Does methylphenidate treatment affect functional and structural ocular parameters in patients with attention deficit hyperactivity disorder? - A prospective, one year follow-up study

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**Purpose:** Methylphenidate hydrochloride, which blocks the reuptake mechanisms of dopamine and norepinephrine, is used in attention deficit hyperactivity disorder (ADHD) treatment. Methylphenidate has many general side effects including ocular findings. In this study, we investigated the long-term effects of methylphenidate treatment on functional and structural ocular parameters. **Methods:** In this prospective study, children with ADHD were evaluated. All patients underwent a detailed ophthalmic examination before methylphenidate treatment. All patients were examined in the 3rd, 6th, 9th, 12th months of methylphenidate treatment. Visual acuities, color vision, pupil diameters, static, dynamic and cycloplegic retinoscopy, intraocular pressure (IOP), anterior chamber depth (ACD), axial length (AL) were evaluated and recorded. **Results:** A total of 22 children were included in this study. The best-corrected visual acuities (BCVA) of all patients for both eyes were 0.0 logMAR, and 90.9% of patients had blue–purple color weakness before the treatment. After 1 year of treatment, none of the patients had any change in BCVA and color vision. However, an increase in myopic values of static retinoscopy and a decrease in hyperopic values of cycloplegic retinoscopy were found. Additionally, accommodation capacities were found to be decreased and AL was found to be increased significantly for both eyes. Pupil diameter, IOP, and ACD values did not change significantly. **Conclusion:** Our results suggest that patients with ADHD may have blue color vision deficiencies because of the decreased retinal dopamine levels. Additionally, structural and ocular parameters, especially accommodation capacity, may be affected by methylphenidate treatment.

**Key words:** Accommodation, attention deficit hyperactivity disorder, axial length, color vision, dopamine, methylphenidate hydrochloride

Attention deficit hyperactivity disorder (ADHD) is a mental disorder of childhood characterized by developmentally atypical inattention and/or hyperactivity and impulsiveness. It is the most common neurodevelopmental disorder in children.[1] Methylphenidate hydrochloride, a sympathomimetic amine, which blocks the reuptake mechanisms of dopamine and norepinephrine, is used in ADHD treatment.[2] As it has a stimulant compound, methylphenidate has many general side effects. Headache, appetite loss, and insomnia are the most common side effects.[3] This drug also has some ocular side effects including dry eyes, blurred vision, pupil dilatation, and accommodation disorders.

There exist some papers demonstrating ocular findings of patients with ADHD receiving methylphenidate treatment, and among these studies, only Larranaga-Fragoso et al. evaluated the temporary ocular changes in 14 children using methylphenidate.[4-6] The vast majority of the up-to-date literature is composed of case reports, small sample-sized cross-sectional studies. In addition, there are no data about the long-term effects of methylphenidate treatment on accommodation and color vision in children with ADHD. In this study, we investigated the 1-year effects of methylphenidate treatment on functional and structural ocular parameters including refraction, accommodation, IOP values, color vision, anterior and posterior segment findings.

**Methods**

The study was conducted in line with the dictates of the Declaration of Helsinki, approved by the local ethics committee (Institutional Review Board [IRB]: number: 01-13-18), and informed consent was obtained from parents of the participants.

In this prospective, observational study, children with newly diagnosed ADHD were included. All patients were diagnosed with ADHD by the same child and adolescent psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for ADHD.[7]

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Patients with any systemic disease, additional ocular pathology other than refractive errors, and history of ocular surgery were not included in the study. In addition, patients who were taking any medication other than methylphenidate were excluded from the study. All patients had not previously received any treatment for ADHD.

Before beginning the study, all patients underwent a detailed ophthalmic examination, and then methylphenidate treatment was started (1–1.25 mg/kg/day). All patients were examined by the same pediatric ophthalmologist in the 3rd, 6th, 9th, and 12th months of methylphenidate treatment.

Best-corrected visual acuity (BCVA) was measured for each eye on a decimal scale (Snellen chart). Cover/uncover test, prism, and alternate cover test for near and distance were performed to assess the presence and measurement of strabismus. Pupillary diameters were measured by an auto-refractometer (Nidek Ark 530A, Nidek Co., Ltd., Japan).

Refractive values of patients were evaluated by static retinoscopy. Static retinoscopy was performed for each eye when the patient was fixed on the largest letter on the Snellen chart at a 6 m distance. Spherical equivalent (SE) refraction values for each eye were noted. Spherical equivalent was calculated as follows: the power of sphere + (cylinder power/2).

Dynamic retinoscopy was performed using the monocular estimate method (MEM). This method, retinoscopy was performed for each eye, whereas the patient was reading the MEM cards clipped to the retinoscope at a 40 cm distance. Accommodation capacities of patients were accepted as the difference between spherical values of static and dynamic retinoscopy values.

