

# The Effect of Methylphenidate on the Hearing of Children with Attention Deficit Hyperactivity Disorder

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## Abstract

**Introduction** There has been a sudden idiopathic hearing loss case presented after methylphenidate treatment in a child with attention deficit hyperactivity disorder (ADHD).

**Objective** This study was performed to reveal the probable ototoxic side effects of methylphenidate use in patients with ADHD.

**Methods** Thirty pediatric patients with ADHD were included in the study. Pure tone audiometry, speech discrimination scores, waves I, III, V absolute latencies and waves I-III, I-V, III-V interpeak latencies at the 80 dB nHL intensity after click stimulus auditory brainstem response (ABR) results were compared before and 3 months after methylphenidate treatment.

**Results** There were no statistically significant difference between pretreatment and posttreatment pure tone and speech audiometry findings and ABR results ( $p > 0.05$  for all parameters).

**Conclusion** Methylphenidate can be regarded as a safe drug regarding ototoxic side effects. Additional studies with a larger sample size and longer follow-up may be needed.

## Keywords

- ▶ methylphenidate
- ▶ attention deficit hyperactivity disorder
- ▶ hearing

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral developmental disease characterized by symptoms of inattention and/or hyperactivity inconsistent with developmental level affecting ~ 3–5% of school aged children.<sup>1</sup> It is the most frequent pediatric neurodevelopmental disorder with a prevalence of 3–12%.<sup>2</sup> It is not only a disease but a social problem, since patients have significant functional disabilities such as lower school success, academic underachievement, difficulties in interpersonal relationships and low self-esteem. It affects the patients' capacity for cognition, perception and attention. Early man-

agement is important because untreated patients have a tendency to substance abuse and antisocial behavior later in life.<sup>1</sup> Exact underlying pathogenesis is not known, a primary deficit in the inhibitory control due to dysfunction in the prefrontal cortex was supposed to be the main cause of hyperactivity or impulsive behavior. Imaging studies showed that there are subtle anomalies in caudate and corpus callosum size and shape with reduction in the right frontal area. In the metabolic studies with positron emission tomography (PET) imaging, abnormalities of cerebral metabolism in the prefrontal and premotor areas of frontal cortex have been detected. As a result, abnormalities in the frontal network (frontostriatal dysfunction) were supposed to be the

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main underlying cause.<sup>3</sup> A cerebellar insult was also proposed, since children with ADHD could hardly perform tasks requiring time discrimination and estimation, which are mainly controlled by cerebellum.<sup>4</sup>

The main first-line treatment protocol for ADHD is the central nervous system (CNS) stimulant pharmacotherapy, including methylphenidate (MTP) and amphetamine. Methylphenidate is the most common prescribed medication in cases of ADHD. The exact mechanism of its beneficial effect for ADHD is not known, but it blocks presynaptic dopamine and norepinephrine reuptake, while also inhibiting monoamine oxidase.<sup>4</sup> It is effective as a first-line treatment protocol in 75–80% of ADHD cases.<sup>5</sup> The Cochrane database system review of 2015<sup>6</sup> pointed out that MTP may improve teacher-reported ADHD symptoms, teacher-reported general behavior and parent-reported quality of life among children and adolescents diagnosed with ADHD. It seems to be a paradox for using a psychostimulant in the treatment of hyperactive patients, but actually, it is the child's *control systems* that are being stimulated.<sup>7</sup>

Methylphenidate is generally a safe drug, with common adverse effects being nausea, stomach pain, decreased appetite, insomnia, and headache. Transient motor tics, chronic tics, dysphoria, mood lability and hallucinations are seen less commonly. Cardiovascular effects with sudden unexplained death may also be seen very rarely.<sup>4</sup> Adverse effects on growth and weight gain are controversial.<sup>5</sup>

Recently, Karapinar et al<sup>8</sup> presented a pediatric patient having sudden idiopathic hearing loss 24 hour after usage of MTP for ADHD. Hearing loss in children may mimic symptoms of ADHD, such as inattention, and it can complicate the treatment options when seen together with ADHD.<sup>9</sup> Since the effect of MTP on the auditory pathway is not known, in this first study, we aimed to show the effects of MTP on hearing and auditory pathways by analyzing the pure tone audiometry, speech discrimination, and auditory brainstem response (ABR) results.

