Hirsutism in a Female Adolescent Induced by Long-Acting Injectable Risperidone: A Case Report

To the Editor: Hirsutism is defined as excess growth of androgen-dependent sexual hair. This condition manifests as male-pattern hair growth in areas in which women normally have little to no hair. The androgen-sensitive areas of the body are upper lips, chin, ears, cheeks, lower abdomen, back, chest, and proximal limbs.[1] Hirsutism affects 5% to 15% of women across all ethnic backgrounds. It is a distressing condition for patients, with unwanted facial hair being one of the most devastating consequences.[2] Physical appearance has always had an impact on status and self-esteem as well as social opportunity.[3] Hirsutism is associated with increased anxiety, depression, self-consciousness, embarrassment, and body dissatisfaction.[4] The stigma of hirsutism and the lack of public knowledge regarding effective therapy prevent some women from seeking treatment.[5] The causes of hirsutism can be divided into 4 categories: idiopathic, drug induced, ovarian, and adrenal.[6] The patient described below suffered from drug-related hirsutism, wherein the development of unwanted facial and body hair was thought to be secondary to pharmaceutical drugs.[2]

Case report. Ms A, a 16-year-old black adolescent girl, presented to the adolescent inpatient psychiatric facility in 2011 with a 1-week history of new-onset mania with psychotic features. Ms A's pediatric history was unremarkable for trauma, abuse, or delayed developmental milestones. Ms A's urine drug screen corroborated her denial of any history of substance abuse. There were no remarkable findings on her past medical or family history.

On presentation, Ms A had pressured speech, racing thoughts, flight of ideas, and insomnia. She had delusions of grandiosity that were exemplified by her claim over the throne of England as its future queen. She also had delusions of paranoia and persecution that were revealed by her belief that her friends were scheming to kill her. She reported auditory hallucinations of people trying to harm her. She also reported visual hallucinations. On mental status examination, she described her mood as "great," and her affect was euphoric. Her speech was pressured; she displayed physical restlessness and impulsiveness.

Ms A's physical examination was within normal limits. Her pregnancy test was negative. She was prescribed 1 injectable formulation of long-acting risperidone 37.5 mg every 2 weeks to ensure medication compliance. Her intramuscular antipsychotic therapy was overlapped with oral risperidone until she showed clinical improvement. Ms A showed gradual symptomatic improvement over the course of the following week and was discharged in stable condition. Oral risperidone was discontinued.

Ms A returned to the inpatient facility after the second injectable dose of risperidone with complaints of bilateral breast enlargement and "milk discharge" from her breasts. She also had excessive hair growth on her upper lips, chin, cheeks, and upper chest. She reported regular menstrual cycles in the preceding 3 months. She reported compliance with injectable risperidone and denied taking any other medications. Galactorrhea and hirsutism were confirmed by physical examination. The pelvic examination result was within normal limits. The urinalysis and urine pregnancy test results were unremarkable. Her serum prolactin level was elevated at 187 ng/mL (reference range in nonpregnant females: 2–29 ng/mL). Prolactin levels > 100 ng/mL are characteristic of prolactin-secreting tumors.[7] She denied headaches or vision changes. Her thyroid-stimulating hormone and free T_4 levels were within normal limits. A computed tomography scan of the head, performed after hospital discharge, showed no masses or lesions in the brain. Long-acting injectable risperidone was discontinued, and she was switched to lithium after appropriate screening. Ms A was discharged after a brief 3-day hospital course. Her galactorrhea resolved after 1 week, and her prolactin level decreased to 40 ng/mL. Her hirsutism gradually resolved after 1 month. Ms A is currently on lithium monotherapy with well-controlled symptoms and no adverse effects.

Table 1. Comparative Risk of Hyperprolactinemia for Various Antipsychotic Medications[a]

Variable	Risk of Hyperprolactinemia
Low-potency first-generation antipsychotics	++
High-potency first-generation antipsychotics	+++
Aripiprazole	0
Clozapine	0
Olanzapine	+
Quetiapine	0
Risperidone	+++
Ziprasidone	+

[a]Based on Gardner et al[19] and Haddad and Sharma.[20]
Symbols: 0 = rare, + = lower risk, ++ = medium risk, +++ = higher risk.

PubMed was searched (1980–2011) using the terms *risperidone, Consta, depot,* and *hirsutism* in various combinations. To our knowledge, there have been no case reports published regarding long-acting injectable risperidone–induced hirsutism.

