CASE REPORT

Antipsychotic-Induced Rabbit Syndrome in a Pediatric Patient

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INTRODUCTION

Rabbit syndrome is an antipsychotic-induced dyskinesia of the mouth, characterized by a fine, rapid, involuntary perioral motion that resembles the chewing motion of a rabbit.[1] The oral movements occur in a vertical direction and can be differentiated from tardive dyskinesia by the lack of involvement of the tongue and by the rhythmic pattern.[2] However, differentiation of tardive dyskinesia or parkinsonism from rabbit syndrome can remain difficult, as the latter may present with features of the other 2 conditions.[1,2]

Since it was first described in 1972, rabbit syndrome has been mainly associated with the typical antipsychotics, primarily high-potency agents such as haloperidol.[3] However, atypical antipsychotics are now used more frequently than in the past, and rabbit syndrome has also been reported in association with olanzapine, aripiprazole, clozapine, paliperidone, amisulpride, and, most commonly, risperidone.[1,2] Here, we report what appears to be the first case of rabbit syndrome in a pediatric patient.

CASE REPORT

An 11-year-old girl had an extensive medical history of developmental issues secondary to early birth trauma.* The birth was complicated, and emergency cesarean section was required because of fetal distress. It is likely that the patient suffered an ischemic insult at this time, which resulted in periventricular leukomalacia and mild cerebral palsy. As a toddler, the patient displayed signs of sleep disturbances, inattentiveness, and delayed speech development. By the age of 6 years, a psychological assessment based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, identified generalized anxiety disorder with features of obsessive–compulsive disorder, attention deficit hyperactivity disorder (combined type), and a learning disorder. Also of note were a history of seizures, motor planning issues, mild tremors, and an episode of what appeared to be antidepressant-induced mania when the patient's medication was changed from fluoxetine to citalopram at age 9 years.

At the time of presentation, in December 2012, the child's anxiety, aggression, and agitation were noted to be worsening. Because she had previously tolerated fluoxetine well, with a partial response, it was decided to restart this drug, even though there was a history of antidepressant-induced mania. Following the change, the patient displayed new tremors in her hands, which were potentially attributable to the fluoxetine. Her medications were adjusted by changing fluoxetine 20 mg to sertraline 25 mg daily, with a short trial of risperidone 0.25 mg daily to manage the worsening aggressive outbursts. At this time, the patient was also receiving lisdexamfetamine 50 mg daily and melatonin 9 mg at bedtime, both of which she had been taking for some time. During the trial of risperidone, the patient showed improvement in many symptoms, including anxiety, mood swings, appetite, social interaction, obsessive tendencies, irritability, and negativity. The hand tremors initially improved following the change from fluoxetine to sertraline, but they eventually returned.

The observation that this patient responded well to risperidone and only partially to antidepressants led to suspicion of an underlying mood disorder. After discussion with the family regarding alternative mood stabilizers, their preference was to continue regularly scheduled risperidone 0.25 mg at bedtime, along with her other medications. Although there was some sustained improvement, regular use of risperidone was not completely successful in adequately controlling her symptoms. There was an absence of a consistent level of mood, and subclinical depressive episodes were frequent, possibly consistent with a cyclothymic disorder. However, the patient did not meet the diagnostic criteria for bipolar disorder. As the family continued to contemplate changing to a mood stabilizer, their preference was to continue the risperidone, at an increased dose (0.25 mg twice daily). Several weeks later, concerns remained about the patient being highly anxious, hyperactive, bossy, and impulsive, with labile mood. At that time, the risperidone dosage was

*The patient's guardian provided consent for publication of this report.

increased again, to 0.5 mg twice daily, and the sertraline dosage was increased to 50 mg daily, before the use of mood stabilizers was attempted. Within several days of these dose increases, and 4 months since initiation of risperidone, the patient began to experience sedation, blurry vision, and worsening tremors, including a facial tic. The tic recurred every 5–20 s along the vertical axis of the mouth and included squinting of the nose. There was no involvement of the tongue, and the patient was unable to voluntarily suppress these movements. Rabbit syndrome was diagnosed, and it was decided to switch from risperidone to quetiapine 75 mg daily; unfortunately, this was associated with worsening of the facial tic. As a result of this problem and the patient's continued symptoms of an underlying mood disorder, lithium 300 mg daily was started as the quetiapine was tapered down.

Over the next several weeks, the patient's facial tic declined in frequency and eventually ceased. According to the Naranjo probability scale for rating adverse reactions,[4] the association between the patient's symptoms and the risperidone could be considered "definite". The lithium seemed better for controlling the patient's mood disorder; however, mild symptoms remained, and the dose of lithium was gradually increased. At the time of writing, in early 2014, the patient was taking lithium 300 mg twice daily, lisdexamfetamine 50 mg daily, sertraline 50 mg at bedtime, and melatonin 9 mg at bedtime. There had been an overall improvement in symptoms in the preceding months, including increased involvement in social activities and improved academic performance. There has been no recurrence of the facial movements since she stopped taking the antipsychotic medications.

