Assessment of retinal findings in children and adolescents with specific learning disorder: A case-control study

Özgül öğrenme bozukluğu olan çocuk ve ergenlerde retinal bulgularının değerlendirilmesi: Bir vaka kontrol çalışması

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SUMMARY

Objective: Specific Learning Disorder; is a neurodevelopmental disorder that arises due to genetic, epigenetic and various environmental factors. The aim of this study is to compare children and adolescents diagnosed with specific learning disorder with healthy controls in terms of intraocular pressure, retinal nerve fiber layer, central macular thickness and choroidal thickness. **Method:** This prospective case-control study included 63 children and adolescents, including 30 with specific learning disabilities and 33 controls. The case and control groups were assessed using 'Schedule for Affective Disorders and Schizophrenia School-Age Children-Present and Lifetime Version Form-DSM-5 Turkish Version for diagnostic interview. Case and control groups were compared in terms of retinal findings by performing intraocular pressure and optic coherence tomography. In the study, various retinal nerve fiber layer quadrants were compared separately for the right and left eyes. **Results:** In the case group, only the right eye superior nasal retinal nerve fiber layer quadrant thickness was found to be lower than the control group. There was no difference between the groups in terms of other parameters. **Discussion:** Our study indicates a lower right eye superior nasal retinal nerve fiber layer quadrant thickness in children and adolescents with specific learning disorder as compared to controls. However, there was no difference between the groups in terms of intraocular pressure and other retinal findings. Longitudinal studies with larger samples are needed in order to generalize retinal findings in specific learning disorder to the population.

Key Words: Choroidal thickness, intraocular pressure, macular thickness, retinal nerve fiber layer, specific learning disorder.

ÖZET

Amaç: Özgül Öğrenme Bozukluğu; genetik, epigenetik ve çeşitli çevresel faktörlere bağlı olarak ortaya çıkan nörogelişimsel bir bozukluktur. Bu çalışmanın amacı, özgül öğrenme bozukluğu tanısı alan çocuk ve ergenleri göz içi basıncı, retina sinir lifi tabakası, santral makular kalınlık ve koroid kalınlığı açısından sağlıklı kontrollerle karşılaştırmaktır. **Yöntem:** Bu prospektif vaka kontrol çalışmasına 30'u özgül öğrenme bozukluğu ve 33'ü kontrol olmak üzere 63 çocuk ve ergen dahil edildi. Vaka ve kontrol grupları, 'Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam Boyu Şekli-DSM-5 Türkçe Versiyonu' kullanılarak değerlendirildi. Olgu ve kontrol grupları göz içi basıncı ve optik koherens tomografi ölçümleri ile retina bulguları açısından karşılaştırıldı. Çalışmada farklı retina sinir lifi kalınlıkları sağ ve sol göz için ayrı ayrı kadranlara ayrılarak karşılaştırıldı. **Bulgular:** Olgu grubunda sadece sağ göz superior nazal kadran retina sinir lifi kalınlığı kontrol grubuna göre daha düşük bulundu. Diğer parametreler açısından gruplar arasında fark yoktu. **Sonuç:** Çalışmamız, özgül öğrenme bozukluğu olan çocuk ve ergenlerde kontrol grubuna göre düşük sağ göz superior nazal kadran retina sinir lifi tabakası kalınlığını göstermektedir. Ancak göz içi basıncı ve diğer retina bulguları açısından gruplar arasında fark yoktu. Özgül öğrenme bozukluğundaki retina bulgularının topluma genellenebilmesi için daha büyük örneklemli boylamsal çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Koroid kalınlığı, göz içi basıncı, makula kalınlığı, retina sinir lifi tabakası, özgül öğrenme bozukluğu.

