The Rebound Effect Associated with Methylphenidate: A Case Report

Efeito Rebound Associado ao Metilfenidato: Caso Clínico

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent neurodevelopmental disorders in children. Psychostimulants, particularly methylphenidate, are first-line pharmacological agents with robust evidence of efficacy and a favorable safety profile. However, abrupt offset of pharmacodynamic effect may precipitate a rebound phenomenon, characterized by transient exacerbation of irritability, hyperactivity, and behavioral dysregulation. This phenomenon is rarely documented in scientific literature and likely underdiagnosed.

An eight-year-old boy with unremarkable past medical and family history presented with longstanding inattention, increased motor activity, and academic underachievement. Other comorbid conditions were excluded. Diagnosis of ADHD was established. Treatment was initiated with extended-release methylphenidate. Daily late-afternoon episodes of marked irritability and increased motor restlessness emerged, consistent with methylphenidate rebound. Add-on administration of immediate-release methylphenidate in the afternoon resulted in effective mitigation of rebound symptoms.

This case study aims to review the semiological characteristics of the rebound effect induced by methylphenidate and the respective therapeutic approach.

KEYWORDS: Attention Deficit Disorder with Hyperactivity/drug therapy; Child; Methylphenidate/adverse effects

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RESUMO

A perturbação de hiperatividade/défice de atenção (PHDA) constitui uma das patologias do neurodesenvolvimento mais prevalentes na infância. Os psicoestimulantes, como o metilfenidato, têm demonstrado elevada eficácia e um perfil de segurança favorável no controlo sintomático desta perturbação. Contudo, associam-se a potenciais efeitos adversos, incluindo o fenómeno de *rebound*, caracterizado pela exacerbação sintomática aquando da cessação do efeito farmacológico. Este fenómeno é escassamente documentado na literatura científica, e, provavelmente, subdiagnosticado.

Uma criança do sexo masculino, com oito anos, sem antecedentes pessoais ou familiares de relevo, foi avaliado em consulta de neurodesenvolvimento por manifesta desatenção, aumento da atividade motora e insucesso escolar. Após exclusão de comorbilidade, foi estabelecido o diagnóstico de PHDA. Foi instituída terapêutica com metilfenidato de libertação prolongada. Observou-se irritabilidade acentuada e aumento da atividade motora ao fim da tarde, compatíveis com efeito de *rebound*. A adição de uma dose baixa de metilfenidato de ação curta durante a tarde resultou num controlo eficaz dos sintomas.

O presente caso visa rever as características semiológicas do efeito de *rebound* induzido pelo metilfenidato e a respetiva abordagem terapêutica.

PALAVRAS-CHAVE: Criança; Metilfenidato/efeitos adversos; Perturbação do Deficit de Atenção com Hiperatividade/tratamento farmacológico

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders of childhood, and has a significant impact on academic achievement, psychological well-being and social functioning.[1] The estimated worldwide prevalence is approximately 7.2%.[2] The core symptoms of ADHD include persistent inattention and/or hyperactivity-impulsivity. Although hyperactivity tends to diminish with age, inattention frequently persists into adulthood.[3] ADHD is often associated with comorbid neurodevelopmental disorders; however, even in their absence, academic performance is frequently compromised.

The American Academy of Pediatrics (AAP) recommends a multimodal approach for school-aged children with ADHD, including pharmacological treatment, parent training in behavior management, behavioral classroom interventions, and educational support.[1] Psychostimulants, particularly methylphenidate and lisdexamfetamine dimesylate, are strongly recommended and highly effective in the treatment of ADHD's core symptoms.[1] In Europe, methylphenidate is considered the first-line pharmacological treatment due to its cost-effectiveness and wide range of available formulations.[4] Its mechanism of action includes inhibition of dopamine and norepinephrine transporters, an affinity for and agonist activity of serotonin 5-HT1A receptors, and redistribution of vesicular monoamine transporter 2. As a consequence, methylphenidate elevates extracellular dopamine and norepinephrine levels.[5]

Methylphenidate has a well-established safety profile, with generally mild and transient side effects. However, its limited daily duration of action may result in rebound symptoms - episodes of marked irritability, impulsivity, and increased motor activity - that may be worse than the baseline as the medication effect wanes. Although the rebound phenomenon is widely recognized in clinical practice, it remains insufficiently documented in the scientific literature.

