Birth and Growth Medical Journal
2025;34(3):128-131. doi:10.25753/BirthGrowthMJ.v34.i3.26248

CLINICAL CASE REPORTS

Methylphenidate-induced dyskinesia, an underrecognized adverse effect In ADHD treatment

Teresa Pinheiro[1] , Carla Maia[2]

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is one of the leading mental and behavioral disorders in childhood and adolescence and remains a clinical challenge for healthcare professionals. Methylphenidate (MPH) is the first-line pharmacological treatment option for children over six years of age, but it is not without side effects. While the most common are mild and reversible upon therapy discontinuation, less recognized complications may occur, such as MPH-induced dyskinesia. Dyskinesia may present acutely, with the sudden onset of involuntary movements shortly after MPH administration (acute dyskinesia) or tardively, developing gradually after weeks of treatment (tardive dyskinesia). The cause of this drug-induced effect remains unclear. Herein is reported the first case in the literature of a patient with ADHD who developed symptoms of acute and tardive dyskinesia while receiving MPH. This case highlights the importance of awareness and early recognition of this rare but potentially stigmatizing adverse effect.

Keywords: attention deficit hyperactivity disorder; dyskinesia; methylphenidate; Pediatrics

1. Department of Pediatrics and Neonatology, Unidade Local de Saúde Entre-o-Douro e Vouga. 4520-211 Santa Maria da Feira, Portugal. ana.pinheiro@ulsedv.min-saude.pt
2. Department of Child and Adolescent Psychiatry, Unidade Local de Saúde Tâmega e Sousa. 4564-007 Guilhufe, Portugal. 60607@ulsts.min-saude.pt

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a leading mental and behavioral disorder in childhood and adolescence and remains a clinical challenge both due to the difficulty in correctly evaluating and diagnosing the condition and in prescribing the right treatment option.[1] The estimated global prevalence in children varies between 5-7.2%,[2-4] with the variation attributed to different research methodologies and age groups, and to changes in diagnostic criteria over the years.[2] Surveys in the United States of America have reported a prevalence of 9.4% in children aged 2-17 years.[2] Studies in Europe reported a prevalence of 8.74%.[5] A recent study evaluated the incidence of ADHD among children in Navarra, Spain, from 2003 to 2019 and reported an incidence ranging from 4.23/1000 in children aged seven years to 1.71/1000 in adolescents aged seventeen years in 2019. The authors reported an increase of 77% from 2003 to 2009, followed by a plateau and a decrease since 2015, reaching rates in 2019 lower than those observed in 2003, which does not corroborate most epidemiologic studies on the subject, which show a continuous increase in ADHD incidence over the years.[5] Boys are twice as likely to be affected as girls, and most patients meet criteria for other mental disorders.[2,4] Male patients often have a concomitant oppositional defiant disorder or conduct disorder, and female patients often have a comorbid disorder such as anxiety or depression.[2]

ADHD is a chronic neurodevelopmental disorder in which patients present with a persistent pattern of inattention and/or hyperactivity and impulsivity that has been present for at least six months, leads to functional impairment in more than one setting, and is present before the age of twelve.[1] Symptoms are progressive and persistent. Around 50-80% of children with ADHD continue to experience symptoms during adolescence, and 40% continue to show signs of the disorder into adulthood.[1]

Treatment options range from psychosocial to pharmacological. European guidelines recommend the use of medication only in patients with moderate to severe symptoms with major functional impact. For patients with mild symptoms, the first option is behavioral training of caregivers.[6] Behavioral and training interventions have been shown to be effective, but continued adherence by patients and families is a key requirement for their success.[2] Nearly two-thirds of children and adolescents diagnosed with of ADHD take medication.[2,7] Several pharmacologic options are available, including psychostimulants such as methylphenidate (MPH) and amphetamines, and non-psychostimulants such as atomoxetine and clonidine. Studies on the efficacy and tolerability of ADHD medications concluded that MPH should be the first pharmacologic choice for children and adolescents with ADHD.[3,4,7] MPH can be used in children as young as six years of age.[8] A review of the literature suggested that MPH is effective in reducing hyperactivity and impulsivity and improving concentration and overall behavior and quality of life in children with ADHD.[9] It also reported improvement in teacher-reported ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life.[9]