## Materials and Methods

Local ethical committee approval was acquired for the present study. Thirty patients diagnosed with ADHD according to the diagnostic and statistical manual of mental disorders (DSM-5)<sup>10</sup> criteria were taken to the current study. There were 17 (56.6%) boys and 13 (43.4%) girls. The mean age was 11.06 (ranging from 6 to 15). All of the patients were treated with the osmotic release oral system MTP medication, brand name Concerta (Janssen Pharmaceuticals Inc., Beerse, Belgium). Otoscopic examinations to all of them were performed by the same physician before the treatment and on the third month control visits. Tympanometry was performed on all patients before audiologic testing. Only the ones with normal otoscopic findings and normal tympanometry (Type A) were taken to the current study. The patients with hearing loss, ototoxic medication use, and previous ear surgery history were excluded. Pure tone audiometry and speech discrimination scores, tested using the AC40 clinical audiometer (Interacoustics, Middelfart, Denmark), as well as

click stimulus ABRs, using BERA 4000 (Homoth Medizin- elektronik GmbH&Co, Hamburg, Germany) were performed on all patients before and 3 months after the treatment. Pure tone averages were calculated using means of four tone (0.5, 1, 2, 4 kHz) frequencies. In the ABR results, waves I, III, V absolute latencies and waves I-III, I-V, III-V interpeak latencies at the 80 dB nHL intensity were assessed. The pretreatment results of each parameter were compared with the posttreatment results statistically.

## Statistical Analysis

All continuous measurements in the pre- and posttreatment pure tone audiometry and speech discrimination results were tested for normality using the Shapiro-Wilk test. The significance value was set at  $p < 0.05$ . As measurements did not display a normal distribution, non-parametric method Wilcoxon signed-rank test was used for independent groups' comparison.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.5 (SPSS, Inc, Chicago, IL). The significance value was set at  $p < 0.05$ .

## Results

All the values of air and bone conduction threshold levels were within their normal limits ( $\leq 15$  dB),<sup>11</sup> both in the pre- and posttreatment results. There was no statistically significant difference between the average pure tone air conduction and the bone conduction threshold levels after treatment in either the right or left ears ( $p = 0.305$  for right ears and  $p = 0.883$  for left ears in the air conduction levels,  $p = 0.726$  for right ears and  $p = 0.589$  for left ears in the bone conduction threshold levels). There was no statistically significant difference for speech discrimination scores for right and left ears when pre- and post-treatment values were compared ( $p = 0.475$  for right ears and  $p = 0.829$  for left ears). Comparison of pure tone audiometry and speech discrimination scores was summarized in ►Table 1.

When ABR results were compared, the Wilcoxon signed-rank test showed no statistically significant difference between pre- and post-treatment values of right ears' wave I absolute latencies. ( $p = 0.226$ ). The paired samples *t*-test also showed that there were no statistically significant differences between the pre- and post-treatment results of other ABR parameters (►Table 2).

## Discussion

In this study, we found that MTP therapy for children with ADHD had no statistically significant effect on pure tone audiometry, speech audiometry and ABR findings.

Hearing and speech development is important for behavioral stability. Children with hearing loss were reported to have significantly more conduct and hyperactivity problems compared with their normal hearing controls.<sup>12</sup> Beside its direct effect, the adverse effect of hearing loss on the language skills can cause communication and behavioral

**Table 1** Comparison of pretreatment and posttreatment results of pure tone audiometry and speech discrimination scores for right and left ears

