Depressive symptoms as a side effect of the sustained release form of methylphenidate in a 7-year-old boy with attention-deficit hyperactivity disorder

Depresivni simptomi kao neželjeni efekat dejstva sporooslobađajuće forme metilfenidata kod 7-godišnjeg dečaka sa hiperkinetičkim poremećajem i poremećajem pažnje

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Abstract

Introduction. Hyperkinetic disorder or attention-deficit hyperactivity disorder (ADHD) is a clinical entity consisting of a cluster of symptoms including hyperactivity, attention disorder and impulse control disorder group. In the context of ADHD etiology we may say that genetic, clinical and imaging studies point out a disruption of the brain dopamine system, which is corroborated by the clinical effectiveness of stimulant drugs, which increase extracellular dopamine in system, which is important both for the comprehension and therapeutical approach to this problem. Today, the best recommended approach regarding children with ADHD is a combination of two therapeutic modalities: pharmacotherapy and behavioral treatment. The first-choice drugs for this disorder belong to the group of sympathomimetics – psychostimulants and atomoxetine (more recently). As the first-choice therapy, methylphenidate in sustained release form has numerous advantages. Like all drugs, methylphenidate has its unwanted side effects. Most common are: loss of appetite, weight loss, sleeping disorders, irritability, headache. These side effects are well-known and documented in the literature. By analysing the available literature we have found cases of psychiatric side effects such as: psychosis, mania, visual hallucinations, agitation, suicidal ideas. We have not found examples of ADHD in children who use increased dosage of sustained release of methylphenidate leading to depressive symptomatology. On the other side, methylphenidate may be prescribed for off-label use in treatment-resistant cases of depression. Case report. The case of a 7-year-old boy diagnosed with ADHD was on a minimal dose of sustained release form of methylphenidate. After initial titration of the drug, i.e. after raising the dose to the next level the boy developed clinical signs of depression. The treatment was ceased and depressive symptoms were withdrawn. Conclusion. Manifestation of depressive symptomatology after dose increase of sustained release form of methylphenidate in a 7-year-old boy with ADHD represents an uncommon side effect. Precise drug activity mechanisms responsible for the appearance of these symptoms remains to be explained.

Key words: methylphenidate; depression; attention deficit disorder with hyperactivity; treatment outcome.

Apstrakt


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zuelne halucinacije, agitacija, suicidne ideje. Nismo našli na prikaze dece sa ADHD kod koje se, pri povećanju doze metilfenidata u sporoslobađajućoj formi, razvila depresivna simptomatologija. S druge strane, metilfenidat se propisuje nestandardno za lečenje rezistentnih slučajeva depresije. 

**Prikaz bolesnika.** U radu je prikazan 7-godišnji dečak sa ustanovljenim ADHD. Dečak je inicijalno primao najnižu dozu sporoslobađajuće forme metilfenidata. Nakon podizanja doze leka na sledeći nivo, kod prikazanog dečaka ispojili su se klinički znaci depresije. Posle obustave tretman, došlo je do povlačenja simptoma depresije. 

**Zaključak.** Pojava depresivne simptomatologije kod 7-godišnjeg dečaka sa ADHD nakon povišenja doze sporoslobađajuće forme metilfenidata predstavlja nepoznat neželjeni efekt ovog leka. Precisan mehanizam dejstva leka koji je odgovoran za pojavu ovih simptoma ostaje nerazjašnjeno.

**Ključne reči:** metilfenidat; depresija; hiperkinetički sindrom; lečenje ishod.

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**Introduction**

Hyperkinetic disorder 1 or attention-deficit hyperactivity disorder (ADHD) 2 is a clinical entity consisting of a cluster of symptoms including hyperactivity, attention disorder and impulse control disorder group 3–6. Actually, it is a syndrome of attention disorder, hyperactivity and other deficits of executive functions. It includes a damaged capability of planning “one’s tasks and executing them” 7.