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INTRODUCTION

Specific Learning Disorder (SLD); is a neurodevelopmental disorder that arises due to genetic, epigenetic and various environmental factors. SLD negatively affects the brain's ability to perceive and process verbal or non-verbal information efficiently (1). The frequency of SLD is determined to be 5-15% depending on the applied diagnostic criteria and the design of study (1, 2). Although SLD is a common disorder in childhood, its etiology has not been clearly established. However, it has been reported in clinical and epidemiological studies that the disorder shows high heritability (3). In genetic studies performed in individuals with SLD, it has been shown that blocking the expression of candidate genes that may contribute to its etiology results in the interruption of neuronal migration and axon guidance (4). In addition, the researchers found that the brain structures of individuals with SLD differed compared to healthy individuals. Findings in the studies include a decrease in planum temporale symmetry, and a decrease in gray matter in the posterior temporal, occipitotemporal, temporoparietal and cerebellar areas (5). In Diffusion Tensor Imaging studies, it was stated that there were structural changes in the white matter in the left temporoparietal and left inferior parietal gyrus regions, and these variations correlated with reading problems. In addition, it has been demonstrated in relation to SLD that an occipitotemporal region referred to as "visual word-form area" participates in whole word recognition function (6). The common point in the above-mentioned studies is that SLD is a biological disorder affecting brain structures.

The retinal layer of the eye originates from the anterior tube during the development process of the brain and is an extension of the central nervous system. Due to this property, it is named as the brain's window to the outside world (7). Optical Coherence Tomography (OCT) has been used in various disciplines in recent years due to its non-invasiveness and rapid assessment of biological tissue layers. Retinal changes that occur particularly during the course of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease and Multiple Sclerosis, etc.) were investigated using OCT (8-10). In addition, OCT has also been used to demonstrate the ocular findings of psychopathologies. It has been stated that retinal neurodegeneration occurs in the course of bipolar affective disorder (BAD) and these findings may show progressive changes during the disease course (11). In the study of Polat et al involving the comparison of OCT values between obsessive compulsive disorder (OCD) and controls, no reduction in retinal nerve fiber layer (RNFL) thickness in OCD cases was found but it was suggested that choroidal thickness may serve important purpose in determining the etiopathogenesis of the disease or in the follow-up of the neurodegenerative condition (12).

Following the detection of changes in OCT parameters in neurodegenerative diseases and psychiatric disorders, research involving OCT in childhood neurodevelopmental diseases have also gained momentum. In the study conducted by Garcia-Medina et al in individuals with autism spectrum disorder (ASD), it was found that these individuals had greater macular and RNFL thickness, increased macular vascular density and macular perfusion compared to controls (13). Hergüner et al in their study comparing children diagnosed with attention deficit hyperactivity disorder (ADHD) and controls in terms of OCT values reported lower nasal RNFL thicknesses in ADHD cases than the controls. It was stated that these findings support the evidence that ADHD involves cortical maturation lag, and this can be measured using retinal findings (14).

A decrease in RNFL and other retinal layer thicknesses in SLD, a neurodevelopmental disorder, was the hypothesis of our study and our speculations were based on previous studies and the above-mentioned concepts. For this purpose, our study aimed to compare and contrast SLD cases with a control group in terms of OCT values. To our knowledge, this is the first study reporting on OCT parameters in children and adolescents with SLD.

METHOD

Participants and procedure

A total of 63 children and adolescents aged between 8-18 years, 30 of them in the case group

and 33 in the control group, were included in the study. The case group consisted of individuals who were already being followed up for or newly diagnosed with SLD in the child and adolescent psychiatry outpatient clinic. The control group consisted of people who were evaluated in the child psychiatry outpatient clinic and had no psychopathological condition or those who visited the ophthalmology clinic for a routine eye examination. Those with concomitant psychopathologies such as ADHD, depression and anxiety disorder were not included in the case group. Individuals on medication usage, known neurological, metabolic, endocrinological etc. diseases, ocular diseases such as glaucoma, retinopathy, or with refractive errors of ± 1 diopters and above were also excluded from the study.

The case and control groups were assessed using 'Schedule for Affective Disorders and Schizophrenia School-Age Children-Present and Lifetime Version Form-DSM-5 Turkish Version (K-SADS-PL-DSM-5-T)' (15) for diagnostic interview. In the clinical interview, the patients were evaluated according to The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). The intelligence level of the case group was evaluated with the WISC-R test. The WISC-R test was applied to those who did not have the intelligence test, but those who had the test within the last year were not asked to retest. Cases with an IQ level of 80 and above as a result of the test were included in the study. During the psychiatric interview, the parents of the case and control groups were asked to fill in a sociodemographic data form. Subsequently, the case and control group were directed to the ophthalmological department for an eye examination.