Color vision was evaluated by the Turkish version of color vision test plates, which were developed by Wang K and Wang W. This text contains 66 plates to test red, green, yellow, and blue color vision. Additionally, color weakness can be classified into three degrees such as mild, moderate, and severe.

Anterior chamber depth (ACD) and axial length (AL) were measured by IOL Master 500 (Carl Zeiss Meditec AG, 07740 Jena Germany). After examination of the anterior segment by slit-lamp biomicroscopy, intraocular pressure (IOP) was measured by applanation tonometer (Tonopen).

After performing the above-mentioned examinations, cyclopentolate 1% one drop was used at 5-min intervals to eliminate accommodation and dilate the pupil. After 45 min, cycloplegic retinoscopy and fundus examination were performed.

While BCVA, color vision, and accommodation capacities were evaluated as functional parameters, pupil diameters, IOP, ACD, AL, and refractive values were evaluated as structural parameters.

**Statistical analysis**

Statistical analyses were performed using the SPSS software version 15. Distribution patterns of the variables were analyzed using visual (histograms) and analytical methods (Shapiro–Wilk test). Descriptive analyses were presented using means ± standard deviation for normally distributed variables and medians (interquartile range: 25–75) for non-normally distributed variables. Statistical analysis between the consecutive measurements of non-normally distributed variables was performed using the Friedman test. Wilcoxon test was performed to analyze the test of significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Statistical analysis between the consecutive measurements of normally distributed variables was performed using repeated-measures analysis of variance. Greenhouse–Geisser correction was used when the sphericity assumption was violated. A P value <0.05 was accepted as statistically significant.

**Results**

A total of 22 children were included in this study. There were 18 boys (81.8%) and 4 girls (18.2%). The mean age was 7.6 (6–13) years.

Before initiation of the treatment, BCVAs of all patients for both eyes were 0.0 logMAR, all of them had normal anterior and posterior segment examination findings. When the ocular alignments of patients were evaluated, all patients were orthophoric. None of the patients had complaints of headache or eye pain before drug treatment.

Non-cycloplegic and cycloplegic retinoscopy values of patients are shown in Table 1. The mean non-cycloplegic SE values for both eyes were mild myopic, and mean cycloplegic SE values for both eyes were mild hyperopic for each examination. During the follow-up, an increase in myopic values was observed in non-cycloplegic refraction, whereas a decrease in hyperopia was observed in cycloplegic values for both eyes. The increase in myopic values was 0.26 D for right eyes and 0.17 D for left eyes. The decrease in hyperopic values was 0.27 D for right eyes and 0.28 D for left eyes. BCVAs did not change during the treatment.

Other structural and functional parameters, including accommodation capacity, pupil diameter, IOP, ACD, and AL values are shown in Table 2. During the follow-up, while accommodation capacities were found to be decreased, AL values were found to be increased significantly for both eyes. Pupil diameter, IOP, and ACD values did not change significantly.

At the initial examination, 20 (90.9%) patients had blue–purple color weakness and 1 (4.5%) had green color weakness. When we evaluated the severity of blue–purple color weakness, 3 patients (13.6%) had mild, 10 (45.4%) had moderate, and 7 (31.8%) had a severe weakness. After 1 year of treatment, none of the patients had any change in color vision findings.

There was no complaint of headache, ocular pain, difficulty with near work, and change in ocular alignment after 1 year of treatment.

**Discussion**

In the present study, we evaluated the effects of methylphenidate hydrochloride both on the functional and structural ocular parameters. We found that most of the patients had blue–purple color weakness at baseline, depending on the action of dopamine on color vision, especially S cones. As a result of the 1-year follow-up of patients after methylphenidate treatment, an increase in myopic values of static retinoscopy and AL, and a decrease in hyperopic values of cycloplegic retinoscopy.
were found as structural changes. The only significant change in functional parameters was a decrease in accommodation capacity.

Methylphenidate hydrochloride is a sympathomimetic amine, acting on dopamine and norepinephrine transporters. Blocking these neurotransmitter transporters decreases the reuptake of dopamine and norepinephrine. This results in increased concentrations of these neurotransmitters in the synaptic region, and methylphenidate has therapeutic implications by these action mechanisms in patients with ADHD. Although accommodation disturbance, dry eye, blurred vision, and mydriasis are listed as ocular side effects of methylphenidate and amphetamine-based psychostimulants in the product monograph, there are not many clinical studies evaluating these side effects.

