

# Unilateral Galactocele In A Boy Who Received Risperidone : A Case Report

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## Abstract

Galactocele, generally occurring in young women during or after lactation, is an extremely rare cause of breast mass in infants and children, particularly in males. Here, we report a 7-year and 5-month-old boy who had a painless mass at his left breast. The hormonal blood test revealed hyperprolactinemia, caused by minimum risperidone dosage. Our purpose was to emphasize the importance of including galactocele as a differential diagnosis in children receiving risperidone presented with breast mass. Furthermore, we would like to encourage establishing a standardized follow-up guideline for pediatric patients receiving this drug.

## Introduction

Risperidone is a second-generation antipsychotic drug. It is a potent inhibitor of the serotonin 5-HT<sub>2</sub> and D<sub>2</sub> receptors. Risperidone is indicated for the acute treatment and maintenance treatment of schizophrenia and other related psychotic disorders, including acute bipolar mania (Germann, Kurylo, & Han, 2012). A previous study showed that risperidone was effective and well-tolerated for the treatment of severe tantrums, aggression, self-injurious behavior in autistic children 5 to 17 years old (McCracken et al., 2002) and Attention deficit/Hyperactivity disorder (ADHD) (Arabgol, Panaghi, & Nikzad, 2015).

### Risperidone for treating ADHD

Attention deficit/Hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders affecting patients' educational failure, interpersonal problem, and delinquency (Biederman et al., 2006). The core symptoms consist of inattentive

behavior and/or hyperactivity/impulsivity. The onset of symptoms must appear within 12 years of life and cause functional impairment. The main treatment of ADHD includes both pharmacologic and nonpharmacologic treatment. Methylphenidate, a psychostimulant, is the first-line psychopharmacologic treatment. It exerts its effect by inhibiting presynaptic dopamine transporters of central adrenergic neurons. It also inhibits norepinephrine transporters. Both mechanisms of action lead to increased synaptic cleft concentration of dopamine, amplifying the dopaminergic neurotransmission. Even though it is an effective treatment and 65% of responders (Hodgkins, Shaw, Coghill, & Hechtman, 2012), side effects such as decreased appetite, insomnia, and adverse emotional effects, are frequently experienced. The second-line drugs for ADHD treatment are clonidine and atomoxetine. Atomoxetine is a selective norepinephrine reuptake

inhibitor, which induces increased concentrations of norepinephrine and dopamine in the prefrontal cortex (Brown, Samuel, & Patel, 2018). In Thailand, atomoxetine is scarcely used because it is expensive and cannot be reimbursed. Extended-release clonidine, approved by the US FDA for adjunctive therapy with stimulant medications in ADHD treatment (Brown et al., 2018), is not available in Thailand. The use of atypical antipsychotics has been risen significantly for treating disruptive behavior disorders and ADHD in children. The most familiar and widely used atypical antipsychotics in Thailand is risperidone, because of its efficacy and safety. Risperidone is indicated for the acute treatment and maintenance treatment of schizophrenia and other related psychotic disorders, including acute bipolar mania (Germann et al., 2012), severe tantrums, aggression, or self-injurious behavior in autistic children. In children with subaverage intelligence, treating with risperidone also showed a significant reduction in both disruptive and hyperactivity symptoms (Aman, Binder, & Turgay, 2004). More recently, evidence showed a significant improvement in ADHD symptoms after 6 weeks of risperidone treatment (Arabgol, Panaghi, & Nikzad, 2015). Common side effects of risperidone are drowsiness, weight gain, headache, dyspepsia, rhinitis, and vomiting.

### Risperidone and hyperprolactinemia

Pituitary prolactin secretion is regulated by neuroendocrine neurons in the hypothalamus, especially in the tuberoinfundibular tract that extends from the arcuate nucleus of the mediobasal hypothalamus (tuberous region) and projects to the median eminence (infundibular region). Neurosecretory dopamine neurons of the arcuate nucleus inhibit prolactin secretion. Hence, prolactin secretion increases when antipsychotic therapy results in dopamine receptor blockade (Freeman, Kanyicska, Lerant, & Nagy, 2000). Antipsychotics vary in affinity for the D2 receptor, rate of dissociation from the receptor, and ability to act on the receptor as both a dopamine agonist (which lowers serum prolactin) and a dopamine antagonist (which increases serum prolactin). Based on adult and pediatric data, the relative potency of antipsychotic drugs in inducing

hyperprolactinemia is roughly risperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole (Correll & Carlson, 2006). The most common presentation of risperidone-induced hyperprolactinemia in children is galactorrhea. Another predictor of hyperprolactinemia is a dosage of antipsychotic prescribed, with increased levels observed at higher doses (Inder & Castle, 2011).