Parameter	Mean	SD	<i>p</i>
Pretreatment right ears' average air conduction threshold	11.86	3.72	0.305
Posttreatment right ears' average air conduction threshold	10.66	3.67	
Pretreatment right ears' average bone conduction threshold	3.66	3.45	0.726
Posttreatment right ears' average bone conduction threshold	3.43	2.58	
Pretreatment right ears' speech discrimination scores	98.5	2.67	0.475
Posttreatment right ears' speech discrimination scores	98	4.03	
Pretreatment left ears' average air conduction threshold	10.23	2.56	0.883
Posttreatment left ears' average air conduction threshold	10.16	3.99	
Pretreatment left ears' average bone conduction threshold	3.83	3.39	0.589
Posttreatment left ears' average bone conduction threshold	3.43	2.52	
Pretreatment left ears' speech discrimination scores	99	2.91	0.829
Posttreatment left ears' speech discrimination scores	99.4	1.4	

Abbreviations: SD, standard deviation.

problems.<sup>12</sup> A slightly higher incidence of ADHD is seen among deaf patients ranging from 3.5–38.7%, especially the ones with acquired hearing loss are at greater risk.<sup>7,13</sup> Parasnis et al<sup>13</sup> postulated that decrement in the auditory

perception in the CNS can cause reorganization of the visual attention from central to peripheral so that individuals can be alert to their surroundings. This decreases the central visual attention scores and impulsive response behavior also

**Table 2** Comparison of pretreatment and posttreatment results of auditory brainstem responses with paired samples *t*-test

Paired samples <i>t</i> test							
	Parameter (millisecond)	Paired differences					Sig. (2-tailed)
		Mean	SD	SE Mean	95% CI of the difference		
					Lower	Upper	
Pair 1	Pretreatment-Posttreatment LE wave I absolute latency	0.02000	0.11371	0.02076	-0.02246	0.06246	0.343
Pair 2	Pretreatment-Posttreatment LE wave III absolute latency	0.00667	0.11171	0.02039	-0.03504	0.04838	0.746
Pair 3	Pretreatment-Posttreatment LE wave V absolute latency	0.03300	0.15322	0.02797	-0.02421	0.09021	0.248
Pair 4	Pretreatment-Posttreatment LE wave I-III interpeak latency	-0.01267	0.15200	0.02775	-0.06942	0.04409	0.651
Pair 5	Pretreatment-Posttreatment LE wave I-V interpeak latency	0.01100	0.19021	0.03473	-0.06003	0.08203	0.754
Pair 6	Pretreatment-Posttreatment LE wave III-V interpeak latency	0.02433	0.14626	0.02670	0.03028	0.07895	0.370
Pair 7	Pretreatment-Posttreatment RE wave III absolute latency	-0.04933	0.17261	0.03151	-0.11379	0.01512	0.128
Pair 8	Pretreatment-Posttreatment RE wave V absolute latency	-0.04867	0.19894	0.03632	-0.12295	0.02562	0.191
Pair 9	Pretreatment-Posttreatment RE wave I-III interpeak latency	-0.00667	0.18087	0.03302	-0.07420	0.06087	0.841
Pair 10	Pretreatment-Posttreatment RE wave I-V interpeak latency	-0.00767	0.23312	0.04256	-0.09471	0.07938	0.858
Pair 11	Pretreatment-Posttreatment RE wave III-V interpeak latency	-0.00033	0.14736	0.02690	-0.05536	0.05469	0.990

Abbreviations: CI, confidence interval; LE, left ear; RE, right ear; SD, standard deviation; SE, standard error.

increase in these individuals. Children with inattention can show functional hearing loss properties without an actual pathology.<sup>14</sup> Moreover, hearing loss accompanying ADHD can complicate the treatment with exaggerating symptoms and need multidisciplinary approach.<sup>7,9</sup> In this manner, if there is an adverse effect of MTP on hearing during the treatment of ADHD, this must be well known.

