Type 3 Case of Yasui Classification

Effects of Kampo Medicines on Loss of Appetite and Irritation Caused by Attention Deficit Hyperactivity Disorder Medication

Kaori Kimata
Kawashima Family Clinic

Abstract

Methylphenidate hydrochloride sustained-release tablets and atomoxetine hydrochloride are preferred drug treatments for attention deficit hyperactivity disorder (ADHD), but both drugs often cause loss of appetite or irritability. In this study, we examined the effects of *shikunshito* and *rikkunshito* administered to alleviate these adverse effects. Although there were cases in which oral administration was not possible due to the taste or formulation, following administration, loss of appetite improved in 1–2 months. Because patients with ADHD are often "inattentive," missed doses did occur; however, it was considered that patients continued taking Kampo because they felt it was effective. Many children with ADHD experience stress related to their condition and may have low self-esteem. Considering such condition of children with ADHD as "qi-kyo (qi deficiency)," *shikunshito* and *rikkunshito* improved gastrointestinal motility and sustained patient motivation.

Keywords: attention deficit hyperactivity disorder, loss of appetite, *shikunshito*, *rikkunshito*

Introduction

Drug treatment for attention deficit hyperactivity disorder (ADHD) includes methylphenidate hydrochloride sustained-release tablets (MPH), covered by health insurance for children since 2007, and atomoxetine hydrochloride (ATX), covered since 2009. As both drugs sometimes cause loss of appetite as a side effect[1)2)], these medications are often discontinued prior to achieving their optimal effects. Reports indicate that *rikkunshito* is an effective treatment for loss of appetite in patients undergoing chemotherapy[3)4)]. In this study, we examined the effects of Kampo medicines administered to treat loss of appetite and irritability due to the administration of MPH and ATX.

Patients and Methods

Patients included 20 pediatric males who visited our developmental outpatient clinic during the 4 years between January 2014 and May 2017 and were prescribed MPH or ATX. They exhibited loss of appetite and irritability, for which Kampo drugs were additionally prescribed. The patients were all males and between 6 and 14 years of age at the time of Kampo medicines administration. Six patients had comorbid autistic spectrum disorder.

ADHD medication doses were ATX 50 mg/day (n = 1), MPH 18 mg/day (n = 8), MPH 18 mg/day (n = 1), ATX 10 mg/day (n = 1), and MPH 27 mg/day (n = 10) (Table 1). Loss of appetite, as a consequence of MPH administration, tended to increase in severity with the dose. It often appeared from the day the medication was administered. We attempted to prevent a significant decrease in daily intake by reducing the amount of school lunch that the children consumed for the first 1–2 weeks after starting the medication, while increasing the number of snacks and amount of food served at dinner. If loss of appetite persisted for ≥1 month or worsened due to environmental changes, Kampo medicines were added.

Rikkunshito extract granules (Tsumura & Co., Tokyo, Japan) at 5.0 g/day or *shikunshito* extract tablets (Osugi & Co., Osaka, Japan) at 12 tablets/day were administered before breakfast and dinner to combat loss of appetite. We explained the taste and formulations of the drugs to the patients and their parents or guardians. In cases where the patient could only tolerate the granulated formulation, *rikkunshito* extract granules were prescribed. If the patient preferred tablets, we prescribed *shikunshito* extract tablets.

In terms of response evaluation, we considered the drugs to be effective if consumption of food increased by more than half at school lunch. The medications were considered ineffective if loss of appetite persisted, or if the dose of MPH or ATX had to be reduced. The medication effects were considered unknown if oral administration could not be continued or evaluation was difficult due to poor medication compliance.

Results

The results of this investigation are depicted in Table 1. Of the 20 patients, 2 took *rikkunshito* extract granules, and 18 patients took *shikunshito* extract tablets. Many of the patients were sensitive to the drug formulation, smell, or taste and therefore refused the granular formulation or could not continue to take the granular formulation because of time constraints. In those cases, *shikunshito* extract tablets, with similar crude products and indications as *rikkunshito*, were prescribed so that the patients could continue to take the medication.

