A Case of Nocturnal Enuresis Associated with Attention-deficit/hyperactivity Disorder Successfully Treated with Guanfacine Monotherapy

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Nocturnal enuresis (NE) is a syndrome associated with abnormal nocturnal urine production, urination mechanism, and sleep arousal.
NE is strongly associated with attention-deficit/hyperactivity disorder (ADHD), and it has been reported that NE occurs in approximately 30% of children with ADHD. There have been several reports on the efficacy of atomoxetine as treatment for NE with ADHD, while the efficacy of guanfacine is still limited.
We report our experience of treating an 10-year-old girl with NE with ADHD with a single dose of guanfacine. The patient first visited our hospital because of difficulty concentrating, restlessness at home and school, and nocturnal incontinence. She was diagnosed with NE with ADHD based on a review of her personal history from her mother. Her NE symptoms improved with guanfacine monotherapy (1 mg/day. The patient weighed 28 kg).

Key words: nocturnal enuresis, attention-deficit/hyperactivity disorder, guanfacine, ADHD-Rating Scale- IV

INTRODUCTION

Nocturnal enuresis (NE) and attention-deficit/hyperactivity disorder (ADHD) are strongly associated and involve central nervous system immaturity [1]. Indeed, clinical features, including urgency and bladder overactivity, have been reported in children with ADHD [2], with NE observed in approximately 30% of children with ADHD [3], and the most frequent complication of NE is ADHD inattentive type [4].

Desmopressin has been recommended as the treatment for NE, and its efficacy has been well demonstrated [5]. In contrast, methylphenidate, atomoxetine, and guanfacine are mainly used for the treatment of ADHD. Among them, the efficacy of atomoxetine as pharmacotherapy for NE associated with ADHD has been reported [6, 7], but reports on the efficacy of guanfacine are limited.

Herein, we report our experience of treating a 10-year-old girl with NE associated with ADHD with a single dose of guanfacine.

CASE PRESENTATION

The patient was a 10-year-old girl who presented to our hospital with complaints of difficulty concentrating, restlessness, and nocturnal incontinence. When she was 7 years old, she visited the pediatrics department of another hospital due to the same complaints as mentioned above. Physical diseases such as renal and urinary tract diseases were ruled out, and she was diagnosed with NE associated with ADHD. She was referred to our hospital because her condition did not improve despite disease education and night alarm therapy she was not taking any medication.

At the first visit, the patient was seated in a restless manner and had dark circles under her eyes. The patient said, “I get yelled at for my restlessness” and “my sleep is too shallow; in addition, I always get scolded for wetting the bed around dawn.” Subsequently, we interviewed her mother to learn about the patient’s personal history. The patient was born at 39 weeks’ gestation, with no indications of delayed language or physical development during childhood. However, as an infant, she did not follow her mother or point to objects of shared interest. Further, she was always restless at home and at nursery school, making it difficult for her to follow instructions. She had many friends, but when they quarreled, she sometimes hit them. In elementary school, her restlessness and difficulty concentrating in class were noticed. She had no problems with her grades, but she was careless. She had nocturnal incontinence about 4–5 times per week, and the nocturnal incontinence was always at dawn. At the time of the first visit, the psychiatric findings of the patient included inattention, hyperactivity, and impulsivity. In addition, nocturnal incontinence was now observed about 2–3 times per a week. She was assessed using the ADHD Rating Scale-IV [8] for household use on the same day. Her total score was 26 points (19 points for inattention, and 7 points for hyperactivity and impulsivity).

A month after our initial examination, the class teacher also came to our hospital with the patient and her mother. We asked the class teacher how the patient was doing at school, and we heard that there were many careless mistakes, such as being restless in class

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and forgetting to write her name on tests. The class teacher then assessed the patient using the ADHD Rating Scale-IV for schools, and the total score was 29 points (20 points for inattention, and 9 points for hyperactivity and impulsivity). Therefore, we diagnosed the patient with NE associated with ADHD (careless type) based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and the patient and her mother were notified of the diagnosis. On the same day, guanfacine treatment was initiated (1 mg/day, the patient weighed 28 kg).