Through this report, the authors aim to review the clinical characteristics and therapeutic strategies associated with the methylphenidate rebound effect, contextualized through the discussion of a clinical case.

CASE REPORT

An eight-year-old boy was referred to the neurodevelopmental clinic due to academic underachievement and inattention, with history of increased motor activity since infancy. He was the second child of healthy non-consanguineous parents. His older sister was healthy. Family history was unremarkable, though fa-

ther reported a history of learning difficulties. The patient had no significant past medical history and was attending the third grade in a mainstream school. Parents reported a normal vision and hearing screening six months prior to evaluation.

Neurodevelopmental and behavioral assessment revealed age-appropriate gross and fine motor skills, and appropriate language development. Verbal and non-verbal cognitive abilities were also within the expected range for age. The patient achieved fluent reading by the end of second grade and was able to write dictated sentences, despite some inconsistent spelling errors. Mathematical performance was more impaired, particularly in subtraction, multiplication and problem--solving tasks. Social interaction were described as generally appropriate, although teachers reported a tendency to dominate peer activities.

From behavioral standpoint, excessive motor activity had been present since approximately 12 months of age. The child ran in inappropriate contexts, talked excessively, had difficulty waiting his turn, and acted impulsively. Parents reported a history of frequent temper tantrums in early childhood, which improved after the age of five. Teachers described frequent classroom disruptions and difficulty working quietly. During evaluation, he was cooperative but noticeably restless.

Attention-related symptoms included frequent careless mistakes, distractibility, disorganization, and avoidance of schoolwork, particularly mathematics. He frequently lost school materials and personal belongings. There were no significant concerns regarding mood, affections, social conduct, sleep, or temperament. Parents also denied tics or other repetitive movements.

Based on DSM-5-TR criteria, a diagnosis of ADHD, combined presentation, was established.[6] Given the child's ability to swallow pills, treatment was initiated with extended-release methylphenidate at 18 mg/day, increased to 27 mg/day after one week, and to 36 mg/day after an additional week (approximately 1.3 mg/kg/day), in combination with behavioral and classroom interventions. A significant improvement in motor activity and attention was observed. The patient complained of transient headache and decreased appetite without weight loss. No significant changes in blood pressure and heart rate were noted. However, parents reported daily episodes of marked irritability, emotional lability, crying, and increased motor activity, occurring in the late afternoon. These episodes were interpreted as explosive behaviors related to a rebound effect as the medication wore off. To address this, an additional 5 mg dose of immediate-release methylphenidate was administered in the afternoon (around 16-17 h), resulting in marked reduction of rebound symptoms without additional adverse or interference with sleep. After six months of treatment, the patient demonstrated sustained improvements in attention, behavior and academic performance.

DISCUSSION

This case involves an eight-year-old boy diagnosed with ADHD, combined presentation, using DSM-5-TR criteria and in accordance with the AAP recommendations.[1,6] ADHD is more common in males than in females.[2] The median age at diagnosis is approximately seven years.[7] Although symptoms of increased motor activity had been present since 12 months of age, diagnosis was established only at eight years, when inattention became more evident with the increasing demands of schoolwork.

The majority of subjects with ADHD also meet diagnostic criteria for another condition.[1] Comorbidities were properly screened, including emotional, behavioral and neurodevelopmental disorders, and physical conditions, as recommended in DSM-5-TR and by the latest AAP guidelines.[1,6] No comorbidities were found; however, inattention and hyperactivity resulted in significant academic impairment, particularly in subjects' sustained attention and executive functioning, such as mathematics.

In line with AAP and European guidelines, the authors initiated pharmacological treatment with a psychostimulant – methylphenidate – given its established efficacy, cost-effectiveness, and availability in multiple formulations.[1,2,4] As the patient was able to swallow pills, a long-acting formulation was selected to improve adherence and simplify the therapeutic regimen.[8] Although short-acting formulations allow greater flexibility, they are associated with lower adherence and a higher potential for rebound symptoms.

The safety profile of methylphenidate is well established, with most adverse effects being mild and transient, including abdominal pain, vomiting, decreased appetite, headache, and insomnia.[9] Methylphenidate is also associated with a modest mean increase in blood

pressure (1-4 mmHg) and heart rate (1-2 beats per minute).[9] However, clinical substantial increase in both heart rate and blood pressure have been reported in 5%-15% of patients.[9] In the present case, no clinically relevant cardiovascular changes were observed, and adverse effects were limited to transient headache and mild appetite suppression without weight loss.