MPH is a central nervous system (CNS) stimulant that acts on dopamine and norepinephrine transporters by blocking the uptake of dopamine and norepinephrine by presynaptic neurons, thereby increasing neurotransmitter levels in synaptic clefts.[4,6-8] This produces a stimulant effect within the CNS, namely in the striatum, nucleus accumbens, and prefrontal cortex.[7,8] The effect in the prefrontal cortex appears to be the most relevant outcome of MPH's therapeutic activity in ADHD, but its effect on the disease is not yet fully understood.[7] MPH is also a weak agonist at the 5HT1A receptor, which is an additional mechanism that contributes to increased dopamine levels and its beneficial effects on ADHD.[7,8] There are several oral formulations available, which are classified according to the rate of release as immediate-release (IR), extended-release (XR), and sustained-release (SR).[8] IR formulations have a peak plasma concentration 1-3 hours after oral dosing and an estimated half-life of 1.5-2.5 hours. SR formulations have an initial peak at 1-2 hours and a second higher peak at an average of 4.7 hours after administration.[7] MPH is metabolized to a compound with little or no pharmacological activity called ritalinic acid. For IR formulations, 78-97% is excreted in the urine and a small percentage is excreted in the feces as ritalinic acid.[7]

Like all drugs, MPH is known to cause side effects that can affect the child's functioning and developmental levels. However, there is still much to learn about this drug because most of the available studies are of short duration, and MPH is sometimes used for prolonged periods of time and during particularly sensitive years when major neurobiological changes occur.[6] Nevertheless, the effects described in the literature are not severe, most are reversible with therapy discontinuation, and there is no evidence of hazardous outcomes.[9] The most common side effects are short-term increases in blood pressure and heart rate, anorexia that may affect growth rate, sleep disturbances, emotional lability, irritability, and a different understanding of experiencing emotions.[3,6,10-12] Tics don't seem to be a side effect of psychostimulants; instead, their occurrence is described as an incidental effect during medication.[6,13] However, MPH can cause other symptoms that are less well known to medical professionals. One of these is MPH-induced dyskinesia.[14] This type of dyskinesia can be divided into acute (AD) and tardive (TD) dyskinesia. Acute dyskinetic reactions are characterized by the sudden onset of dyskinetic movements (abnormal, involuntary, and uncontrolled movements) after administration of MPH and their complete regression upon discontinuation, with an "on and off" type of effect. AD is thought to be caused by an elevated concentration of MPH, which leads to overstimulation of dopamine receptors and blockade of their transporters, increasing extracellular dopamine levels. On the other hand, TD is characterized by the slow onset of dyskinetic symptoms that appear weeks

after the first MPH intake. They resolve months after therapy discontinuation. TD appears to be related to the development of dopamine receptor hypersensitivity caused by chronic MPH use.[10,11,14] These movements typically affect the face, orofacial region (lips and perioral region, and upper and lower extremities (arms, wrists, hands, fingers, legs, knees, ankles, and toes).[14] MPH-induced dyskinesia is often seen in children prescribed a combination of medications or in children with ADHD and developmental delay, but it has also been described in otherwise healthy children without the use of concomitant medications.[11] There are no known risk factors for the development of these drug-induced movements.[15] They are usually not dangerous or painful, but may be observed by third parties, causing the children to suffer from social stigmatization. Consequently, there is a need to control or minimize the movements. One of the options in AD is to change the MPH formulation from an IR to an XR or SR formulation so that the drug concentration increases more gradually. Another option is the use of biperiden, a centrally acting anticholinergic drug that is thought to act by competitive antagonism of acetylcholine at cholinergic receptors in the corpus striatum, although its exact role is still uncertain.[15] There are currently no treatments for MPH-induced TD.