Two months after our initial examination, the patient said, "Since I started taking the medicine, I can sleep well at night, I've lost the dark circles under my eyes, and the number of times I wet my bed has decreased," and "I was told by my family that l was calm." Thus, the time zone of nocturnal incontinence has not changed, but the frequency of nocturnal incontinence decreased to about once per week.

Six months after our initial examination, the ADHD Rating Scale-IV score for household use was completed again, and the total score was 18 points (14 points for inattention and 4 points for hyperactivity and impulsivity). The ADHD Rating Scale-IV for schools was also completed again, and her total score was 21 points (18 points for inattention and 3 points for hyperactivity and impulsivity). Although her carelessness persisted, her hyperactivity and impulsivity improved. At school, she was able to attend classes more calmly and get along well with her friends. Nocturnal incontinence also improved, and the patient and her mother appeared to be relieved.

At present, one year has passed since our initial examination, and the patient has had no nocturnal incontinence for more than six months.

DISCUSSION

We report the case of a 10-year-old girl with NE associated with ADHD that was successfully treated with a single dose of guanfacine. The prevalence of NE in children aged 6–12 years ranges from 1.5% to 8.9% [9], with a relatively high rate of spontaneous remission of 10–15% per year after school age [9]. However, considering that the incidence of ADHD in children with NE is 3.4 times higher than that in a non-NE group [10], some cases of NE persist into adulthood, and the psychological burden on the individual is large. Therefore, the therapeutic significance of NE is considered quite high.

In addition to nocturnal alarm therapy [11], medications such as tricyclic antidepressants [12] and desmopressin [5] have been reported to be effective in the treatment of NE. However, atomoxetine [6, 7, 13], a drug for ADHD, and clonidine, an antihypertensive agent, have been reported to be effective in the treatment of NE associated with ADHD [14].

There are two factors that may have contributed to the improvement of NE in this case.

First, the guanfacine used in this case had some effect on the locus ceruleus nucleus. Atomoxetine was shown to improve ADHD symptoms by increasing dopamine and noradrenaline in the prefrontal area and nucleus accumbens by inhibiting dopamine and noradrenaline transporters in the plasma membrane of presynaptic terminals [13]. Clonidine, a presynaptic α2-adrenoceptor agonist, was shown to decrease norepinephrine by inhibiting the sympathetic nervous system [14]. Noradrenaline is produced in the locus ceruleus and spreads throughout the brain, where the micturition center is thought to be located [15]. The locus ceruleus is activated by the stimulation of bladder development during sleep, especially during deep sleep [16]. In addition, the locus ceruleus is axonally linked to the hypothalamus, where vasopressin, an antidiuretic hormone, is produced [17]. Thus, the locus ceruleus is highly associated with NE, and clonidine, similar to atomoxetine, may act in some way on the locus ceruleus to improve NE. Therefore, guanfacine used in this case is a postsynaptic α2-adrenoceptor agonist [18], and although its receptor is different from that of clonidine, it seems to have contributed to the improvement of NE through a similar mechanism.

Second, guanfacine improved the patient's sleep quality. It has been reported that both clonidine and guanfacine improve sleep quality by decreasing rapid eye movement (REM) sleep [18], which increases the rate of deep sleep in non-REM sleep. One of the causes of NE in this case was considered to be the immature diurnal secretion of antidiuretic hormone, which resulted from poor sleep quality. Improvements in sleep quality likely led to the secretion and action of antidiuretic hormone, which resulted in the improvement of NE.

In addition to the above two points, another factor contributing to improvements in the present case was thought to be that the self-esteem of the patient increased with the reductions in carelessness, hyperactivity, and impulsivity induced by guanfacine, and that the treatment volition for NE improved.

However, since the index of improvement in NE in this case was based on the subjective view of the mother, and the patient was only observed for a short treatment period, the possibility of natural improvement in NE cannot be denied. Though larger case studies are required to validate our results, this case demonstrates that nocturnal enuresis associated with ADHD can be successfully treated with guanfacine monotherapy.

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Dr. Takahashi has no conflicts of interests to disclose.

INFORMED CONSENT

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. This informed consent is maintained in the medical records for this patient.

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