DOI: 10.5455/bcp.20120731061626

Possible Methylphenidate Related Hoarseness and Disturbances of Voice Quality: Two Pediatric Cases

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ÖZET:

Metilfenidat ile olası ilişkili ses kısıklığı ve ses kalitesinde bozulma: iki çocuk olgu

Dikkat eksikliği hiperaktivite bozukluğu tedavisinde kullanılan metilfenidat, çocuklarda genel olarak güvenli bir ilaç olsa da, özellikle büyüme gelişme, kardiyovasküler sistem, iştah ve uyku kalitesi üzerine olan yan etkilerinin dikkatli takibi gereklidir. Bu olgu sunumunda metilfenidat kullanımı ile ilişkili, ilaç kesimine yol açan ses kalitesinde bozulma, ses kısıklığı geliştiren iki erkek çocuğunu sunmaktayız. Bu iki olgudaki disfonik bulgular, metilfenidatın santral sinir sistemi ve sempatik sinir sistemi üzerine olan direkt etkileri ile ilişkili olabilir.

Anahtar sözcükler: Metilfenidat, dikkat eksikliği hiperaktivite bozukluğu, ses bozuklukları, disfoni, ses kısıklığı

Klinik Psikofarmakoloji Bülteni 2012;22(3):278-82

ABSTRACT:

Possible methylphenidate related hoarseness and disturbances of voice quality: two pediatric cases

Although methylphenidate is generally a safe drug in children for treatment of attention deficit hyperactivity disorder, it is necessary to monitor carefully its side effects especially on growth and development, the cardiovascular system, appetite and quality of sleep. In this case report, we present two male children who developed disturbances in voice quality and hoarseness associated with methylphenidate use, which required drug discontinuation. Dysphonic symptoms in these two children may be related to methylphenidate's direct effects on the central and sympathetic nervous systems.

Key words: methylphenidate, attention deficit hyperactivity disorder, voice disorders, dysphonia, hoarseness

Bulletin of Clinical Psychopharmacology 2012;22(3):278-82

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Gönderme tarihi / Date of submission: 19 Aralık 2011 / December 19, 2011

Kabul tarihi / Date of acceptance: 31 Temmuz 2012 / July 31, 2012

Bağıntı beyanı:
O.Y, A.A.A, B.A.S, T.T.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
O.Y, A.A.A, B.A.S, T.T.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder characterized by attention deficit and/or impulsivity-hyperactivity and emotional instability (1).

Methylphenidate is the most frequently prescribed drug for the children with ADHD (2). Methylphenidate is a generally safe drug, available for many years for children and adolescents. The most common side effects of methylphenidate are; insomnia, loss of appetite, weight loss, abdominal pain and headache (3).

Hyperactivity-impulsivity symptoms of ADHD with respect to speech pattern are; interrupting mutual conversation of others, talking loudly, not being able to play silently, answering before the completion of questions, excessive talking, nonsense and inappropriate vocalizations. Symptoms that can be seen related with attention deficit are; unable to carry on conversations and answering inappropriately. Although there are many studies investigating developmental language and speech disorders in chidren with ADHD, there are little or no studies examining vocal and acoustic parameters in this patient group (4).

In a study conducted by Hamdan and his research team, published in 2007; it was found that children with ADHD speak louder, experience further hoarseness, puffiness-shortness of breath (audible air turbulance), vocal strain (hyperfunctional voice/dysphonia) and had lower fundamental voice frequency (coarse sound). According to researchers, these findings can be related with risk factors for childhood voice disorders (dysphonia) like the misuse and abuse of voice which are seen more common in ADHD (4).

In an internet website (ehealth-me) supported by American Food and Drug Administration (FDA) where individuals give feedback about side effects of the drugs they use, among 245 people who reported side effects associated with methylphenidate only one individual (0.41%) reported hoarseness and disturbance of voice quality. However these datas are scientifically controversial, as they are based on subjective individual observations (5). As we know, two cases we report in this presentation are the first report of methylphenidate related disturbance of voice quality in the scientific literature.

CASE 1

10 years old, fifth grade elementary school male student, referred to third grade health institution (university hospital) with the guidance of his teacher, with the complaints of attention deficit, distractibility in class, excessive talking in the lessons, restlessness on his seat, able to complate his homework in a long time, not able to study for a long time. Patient was living in a metropolitan area with his high school graduate mother who doesn't work, university graduate father who works as sergeant in the army and high school student older sister. According to anamnesis given by father; patient had hyperactivity and susceptibility to accidents, especially prominent after he began walking. Also in preschool class his teachers complaint about his hyperkinesis. Just after he began to elementary school his teacher complaint that he was generally standing up inappropriately, making unsense vocalizations, unable to listen teacher, daydreaming in the classroom. He was able to complete his homeworks in a long time which can be actually completed in a short time, because of his continual breaks, wandering and daydreaming. In the fifth grade his academic success decreased significantly.