Symptoms of elevated prolactin can occur as a direct result of prolactin's physiologic effect on breast tissue (breast enlargement or engorgement, and galactorrhea) or indirectly through hypogonadism related to decreased FSH and LH (amenorrhea or oligomenorrhea, decreased libido, and erectile dysfunction). Hyperprolactinemia also increases the risk of breast tumor (Byerly, Suppes, Tran, & Baker, 2007), pituitary tumor (Holt & Peveler, 2011), and reduce bone density (Naidoo, Goff, & Klibanski, 2003). Intervention must be provided, if serum prolactin is elevated and the patient has clinical symptoms of hyperprolactinemia. The recommendation is to discontinue risperidone and switch to a prolactin-sparing antipsychotic such as aripiprazole. If serum prolactin exceeds 200 ng/ml or is persistently elevated despite switching to a prolactin-sparing antipsychotic, obtain an MRI of the sella turcica to look for a pituitary adenoma or parasellar tumor (Casanueva et al., 2006; Haddad & Wieck, 2004).

### Galactocele

A galactocele is defined as a cystic lesion filled with milk or milk-like fluid (Boyle, Lakhoo, & Ramani, 1993). Galactocele is most commonly found in young fertile women during or after breastfeeding (Kim et al., 2006). This lesion is exceedingly rare in pediatric patients, and only a few reported in male infants (Obrist, Schwabegger, Brunhuber, Schafer, & Kreczy, 2003; Perez-Boscolo et al., 2009; Vlahovic et al., 2012). The cause may be multifactorial (Poiana, Chirita, Carsote, Hortopan, & Goldstein, 2009), several specific factors had been postulated. These factors include a history of trauma or inflammation leading to breast cyst formation, prolactin-induced galactocele, the presence of secretory breast epithelium, and ductal obstruction

(Boyle et al., 1993). This article presented another case of a pediatric patient who developed galactocele after taking risperidone for 14 months. This case is especially interesting because galactocele is a rare side effect, specifically in boys treated with low doses of this medication.

## Methods

### *Study design: Case study*

This case report was conducted at the Faculty of Medicine, Siriraj Hospital. A 7-year-and-5-month-old Thai boy presented with a painless mass in the left breast for two days. There was no nipple discharge and no history of trauma or infection to the breast. Our patient was afebrile and had neither headache nor vomiting. He had no weakness, normal vision, and normal urination. His underlying diseases include Barakat syndrome (end-stage renal disease on peritoneal dialysis, hypoparathyroidism), global developmental delay and hyperactivity. He presented at 5 years and 9 months with hypocalcemic seizure with family history of hypoparathyroidism and bilateral sensorineural hearing loss in his father and sister. The blood test showed severe hypocalcemia (total calcium 4.8 mg/dl), hypoparathyroidism (parathyroid hormone 67.1 pg/ml), and chronic renal failure (blood urea nitrogen 92.6 mg/dl, serum creatinine 5.57 mg/dl). Renal ultrasound revealed bilateral renal hypoplasia. He was diagnosed with Barakat syndrome right then and was treated with peritoneal dialysis, calcium, and active vitamin D supplementation. He was also diagnosed with moderate to severe global delayed development. The developmental assessment revealed: Personal-social DQ 43, Fine motor DQ 26, Language DQ 35, and Gross motor DQ 43. Physical examination was unremarkable. He had a normal eye and hearing exam. His chromosome study was 46, XY and FMR1 gene was found normal size 29 CGG repeats. He received a developmental stimulation program and speech therapy at Siriraj hospital. A mother reported that he was restless and did not cooperate in the treatment program. Therefore, he was also diagnosed at 6 years and 3 months of age with hyperactivity and risperidone was prescribed instead of methylphenidate due to failure to thrive. Risperidone dosage was

elevated to 0.5 mg daily from the age of 6 years and five months with better behavior and cooperation during therapy sessions. At the age of 7 years and 5 months, he came with a painless left breast mass two days prior to hospitalization. Physical examination revealed a painless, movable cystic mass just beneath the left nipple, with a diameter of 3 cm. The overlying nipple and skin were normal, and there was no nipple discharge. The right breast was normal. Both testes were in the scrotum, and they had normal size. The body length was 108 cm (< 3rd percentile), and the body weight was 23.3 kg (25th to 50th percentile). There was no sign of puberty, hirsutism, or other abnormal pigmentation. Neurological examination and visual field were unremarkable. He was diagnosed with breast abscess and operation for incision and drainage was done.

