



## CASE REPORT

# Risperidone-induced Enuresis Continuum in Two Pediatric Cases

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### ABSTRACT

Risperidone is an atypical antipsychotic agent, widely used in the management of anger, aggression, and behavioral problems in children and adolescents. Its use in children and adolescents is safe, and the most frequently reported side-effects are weight gain, listlessness, and increased appetite. Enuresis is a rare complication following risperidone use. This report describes two pediatric cases of enuresis developing following a risperidone use. The first case was a 9-year-old boy diagnosed with attention-deficit/ hyperactivity disorder with combined presentation and oppositional defiant disorder. Diurnal and nocturnal enuresis began on the fifth day of 0.5 mg risperidone therapy and resolved four days after discontinuation of risperidone. The second patient was a 13-year-old boy diagnosed with Down syndrome, intellectual disability, and conduct disorder. Diurnal and nocturnal enuresis started on the third day of 1 mg/day risperidone therapy and resolved 10 days after discontinuation of risperidone. Both patients were subsequently started on aripiprazole, with a low  $\alpha$ -1 adrenergic blocking effect, and no enuresis occurred during their follow-up visits.

Cases of both nocturnal and diurnal enuresis following risperidone use are rare in the previous literature. In addition to the central dopamine blocking caused by antipsychotics, mechanisms such as peripheral  $\alpha$ -blockage involvement in relaxation of the urethral muscles and blocking of the pudendal muscles with 5-HT<sub>2</sub> and 5-HT<sub>3</sub> antagonism have also been implicated in urinary incontinence. This report is important in terms of emphasizing the rare side-effect of both nocturnal and diurnal enuresis following a risperidone use. Considering also the adverse impact of urinary incontinence of patients' quality of life, it is important for clinicians to be aware of such a side-effect in order to increase compliance with treatment in patients.

**Keywords:** Antipsychotic, diurnal enuresis, nocturnal enuresis, risperidone, side effect

## INTRODUCTION

Enuresis is defined as involuntary urinary incontinence occurring after the age when control should be established. It is classified as nocturnal only, diurnal only, or both (continuum) (1). Although enuresis is seen in some psychiatric disorders or as a side-effect of antipsychotics, it is thought to be undiagnosed or reported less frequently by patients than is actually the

case because it is distressing and embarrassing or from a reluctance to ask clinicians (2). In the literature, various psychotropic agents have been reported to be capable of causing enuresis. Enuresis was determined in 20.7% of 82 patients using clozapine in one cohort study, while lower but significant enuresis was reported in subjects using olanzapine, quetiapine, and risperidone (3). Although the incidence of enuresis following risperidone use is very low, there has recently been an increase in the numbers of cases of nocturnal and diurnal enuresis following risperidone use in children and adolescents (4,5). In the majority of cases reported to date, enuresis has developed when risperidone was used in combination with selective serotonin reuptake inhibitors (SSRIs) or

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other antipsychotics (3). Our review of the literature revealed few data concerning enuresis continuum following a risperidone use (6,7).

Risperidone is an atypical antipsychotic agent with D2 and 5HT2 antagonism, widely used in the treatment of children and adolescents. It has been shown to be effective in behavioral disorders such as hyperactivity, irritability, self-harm behavior and stereotypes (8). While its use is safe in children and adolescents, the most frequent side-effects are increased appetite, weight gain, listlessness, and sedation (9). The reported incidence of risperidone-induced enuresis in the literature is less than 1% (10).

In this case report, we present two pediatric age patients in whom both diurnal and nocturnal enuresis developed shortly after the initiation of risperidone therapy and in which diurnal and nocturnal urinary continence was restored following the discontinuation of treatment.