The patient was diagnosed as ADHD and short acting, immediate release methylphenidate was prescribed with a daily dosage of 5 mgr. twice a day. In the first control after the two weeks of initial treatment, it was observed that although there had been significant improvement in his attention deficit symptoms, as a side effect; disturbance of voice quality, hoarseness and bifurcation-strain and over vibration of voice had been observed by both teacher and the family after the drug initiation. His teacher noticed that condition when he made him read passages in the class and his family realised that side effect as hoarseness and reduction in the height/amplitude of his voice just after he had taken his evening dose. His parents who linked that condition with medication, didn't observe any symptom when the child didn't take the drug. Patient was consulted to otolaryngology department. In the consultation laryngitis or other organic conditions causing hoaseness hadn't been observed with physical and endoscopic examination. So as the morning dose had been taken by the child, hoarseness and reduction in the voice amplitude was evident during the first psychiatric control. One day after child and his parents were appointed without getting the morning dose and no symptom was observed at first and after half an hour we made the child take the drug in our outpatient clinic, and this time hoarseness was evident. His voice quality returned to normal, three hours after he had taken the drug. Methylphenidate was discontinued as there had been significant disturbance of his voice. Atomoxetine with the dosage of 18 mgr/day was prescribed. The dosage of atomoxetine was gradually increased to 40 mgr/day in two months. Patient improved significantly with this treatment without any important side effect.

CASE 2

11 years old, sixth grade elementary school male student attended to second grade health institution (public hospital) with the recommendation of guidance counselor of his school for the symptoms of forgetfulness, academic failure, attention deficit, daydreaming, not able to participate in lesson, difficulty of understanding instructions, restlessness on his seat and shyness. He was the fourth child of high school graduate father who works as official and elementary school graduate mother. Patient whose motor development was normal, always had been overactive compared to his peers. The patient who had slower speech development

compared to his elder siblings began stuttering at the age of 3,5. His fluent language disorder continued ondulantly until he started to preschool class and in this period his expressive language abilities gradually rose but his phonological problems were stil evident. His phonological problems gradually disappeared during elementary school years. He was among one of the last students to learn reading and writing in the first grade. His teacher stated his parents that he had lower academic abilities than his peers, because of learning-perception difficulties and attention disorder. Although he had no significant conduct problems, he was always restless on his seat and interested and distracted with something other than lesson and seemed to be absent-minded in the classroom. At the begining his writing was described as unreadeble and had scrambled and skipped letters. As his speed and pace of reading had been slower than his classmates, with time he reached their pace. He was always in need of supervision when he was studying, otherwise it was taking very long time to finish his homework. It took long time for him to memorize multiplication table, however his mathematic was always better than his other lessons. He had difficulty particullarly in foreign language class. His memory, memorization and reciting was weak. He always confused directions and had clumsiness. He was disorganized and untidy when he was studying. He was constantly forgetting or losing his possessions in the school. He was always described as avoidant and shy by teachers. He wasn't able to come close to his classmates. He was getting too excited and anxious when teacher wanted him to answer the questions. With the sixth grade his academic success decreased significantly.

The patient was diagnosed with specific learning disorder, ADHD and social anxiety disorder and prescribed OROS-methylphenidate with the daily dosage of 18 mgr. At the second week routine control, he was experiencing side effects like significant appetite loss, drowsiness, however disturbance of voice and hoarseness were the main side effects that the family pointed out. These stated side effects have occured on everyday since the first day of the medication and haven't been observed on drug holidays and always have started short after the single morning dose and decraesed gradually to diner time and disappeared until before the bed time. The patient was referred to otolarngology department. In the consultation no organic pathology was detected with respect to clinical and endoscopic observation. OROS-methylphenidate was discontinued and atomoxetine was prescribed with the dosage of 18 mgr/day. In the course of treatment the dosage was gradually raised to 40 mgr/day. Attention deficit, difficulty of concentration significantly decreased and his academic achievement significantly increased. He had no symptom of hoarseness and disturbance of voice quality. The patient is stil being followed with the same drug treatment in our outpatient clinic.

DISCUSSION

3% and 9% of the general pediatric population has voice disorder symptomatology. To diagnose voice disorder in children, voice of the child shouldn't be appropriate to his age and gender, in respect to height/amplitude, pitch and quality of voice (6).

Although abuse of voice is seen in ADHD (4), ADHD is not generally perceived as a risk factor for childhood voice disorders (4,7). Hearing problems, upper respiratory tract infections, living in a large family, living in a noisy home and environment, need to talk loudly, competition for talking and speech duration, chronic cough, excessive throat clearing increase the risk of childhood voice disorders (7).

