

CLINICAL CASE ROUNDS IN CHILD AND ADOLESCENT PSYCHIATRY

Low-Dose Risperidone-Induced Oculogyric Crises in an Adolescent Male with Autism, Tourette's and Developmental Delay

Tamara Masliyah MD, FRCPC¹; Yasser Ad-Dab'bagh MD, FRCPC¹

Abstract

This article will review the case of a young patient with mental retardation^a, autistic disorder, and Tourette Syndrome who exhibited a favourable treatment response preferentially to risperidone. His presentation, however, was complicated by an exquisite sensitivity to risperidone displayed in the form of recurrent oculogyric crises. In this article, we will outline a review of the case, a survey of the incidence and risk factors of oculogyric crises, as well as a review of the literature on risperidone sensitivity, followed by a review of alternate options for the prevention of oculogyric crises.

Key words: autistic disorder, Tourette Syndrome, mental retardation, oculogyric crisis, dystonic reaction

Case Report

This is the case of a 15 year old white male with autistic disorder, moderate mental retardation^a, and Tourette Syndrome who presented with a four to five month history of increased self-injury (flicking and hitting his nose at a rate of 20 to 50 times per hour), as well as vocal tics (at baseline he emitted high-pitch yelling-type sounds at a rate of 100-200 times an hour), and complex-motor tics, in the form of grabbing and pinching. Of note, the patient had a significantly low BMI of 17 as well as a diagnosis of gluten enteropathy.

Several changes that occurred around the time of symptom onset which may have precipitated or exacerbated his symptoms include: a change in school several months prior to the onset of symptoms with subsequent loss of a close female friend; a close caregiver departing for several months; the relative loss of a supportive brother who had been involved in a time-consuming school project; and, the onset of puberty.

There was an extensive past history of pharmacological attempts to minimise his symptoms including a previous trial of olanzapine 5 mg daily which was discontinued after two weeks due to lack of effectiveness and excessive sedation. Sertraline was also trialed at 25 mg for several weeks and increased to 50 mg which was subsequently discontinued due to worsening agitation. A trial of clonidine was also reported to have caused worsening agitation.

Historically, this patient appeared to respond preferentially to low-dose risperidone. Initially, risperidone was initiated at a dose of 0.25 mg in the morning and 0.5 mg at night to address the self injurious behaviors as well as the vocal and motor tics. In addition to this, occupational therapy-generated behavioral interventions were introduced to address anxiety and self injury.

A favorable change in frequency of self-injurious behaviors as well as motor and vocal tics was reported on day one and day two of these medications, however, the patient experienced an oculogyric crisis (OGC) soon after this. The dose of risperidone was subsequently reduced to 0.125 mg in the morning and 0.25 mg in the evening and increased to 0.25 mg twice a day after 10 days.

Two days following this increase, an OGC reoccurred. In an attempt to address this, diphenhydramine 12.5 mg twice daily

^a Although the DSM-IV TR uses the term "Mental Retardation," the trend in the literature is to substitute for the term "intellectual disability."

¹ Department of Psychiatry, University of Ottawa, Ottawa, Ontario

Corresponding email: tmasliyah@gmail.com

Submitted: October 1, 2010; Accepted: May 26, 2011

and 25 mg in the evening was given concurrently with risperidone 0.25 mg twice daily and 0.125 mg in the evening. This resulted in a decrease in the frequency, intensity and duration of the OGCs and a small improvement in behavioral symptoms with minimal observed sedation.

Finally, the diphenhydramine was replaced with benzotropine 1 mg three times daily which allowed for the titration of risperidone up to 1 mg total daily (in three divided doses) with resolution of the oculogyric events. This titration took approximately 3 months to achieve.

A recent follow-up once he stabilized on a higher dose of risperidone - up to 0.5mg TID (which was a slower 6 month titration) showed a reduction of yelling to 50/day and grabbing/pinching to 20/day and self-injury to about 5/day. These improvements appeared to be dose-dependent. While he remains highly symptomatic, these gains have had huge impacts on quality of life for the patient and his family.

Incidence of Dystonic Reactions

Since the emergence and widespread use of atypical antipsychotic agents, the incidence of dystonic reactions including OGCs has fallen. For general adult psychiatric patients on antipsychotic medications, the overall incidence of dystonic reactions is approximately 2% (Nochimson, 2008).

In a double-blind placebo controlled trial of risperidone involving 101 children and adolescents with autistic disorder who were taking 0.5-3.5 mg of risperidone per day (mean dose of 2.08 mg/day), it was found that after six months, extrapyramidal symptoms were no more common on risperidone when compared to placebo (Aman et al., 2005).

