Gülhane Tıp Dergisi 2006; 48: 169-171

OLGU SUNUMU

Ischemic stroke associated with the use of short term oral methylphenidate

Canan Kocaman (*), Olcay Işık (*), Gülseren Arslan (*), Ender Aksüyek (*), Rengin Şiraneci (*)

Summary

Methylphenidate is a central nervous system stimulant used for the treatment of attention deficit hyperactivity disorder and narcolepsy. In this report, a 9-year-old boy with cerebral ischemic stroke developing after the short term use of oral methylphenidate is presented. The experience of our patient and a review of the literature suggest that consumption of oral methylphenidate may be a potential predisposing factor for stroke.

Key words: Methylphenidate, ischemic stroke, short term use

Özet

Kısa süreli oral metilfenidat kullanımı ile ilişkili iskemik inme

Metilfenidat, dikkat eksikliği-hiperaktivite hastalığı ve narkolepside kullanılan bir santral sinir sistemi stimülanıdır. Bu makalede, kısa süreli oral metilfenidat kullanımını takiben serebral iskemik inme gelişen 9 yaşında bir erkek çocuğu sunulmaktadır. Bizim hastamızdaki deneyimimiz ve literatür incelemesi, oral metilfenidat kullanımının inme için potansiyel predispozan bir faktör olabileceği fikrini desteklemektedir.

Anahtar kelimeler: Metilfenidat, iskemik inme, kısa süreli kullanım

***S.B. Bakırköy Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Nörolojisi Ünitesi, İstanbul**

Ayrı basım isteği: Dr. Olcay Işık, Büyükşehir Mah., Bahçeli Sok. A/18A Kat: 5, Daire: 22, Beylikdüzü, Büyükçekmece, İstanbul
E-mail: isik_orkun@hotmail.com

Makalenin geliş tarihi: 15.08.2005
Kabul tarihi: 28.04.2006

Giriş

Methylphenidate (MP) is a piperidine-derived central nervous system (CNS) stimulant (1). It is commonly used for the treatment of attention deficit hiperactivity disorder (ADHD) among children and of narcolepcy in adults (1). Some studies suggest possible therapeutic uses for methylphenidate in elderly patients with depression (2), patients with post-stroke depression (3), those with human immunodeficiency virus infection (4), those with traumatic brain injury (5), and cancer patients (6). This drug is related to amphetamine and other psychostimulants.

In the brain, MP increases the extracellular levels of dopamine and norepinephrine in a manner similar to cocaine and amphetamine (7). MP blocks the dopamine transporters in the presynaptic cell membrane, leading to increased extracellular levels of dopamine, and affects the cortex, medulla and bulbus. However, unlike the other two psycho-stimulants (cocaine and amphetamine), MP does not affect the serotonergic system (8,9), and hence, it has been used as a tool in animal experiments for characterizing dopamine-behavior relationship without a serotonin effect (9). MP's behavioral profile in rats, including induction of locomotor activity and stereotypes, resembles those of cocaine and amphetamine. Chemically similar to cocaine and other simulants, MP presents a pragmatic paradox (10); it decreases activity and increases the ability to concantrate in children with ADHD. Despite decades of experience with methylphenidate, however, limited information is available regarding the incidence of neurologic complications with use as a stimulant.

Neurologic complications following long term oral methylphenidate therapy have been reported (10). This report describes a child who suffered from a rare neurologic complication, ischemic stroke following the use of short term oral methylphenidate for ADHD.

Case Report

A 9-year-old boy suddenly developed left-sided weakness without loss of consciousness while having breakfast. His weakness progressed

over the next one hour. He was in good general health before the incident. He had no significant medical history. His prenatal, natal and postnatal histories were normal. He had no similar symptoms in the past. His family members had no risk factors for any vascular disease. He had used methylphenidate hydrochloride tablets (60 mg per day by mouth) for the last 6 months. It had been started by a pediatric psychiatrician for the attention deficit.

General physical examination with emphasis on the cardiovascular system showed no abnormalities. His blood pressure was 100/70 mmHg on admission and it was normal during hospitalization. There was no evidence of needle puncture, superficial venous thromboses over the extremities, nasal mucosal ulceration or septum perforation. At neurologic examination, mental state and speech were normal. There was a left central facial palsy. Other cranial nerves were intact. Funduscopic examination showed a normal vascular pattern and optic disc. There was no visual field defect. Right upper and lower extremites had normal muscle tone and strength, whereas the left extremities had decreased muscle tone. Left upper extremity strength was 2/5 both proximally and distally. Left lower extremity strength was 1/5 and 2/5 at proximal and distal, respectively. Muscle bulk was normal. Muscle stretch reflexes were diminished throughout on the left side in comparison to right. There was no sensory loss or extinction. The plantar reflex was upgoing on the left. There were no primitive reflexes. There was no evidence of limb incoordination or cerebellar ataxia out of proportion to weakness. He was not able to walk at the time of presentation.

