Case Report
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Manic Symptoms Due to Methylphenidate Use in an Adolescent with Traumatic Brain Injury

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Almost one-fifth of children who sustain a traumatic brain injury (TBI) are under the risk of attention problems after injury. The efficacy and tolerability of methylphenidate (MPH) in children with a history of TBI have not been completely identified. In this case report, MPH-induced manic symptoms in an adolescent with TBI will be summarized. A male patient aged 17 years was admitted with the complaints of attention difficulties on schoolwork and forgetfullness which became evident after TBI. Long-acting MPH was administered with the dose of 18 mg/day for attention problems. After one week, patient presented with the complaints of talking to himself, delusional thoughts, irritability and sleeplessness. This case highlights the fact that therapeutic dose of MPH may cause mania-like symptoms in children with TBI. Close monitarization and slow dose titration are crucial when considering MPH in children with TBI.

KEY WORDS: Brain injuries; Adolescent; Methylphenidate; Bipolar disorder.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in children, resulting in numerous physical, behavioral and cognitive deficits.[1] Cognitive deficits may involve problems with attention, memory and executive functions that worsen with increasing TBI severity.[2-4] Attention deficit hyperactivity disorder (ADHD) that develops after injury without evidence of preinjury ADHD is often referred to as secondary ADHD.[5]

Methylphenidate (MPH), a well-accepted treatment for ADHD, may be associated with behavioral adverse effects.[6] Amongst these reactions, psychotic symptoms are the most terrifiying ones for families. Although firstly reported in the early 1970s, the terminology of psychotic symptoms due to MPH use has not been well described. The first report of stimulant-induced psychosis and/or mania symptoms in children included three cases and used the definition of 'methylphenidate hallucinosis'.[7] In these cases, hallucinations were the prominent presenting symptoms. In later reports, the term 'toxicosis' has been used to distinguish transient psychotic symptoms associated with stimulant use.[8] Toxicosis term specifically indicates that the psychotic-like or mania-like symptoms resolve following discontinuation of stimulant. When the adverse reaction symptoms continue or recur after discontinuation, a rediagnosis of bipolar disorder or schizophrenia may be considered.[8]

The efficacy and tolerability of stimulants in children with a history of TBI have not been completely identified. In this case report, the emergence of manic symptoms with MPH use in an adolescent with TBI will be summarized. Informed consent was obtained from the patient's parents.

CASE

A male patient aged 17 years was admitted to the child and adolescent psychiatry clinic with the complaints of attention difficulties on schoolwork and forgetfullness. Patient's medical history revealed that he had a car accident 3 months ago which included a TBI. Upon admission to emergency room, his Glasgow Coma Scale score was 6/15. At the time of the accident, his neurologic assessment was marked with upper and lower muscular weakness, memory deficits and frank mutism. This clinic picture resolved in 2 months; however, he has been speaking slowly since then. Before the accident, he was reported to

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have a succesfull academic life in both elementary and secondary school. He never had attention problems, hyperactivity or impulsivity. Prior psychiatric history of the patient did not reveal any psychiatric disorder diagnosis. There was no known history of psychiatric disorders in both parents and extended family members. After the accident, he had difficulty on sustaining attention on school work and forgetfulness on daily duties. He described himself as "I study hard and try to do my best but I am far from my previous academic performance. I can't focus, can't sustain my attention and I do simple mistakes". Deficits in cerebellar tests, slow speech and difficulty at walking on hills were evident in his neuorologic examination. His magnetic resonance imaging (MRI), which was performed 10 days after the injury, revealed postinjury findings on the right frontal lob, lef temporal lobe and corpus callosum (Fig. 1). Sleep and awake electroencephalography (EEG) of the patient was also obtained on the 7th day after injury. Sleep EEG showed 4-6 Hz theta waves mixed with V waves and sleep spindles. Awake EEG showed 8-9 Hz alpha waves in posterior regions. There were no cerebral assymetry, focal slowing or epileptiform discharges.