We found that patients often forgot to take the drugs before dinner. Twelve patients took their medication only once in the morning, and 8 patients took their medications twice per day, every morning and evening. Appetite stimulation effects were "good" in 16 cases, had "no effect" in 3 cases, and were "unknown" in 1 case. Ten patients out of the 16 that exhibited a "good" response to the drug discontinued the medication within 2 months. In 14 cases, administration of Kampo medicines was started between July and November, indicating that more patients appeared to experience loss of appetite during summer or at the start of sports day practice.

There was no case in which drug therapy for ADHD was discontinued due to sustained loss of appetite. In 1 case, the dose was reduced due to loss of appetite and nausea, and in another case, the dose was reduced because the patient's ADHD symptoms improved.

Three cases exhibited irritability and frequent episodes of crying in addition to loss of appetite; therefore, we added 2.5 g/day of *kanbakutaisouto* (Tsumura & Co., Tokyo, Japan) before dinner. In 3 cases with continuous irritability and agitation, *shikunshito* was discontinued and switched to *daisaikoto* extract tablets (Osugi & Co., Osaka, Japan) at 6 tablets/day before breakfast. After switching Kampo medicines, the patients with irritability showed improvement in symptoms. The following Kampo medicines were additionally prescribed: *hangekobokuto* for severe anxiety (n = 1); *shokenchuto* for repeated abdominal pain (n = 2); *goreisan* for nausea (n = 1); and *hangeshashinto* for sustained diarrhea (n = 1). Due to the small sample size, individual examinations of each side effect were not performed.

Case presentation

Case 10: A 10-year-old 5th grade male student.

At first consultation: The patient was in 3rd grade. He visited the clinic accompanied by his mother.

Chief complaint: The patient was advised by his classroom teacher to consult a developmental outpatient clinic for his poor conduct in the classroom.

Patient's complaints: difficulty in listening to others, often spilling drinks; often getting lost during early childhood, restlessness at home, and frequent movement.

Parental concerns: If medicine improved the patient's condition, the mother requested that pharmacological treatment be initiated. The patient's mother also wanted to better understand the patient's psychological status.

Perinatal period: Unremarkable.

Developmental history: During early infancy, the patient was sensitive to sound and was a shallow sleeper. He did not exhibit stranger anxiety.

At 1 year of age, the patient started running as soon as he started walking. Patient had delayed speech and began speaking words at the age of 22 months.

At 2 years of age, he had difficulty understanding, even when auditory information was repeatedly presented. He liked to climb to high places and was restless, with frequent movement. At 3 years of age, he frequently misbehaved, despite warnings, and was restless. He showed great interest in letters and numbers. At 4 years of age, he showed no avoidance of dangerous activities and required repeated redirection. He talked about many things, but did not understand the feelings or positions of others. He was obsessed with winning and losing and had trouble maintaining friendships. Additionally, he often forgot his belongings.

[ADHD checklist (behavioral questionnaire) for children aged ≥6 years]

Inattention (7 points): does not pay attention to details while studying; has difficulty focusing on activities; cannot listen to instructions to the end; avoids tasks; often gets distracted; has difficulty learning tasks and activities in order; does not seem to hear when being spoken to.

Hyperactive/impulsive (5 points): restless and keeps moving; cannot keep still; talkative; answers questions without listening to the end; leaves seat when required to be seated.

Treatment course:

We encouraged the family, especially the mother, and the classroom teacher to understand the developmental characteristics of ADHD and discussed the following recommendations: (1) adjustment of the environment, such as reducing wall hangings that may be distracting; (2) how to talk to the patient, such as giving instructions separately for each item, and sending a signal to pay attention; and (3) how to support the patient when he gets in trouble. We had an individual interview with the patient once a month, where we observed the patient could not help touching whatever he saw, frequently turned around in his chair, switched from one topic to another during conversations, and constantly moved around during games, indicating an inability to complete a conversation or a game to some extent. MPH (CONCERTA®) was started for hyperactivity and impulse control. The patient started taking MPH at 18 mg/day during the summer vacation prior to the 3rd grade, and loss of appetite appeared on the first day of drug administration. Starting in September, we reduced the amount of food served during school lunch by half and increased the amounts of snacks and dinner.