Different studies have examined refractive errors in patients with ADHD using methylphenidate treatment. \cite{2} The study by Fabian et al.\cite{3} and Gronlund et al.\cite{4} were case-control studies and the results of healthy and ADHD patients were compared. Similar SE values were found between the two groups in both studies. In the study of Gronlund et al.,\cite{4} although the mean period of drug usage was 19.5 months, children who had been on medication for only 2 months were also included in the study. Additionally, all these children were not taking methylphenidate treatment, whereas some were taking amphetamine treatment. In Fabian et al.'s study, although 56 patients were compared with 66 healthy controls, only 15 of the children in the ADHD group were receiving methylphenidate treatment. These data cannot be generalized as the results of methylphenidate treatment because of the cross-sectional design of the studies and not all patients used methylphenidate and those using methylphenidate had different periods of use. The study of Larranaga-Fragoso et al.\cite{6} is the only prospective study that evaluates the ocular effects of methylphenidate. In that study, 14 children with ADHD

| Table 1: Non-cycloplegic and cycloplegic retinoscopy values of patients at baseline and during the methylphenidate treatment at 3-month intervals |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Baseline        | Third month     | Sixth month     | Ninth month     | Twelfth month   | P               |                 |
| Non-cycloplegic (D) RE | -0.09±1.34     | -0.09±1.29     | -0.18±1.21     | -0.28±1.23     | -0.35±1.20     | 0.065           |                 |
|                 | (-0.62/+3.12)   | (-3.62/+2.12)   | (-3.25/+2.00)   | (-3.88/+1.50)   | (-3.50/+1.75)   |                 |                 |
|                 | -0.22±1.27     | -0.12±1.16     | -0.18±1.17     | -0.25±1.24     | -0.39±1.29     | 0.031           |                 |
|                 | (-3.75/+2.25)   | (-2.88/+2.00)   | (-2.88/+2.00)   | (-3.88/+2.00)   | (-4.00/+2.00)   |                 |                 |
| Cycloplegic (D) RE | +0.70±1.41     | +0.58±1.29     | +0.51±1.32     | +0.43±1.25     | +0.19±1.41     | <0.001          |                 |
|                 | (-2.50/+3.75)   | (-2.50/+2.38)   | (-2.88/+2.75)   | (-3.25/+2.38)   | (-3.25/+2.38)   |                 |                 |
|                 | +0.71±1.42     | +0.57±1.36     | +0.48±1.39     | +0.43±1.27     | +0.07±1.51     | <0.001          |                 |
|                 | (-2.62/+3.75)   | (-3.12/+2.38)   | (-2.88/+2.38)   | (-3.12/+2.25)   | (-4.00/+2.25)   |                 |                 |

D: Diopter, LE: left eye, RE: right eye. Refractive values are presented as mean±standard deviation (minimum-maximum)

| Table 2: Ocular parameters of patients at baseline and during the methylphenidate treatment at 3-month intervals |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Baseline        | Third month     | Sixth month     | Ninth month     | Twelfth month   | P               |                 |
| Accommodation capacity (Diopter) RE | 4.0 (2.5-6)     | 3.625 (2-6)     | 3.625 (2.5-6)   | 3.625 (1.5-6)   | 3.625 (1.25-6)  | 0.009           |                 |
|                 | 3.75 (2.5-6)    | 3.625 (2-6)     | 3.625 (2.5-6)   | 3.625 (1-6)     | 3.265 (1-6)     | 0.055           |                 |
| Pupil diameter (mm) RE | 5 (4-7)         | 5 (4-7)         | 5 (4-8)         | 5 (4-7)         | 5 (4-8)         | 0.221           |                 |
|                 | 5 (4-7)         | 5 (4-7)         | 5 (4-8)         | 5 (4-7)         | 5 (4-8)         | 0.221           |                 |
| c/d ratio RE | 0.26±0.13       | 0.28±0.14       | 0.28±0.14       | 0.29±0.14       | 0.29±0.14       | 0.005           |                 |
|                 | 0.25±0.15       | 0.27±0.16       | 0.27±0.16       | 0.28±0.16       | 0.29±0.16       | 0.002           |                 |
| IOP (mmHg) RE | 15.2±3.1        | 14.5±3.4        | 14.0±2.7        | 14.7±2.3        | 14.1±2.7        | 0.617           |                 |
|                 | 14.8±3.0        | 14.4±3.5        | 13.8±2.6        | 14.5±2.2        | 13.9±2.4        | 0.879           |                 |
| ACD (mm) RE | 3.53±0.23       | 3.56±0.24       | 3.55±0.24       | 3.55±0.23       | 3.55±0.23       | 0.780           |                 |
|                 | 3.54±0.24       | 3.57±0.24       | 3.58±0.25       | 3.58±0.25       | 3.58±0.23       | 0.190           |                 |
| AL (mm) RE | 22.97±0.97      | 23.03±0.99      | 23.08±0.99      | 23.13±0.98      | 23.19±0.98      | <0.001          |                 |
|                 | 22.96±0.95      | 23.01±0.96      | 23.05±0.96      | 23.10±0.95      | 23.15±0.95      | <0.001          |                 |