These symptoms must be expressed in that particular degree and range (be general), so as to provoke important difficulties in functioning in different areas of everyday life (home, school, work, social relations, etc.).

The disorder appears at around two-three years of age but is not recognized in most cases before starting to attend school, where a high degree of self-control is requested concerning behavior, attention and perseverance in activities which demand longer cognitive engagement. The leading place in the origin of this disorder (etiology) have biological mechanisms of neurotransmission regulation in the central nervous system (CNS) 8,9. In the context of ADHD etiology we may say that genetic, clinical and imaging studies point out a disruption of the brain dopamine system, which is corroborated by the clinical effectiveness of stimulant drugs, which increase extracellular dopamine in the brain. Basically, it is a biological and not psychological disorder, which is important both for the comprehension and therapeutic approach to this problem.

Today, the best recommended approach regarding children with ADHD is a combination of two therapeutic modalities: pharmacotherapy (psychostimulants and atomoxetine) and behavioral treatment 10–15. The first choice drugs for this disorder belong to the group of sympathomimetics as follows: psychostimulants and atomoxetine (more recently) 12–15. As the first choice therapy, methylphenidate in a sustained release form has numerous advantages 17. It helps to preserve one’s privacy and avoid stigmatization at school, which considerably improves the compliance.

**Case report**

We presented a 7-year-old boy referred to the Clinic when he was 6. The boy was not able to sit still (in continuous movement), stay at one place for a longer period of time. The speech-language therapists could not work with him, his mother “did not know what to do” and “was constantly running after him”.

The boy was born as a second child, his parents were young and healthy. The mother had a regular pregnancy, delivery was “somehow difficult”. At birth, the boy did not breathe for a couple of minutes (APGAR score 7) and spent 10 days in the incubator. Weight at birth was 4 kg. Cranial ultrasonography presented no abnormalities. At the age of one and half a month the boy was diagnosed with hypotonia and torticolis by the pediatric neurologist. The repeated cranial ultrasonography test was normal. Electroencephalogram (EEG) showed the presence of epileptic paroxysmally dysrhythmic activity. The boy had no seizures. Antiepileptic treatment “for preventive reasons” (valproic acid) started from the 2nd year of age.

Motoric development milestones were at the limits for the boy's age, but there was slowness in speech and cognitive development, so the boy was submitted to continuous development stimulation and speech-language treatment. Valproic acid was withdrawn after a 3.5-year period.

Family history showed no important signs of inheritance-relevant health problems. At admission the boy was well developed for his age and well-brought-up. The boy was in constant movement, used to open closet doors and drawers, run through the office, it was not possible to keep him at the same place for a longer period of time. The boy was motorically agile, smiling, in a good mood, and emotionally warm. His non-verbal communication was short, and verbal communication difficult. Speech was dysphasic (dysphasia expressiva) with frequent repeating of words, from time to time speaking in the third person.

Fascinated by the strip, the boy was constantly rolling it around his hand. Neurological finding was regular.

The finding of neurological examination was regular; psychological assessment showed that intellectually the boy was at the level of mild mental retardation; laboratory analyses of blood and urine showed results in the referential limits; screening for ADHD-IOWA Conner’s scale was 29; electroencephalogram background activity was regular; magnetic resonance imaging (MRI) showed no abnormalities; no drug treatment, while reeducation and stimulation of development such as speech language treatment in continuity were recommended.