Drugs known to be associated with hirsutism include glucocorticoid, cyclosporine, phenytoin, diazoxide, minoxidil, and some antipsychotic medications.[2]

Risperidone was the first second-generation antipsychotic to be formulated as a long-acting injectable form in 2003. The main release of risperidone long-acting injectable begins around weeks 2 or 3 postinjection, and levels build up rapidly over weeks 3 and 4.[8] Risperidone long-acting injectable takes about 8 weeks to reach steady plasma levels and therefore needs to be supplemented with repeated injections and oral antipsychotic treatment for the initial 4 to 6 weeks.[9] A study[10] indicates that brain dopamine receptor occupancy at steady-state plasma levels of risperidone long-acting injectable are in the range found in patients effectively treated with 2–6 mg of oral risperidone. Clinical reviews of risperidone long-acting injectable have reported elevated prolactin levels. Studies monitoring patients who switched from oral risperidone therapy to 12 weeks of risperidone long-acting injectable therapy showed a significant reduction in serum prolactin, albeit elevated above normal. Only 1.3% of patients experienced treatment-emergent adverse effects, such as galactorrhea, menstrual irregularity, and sexual dysfunction, that were possibly related to prolactin elevation.[8]

Antipsychotics cause an elevation in prolactin levels by blocking the dopamine inhibition on the pituitary gland.[11] The efficacy and side effects of antipsychotics are due to their direct blockade of dopamine release in the mesolimbic tract, the tuberoinfundibular tract, and the nigrostriatal tract. Blockade of dopamine receptors in the tuberoinfundibular tract removes the inhibitory effect that dopamine has on the lactotrophs in the pituitary, resulting in unregulated prolactin secretion. Studies show that risperidone strongly increases prolactin (by 45–80 μg/L) compared to other antipsychotics that show intermediate (by 17 μg/L) to moderate (by 1–4 μg/L) increases. The prolactin increase with risperidone appears to be unrelated to dosage.[12]

The association between hyperprolactinemia and hirsutism was first described in 1975.[13] The study found that all women with the amenorrhea-hirsutism syndrome had elevated prolactin levels without any evidence of a pituitary tumor.[13]

Hyperprolactinemia may induce hirsutism via several mechanisms. Prolactin inhibits the hepatic synthesis of sex hormone–binding globin, thereby raising the concentration of plasma-free (unbound) testosterone.[6] An elevation in the plasma-free testosterone level is the most consistent endocrinologic finding in hirsutism.[14] Prolactin also synergizes with luteinizing hormone and

stimulates testosterone synthesis. Hyperprolactinemia stimulates adrenal formation of the prohormone dehydroepiandrosterone sulfate,[7] which is metabolized to testosterone in peripheral tissues such as fat.[15] Hirsutism is a result of increased terminal hair growth secondary to excessive androgen action on terminal hair follicles. Elevated androgen levels are found in 60% to 80% of hirsute females.[16]

The quantity of secreted androgens, the peripheral conversions of androgen to its end products, the amount of free androgen in circulating blood, the metabolic clearance rate, and the sensitivity of the hair follicles are all major contributors to hirsutism.[6]

Minoxidil is thought to treat androgenic alopecia via its vasodilatory and potassium channel opening effects. It is speculated that widening blood vessels and opening potassium channels allow more oxygen, blood, and nutrients to the follicle, which inadvertently lead to hair growth.[17] Risperidone has α_2 antagonist properties, which result in vasodilation, albeit with an undetermined potency.[18] The authors hypothesize that risperidone's vasodilatory effects could be contributory to its adverse effect of hirsutism in the manner similar to minoxidil's effect on androgenic alopecia. Comparative risk of hyperprolactinemia of various antipsychotic medications is shown in Table 1.[19,20]

Assessment of hirsutism should involve clinical examination and the patient's view of how he or she is affected psychologically. Treatment of hirsutism involves treating the underlying cause and removal of the unwanted facial hair using various treatments (eg, mechanical, pharmacologic, laser/photoepilation).[2,21] In our patient, hirsutism resolved after discontinuation of long-acting injectable risperidone.

This case brings awareness to clinicians of the possibility of hirsutism with the use of antipsychotic medications. We believe it is important for clinicians to understand that long-acting injectable risperidone can potentially induce hirsutism. Clinicians should monitor patients for developing hirsutism following long-acting injectable risperidone administration.

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