## CASE PRESENTATIONS

### Case 1

A nine-year-old boy was brought to our outpatient clinic by his mother due to hyperactivity, inability to remain in one place, excessive talking, lack of interest in lessons, inattentiveness, forgetfulness, losing his belongings, low academic grades at school, arguing with elders, and conflict with his peers and sibling. According to information elicited from the family and teacher, the patient had been hyperactive since pre-school, was frequently involved in accidents, had been lacking interest in lectures since year one of elementary school, talking in class, forgetful and absent-minded, lost his belongings, and had fought with his peers and sibling, argued with elders and defied rules during the previous year. The patient was 132 cm tall and weighed 28 kg. No pathology was determined at physical examination. The patient had been delivered by cesarean section delivery at 34 weeks, had a surviving twin sibling, had received incubator care for one week, walked at the age of 10 months, began forming sentences at 16 months, established diurnal fecal

and urinary continence at two years and nocturnal urinary continence at three years. No enuresis or encopresis were present in the family history, and the twin sibling was under monitoring at an external center with a diagnosis of attention-deficit / hyperactivity disorder (ADHD). In his psychiatric exam, his intelligence was normal (IQ=110) and ADHD combined type and Oppositional Defiant Disorder (ODD) were determined based on DSM-5 diagnostic criteria. The patient was started on methylphenidate at 36 mg/day. At his follow-up exam after two months, despite an increase in interest in lessons and attention and a decrease in hyperactivity and talking in class, we learned that the patient's irritability, arguing with elders and fighting with his sibling persisted. The ODD symptoms persisted, and risperidone 0.5 mg/day was added to treatment. One week later, the patient represented to our outpatient clinic due to diurnal enuresis at least twice a day and nocturnal enuresis 1-2 times nightly that began on the fifth day of treatment. The patient's familial and medical history, urological examination and laboratory tests were within normal range. The fact that enuresis did not develop while receiving methylphenidate therapy but occurred after the addition of risperidone suggested risperidone-induced enuresis continuum. Risperidone therapy was stopped, and treatment continued with methylphenidate 36 mg/day. At evaluation two weeks subsequently, we were informed that diurnal and nocturnal enuresis resolved four days after discontinuation of risperidone therapy. His Naranjo adverse drug reaction probability scale score was 6 for the drug (11). It suggests a probable association between risperidone and emergence of symptoms of enuresis. ODD-related symptoms persisted, and aripiprazole 5 mg/day was added to the patient's treatment. No enuresis was observed during three-month follow-up with aripiprazole 7.5 mg/day and methylphenidate 36 mg/day therapy. Written consent was received from the patient and his family for the publication of this report.

### Case 2

A 13-year-old boy patient with Down syndrome was brought to our outpatient clinic by his parents due to

hyperactivity, irritability, self-mutilative behavior and damaging his surroundings. At interview with the family, we learned that the patient had been hyperactive and restless since the age of four years, and that for the previous two years he had bitten his arms, hit his head against the wall, and thrown objects when felt irritable, and had bitten his parents' arms when his demands were not met. There were no deteriorations of the patient's sleep and appetite and there were no psychomotor hyperactivity and psychomotor retardation. The patient had a previous psychiatric presentation to another center. He had been started on risperidone therapy, but the family had not used it. The patient had been delivered by the spontaneous vaginal route at 39 weeks and had been diagnosed with Down syndrome via karyotype analysis at the age of one year. He had walked at two years, been able to form two-word sentences at five years, and established diurnal urinary control at four years of age and nocturnal control at five years of age. He received special education and was unable to care for himself. No remarkable impairment was observed in terms of mood disorder. Intellectual disability (ID) and conduct disorder (CD) was diagnosed based on DSM-5 diagnostic criteria, and the patient was gradually started on 1 mg/day risperidone therapy. Two weeks subsequently, the patient represented to our clinic when symptoms of diurnal enuresis two to three times daily and nocturnal enuresis one or two times nightly that manifested on the third day of drug therapy failed to resolve. The patient's familial and medical history, urological examination and laboratory tests were within normal limits. The situation was assessed as risperidone-induced enuresis continuum, and risperidone therapy was stopped. At follow-up one month later, we learned that the diurnal and nocturnal enuresis had resolved entirely 10 days after discontinuation of risperidone. His Naranjo adverse drug reaction probability scale score was 6 for the drug (11), suggesting a probable association between risperidone and emergence of symptoms of enuresis. The patient's behavioral problems persisted, and aripiprazole 5 mg/day was added to treatment. No enuresis has been observed in the subsequent two months. Written consent

was received from the patient's family for the publication of this report.