As a result of analyses and differential-diagnostic considerations of DSM/IV&MKB/10 criteria the patient was diagnosed with: ADHD, mild mental retardation, and dysphasia evolutionis expressiva.
The diagnosis of ADHD was confirmed. The benefits and risks of the proper use of methylphenidate (sustained release form) as well as alternative treatments were discussed with the mother before prescribing stimulants. We started with a low dose. Therapeutic response was positive. The mother said that: “Now the boy can sit still even for half an hour, his words fund has increased, he rediscovered his toys from the past, wants to draw and write, is more reasonable, with less compulsive repeating of what has nothing to do with the environment”. The mother was satisfied, looked at him for the first two days with belief. The doctor and speech-language therapist were very satisfied with him. After starting the therapy, the boy had (during 7 days) transitory sleep disorders (woke up early) and eating disorder (loss of appetite). Laboratory analyses of blood and urine, body weight and height and screening for ADHD-IOWA Conner’s scale were monitored monthly: low and transient loss of appetite and loss of weight (3 kg for 5 months ) growing up 2 cm and ADHD-IOWA Conner’s scale index 18 were notified.

For five months the boy was at the same lowest dose. The mother reported a certain “activity progression, the boy was getting better, but is constantly moving”. With mother’s agreement, the dosage was increased (the next dose entity).

Three days after the increased therapy the mother phoned disturbed saying that: “The boy is sad, but not calm, cries a lot, eats less, is more anxious, wakes up at night, never has been like this, she cannot recognize him.” At the next control, 4 days after introducing this treatment: “He looks sad, speaks with a low wailing voice; continually repeats: “I cried, I cried, I am sad”, being in continuous movement, with something in his hand, irritable. Mother said: “When he is not sad, he is angry”. The treatment of a sustained release form of methylphenidate was interrupted. At the control two days later, the mother said “He is as before, unrestrained, nothing can be done with him, but he is in a good mood again, he laughs”. The patient remained further at the lowest dose of the drug which he still takes, attending a pre-school institution.

Discussion

Methylphenidate is a psychostimulant drug approved for treatment of ADHD, postural orthostatic tachycardia syndrome and narcolepsy. It may also be prescribed for off-label use in treatment-resistant cases of lethargy, depression, obesity. The accepted model of dopamine deficits in brain is the most probable cause of ADHD dictate therapeutical approach.

Methylphenidate increases levels of dopamine and norepinephrine in the brain through reuptake inhibition of the monoamine transporters 8,9. Like all drugs, methylphenidate has its unwanted side effects. Most common are: loss of appetite, weight loss, sleeping disorders, irritability, headache, stomach ache, skin rash, development or worsening of tics, slow growing 17,18. These side effects are well-known and documented in the literature. Most side effects are minor and disappear over time or the dosage level is lowered. By analysing the available literature we have found cases of psychiatric side effects such as: psychosis, mania, visual hallucinations, agitation, suicidal ideas. We have not found cases of ADHD in children with an increased dosage of sustained release of methylphenidate leading to depressive symptomatology. On the other side, methylphenidate may be prescribed for off-label use in treatment-resistant cases of depression.

A dramatic switch in behaviour in our patient due to medication (dose increase and drug interruption) gave a clear confirmation of the biologic basis of the disorder. At the same time, it opened a question: How can (dose-dependent) methylphenidate lead to the appearance of depressive symptoms when its basic activity is absolutely opposed?

Is this maybe a paradoxical effect which has not been recognized till now and which represents the expression of individual hypersensitivity? Or is it a heterogeneous group of disorders where the same symptoms were acquired by other biological means? The conceptualisation of ADHD over time (postencephalitic parkinsonism, minimal cerebral dysfunction...) sustains this possibility 5.

Differential-diagnostic considerations include the possibility of comorbidity in affective disorder which, although rarely, appears in children 3,5,19. It is known that stimulant drugs may exacerbate symptoms and reveal them for the first time in children with previously unrecognized psychiatric illnesses. The presented patient had neither signs nor anamnestic data regarding possible elements of affective disorder. No cases of affective disorder in family history had been found, as well.

Conclusion

Manifestation of depressive symptomatology after dose increasement of the sustained release form of methylphenidate in a 7-year-old boy with ADHD represents an uncommon adverse effect of the drugs. Precise mechanisms responsible for the appearance of these adverse effects cannot be explained, at the moment.

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