The following laboratory tests or investigations showed normal results: complete blood count with differential, sedimentation rate; blood chemistry and electrolytes, plasma homocystein level, C-reactive protein and lipid profile; serum protein electrophoresis; serum VDRL, anti-HIV, anticardiolipin, antinuclear and ds-DNA antibodies; serum protein C, protein S, antithrombin III, 20210 A gen mutation, factor V Leiden and activated partial thromboplastin time; liver enzymes; urinalysis; CSF analysis including electrophoresis; ECG, chest X-ray and transesophageal echocardiography.

Brain MR scan showed acut infarction involving the caput of right caudate nucleus, putamen and adjacent anterior limb of the internal capsule (Figure 1). Magnetic resonance angiography was normal. His recovery stage was uneventful. However, convulsion appeared 3 months later, and anticonvulsion therapy was started. The medical therapy was only salisilat preparation after this acut infarction. Physiotherapy program was continued approximately 3 months. After this therapy program, his neurological deficit was minimal. His convulsion did not recur later. He is under follow-up program of the Department of Pediatric Neurology.

Discussion

Stroke is relatively rare in childhood. Incidence of ischemic stroke in pediatric population is 0.6 to 3.3 in 100 000 children. Ratio of ischemic to hemorrhagic stroke is 1/1.5 in childhood (11). Many strokes in children do not have a known etiology or a complication of a disease originating outside the central nervous system (CNS). Congenital heart disease, sickle cell disease, vasculitis, infection, hypercoagulable states, trauma and drugs are the usual causes of childhood stroke (11).

In the etiology, after eliminating all the causes, the main cause of stroke may be use of a drug, especially psychostimulant agents as in our case. Amphetamine has been implicated in the etiology of cerebral vas-

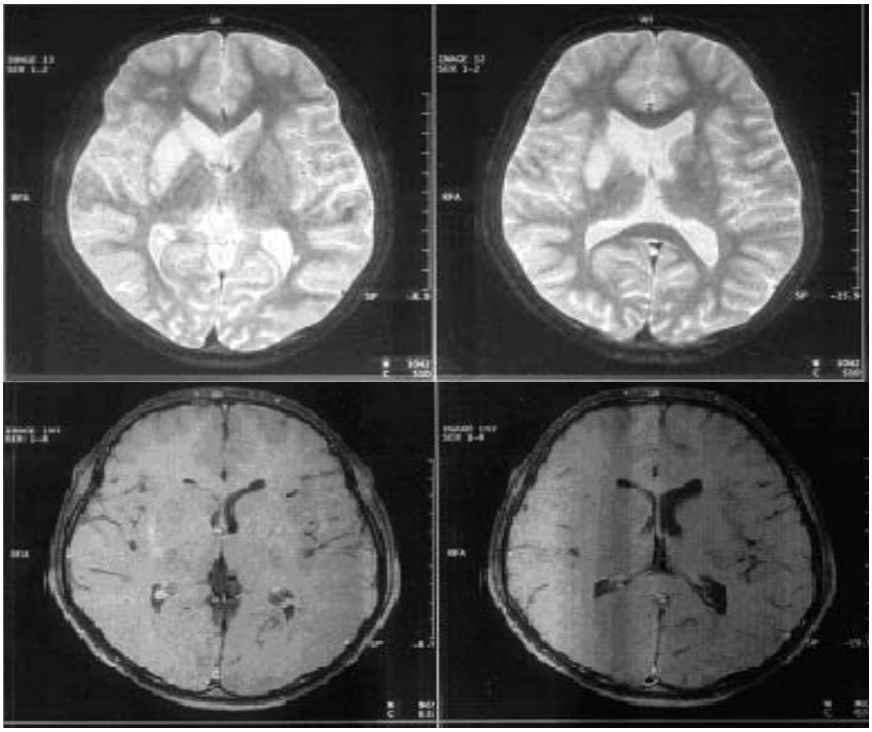

Figure 1. Cranial magnetic resonance scans show acut infarction in the caput of right caudate nucleus, putamen and adjacent anterior limb of the internal capsule on the T1 and T2 sequences

culitis and stroke. MP, which is structurally and pharmacologically similar to amphetamine and cocain, is widely used in the treatment of hyperactivity and attention deficit disorder in children. Although psychiatrists and pharmacologists have used it to treat ADHD for 40 years, they have never known completely how it worked (10). Earlier research has shown that cocain blocks about 50% of dopamine transporters, leading to a surfeit of dopamine in the synapse and a hit of pleasure. Because of MP's chemical similarities to cocaine, pharmacologists thought that it might work in the same way, only less potently, blocking fewer transporters. Animal studies with high doses of MP indicated that this could be the case (10).