Despite the overall therapeutic benefit, the parents reported daily late-afternoon episodes of marked irritability, emotional lability, crying, and increased motor activity occurring as the medication effect diminished. These episodes were interpreted as a rebound phenomenon – a concept widely recognized in clinical practice but insufficiently characterized in the scientific literature. Rebound refers to a transient exacerbation of behavioral symptoms, including irritability, temper tantrums, hyperactivity, and agitation, occurring as the pharmacological effect of the stimulant wanes, in some cases, exceeding baseline symptom severity.[8,10,11] Episodes can be quick or last more than one hour and may be severe enough to lead caregivers to discontinue medication.

Despite its frequent mention in clinical settings, rebound is not explicitly addressed in standard medical references, Food and Drug Administration or European Medicines Agency product labeling, and it is absent from current ADHD clinical guidelines.[1,4] While agitation and restlessness are occasionally listed as adverse effects, the timing of symptom onset is rarely specified, limiting the clinician's ability to distinguish rebound from other medication-related adverse effects. Notably, the American Academy of Child and Adolescent Psychiatry (AACAP) is one of the few organizations to explicitly mention rebound associated with methylphenidate in its "ADHD Parents' Medication Guide".[11] Overall, few studies have specifically investigated this phenomenon.

Sarampote *et al* (2002) reported a case of significant irritability and aggression coinciding with the wearing-off period of methylphenidate, leading to medication discontinuation.[12] In a controlled trial, Carlson *et al* (2003) described severe rebound effects associated with short-acting stimulants (predominantly methylphenidate), manifested by sadness, crying, irritability, and euphoria as medication effects subsided.[10] Long-acting formulations are associated with a lower risk of rebound effects compared with short-acting formulations; however, such effects may still occur with long-acting preparations, as demonstrated in the present case.[8]

The prevalence of methylphenidate-related rebound is unclear. Masi *et al* (2022), in a retrospective observational study, identified rebound symptoms in 16 of 480 children (approximately 3.3%) aged six to 18 years, on short-acting methylphenidate, including one severe case.[13] Carlson *et al* (2003) reported severe rebound effects in 8.7% of 149 children with ADHD, aged five to 12, treated with short-acting stimulants.[10]

Rebound symptoms may result from a rapid decline in stimulant central nervous system concentrations, with "rapid metabolizers" potentially being at increased risk.[8] Although the concept of "rapid metabolizers" is commonly linked to cytochrome P450 variability, methylphenidate is primarily hydrolyzed by hepatic carboxylesterase 1 (CES1).[14] Interindividual variability in CES1 activity may influence drug exposure.

Currently, no standardized therapeutic approach exists. In a pharmacological trial that attempted to characterize methylphenidate rebound, Greenhill *et al* (2001) reported an improvement in irritability following the addition of a third dose of short-acting methylphenidate in the afternoon.[15] Consistent with AACAP recommendations and these findings, a low dose of immediate-release methylphenidate was added shortly before the expected decline of long-acting morning dose, resulting in clear clinical improvement.[11,15] This strategy likely mitigates abrupt decreases in central nervous system stimulant levels. However, the overall effectiveness and generalizability of this approach remain uncertain. Alternatively, if methylphenidate is not tolerated, a switch to an alternative stimulant, such as lisdexamfetamine dimesylate, may be considered, as part of the standard ADHD pharmacotherapy.[4]

TO CONCLUDE:

1. When caregivers report agitation or increased motor activity after the initiation of methylphenidate, clinicians should carefully assess the timing of symptom onset;
2. The diagnosis of methylphenidate-associated rebound effect should be considered in cases of irritability and hyperactivity occurring as the therapeutic effect diminishes;
3. Administration of a low dose of immediate-release methylphenidate before the wearing-off period of extended-release morning formulation may attenuate rebound symptoms.

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FP and STO - Conceptualization, data curation, writing--original draft, review and editing.

MLC - Conceptualization, data curation and writing-original draft,

MP - Conceptualization, project administration, supervision, validation, writing-original draft, review and editing.

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