Ocular Examination

After a routine eye examination, OCT was performed on the participants to evaluate retinal findings (RNFL, central macular and choroidal thickness). Single-layer retinal analysis was performed with commercial spectral domain OCT (SD-OCT) (Spectralis; Heidelberg Engineering, Heidelberg, Germany) with a approximately 840-nm wavelength. Choroidal thickness was measured using a SD-OCT device (Spectralis: wavelength, 870 nm; Heidelberg Engineering, Germany) with an enhanced depth-imaging mode after pupil dilation. The OCT images were assessed by same ophthalmologist.

Statistical Analyses

SPSS 22.0 package program was used for statistical analysis. Variables were evaluated for normal distribution using the Kolmogorov Smirnov and visual methods (histograms and probability plots). Average and standard deviation were used for normally distributed variables for descriptive statistics. Student t test was used to evaluate the differences in parametric data. MannWhitney U test was used to evaluate non-parametric data. Chi square test was used to evaluate categorical data. p value $<0,05$ was considered statistically significant.

Ethics Statement

This prospective case-control study was conducted between December 1, 2019 and October 31, 2020 upon obtaining the approval of Ethics Committee (Date: 01.11.2019, Protocol Number: 2019/2151). Participants were provided with information according to the Declaration of Helsinki before they enrolled in the study. Written consent was obtained from those gave their consent.

RESULTS

The study involved a total of 63 children and adolescents: 30 (10 girls / 20 boys) in the case group and the 33 participants (14 girls / 19 boys) in the control group. The mean age of the case group was 9.76 ± 2.26 years, and that of the control group was 9,78 ± 2,36 years. The two groups did not differ significantly in gender and age ($p = 0,458$, $p = 0,971$, respectively). The characteristics of the patient education received by the case group regarding SLD were recorded. The average age of children starting special education was determined to be 8,19 ± 1,93 years and the average duration of education was 2 hours / week. Results are provided in Table 1. Subsequently, the case and control groups were compared in terms of RNFL, central macular thickness, and choroidal thickness. Superior nasal

Tables

Table 1: Investigation of SLD cases in relation to the education they received

	n	%
Reason of visit		
Treatment and Follow-up	7	23,3
Medical report	23	76,7
Special education		
Present	21	70
Absent	9	30
Inclusive education at school		
Present	19	36,7
Absent	11	63,3
Benefit from special education		
Little	3	14,3
Moderate	6	28,6
Substantial	9	42,9
Very substantial	3	14,3
Source of information on SLD		
Child and adolescent psychiatry	13	61,9
Private educational institution	10	47,6
Internet/Social media	5	23,8
Other families with SLD	2	9,5

quadrant RNFL thickness for the right eye in the SLD group was significantly lower than the control group (p = 0,012). There was no statistically significant difference between the case and control groups in terms of other variables. Results are given in Table 2.

Table 2: Comparison of the case and control groups in terms of IOP and OCT values

Variable	Case Group (n=30)	Control Group (n=33)	P value
	Mean–SD	Mean–SD	
Right IOP	15,73–2,79	15,03–1,89	0,243
Left IOP	15,43–2,77	14,87–1,55	0,326
Right santral macular thickness	216,73–12,39	217,45–11,89	0,814
Left santral macular thickness	218,30–11,75	217,66–12,53	0,837
Right choroidal thickness	317,60–47,78	317,36–56,71	0,986
Left choroidal thickness	329,60–57,35	315,84–59,46	0,355
Right RNLF			
Nasal Superior	102,73–16,32	113,39–16,13	0,012*
Nasal	79,86–13,35	75,42–13,38	0,193
Nasal Inferior	113,73–21,76	116,33–21,97	0,639
Temporal Inferior	140,56–17,62	141,60–16,91	0,812
Temporal	74,73–10,80	78,21–10,70	0,205
Temporal Superior	142,30–22,91	143,66–20,49	0,804
Global	101,03–9,58	102,75–8,18	0,444
Left RNFL			
Nasal Superior	134,63–19,55	140,96–18,78	0,195
Nasal	71,50–9,35	74,72–11,85	0,238
Nasal Inferior	140,50–26,05	146,45–22,67	0,336
Temporal Inferior	114,56–22,58	113,87–20,88	0,900
Temporal	80,13–15,83	74,57–14,26	0,148
Temporal Superior	116,46–19,39	123,45–23,40	0,204
Global	101,20–9,46	123,45–23,40	0,450