However, in a retrospective chart review involving adolescents and youth with developmental disabilities treated with atypical antipsychotics conducted by Friedlander et al. (Friedlander, Lazar, & Klanicnik, 2001), the rate of oculogyric dystonia with risperidone and olanzapine treatment was found to be significantly higher at 10% and 14%, respectively.

On an additional note of interest concerning the risk of tardive dyskinesia, one study found the annual risk of tardive dyskinesia in adults with schizophrenia treated with quetiapine to be 0.7% while another found the annual risk of tardive dyskinesia in adults with schizophrenia or schizoaffective disorder treated with risperidone to be 0.6% (Kane, 2004). According to the retrospective chart review conducted by Friedlander et al. (2001), the rate of dyskinesic movements with risperidone in developmentally disabled youth was 5% and this appeared to be the case within one year of treatment.

Risk Factors for Neuroleptic-Induced Dystonic Reactions

The incidence of dystonic reactions is greater in males than in females and more common in younger age groups. Dystonic reactions occur most commonly in the first few days of antipsychotic initiation, and at higher potency or dose of antipsychotic formulation as well as with rapid titration of the antipsychotic medication.

Recent use of alcohol or cocaine is also a risk factor, as these substances cause release and subsequent depletion of dopamine in the central nervous system.

In addition, individuals who have the slow metabolizer genotype at cytochrome P450, subclass 2D6 (responsible for most of risperidone's metabolism) could also exhibit an atypical sensitivity to risperidone which may manifest via dystonic reactions at low dosages (Coffey, Bott, & de Leon, 2005).

In addition, youth with intellectual disability appear to be at increased risk for neuroleptic-induced movement disorders (Friedlander et al., 2001).

There is also some speculation into the connection of Tourette Syndrome and the increased potential to develop dystonic reactions. As noted by Pringsheim (Pringsheim, Freeman, & Lang, 2007), Tourette Syndrome can be associated with tics in the form of dystonic tics (not induced by antipsychotic medication). In addition, there is a case report describing a three-generation family in which Tourette Syndrome and dystonias congregate (Nemeth et al., 1999). This brings forth the question of the possibility of increased susceptibility of children with Tourette Syndrome to developing antipsychotic-induced dystonic reactions.

Review of the Literature

There have been several other case reports which describe risperidone sensitivity in the form of severe dystonic reactions, however none that have outlined sensitivity at doses as low as those reported in the case above.

In the aforementioned study conducted by Friedlander et al. (2001) which consisted of a retrospective chart review involving adolescents and young adults with developmental disabilities treated with atypical antipsychotics, four out of the forty patients who were treated with risperidone had documented OGCs.

One report (Takhar & Manchanda, 1996) described an antipsychotic naïve 17 year old male with schizophrenia who developed an acute dystonic reaction several hours after his second day of a 2 mg dose of risperidone.

An additional noteworthy case report (Fountoulakis, et al., 2006) described an 18 year old male with Tourette Syndrome who experienced an acute dystonic reaction characterized by oculogyric crisis, facial muscle spasm and torticollis on the third day of treatment with aripiprazole 10 mg per day.

Alternate Options for the Prevention of Oculogyric Crises

Several other anticholinergic medications could be considered for the prevention of oculogyric crises such as those used primarily in the treatment of Parkinson's disease, for example, trihexylphenidyl, biperiden, orphenadrine, and procyclidine.

The potential concern with the use of these medications is their capability of inducing anticholinergic-related cognitive changes in an already cognitively impaired individual.

In patients who are refractory to anticholinergic medication or for those in whom anticholinergic use is contraindicated, benzodiazepines have been used, however, their usage is primarily in the treatment of acute dystonic reactions as opposed to their prophylaxis (van Harten, Hoek, & Kahn, 1999).

Lastly, amantadine, an agent with dopamine agonist activity which is also used in the treatment of Parkinson's disease, can be a useful alternative to anticholinergic medications (Fayen, Goldman, Moulthrop, & Luchins, 1998). This may be particularly useful in patients with underlying cognitive impairment who are especially vulnerable to the cognitive effects of anticholinergic medications. However, amantadine can occasionally cause worsening of psychotic symptoms, nightmares, insomnia and mood disturbances (Bezchlibnyk-Butler & Virani, 2007).

Discussion

Upon reviewing this case, one might ask – why the persistence in the use of risperidone? We persevered in our treatment with risperidone for several reasons. Risperidone has been found to be superior among the atypicals in the treatment of Tourette Syndrome (Doskoch, 2002). It has also shown the most promise among the atypicals in the treatment of children with autistic disorder, as well as children with mental retardation, particularly with respect to self-injurious behaviour (Sadock & Sadock, 2003).