CASE REPORT

The authors report the case of a 10-year-old girl referred to a Child and Adolescent Psychiatry consultation for challenging/oppositional behavior, sleep disturbance, and parental dysfunction. She had a personal history of ependymoma treated with surgery, chemotherapy, and radiotherapy until 2015, growth hormone deficiency treated with growth hormone, hypothyroidism treated with levothyroxine, and bladder dysfunction treated with oxybutynin. Psychological assessment revealed significant difficulties in concentration and immediate and working memory, with significant limitations in quality of life, particularly in emotional and academic regulation. The Wechsler Intelligence Scale for Children (WISC-III) showed a verbal intelligence quotient (IQ) of 84, an achievement IQ of 70, and a total IQ of 72. The girl attended school in a regular education course with measures to support learning and inclusion, in accordance with Decree-Law 54/2018 of the Portuguese General Directorate of Education, and received speech therapy and psychological support at school.

The girl was initially treated with risperidone 0.03 mg/Kg/day (0.75 mg) with improvements in impulsivity control. At the beginning of the 2020/2021 school year, she was prescribed IR MPH 0.6 mg/Kg/day (10 mg in the morning and 5 mg at lunchtime) for complaints of inattention, with a good response in terms of attention. However, thirty minutes after taking MPH, the mother reported masticatory-type movements with repetitive movements of the orofacial, labial, and jaw muscles and tongue extrusion. These movements regressed at the end of the day and were absent during the weekend when the girl was not under the effect of MPH. Pharmacotherapy was changed to long-acting MPH 0.75 mg/Kg/day (18 mg/day). With this therapy, the patient initially maintained orofacial dyskinesia, albeit to a lesser extent, which decreased over time to complete resolution. However, after a few months of treatment, she developed repetitive movements of the upper limbs, namely combing and curling her hair, which occurred only under the effect of medication. She is currently on ER MPH 0.83 mg/Kg/day (20 mg/day) with no reports of orofacial dyskinesia, but maintains repetitive movements of the extremities, especially during activities that require concentration.

DISCUSSION

ADHD is one of the most common behavioral disorders diagnosed in children. It causes a variety of symptoms that can lead to functional impairment. MPH is the first-line pharmacological treatment for children over six years of age, but is not without side effects. The most common side effects are mild and reversible with therapy discontinuation. MPH-induced dyskinesia is characterized by the sudden onset of dyskinetic movements after MPH administration (AD) or the development of dyskinetic movements after a few weeks of treatment (TD). The cause of this drug-induced effect remains unclear. With this case report, the authors aim to raise awareness of the development of MPH-induced dyskinesia, as these movements may occur at any time during treatment and at appropriate therapeutic doses. To the authors' knowledge, this is the first case reported in the literature of a patient receiving MPH for ADHD who developed both AD and TD symptoms.

CONCLUSION

ADHD is one of the most common behavioral disorders in children. MPH is the first-line pharmacological treatment for children with ADHD over the age of six. MPH-induced dyskinesia is an effect that is little known to healthcare professionals. Its etiology is still unclear and it can be divided into acute and tardive dyskinesia. The acute form typically has an "on and off" type of action, while the tardive form is characterized by movements that usually appear weeks into the duration of treatment. Biperiden has been described as effective in AD treatment, but no treatment options are available for TD.