A diagnosis of major neurocognitive disorder due to TBI was made and osmotic release oral system (OROS) MPH was administered with the dose of 18 mg/day for attention problems. After one week, patient was admitted to the clinic with the complaints of talking to himself, delusional thoughts, irritability and sleeplessness. He was reported to speak everyone that he and his father were prophets. He was reported to be more talkative than usual especially in social situations. His psychiatric interview revealed elevated mood, incongruent affect and delusional thoughts about his mission to save the world. The patient's Young Mania Rating Scale (YMRS) score was 29. His general pediatric and neurologic evaluation did not reveal any additional findings. The Naranjo adverse drug reaction probability scale score was 8. With the suspect of a medication induced adverse reaction, MPH was discontinued and all of the symptoms resolved in 3 days. Three days after the discontinuation of MPH, YMRS score decreased to 4.

DISCUSSION

Almost one fifth of children who sustain a TBI are under the risk of attention problems after injury.[9] Children with severe TBI are shown to have a greater risk for developing postinjury attention problems.[10] The consequences

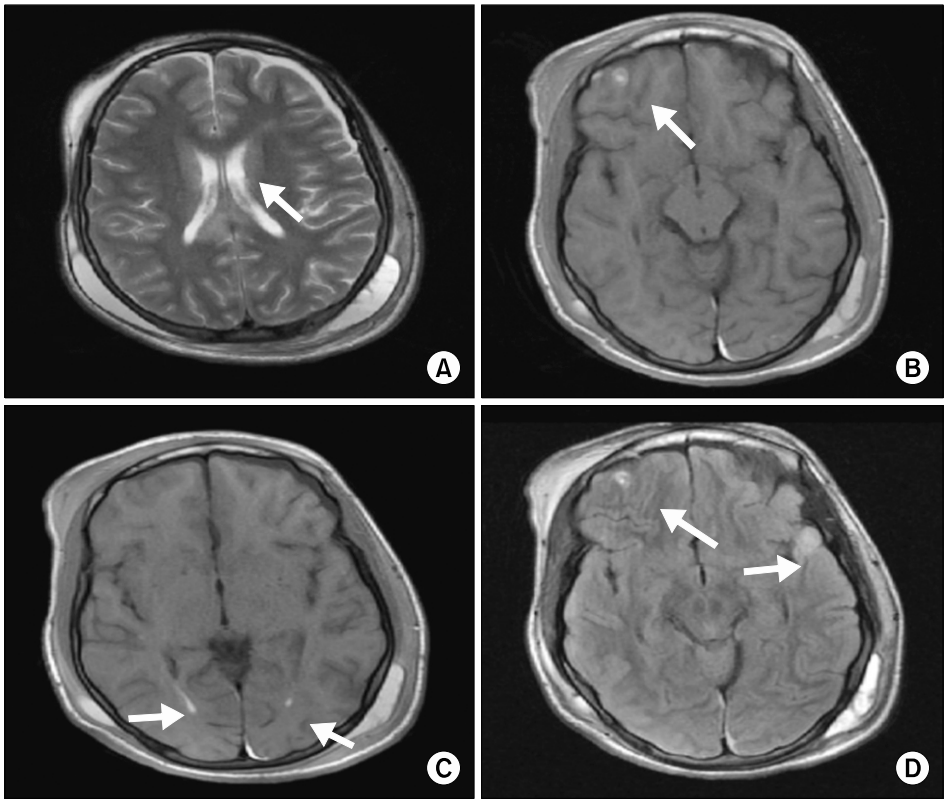

Fig. 1. (A) On the T2-weighted axial image, increased focal signal intensity in corpus callosum. (B) On the T1-weighted axial image, hemorrhage and contusion in right frontal lobe grey matter. (C) On the T1-weighted axial image, minimal intraventricular hemorrhage. (D) On the fluid-attenuated inversion recovery (FLAIR) examination axial image, contusion and related increase in focal signaling in the right frontal and left temporal lobes grey matter.

of attention problems may extend beyond school functioning and can have negative impacts on a child's social relationships, emotional well-being, self esteem and quality of life.[11)]

Despite the high burden of attention problems in children and adolescents after TBI, only a limited number of controlled studies, all with small sample size and short duration, have been conducted to date. In an early study by Williams *et al*.,[12)] no signifficant effect of MPH was reported in 10 children with mild-to-severe head trauma. Mahalick *et al*.[13)] studied 14 children with TBIs of varying severity and MPH treatment resulted in significantly greater scores on the study measures of attention when compared with placebo. A chart review on 10 children with TBI has also shown positive findings on attention and behavior.[14)] A recent placebo controlled study, in which only five children with TBI have completed the study procedures, reported a small but significant effect on attention and hyperactivity with psychostimulants.[1)] Of note, none of the mentioned studies focused on the possible adverse effects of MPH and treatment associated mania or psychosis was not reported.