IOP: Intraocular Pressure, RNFL: Retinal Nerve Fiber Layer

DISCUSSION

In this prospective case-control study, individuals with SLD were compared with healthy controls in terms of intraocular pressure (IOP) and retinal findings. As a result of statistical analysis, regardless of variables such as gender or age, individuals with SLD were found to have lower right eye superior nasal RNFL quadrant thickness than controls. IOP, choroidal thickness and central macular thickness were not significantly different between the groups.

In recent years, there are many studies designed for addressing the ocular symptoms of psychopathologies. In studies on patients with psychotic and mood disorders, the decrease in RNFL thickness was interpreted as an indicator of the progressive neurodegeneration seen in these disorders. It has been stated that OCT can be used in the diagnosis and follow-up of these diseases (11,16,17). Hergüner et al compared 45 children with ADHD with 45 healthy controls in terms of RNLF, macular thickness and macular volume, and reported a decrease in RNFL thickness only in the nasal quadrant in the case group. It was suggested that this may be caused by lag in cortical development in ADHD (14). However, in a study by Işık et al comparing ocular findings of ADHD cases who received treatment with ADHD patients who did not receive treatment and healthy controls indicated no significant difference in RNFL between the groups (18). In this study, only global RNFL measurement was made. In our study, we found a significant decrease in thickness in the nasal superior RNFL quadrant in children and adolescents with SLD as compared to healthy controls. Our study differs from other studies in the sense that it compares RNFL measurements for both the right and left eyes separately in 7 distinct quadrants. However, the variation detected only in a single quadrant may suggest that SLD is more of a neurodevelopmental disorder rather than a global neurodegenerative disease.

Another parameter evaluated in neurodevelopmental disorders is macular thickness. In studies on ADHD conducted by Hergüner et al and Işık et al, no difference was detected in macular thickness

between the groups (14, 18). However, in contrast to above-mentioned studies, studies by Sánchez-Guillén et al and Atas et al found a lower central macular thickness in an ADHD group (19, 20). In a study conducted on autism spectrum disorder, another neurodevelopmental disorder, higher macular thickness was found in individuals with ASD compared to controls (21). In our study, no difference was found in the right and left eye central macular thickness between SLD cases and the control group. This suggests that SLD may have a different disease mechanism compared to other neurodevelopmental disorders.

In a study comparing children with anxiety disorder and controls, it was found that central choroidal thickness was higher in the group with anxiety disorder (22). Similarly, choroidal thicknesses were found to be higher in patients with obsessive-compulsive disorder and conversion disorder (23,24). However, no difference was detected in choroidal thickness between the groups in our study. The lack of difference between the groups may be due to the small sample size or the lack of measurement for different fields.

Limitations

Our study is a strong one in terms of assessing retinal findings in a disorder that is classified as a neurodevelopmental disorder with a high prevalence. However, our findings should be interpreted while taking the limitations into consideration. The limitations of our study include the cross-sectional nature of the study and the relatively small sample size. In addition, the fact that accompanying disorders such as attention deficit hyperactivity disorder were excluded from the study and these disorders were not studied can be counted among the limitations.

CONCLUSION

In conclusion, our study indicates a lower right eye superior nasal RNFL quadrant thickness in children and adolescents with SLD as compared to controls. However, there was no difference between the groups in terms of IOP and other retinal findings. Longitudinal studies with larger samples are needed in order to generalize retinal findings in individuals with SLD to the general population.

Conflicts of interest: The authors declare that they have no conflict of interest.

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