In exploring the question of why this patient displayed such extreme sensitivity to risperidone, we performed a serum risperidone level in order to rule out the possibility that this patient had a slow metabolizer genotype at cytochrome P450, subclass 2D6. This, however, did not appear to be the case based on the serum value we obtained of 14.4 nmol/L (with the therapeutic range for adults with schizophrenia being 19–269 nmol/L on much higher dosages) as we would have expected a much higher serum value in the case of a slow metabolizer, and we have anecdotally found such a serum level to be common among children on twice as high a daily dosage of risperidone. (Of note, pediatric reference ranges have not yet been established).

Based on this result, we also inferred that the patient's risperidone sensitivity was likely primarily an issue of low volume of distribution. As is the case with most psychotropics and CNS medications, risperidone is highly

lipophilic. Thus we have interpreted the serum risperidone level we obtained as being higher than expected and was attributed to the patient's reduced body fat as reflected by his low BMI.

Other risk factors which likely contributed to this patient's presentation include intellectual disability, male gender, young age and, possibly, co-morbid Tourette Syndrome.

Conclusions

Idiosyncratic risperidone sensitivity, presenting in the form of oculogyric crises, is probably uncommon in occurrence. However, such sensitivity can present in certain patients on low-dose risperidone who have a significantly low volume of distribution. Age, gender, intellectual disability and co-morbid Tourette Syndrome may be contributing factors.

On a final note, in light of the medication-sensitivity illustrated in this case, we would like to remind prescribers to start at a low dose and titrate slowly in children, particularly those with intellectual disability.

References

- Aman, M. G., Arnold, L. E., McDougle, C. J., Vitiello, B., Seahill, L., Davies, M.,...Lindsay, R. L. (2005). Acute and long-term safety and tolerability of risperidone in children with autism. *Journal of Child and Adolescent Psychopharmacology*, 15(6), 869-84.
- Bezchlibnyk-Butler, K., & Virani, A. S. (2007). *Clinical Handbook of Psychotropic Drugs*, 17th E, Hogrefe & Huber. Cambridge, MA.
- Coffey, G. L., Botts, S. R., & de Leon, J. (2005). High vulnerability to acute dystonic reactions: A case of antipsychotic exposure and uncontrolled seizure activity. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 29(5), 770-774.
- Doskoch, P. (2002). Beyond Psychosis: Using atypical antipsychotics in children with Tourette's Syndrome or Conduct Disorder. *Neuropsychiatry Reviews*, 3(1).
- Fayen, M., Goldman, M. B., Moulthrop, M. A., & Luchins, D. J. (1988). Differential memory function with dopaminergic versus anticholinergic treatment of drug-induced extrapyramidal symptoms. *American Journal of Psychiatry*, 145(4), 483-6.
- Fountoulakis, K. N., Siamouli, M., Kantartzis, S., Panagiotidis, P., Iacovides, A., & Kaprinis, G. S. (2006). Acute dystonia with low-dosage aripiprazole in Tourette's disorder. *Annals of Pharmacotherapy*, 40(4), 775-7.
- Friedlander, R., Lazar, S., & Klancnik, J. (2001). Atypical antipsychotic use in treating adolescents and young adults with developmental disability. *Canadian Journal of Psychiatry*, 46, 741-745.
- Kane, J. M. (2004). Tardive dyskinesia rates with atypical antipsychotics in adults: Prevalence and incidence. *Journal of Clinical Psychiatry*, 65(suppl 9), 16-20.
- Nemeth, A. H., Mills, K. R., Elston, J. S., Williams, A., Dunne, E., & Hyman, N. M. (1999). Do the same genes predispose to Gilles de la Tourette syndrome and dystonia? Report of a new family and review of the literature. *Movement Disorders*, 14(5), 826-31.
- Nochimson, G. (2008). Toxicity, medication-induced dystonic reactions: Treatment & medications. *eMedicine*, Sept 30.
- Pringsheim T, Freeman, R., & Lang, A. (2007). Tourette syndrome and dystonia. *Journal of Neurology, Neurosurgery, and Psychiatry*, 78, 544.
- Sadock, B. J., & Sadock, V. A. (2003). *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*, 9th Ed. 2003. Lippincott Williams & Wilkins.
- Takhar, J., & Manchanda, R. (1996). Acute dystonic reaction with risperidone. *Canadian Journal of Psychiatry*, 41(1), 61-2.
- Van Harten, P. N., Hoek, H. W., & Kahn, R. S. (1999). Acute Dystonia induced by drug treatment. *BMJ*, 319(7210), 623-626.