## DISCUSSION

This report describes two pediatric age patients of diurnal and nocturnal enuresis occurring during risperidone therapy and rapidly entering remission following drug discontinuation, one patient being mentally normal and the other with neurodevelopmental retardation. Enuresis developing during risperidone therapy and resolving after discontinuation of treatment suggests a causal relation between risperidone and urinary incontinence. Previous cases and studies in the literature support such a relation (3,5-7). While the mechanisms involved in atypical antipsychotic-related enuresis are not yet fully understood, several theories have been proposed. These include overflow incontinence associated with urinary retention mediated by anticholinergic activity (12), decreased internal urethral sphincter tonus associated with  $\alpha$ 1 adrenergic blockage (13), pudendal reflex blockage via 5HT2 or 5HT3 antagonism (14), and decreased dopamine in the basal ganglia or imbalance between norepinephrine and dopamine in the basal ganglia (15). Waking for bladder emptying being prevented by the sedative effects of antipsychotics can also result in enuresis (16).

Risperidone primarily behaves as a dopamine type 2 (D2) and serotonin 2A (5HT2A) receptor antagonist, and also exhibits a powerful blocking effect on  $\alpha$ -1 and  $\alpha$ -2 adrenergic receptors. The  $\alpha$ -1 adrenergic system regulates internal urethral sphincter tonus (13). It is thought to lead to urinary incontinence by reducing internal urethral sphincter tonus with its adrenergic blocking effect. We think that risperidone might cause urinary incontinence with its antagonist effect on urethral sphincter  $\alpha$ -1 receptors.

The sedative effects of risperidone may lead to inability to wake and thus result in nocturnal enuresis. Since our case experienced enuresis not only during at night, and since the parents reported no waking

difficulties enduring risperidone therapy, enuresis did not seem to be sedation-related. Cases of enuresis continuum following risperidone use are very rare in the literature. Our report differs in that all previous cases have been diagnosed with autism (6,7). Both diurnal and nocturnal enuresis in both our cases resolved rapidly after discontinuation of risperidone, and no recurrence of incontinence occurred after switching to aripiprazole, another atypical antipsychotic with a low  $\alpha$ -1 adrenergic blockade effect. Aripiprazole is an atypical antipsychotic agents with partial agonist effects against dopamine D2 and serotonin type 1A (5HT1A) receptors and a full antagonistic effect against 5HT2A receptors, and with a low  $\alpha$ -1 adrenergic blockade effect (17). Although it is effective in the treatment of enuresis developing from antipsychotic therapy due to this low  $\alpha$ -1 adrenergic blockade effect, aripiprazole, it has also been reported to have led to diurnal enuresis in a five-year-old girl (5).

Reported risk factors for enuresis include a history of primary enuresis (18), male gender (19) and combined new generation antipsychotic use (3). Male gender may have been a facilitating factor in both our cases. The majority of cases of risperidone-induced enuresis have been reported in children with autism and developmental disabilities (5-7). Our report was also different due to the fact that our first patient was developmentally normal.

Although antipsychotic-induced incontinence is self-limiting and no therapeutic intervention is recommended, examination of the current literature shows that the majority of pediatric cases of enuresis developing after risperidone use have not resolved spontaneously (7). Possible interventions for this side-effect developing in association with antipsychotic agents include behavioral measures (such as reducing liquid intake in the evenings, and waking the patient for urination), the prescription of minimally effective antipsychotic agents, drug discontinuation (20), using drugs such  $\alpha$ -agonists (such as ephedrine) (13), and treatment modification to another antipsychotic agent with low  $\alpha$ -1 adrenergic blockade (7).

In the light of the information in the literature, and considering the impact of this side-effect on the quality of life of patients and families and on compliance with

treatment, we also discontinued risperidone therapy in both our cases and replaced this with aripiprazole.

In conclusion, our cases are important in terms of highlighting the rare side-effect of nocturnal and diurnal enuresis following risperidone use. Considering also the adverse effect of urinary incontinence on quality of life, clinical psychiatrists should be aware of such a side-effect in order to increase patients' compliance with treatment.

**Patient informed consent:** Written informed consent was obtained from the patient for the publication of the case report.

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