When sports day practice started in early September, he also experienced loss of appetite in the evening and his daily intake decreased to about half of pre-medication levels. Because the patient was unable to take the granulated formation, we prescribed *shikunshito* extract tablets–at 12 tablets /day before breakfast and dinner. Although the patient was actually taking *shikunshito* only before breakfast, his appetite improved about 1 week after starting the medication. At this time, the patient was eating half of his school lunch and all of his dinner each day. After the sports day ended in October, he started to eat the full amount of school lunch. After 1 month, his appetite improved, and *shikunshito* was discontinued.

After starting MPH at 18 mg/day, he could remain calm in class for longer periods and required less frequent redirection by the classroom teacher. However, while learning at home, he often cried for hours.

In the 4th grade, he started to receive special guidance, in addition to his general classwork. At our clinic, we started to provide social skill training with the help of a psychotherapist and separately interviewed the patient and his mother. When practice for the sports day started in September, the patient found it difficult to focus and participate during class. He continued to be absentminded and spent time playing alone with his hands, disconnected from class activities. Then MPH dose was increased to 27 mg/day. While the patient was under observation, his appetite decreased, and he was barely able to eat school lunch. Beginning in

November, we prescribed *shikunshito* extract tablets at 6 tablets/day before breakfast.

After taking Kampo medicines, his appetite returned to the same level as when he was taking 18 mg/day of MPH, and he was once again able to eat half of his school lunch. After increasing MPH dose to 27 mg, he was able to listen to instructions in group settings and throughout the day. He remained calm and participated in class while at school, and he was more easily able to complete his homework. At present, the patient has been taking MPH at 27 mg/day for 6 months along with *shikunshito*.

Discussion

MPH suppresses hyperactivity and impulsivity, hallmark symptoms of ADHD, by activating the dopaminergic nervous system. MPH also suppresses eating behaviors, which can lead to a loss of appetite[1)2)]. Loss of appetite is generally self-limiting and improves within 2–3 weeks, but if it does not improve, this adverse effect can alleviate by withdrawing the drug during weekends or reducing the drug dosage. There have been reports on the effects of *rikkunshito* on loss of appetite during chemotherapy[3),4)], and we hypothesized that Kampo medicines would have similar effects on loss of appetite caused by MPH or ATX.

The crude products of *rikkunshito* are ginseng, *Atractylodis* Rhizoma, *Poria*, licorice, *Pinelliae* Tuber, citrus unshiu peel, ginger, and Z*izyphi* Fructus, and it is combined with *shikunshito* and nichinto. In addition to the digestion and food absorption effects of *shikunshito*, *rikkunshito* has the effects of *Pinelliae* Tuber and therefore suppresses nausea and vomiting due to fluid retention in the stomach and the effects of *Citri Unshiu* Pericarpium, which reduces gastric fluid retention and sputum. Similar to *shikunshito*, *rikkunshito* also tonifies qi. It is used to treat fatigue, nausea, loss of appetite, chronic gastritis, and symptoms of gastroptosis. *rikkunshito* enhances appetite and gastrointestinal motility by its antagonistic effects on serotonin 2 receptors. A report describes the effects of *rikkunshito* for stress-related loss of appetite, focusing on serotonergic neurons involved in eating behavior[4)].

Shikunshito consists of *Ginseng* Radix, *Atractylodis* Rhizoma, *Poria*, *Glyzirrhizae* Radix, *Zingiber* Rhizoma, and *Zizyphi* Fructus. A combination of *Ginseng* Radix, *Atractylodis* Rhizoma, *Poria*, and *Glyzirrhizae* Radix are the crude products of *ninjinto*, to which *Poria* is added instead of *Zizyphi* Fructus. Its diuretic effects are enhanced, and it is more effective for phlegm-dampness pattern than for *ninjinto*. This formulation tonifies qi and is used to treat impaired digestion and absorption (weakness of the stomach and spleen)[5)]. The difference between *rikkunshinto* and *shikunshito* is that *shikunshito* contains neither *Pinelliae* Tuber, which suppresses nausea and vomiting due to gastric fluid retention, nor *Citri unshiu* Pericarpium, which removes phlegm; thus, *shikunshito* has no effect on nausea.