ACD: anterior chamber depth, AL: axial length, LE: left eye, RE: right eye. Ocular parameters are presented as mean±standard deviation or median (interquartile range 25-75)
were evaluated before the treatment of methylphenidate and after the third and ninth months of treatment. They found mild myopic values for non-cycloplegic refraction and mild hyperopic values for cycloplegic refraction. They did not report a significant difference in the SE values between baseline and the ninth-month examination. Similar to the study of Larranaga-Fragoso, we evaluated the effects of methylphenidate treatment on ocular parameters. However, our study population had more subjects (22 patients), and we followed the patients for 1 year with 3-month intervals. Similar to the previous study, we found mild myopic values for non-cycloplegic refraction and mild hyperopic values for cycloplegic refraction. Additionally, there was a significant increase in myopic values for non-cycloplegic refraction and a significant decrease in hyperopic values for cycloplegic refraction for both eyes during the follow-up period. As already known, a myopic shift can be seen with age. Besides, it was shown that a decrease in retinal dopamine concentrations caused a deprivation of myopia or lens-induced myopia. Although methylphenidate increases the concentration of dopamine in the presynaptic region, it is not known whether this increase occurs in the retina. If retinal dopamine levels increase with methylphenidate treatment, refractive value changes in these patients may not only be age-related but may also be affected by treatment. Therefore, the myopic shift observed with age may be lesser in patients treated with methylphenidate. It would be appropriate to compare these children with the healthy control group to understand whether 1-year follow-up change in SE values is the result of the effect of methylphenidate on retinal dopamine or it is only due to the age-related changes.

Another reported ocular side effect of methylphenidate is accommodation disorders. Fabian et al. did not find any difference between children with the diagnosis of ADHD and the healthy control group in terms of accommodation amplitudes. However, only 27% of children were under methylphenidate treatment. Soyer et al. reported a 9-year-old child with a significant decrease in visual acuity secondary to accommodation disorder after being treated with methylphenidate and lisdexamfetamine. Our study is the first study that evaluated the effect of methylphenidate on accommodation amplitude. We found a significant difference between the accommodation capacities before and after 12 months of methylphenidate usage. Although a decrease in accommodation amplitude was observed with drug usage in these children, they did not complain about any blurred vision because they could still accommodate. This finding suggests that children with a longer duration of methylphenidate treatment may develop blurred vision due to a decrease in accommodation capacities.

One of the conditions that should be considered during treatment with stimulants such as methylphenidate, is the presence of glaucoma. Because of their weak anticholinergic effect and inhibition of the reuptake of noradrenaline in the synaptic region, they can induce angle-closure or worsen chronic angle-closure glaucoma. In addition, these drugs have been reported to cause transient elevation of IOP without causing angle closure. Lu et al. reported a 10-year-old boy with bilateral open-angle glaucoma during the treatment with methylphenidate. There was no difference between the IOP values and c/d ratios before and 9 months after the treatment in the study of Larranaga-Fragoso. However, they found a decrease in ACD values between the baseline and ninth-month examinations, and they suggested to be careful about angle closure during the treatment. In our study, similar to the study of Larranaga-Fragoso et al., we did not find any difference between IOP values before and after methylphenidate usage for 12 months. We also did not find any significant difference between baseline and 12th-month ACD values.

Previous studies showed that ADHD has been associated with color perception problems. These patients had impaired performance on processing colored stimuli, particularly for blue color and they responded more slowly to blue stimulus shapes compared to healthy controls. The pathophysiology of blue color perception problems in these patients is thought to be related to retinal dopamine deficiency. Dopamine is one of the major neurotransmitters in the retina and it plays a role in the color perception mechanism. A decrease in retinal dopamine affects the short-wavelength chromatic pathway, and blue–yellow color discrimination is impaired. It is known that different conditions that cause changes in the retinal dopamine levels such as Parkinson’s disease, Huntington’s disease, Tourette syndrome, cocaine withdrawal, and normal aging, are associated with blue–yellow color vision loss. Because the mechanism of methylphenidate increases dopamine levels, we evaluated the effect of treatment on color vision. We found that 90.9% of patients had blue–purple color vision weakness at baseline. This finding is consistent with the decrease in dopamine levels observed in patients with ADHD. However, none of the patients had any change in color vision test at the 12th month of treatment. This may be because the methylphenidate dose does not increase the level of retinal dopamine.

**Conclusion**

This study suggests that patients with ADHD may have blue color vision deficiencies because of the decreased retinal dopamine levels. Additionally, structural, and ocular parameters, especially accommodation capacity, may be affected by methylphenidate treatment. Therefore, ocular side effects should be taken into consideration, and ophthalmic examination of patients should be performed at regular intervals during methylphenidate treatment.

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**Conflicts of interest**

There are no conflicts of interest.

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