusion DSM-IV-TR criteria of bipolar disorder [14].

The cases and controls also had a complete ophthalmologic examination, including assessment of best-corrected visual acuity (*BCVA*), intraocular pressure (IOP) measurement, slit lamp biomicroscopy, and dilated fundus examination. Only participants with BCVA of 20/20 or better with normal IOP included. Exclusion was posterior pole pathology including optic nerve and retinal pathology and any media haziness that causes interruption in ocular and OCT examination. More exclusion was psychiatric and neurological diseases with gray matter defects and consequently RNFLT diminution such as multiple sclerosis, dementia, substance abuse (30) and finally for decreasing interfering factors, obsessive compulsive disorder.

All eyes underwent a peripapillary RNFLT measurement by OCT (3D OCT-1000, Topcon Corporation, Tokyo, Japan). OCT was done by an experienced optometrist who was masked to the patients' group. Scans with a quality factor <60 and blinking during the scanning process were excluded. It was performed for every eye on a circle at 3.4 mm around the optic disc in four superior, temporal, inferior and nasal quadrants. The thickness of each quadrant and the mean of all were used for analysis.

The mean age of bipolar patients was 32.5 ± 9.3 and controls 31.2 ± 9.5 years. 80% of both groups were males. Smokers in case group were 60.0%, significantly higher than in control subjects (23.7%). It also evident for duration of smoking period in which cases had 10 years of smoking versus 5 years in controls and 16.5 *versus* 10 for number of cigarettes per day. Mean IOP was 13.6 ± 1.7 and 13.7 ± 1.9 for cases and controls respectively. In comparing characteristic of cases to controls, the only meaningful difference was in percent of smokers (p value=0.004).

There was no statistically significant relation between the mean

OCT thickness and the depression episode number nor manic episode number (P=0.960 and P=0.627). We found no statistically significant relation between the mean OCT thickness and age of onset (P=0.421). There was no statistically significant relation between the mean OCT thickness and smoking in two groups (P=0.728 and P=0.424 in the case and control groups respectively). This relation was not found even with the number of cigarette smoking (P=0.794 and 0.191 in case and control groups, respectively). No relation was found with smoking duration (P=0.934 and P=0.546 in case and control groups respectively).

Age of onset in patients group was 23.2 ± 5.4 year. Previous occurrence of psychosis was 66.7% and most of the patients (83.3%) were psychotic at the time of OCT scan. Most of patients (86.7%) had only one episode of mania. A significant proportion of patients had no episode of depression (46.7%) and 36.7% had only one episode. Among these variables only duration of disease had statistically significant relation to the RNFLT (Table 1). Also, we assessed the relation of any kind of disorder (mania or depression) at present time with RNFLT and we didn't find any statistically significant relation (P=0.399).

The mean RNFL thickness was 99 ± 8, 106 ± 8 mμ in the case and control groups respectively. This difference was statistically significant

Variable		Value	P-value for relation with RNFLT§
age of onset	Mean ± SD	23.2 ± 5.4	0.421
	Median (range)	22 (14 to 42)	
Duration	Mean ± SD	10.6 ± 8.6	0.040
	Median (range)	9.5 (0 to 30)	
Psychosis	No	5 (16.7%)	0.733
	Yes	25 (83.3%)	
HxPsychosis	No	10 (33.3%)	0.828
	Yes	20 (66.7%)	
Depression Episode Number	0	14 (46.7%)	0.960
	1	11 (36.7%)	
	2	3 (10.0%)	
	3	1 (3.3%)	
	4	1 (3.3%)	
Manic Episode Number	0	2 (6.7%)	0.627
	1.0	24 (80.0%)	
	2.0	4 (13.3%)	

§ Based on GEE analysis

Table 1: Specifications of variables in the case group and their relations with RNFLT.

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(p=0.001). In comparison of the mean RNFLT's of different quadrants in the case and control groups, inferior, superior, nasal quadrants were statistically significant (p<0.001) (0.040) (0.005), temporal quadrant was not reached to the significant level (p=0.907).

There are only few studies on OCT in psychiatric disorders that was exclusive to schizophrenia and none on bipolar disorder but they are compatible with our result showing decreasing of RNFLT (5, 7) this is in line with studies on gray matter deficit in bipolar disorder [10,15]. We also observed statistically significant reduction of the peripapillary RNFLT in inferior, superior, and nasal quadrants in bipolar disorder when compared with controls. In one previous study, only nasal quadrant of the schizophrenic patients was reduced when compared with controls [7].

In the other hand, our study concluded that duration of disease had statistically significant relation to the RNFLT. Other studies also showed that duration of schizophrenia was correlated to RNFL thinning, macular thinning, and reduction of macular volume [16] and severity of symptoms to smaller macular volume [17].

Also psychosis is a common feature of bipolar disorder but 83% of cases in our study had psychosis at the time of scan that is relatively higher than typical bipolar population. Because of probably significance of psychosis in gray matter loss, the psychosis could independently cause the decreasing of RNFLT. However there is no study on effect of psychosis on OCT, instead there are studies that show gray matter and structural changes [18,19]. So another study with nonpsychotic bipolar subject needed.

Despite the patients and control group ages are matched, young population age could act as a confounding variable due to a relationship between age and decreasing RNFL thickness [20,21], in the way that lead to lower intensity of gray matter loss due to evidence that shows a more progressive brain aging changes in bipolar patients compare to normal population [22].

The only meaningful difference in comparing characteristics of cases to controls was in percent of smokers (p value=0.004). Until this day, there is no research on the effect of smoking on OCT in general or on gray matter loss in bipolar smokers patients but there are studies showing gray matter loss in schizophrenic smokers [23], and in smokers versus non-smokers [20,21], also on previous studies of OCT in schizophrenia, smoking were not take to account. So we proposed future study for more clarification in effect of high rate of smoking on our result.

Most of cases in our study had psychosis at the time of scan (83%); this is different from typical bipolar patients. Because of probably consequence of psychosis in gray matter loss, the psychosis could independently cause the decreasing of RNFLT. So, we are suggesting another study with nonpsychotic bipolar subject needed [24,25].

Our study showed peripapillary RNFLT decreases in bipolar disorder and OCT can be used for detecting severity and duration of disorder, but most of our cases previously had not MRI scans, and also our cases had relatively few episodes of mania. In future more longitudinal studies should be done with enrolment of the longstanding nonpsychotic bipolar cases with more episodes of mania by doing subgroup analysis depending on duration of illness, number of the episodes of mania, and MRI findings to correlate RNFLT decrease to disease duration and activity.

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