Rikkunshito extract granules at 5.0 g/day or *shikunshito* extract tablets at 12 tablets/day before breakfast and dinner were prescribed for loss of appetite secondary to ADHD treatment drugs. In cases in which oral administration was continued, the effects of *rikkunshito* and *shikunshito* appeared in 1–2 months. A patient who could barely eat school lunch was soon able to eat more than half with improvement in appetite. Once patients adapted to the environmental changes and the temperature became cooler, those patients who wanted to discontinue Kampo medicine and those who frequently forgot to take their medication discontinued use within 2 months. The 3 patients who continued Kampo medication for 4–10 months continued to eat smaller school lunches, as did patients who were picky eaters. In these individuals, Kampo was continued over time. One patient continued taking *shikunshito* for 9 months. In this case, his appetite completely recovered to the extent that he consumed more than 1 serving of school lunch, but because Kampo medication helped him

stay calm, administration was continued. Soon after that, his MPH dose was reduced.

Regarding the time when Kampo medicines were initiated, 14 cases (70%) started during summer or fall when practices for field day were being held. In these cases, loss of appetite may have been caused by higher environmental temperatures and increased humidity as well as deterioration of ADHD symptoms due to changes in school–life rhythm.

There were many cases in which continuing medication was difficult due to the developmental characteristic of "inattention." In 12 cases (60%), despite being instructed to take medication twice per day, before breakfast and dinner, patients were actually taking only 1 dose per day in the morning. However, they were able to continue taking Kampo medicines every day because they experienced an effect from the medication. If continuously taken twice per day in the morning and evening, the appetite-stimulating effects can be increased. Therefore, medication counseling is necessary in the future. Children with ADHD are often cautioned and restricted in their behaviors due to developmental characteristics, and they are under continual life stressors. If we consider the condition of these children, whose self-esteem declines by repeated failures due to inattention, as "qi deficiency", *rikkunshito* and *shikunshito* can enhance motivation in addition to improving gastrointestinal motility.

Among the 6 cases that showed worsened irritability and agitation during the administration of ADHD medication, *kanbakutaisoto* extract granules were added in 3 cases, and the medication was switched to *daisaikoto* extract tablets in the other 3 cases. In both groups, irritability improved, indicating that the medication was effective; however, the sample size was small, and future studies with more cases are necessary.

Summary

When *rikkunshito* or *shikunshito* was administered for loss of appetite secondary to treatment with ADHD medicine, 16 out of 20 cases showed improvement. In addition, among the 16 cases that showed improvement, 10 cases were able to finish taking Kampo medicines within 2 months. There was no case in which ADHD medicine had to be discontinued due to persistent loss of appetite.

The abstract of this paper was presented at the 45th Japan Pediatric Oriental Medicine Society Annual Meeting (Nagoya, 2017).

References

1) Miyajima Y., Pharmacotherapy of attention deficit hyperactivity disorder (ADHD), J. Pediatr. Pract. 77:866–869, 2014.
2) Negoro H., Kyo M., Treatment of loss of appetite appeared during ADHD pharmacotherapy in children; Effect of mosapride citrate sustained release tablets on methlphenidate hydrochloride sustained-release tablet-induced loss of appetite, Clinical Psychiatry 17:669–676, 2010.
3) Ohno T., Mochiki E., Kuwano H., Side effects of chemotherapy and traditional Chinese medicine, Loss of appetite-*rikkunshito* . Journal of Clinical Surgery 68:1340−1344, 2013.
4) Yakabu Y., Action mechanisms of traditional Chinese medicine (1) *rikkunshito* and appetite control mechanisms mediated by ghrelin, Clinical Gastroenterology 28:221–230, 2013.
5) Inaki M., Fundamentals and practical guidance-Important Kampo Prescription Manual 25, *Shikunshito*. Kampo Practice 13:15–18, 1994.