## Results

A milk-suspected, whitish liquid was found inside the mass. No organism and white blood cells were found on the liquid's Gram stain, and the culture showed absolutely no growth. Therefore, additional blood test was done. The results showed hyperprolactinemia (prolactin level 567 ng/ml), hypercholesterolemia (206 mg/dl), hypertriglyceridemia (178 mg/dl), impaired fasting glucose (fasting blood glucose 101 mg/dl), and normal thyroid function test. All of which excluded panhypopituitarism. Primary diagnosis was risperidone-induce hyperprolactinemia and galactocele. Risperidone was discontinued, and methylphenidate was prescribed instead, but he developed severe mood lability and irritability, so methylphenidate was intolerable and had been stopped. A month after risperidone discontinuation, prolactin level was reduced to 22 ng/ml; and, no new breast lumps were formed. Therefore, we treated his mischievous symptoms with 2 mg/day of aripiprazole. The symptoms were controllable with good response.

## Discussion

Hyperprolactinemia occurs in up to 70% of patients taking antipsychotic drugs (Montgomery et al., 2004). They increase prolactin levels through their primary

mechanism of dopamine (D2) receptor antagonism. Dopamine inhibits prolactin secretion; thus dopaminergic inhibition increases prolactin release in the hypothalamic tuberoinfundibular tract (Ajmal, Joffe, & Nachtigall, 2014; Peuskens, Pani, Detraux, & De Hert, 2014) and leads to hyperprolactinemia. Hyperprolactinemia is one of the causes of galactocele in children (Vlahovic et al., 2012; Vlahovic, Djuricic, & Todorovic, 2015). High prolactin level induces milk production but not being to drain. The most common causes of hyperprolactinemia are side effects from medication, especially antipsychotics and antidepressants. Prolactinoma, or a prolactin hormone-producing pituitary tumor, is another common cause. It is suspicious if neurological and visual field examinations are abnormal. Long-term or in adequately treated primary hypothyroidism is also one of the common causes of hyperprolactinemia, can cause pituitary hyperplasia that may mimic a pituitary tumor (Cannavo et al., 2003). Galactocele is an exceedingly rare presentation. From 2005 to the present, Galactocele has been found in only 13 people who took risperidone, most commonly in boys (92%), aged 2-9 years (87.5%), and have taken the drug for 6-12 months (100%). Once risperidone - induced galactocele is suspected, there will be a minimal risk for unnecessary surgery. Risperidone must be discontinued and replaced by other antipsychotic that rarely induced hyperprolactinemia such as aripiprazole, olanzapine, clozapine, and quetiapine (Inder & Castle, 2011), if indicated. Our patient had no abnormalities in neurological and visual field examinations. The blood test did not indicate pituitary tumor. Particularly, the symptoms appeared after taken risperidone for 14 months. A provisional diagnosis of risperidone-induced hyperprolactinemia was given. In this case, even though he had a low dosage of risperidone, he developed symptomatic hyperprolactinemia. This may be because of chronic renal failure. Previous studies showed that prolactin could not be sufficiently excreted through dialysis. The accumulation of risperidone metabolites could induce unfavorable symptomatic hyperprolactinemia (Sievertsen, Lim, Nakawatase, & Frohman, 1980).

Although risperidone can elevate prolactin level up to 200 ng/ml (Kearns, Goff, Hayden, & Daniels, 2000), our patient's prolactin level was even higher. Therefore, worse side effects of hyperprolactinemia cannot be excluded. We monitored prolactin level after risperidone discontinuation. If the level was still high, MRI brain must be applied. In our patient, serum prolactin subsides to normal after stoppage of risperidone (lower than 25 ng/ml) (Casanueva et al., 2006).

Currently, antipsychotic prescription in pediatric patients is increased. In addition to hyperprolactinemia, other side effects include increasing appetite, weight gain, sedation, extrapyramidal and metabolic abnormalities (McNeil, Gibbons, & Cogburn, 2020). Moreover, the unfavorable outcome of long-term risperidone use is also recognizable, included breast cancer (Byerly et al., 2007), pituitary tumor (Holt & Peveler, 2011), and sexual dysfunction (Serretti & Chiesa, 2011). Therefore, pediatricians and pediatric psychiatrists should pay attention to and monitor the side effects of risperidone. A concrete practice guideline for risperidone treatment is beneficial

## Summary

Galactocele is a rare entity that should be included in the differential diagnosis of breast mass in a male child receiving risperidone. The physicians have to keep in mind that low dose could also cause serious adverse events, especially in patients with discretion defects. Finally, we hope that our case report will facilitate the physicians to increase awareness and monitor the side effects caused by risperidone in pediatric patients. We encourage the establishment of future guidelines for risperidone treatment. We are thankful to our patient, who gave us an informed consent for publishing his information as a case report.

## Limitation

Because this case report did not contain the imaging and pathologic results of breast mass; however, the results of other laboratory tests are sufficient to be diagnosed as galactocele. This is the first case of pediatric patients at Siriraj hospital to be identified as

risperidone-induced galactocele, so there is no case series' information that can be used to determine the dosing and duration of risperidone usage, as well as other risk factors that cause this side effect.

## Conflict of Interest

The authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs described in this report.

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