DISCUSSION

The exact mechanism of rabbit syndrome remains unknown, and the literature suggests conflicting causes. For example, it has been suggested that rabbit syndrome may be similar to drug-induced Parkinson disease, whereby a hypercholinergic state arises secondary to dopamine blockade.[2] Alternatively, it has been postulated that the mechanism is similar to that of tardive dyskinesia, being characterized by a state of cholinergic hypofunction due to dopaminergic hypersensitivity.[2] The former hypothesis is supported by clinical evidence, as the symptoms of rabbit syndrome tend to disappear with anticholinergic treatment, whereas the symptoms of tardive dyskinesia tend to worsen upon treatment.[5,6] Although physiologic and clinical differences do exist among rabbit syndrome, tardive dyskinesia, and parkinsonism, a clear diagnosis of rabbit syndrome can be difficult to confirm, as features of each condition may be present simultaneously.[6]

The main diagnostic features that differentiate rabbit syndrome from other extrapyramidal syndromes are its high specificity to the buccal region and the lack of lingual involvement.[1,2] In contrast to rabbit syndrome, which is characterized by rapid, rhythmic movements along the vertical axis of the mouth, tardive dyskinesia is better characterized as slow, less regular movements that may occur in all directions and, importantly, that involve the tongue.[7] Additionally, unlike the symptoms of rabbit syndrome and parkinsonism, the symptoms of tardive dyskinesia tend to cease during stage 1 non-REM sleep.[7]

Fortunately, rabbit syndrome appears readily treatable by reducing the dose of the offending antipsychotic, and it typically resolves within several days of treatment with an anticholinergic agent.[1,2,8] Several studies have noted that switching to atypical antipsychotics with stronger anticholinergic properties, such as olanzapine, clozapine, and quetiapine, may be an alternative to using anticholinergics.[9,10] This strategy has the additional benefit of simultaneously treating the underlying disorder.[9,10] However, in the case reported here, the patient exhibited worsening of symptoms following the switch to quetiapine, which may suggest a physiologic mechanism similar to that of tardive dyskinesia.[6]

Like other atypical antipsychotics, risperidone is a selective antagonist of serotonergic and dopaminergic receptors. At higher doses, risperidone's dopamine antagonism may predominate, leading to an increased rate of extrapyramidal side effects.[7] Indeed, some studies have shown an increased incidence of extrapyramidal symptoms associated with increasing doses of risperidone in adolescents.[11] The first case of rabbit syndrome caused by risperidone was published in 1999,[8] and a total of 9 risperidone-associated cases in adults have been reported to date, making risperidone the most common atypical antipsychotic associated with rabbit syndrome.[2] The lower prevalence of rabbit syndrome associated with other atypical antipsychotics may be a result of more favourable serotonin-to-dopamine receptor affinity ratios.[12] Other risperidone-related factors to consider are patient-specific polymorphisms, such as poor metabolism by the cytochrome P450 2D6 isozyme; in these patients, exposure to the drug can be increased, with potential for adverse effects.[13]

CONCLUSION

Although the prevalence of rabbit syndrome is reported to be 1.5%–4.4% with the typical antipsychotics,[14] no studies examining its prevalence with the use of atypical antipsychotics were identified. Typically, the onset of rabbit syndrome is slow, and it appears after months to years of treatment.[2] The patient described here, an 11-year-old girl, experienced rabbit syndrome after 4 months of treatment with risperidone, within days following a dosage increase from 0.5 mg daily to 1.0 mg daily. Although treatment of rabbit syndrome with anticholinergics has been associated with faster symptom resolution (i.e., within days), in this patient the symptoms resolved spontaneously over a period of several weeks after the antipsychotics were stopped, which suggests that rabbit syndrome may not require active treatment.

References

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CORRECTION

Pharmacists' Perceptions of the Influence of Interactions with the Pharmaceutical Industry on Clinical Decision-Making: Correction

An article reporting results of a survey concerning the influence of interactions with the pharmaceutical industry[1] contained two errors introduced in the course of editing:

(1) On page 381, the second paragraph before the Discussion section should read as follows:

> Respondents were about evenly split in terms of agreement with the statement "My relationship to the pharmaceutical industry promotes my professionalism and helps me care for my patients": 44% (96/220) disagreed [not "agreed"] or somewhat disagreed whereas 37% (81/220) agreed or somewhat agreed.

(2) On page 384, in the paragraph about study limitations, the fourth sentence should read as follows:

> For example, a disproportionately large [not "small"] number of very experienced pharmacists participated, so these results may not reflect the views of younger pharmacists.

We apologize for these errors and any inconvenience or misunderstanding they may have caused.

Reference

1. Tejani AM, Loewen P, Bachand R, Harder CK. Pharmacists' perceptions of the influence of interactions with the pharmaceutical industry on clinical decision-making. *Can J Hosp Pharm*. 2015;68(5):378-85.

CORRECTION

Playing in the Sandbox: Considerations When Leading or Participating on a Multidisciplinary Research Team: Correction

Lisa Dolovich's Research Primer article in the September–October 2015 issue of *CJHP*, concerning multidisciplinary research teams,[1] should have included the following acknowledgement: "The author thanks Melissa Pirrie and Kalpana Nair for their presubmission review and helpful comments to improve this manuscript."

We apologize for this oversight.

Reference

1. Dolovich L. Playing in the sandbox: considerations when leading or participating on a multidisciplinary research team. *Can J Hosp Pharm*. 2015;68(5):401-5.