The risk of stimulant-induced psychosis and/or mania symptoms in children as estimated as 1 in 400.[8)] In a significant proportion of cases, toxicosis symptoms develop at the theraupatic doses of stimulants.[15)] Presenting symptoms usually emerge shorty after the start of the treatment or with a dose increase. In the great majority of such reports, behavioral symptoms resolve within a week after discontinuation.[16)] In accordance with the literature, manic symptoms started within the first week of MPH treatment, and rapidly subsided with discontinuation in our case. It has been shown that stimulant induced toxicosis symptoms are highly similar to those of bipolar disorder or schizophrenia.[8)] Symptoms may include euphoria, grandiosity, paranoid delusions, confusion and auditory hallucinations.[8,16)] Bizarre behaviors, hallucinations involving visual and/or tactile sensations of insects, snakes, or worms were also reported, especially in younger children.[17)] Our case also presented with grandiose delusions with religious content and socialy disinhibited behaviors which are commonly reported in manic episodes. In the differential diagnosis, bipolar disorder manic episode might be a possibility. However, the short duration of symptoms and the direct relationship with MPH use do not fit the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) criteria.[18)] Moroever, MPH-induced mania symptoms must be considered as a different clinical entity than the highly hereditery bipolar disorder. Acute onset of clinical picture, absence of mood symptoms in the prior psychiatric history and the lack of the family history in the present case are against a bipolar disorder diagnosis.[17)] In light of the available research and the suggested terminology, toxicosis term appears to be the best description of the case.

Although not completely identified, the emergence of psychotic symptoms may be related with the mechanism of action of MPH. MPH mainly works via the reuptake inhibition of dopamine, and less prominently noradrenaline, in the striatal regions. Effects on selected frontal and temporal regions were also observed with MPH use.[19)] Increased dopaminergic and/or noraderengic transmission with MPH, especially in higher doses, may be associated with psychotic/manic symptoms.[8)] Although stimulant-induced toxicosis appears to be an idiosyncratic reaction, some risk factors have been proposed. The use of high doses, premorbid ADHD symptoms and mental retardation were suggested to be related with an increased risk.[20)]

In the present case, the disrupted brain regions, as shown by the MRI findings, might give rise to a vulnerability for this behavioral adverse reaction. Right frontal, left temporal regions and corpus callosum, which were injuried in our case, are among the shown regions for the neurobiology of bipolar disorder in children and adolescents.[21,22)] Deficits in executive functions, visual-motor responses and working memory were reported in children with traumatic lesions on corpus callosum.[23)] The previous literature on mania symptoms after TBI is limited. Some studies have shown that multifocal lesions, mainly in temporal poles, are associated with mania.[24)] Both left and right temporal lesions were found to be linked with mania symptoms.[25,26)] A previous review on 66 adult TBI patients have shown the incidence of mania as 9% within 12 months of follow-up.[27)] There is evidence that severe TBI and male gender are associated with an increased risk of mania.[28,29)] The relationship between age and mania has not been specifically documented, however, younger age has been found as a risk factor for psychiatric disorders after TBI.[30,31)] In our case, diffuse disruptions in fronto-temporal grey matter might have resulted with an increased vulnerability to manic symptoms. Since these vulnerable regions are also among the shown target regions of MPH, an additive effect of MPH might have occured. In other words, MPH use might have led to either irreguler or overt activity in the brain regions which were already disrupted with the head trauma. Eventually, the additive effects of head trauma and MPH use might have resulted in the

emergence of manic symptoms in our case, which did not have any premorbid psychiatric history.

This case highlights the fact that therapeutic dose of MPH may cause mania-like symptoms in children with TBI. Close monitarization and slow dose titration are crucial when considering MPH in children with TBI.

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