Amphetamine-induced vasculitis was first described in drug abusers in 1970 (12); the pathophysiology and pathology of the vascular abnormalities, particularly in the central nervous system, remain poorly understood. Lymphocytic infiltration around brain arterioles has been produced experimentally in monkeys with repeated intravenous administration of methamphetamine (13). Intravenous MP, like methamphetamine, can produce angiographic changes including decreased vessel calibre and absence of filling in small middle cerebral artery branches (14). Recent clinical reports have reported associated irregularity and partial occlusion of small cerebral vessels with oral amphetamine use in non-drug abusers (15). Given its pharmacological similarity to amphetamine, the association of MP with cerebral arteritis is not unexpected, yet has not been previously reported.

A clinical report by Trugman described an 12-year-old patient with hemidystonia, few years after experiencing ischemic cerebral infarction. The patient was diagnosed to have ADHD at age five and treated with MP 20 mg per day until age 12 when right hemiparesis and aphasia suddenly developed. Cerebral angiography showed occlusion of the left anterior cerebral artery and a branch of the left middle cerebral artery. Brain MRI confirmed infarction in the left striatum and internal capsule (16).

Schteinschnaider et al. reported an eight-year-old boy with ADHD, who developed repeated episodes of hemidystonia and ataxia, while receiving MP 20 mg daily for 18 months. An MRI showed thalamic infarction, and an angiogram revealed occlusion of both cerebral arteries (17).

The occurence of acut infarction involving the caput of right caudate nucleus, putamen and adjacent anterior limb of the internal capsule following the use of short term oral methylphenidate in our patient who did not have any known risk factor for cerebrovascular disease, suggests an association between this drug and cerebral infarction. It seems justified to consider the use of short term oral methylphenidate as a potential predisposing factor for stroke in this patient.

We draw your attention to the risk of using oral MP, which is taken by many children in recent years. Although the pathogenesis of this cerebral infarction is unclear, we believe that physicians who prescribe this drug should be aware of this potential possibility.

References

1. Challman TD, Lipsky JJ. Methylphenidate: its pharmacology and uses. Mayo Clin Proc 2000; 75: 711-721.
2. Jansen IH, Olde Rikkert MG, Hulsbos HA, Hoefnagels WH. Toward individualized evidence-based medicine: five "N of 1" trials of methylphenidate in geriatric patients. J Am Geriatr Soc 2001; 49: 474-476.
3. Johnson ML, Roberts MD, Ross AR, Witten CM. Methylphenidate in stroke patients with depression. Am J Phys Med Rehabil 1992; 71: 239-241.
4. Hinkin CH, Castellon SA, Hardy DJ, et al. Methylphenidate improves HIV-1 associated cognitive slowing. J Neuropsychiatry Clin Neurosci 2001; 13: 248-254.
5. Glen MB. Methylphenidate for cognitive and behavioral dysfunction after traumatic brain injury. J Head Trauma Rehabil 1998; 13: 87-90.
6. Rozans M, Dreisbach A, Lertora JJ, Kahn MJ. Paliative uses of methylphenidate in patients with cancer: a review. J Clin Oncol 2002; 20: 335-339.
7. Meririnne E, Kankaanpaa A, Seppala T. Rewarding properties of Methylphenidate: sensitization by prior exposure to the drug and effects of dopamine D1- and D2- receptor antagonists. J Pharmacol Exp Ther 2001; 298: 539-550.
8. Koe BK. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. J Pharmacol Exp Ther 1976; 199: 649-661.
9. Segal DS and Kuczenski R. Escalating dose-binge treatment with methylphenidate: role of serotonin in the emergent behavioral profile. J Pharmacol Exp Ther 1999; 291: 19-30.
10. Vastag B. Pay attention: ritalin acts much like cocaine. JAMA 2001; 8: 22-29.
11. Kirkham FJ, Prengler M, Hewes DKM, Ganesan V. Risk factors for arterial ischemic stroke in children. J Child Neurol 2000; 15: 299-307.
12. Citron BP, Halpern M, Mc Carron M, et al. Necrotizing angiitis associated with drug abuse. N Engl J Med 1970; 283: 1003-1011.
13. Rumbaugh CL, Bergeron TR, Scanlon RL, et al. Cerebral vascular changes secondary to amphetamine abuse in the experimental animal. Radiology 1971; 101: 345-351.
14. Rumbaugh CL, Fang HCH, Higgins RE, et al. Cerebral microvascular injury in experimental drug abuse. Invest Radiol 1976; 11: 282-294.
15. Harrington H, Heller HA, Dawson D, et al. Intracerebral hemorrhage and oral amphetamine. Arch Neurol 1983; 40: 503-507.
16. Trugman JM. Cerebral arteritis and oral methylphenidate. Lancet 1998; 1 (8585): 584-585.
17. Schteinschnaider A, Plaghos LL, Garbugino S, et al. Cerebral arteritis following methylphenidate use. J Child Neurol 2000; 15: 265-267.