In the differential diagnosis of hoarseness in children neurological (paresis/paralysis, neuromuscular diseases, central nervous system injury, spasmodic dysphonia), inflammatory/infectious (laryngitis, gastroesophageal reflux, rheumatoid arthritis), neoplastic/anatomic (nodule, polip, granuloma, cysts, papillomatosis, laryngeal web), traumatic, iatrogenic causes involve. Also asthma, chronic cough, cystic fibrosis, synusitis, postnasal drip, adenoid vegetation, juvenile rheumatoid arthritis, hypothyroidism can cause impairment of voice (8).

In these two cases we presented, we didn't consider any stated organic causes above, which leads to impairment of voice quality and hoarseness according to otolaryngological examination and endoscopic investigation. The cases presented hoarseness and disturbance of voice quality, that began on the first day of methylphenidate treatment and that didn't relapse with drug discontinuation and that were clearly evident during the action of immediately release methylphenidate and OROS-methylphenidate (respectively 3-4 hours and 12 hours) (9). These symptoms weren't based on subjective observation of an individual, were based on observation of

two and more individuals, also the variation in the quality of voice can be observed in the outpatient clinic when the drug was taken and not taken. According to all these symptoms and observations, we think that hoarseness, dysphonic symptoms are related with methylphenidate use in these two cases. Observed symptoms were as severe as need to stop the medication and were disturbing quality of life significantly in both cases.

According to the Naranjo 1981 classification, +5 point was calculated (+5-8 possibly related side effect) for the hoarseness and impairment of voice quality associated with methylphenidate for these patients (10). In the both cases side effect started with drug use and symptoms occured just after the drug intake. Also in the both cases there hasn't been any side effect on the drug holidays and side effects were relapsing after the recurrent doses. All these signs indicate that in the both cases disturbance of voice quality and hoarseness is possibly related with methlphenidate.

One of the well known side effect of methylphenidate is; leading to development and exacerbation of tics (9,11). Although there has been rarely reported vocal tics which lead to varied usage of voice (12), we didn't consider tic disorder for the differential diagnosis. We disregard vocal tic or compulsive behaviour like tic for differential diagnosis because of the; absent of the simple-uncomplicated motor and vocal tics, hoarseness which continues during drug action, non-episodic course, disappearence of dysphonia when the drug action diminishes, absent of the urgency sensation, not having somatosensory phenomena urging to exhibit tics and absent of the cognitive component. It is known that increased anxiety levels can cause disturbance of voice quality and functional dysphonia (12). As methylphenidate has a anxiogenic profile (9,11), it can be assumed that disturbance of voice quality can be related with increased anxiety, but neither cases exhibited autonomic, physical and mental symptoms supporting heightened anxiety, neither we have enough evidence to expose this linkage.

As we know in the medical literature, there has been a single research to date investigating psychostimulants and their effect on vocal-acoustic parameters in which Congologlu and his colleagues determined decreased fundamental frequency of voice and related variance of speech resonance and increase in the absolute jitter levels with methylphenidate use on children with ADHD. According to the investigators methlyphenidate can adjust and tune the voice with the suppression of motor speech centrally (with its action on brain) (13). Interestingly symptoms of our patients are consistent with Congologlu's research findings, because decreased fundamental frequency (coarsening of voice) and increased jitter levels (bifurcation of voice and increase in vibrancy) (13) might explain coarsening and bifurcation and over-vibration of voice and hoarseness in which our cases exhibit during methylphenidate's time course of drug action.

In these two cases disturbance of voice quality during methylphenidate use can be directly related with methylphenidate's direct effect on central nervous and sympathetic nervous systems (9,14). Developing and disappearing dysphonic symptoms during the time course of drug action supports this view. But it is difficult to conclure about the pathophysiology of this condition. Additionally findigs of autonomic dysfunction anomalies like parasympathetic dominancy in children with ADHD which can be balanced with medication for ADHD (14), complicates the utter interpretation. It is interesting that we couldn't observe hoarseness with atomoxetine which has similar peripheric autonomic effects (15,16). Although not a psychostimulant, atomoxetine also acts through central noradrenaline and indirectly through dopamine similar to methylphenidate (17), but methylphenidate acts on prefrontal cortex and many other brain regions more extensively and more broadly, however effects of atomoxetine are seemed to be restricted with prefrontal cortex and cerebellum (17,18). Due to central variation of action, atomoxetine may not cause hoarseness on these cases. Although methylphenidate and atomoxetine has similar periferic autonomic-sympathetic effects, their effect sizes might be different too (9,14-16), and this variation may explain the observed disturbance of voice quality with methylphenidate but not with atomoxetine.

As we know this case report is the first paper, reporting hoarseness and disturbance of voice quality associated with methylphenidate. Researchs investigating side effect and safety profile of drugs used for ADHD (atomoxetine, amphetamine and derivates, methylphenidate, modafinil) have not yet reported disturbance of voice quality and hoarseness to date (11).

Clinicians must keep in mind about methylphenidate related disturbance of voice quality as a rare side effect and only if organic and other causes are excluded, must be considered for differential diagnosis.

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