Methylphenidate is a 1:1 mixture of two isomers, dextro-threo-methylphenidate and levo-threo-methylphenidate. When taken orally, it goes under enteric and hepatic reesterification process to ritalinic acid. The D-isomer of MTP is the pharmacologically active part.<sup>15</sup> It is a sympathomimetic drug that has similar morphology with endogenous catecholamines. Methylphenidate is thought to act in the CNS by enhancing noradrenergic and dopaminergic neurotransmission and blocking presynaptic reuptake of these transmitters; it also inhibits monoamine oxidase.<sup>3,4</sup> At the end, it increases the extracellular dopamine and noradrenaline concentration in the prefrontal cortex, striatum and nucleus accumbens. With up-regulated dopamine transporter activity, it also attenuates the striatal neural activity.<sup>16</sup> Central acting property of MTP was shown with functional magnetic resonance imaging studies that single dose application increased the frontostriatal network, mostly the inferior frontal gyrus.<sup>17</sup> With positron emission tomography (PET) studies, it was demonstrated that MTP primarily increased the norepinephrine concentration in the thalamus and locus cereleus, whereas it enhanced dopamine transmission mostly in the striatum.<sup>18,19</sup> Methylphenidate also normalizes the impaired auditory information processing in ADHD with normalizing the auditory event related potentials.<sup>20</sup>

Psychostimulants including MTP are among the safest drugs in the treatment of ADHD. Most of the side effects of stimulant treatment are dose dependent, mild to moderate in severity and decrease with reduction of the dose and changing the timing of the medication. They commonly subside in the first 1 to 2 weeks of treatment, whereas the adverse effects are also the leading cause of medication interruption.<sup>21</sup> The most common side effects of MTP are nausea, stomach pain, decreased appetite, insomnia, and headache.<sup>4</sup> Less commonly seen are tics, dysphoria, mood lability and hallucinations.<sup>4</sup> Cardiovascular side effects are seen very rarely, tachycardia and palpitation are seen in up to 5% of cases.<sup>22</sup> The ear, nose and throat side effects of MTP include cough, nasal congestion, nasopharyngitis, pharyngitis and rhinitis, which are rarely seen. Dry mouth is seen more commonly, with up to 12–24% of cases.<sup>22</sup> Regarding otologic adverse effects, otitis media<sup>23</sup> and sudden idiopathic hearing loss<sup>8</sup> were reported. In the case report presented by Karapinar et al,<sup>8</sup> an 8-year-old girl admitted with sudden sensorineural hearing loss, 24 hours after the initiation of treatment with MTP. The probable underlying causes were excluded with routine blood tests and magnetic resonance imaging studies. Despite full dose steroid treatment and hyperbaric oxygen therapy, significant improvement in the affected ear could not be achieved. In a recent questionnaire study investigating the adverse effects of medications used in

ADHD treatment,<sup>24</sup> 2 out of 200 children (1%) with MTP monotherapy and 1 out of 200 children (0.5%) with MTP + melatonin therapy were postulated to have hearing problems during treatment, according to their parents, but the type and degree of the hearing losses and their relationship with the treatment were not given. Since the main effect of MTP is on the CNS, the effect of treatment on the retrocochlear auditory pathway was also investigated in our study. In the ABR results, a normal wave I latency with delayed wave I-III or wave I-V interpeak latency suggests a retrocochlear pathology; speech discrimination scores are also disproportionately reduced compared with pure tone average threshold values in the audiometry.<sup>25</sup> We found that all of the results of pure tone and speech audiometries were within the normal limits and there was no statistically significant difference after the therapy with MTP. Retrocochlear pathway investigation with wave I-III, wave I-V interpeak latencies and speech discrimination scores did not present any adverse effects after treatment. Although the hearing loss was attributed to the MTP medication, the case report presented by Karapinar et al<sup>8</sup> may be a coincidence of MTP therapy and sudden hearing loss in the same patient. Another possibility is the endolymphatic hydrops causing sensorineural hearing loss, because the patient had aural fullness and the hearing loss had progressively worsened. Finally, an accompanying perilymph fistula as a reason of progressive sensorineural hearing loss could not be excluded.

## Conclusion

In conclusion, this preliminary report may present that MTP can be regarded as a safe drug without adverse effects on pure tone, speech audiometry findings and auditory brainstem response results in patients with ADHD. Additional studies with a larger number of patients and longer follow-up periods or experimental studies with cochlear electron microscopic findings may be more supportive for investigating its ototoxic side effects.

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