AUTHORSHIP

Teresa Pinheiro – Conceptualization; Investigation; Resources; Writing - original draft; Writing – review & editing;

Validation

Carla Maia – Conceptualization; Writing – review & editing; Supervision; Validation

REFERENCES

1. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. Cleve Clin J Med. 2015 Nov;82(11 Suppl 1):S2-7. doi: https://doi.org/10.3949/ccjm.82.s1.01.
2. Wolraich ML, Jr JFH, Allan C, Chan E, Davison D, Earls M, *et al*. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4):e20192528. doi: https://doi.org/10.1542/peds.2019-2528.
3. Cortese S, Adamo N, Giovane CD, Mohr-Jensen C, Hayes AJ, Carucci S, *et al*. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. The Lancet Psychiatry. 2018;5(9):727-38.
4. Faraone SV. The Pharmacology of Amphetamine and Methylphenidate: Relevance to the Neurobiology of Attention-Deficit/Hyperactivity Disorder and Other Psychiatric Comorbidities. Neurosci Biobehav Rev. 2018;87:255-270. doi: https://doi.org/10.1016/j.neubiorev.2018.02.001.
5. Leache L, Arrizibita O, Gutiérrez-Valencia M, Saiz LC, Erviti J, Librero Jn. Incidence of Attention Deficit Hyperactivity Disorder (ADHD) Diagnoses in Navarre (Spain) from 2003 to 2019. Int J Environ Res Public Health. 2021;18(17):9208. doi: https://doi.org/10.3390/ijerph18179208.
6. Espadas M, Insa I, Chamorro M, Alda-Díez JA. Efectos secundarios del metilfenidato en población infantil y juvenil. Rev Neurol. 2018;66(5):157-162.
7. Shellenberg TP, Stoops WW, Lile JA, Rush CR. An update on the clinical pharmacology of methylphenidate: therapeutic efficacy, abuse potential and future considerations. Expert Rev Clin Pharmacol. 2020;13(8):825-833. doi: https://doi.org/10.1080/17512433.2020.1796636 .
8. Verghese C, Abdijadid S. Methylphenidate: StatPearls Publishing, Treasure Island (FL); 2021 May 4, 2021. www.ncbi.nlm.nih.gov/books/NBK482451/.
9. Storebø O, Ramstad E, Krogh H, Nilausen T, Skoog M, Holmskov M, *et al*. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD) (Review). Cochrane Database of Systematic Reviews. 2015(11).
10. Lee M, Wang L. Methylphenidate-induced Orofacial Dyskinesia: Report of Two School-age Boys in Taiwan. Hong Kong Journal of Paediatrics (new series). 2017;22(2):107-9.
11. Senecky Y, Lobel D, Diamond GW, Weitz R, Inbar D. Isolated orofacial dyskinesia: A methylphenidate-induced movement disorder. Pediatric Neurology. 2002;27(3):224-6.
12. Gokcen C, Karadag M, Aksoy I. Methylphenidate Induced Lip and Tongue Biting. Clinical Psychopharmacology and Neuroscience. 2018;16(2):218-20.
13. Millichap JG. Risk of Tics with Psychostimulants for ADHD. Pediatric Neurology Briefs. 2015;29(12):1.
14. Keresztény Á, Ferenczi-Dallos G, Velő S, Gádoros J, Balázs J. Dyskinesia in Treatment-Naive and Stimulant-Treated Children With ADHD. J Atten Disord. 2020;24(7):981-989. doi: https://doi.org/10.1177/1087054716679262.
15. Arslan EA, Arslan E, Kılınç A, Göksu Ö. Effect of biperiden treatment in acute orofacial and extremity dyskinesia with methylphenidate therapy. Pediatr Emerg Care. 2018;34(11):e217-e218. doi: https://doi.org/10.1097/PEC.0000000000001102.

CORRESPONDENCE TO

Teresa Pinheiro
Department of Pediatrics and Neonatology
Unidade Local de Saúde Entre Douro e Vouga
Rua Dr. Cândido Pinho 5
4520-211 Santa Maria da Feira
Email: ana.pinheiro@ulsedv.min-saude.pt

Received for publication: 18.01.2022
Accepted in revised form: 14.11.2022