

Galactorrhea and Gynecomastia in a Hypothyroid Male Being Treated With Risperidone

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Elevation of prolactin levels among patients treated with psychotropic medications and the treatment of hyperprolactinemia have been described over the past three decades (1–7). Prolactin secretion by the anterior pituitary is inhibited by dopamine. Conversely, blockade of dopamine receptors in the tuberoinfundibular pathways results in elevation of prolactin (8), which can lead to gynecomastia (excessive development of the male mammary glands), galactorrhea (white discharge from the nipple), and amenorrhea (absence of menses) (9). Bromocriptine has been used in the treatment of galactorrhea and amenorrhea due to hyperprolactinemia (7).

Head trauma can adversely affect anterior pituitary function. Anterior pituitary hormones include growth hormone, gonadotropins (follicle-stimulating hormone and luteinizing hormone), corticotropin (ACTH), and thyrotropin. Some or all may be affected by head trauma (10–14).

Risperidone is a newer, atypical neuroleptic that is a benzisoxazole derivative (15). It is an atypical antipsychotic agent with 5-HT_{2A} blockade greater than D₂ receptor blockade. A

recent report described two female patients treated with risperidone who developed galactorrhea (6). One was treated by stopping risperidone and substituting thioridazine, a typical D₂ receptor blocker. The second patient was treated with bromocriptine 2.5 mg twice daily while risperidone was continued.

We present a case of risperidone-induced galactorrhea and gynecomastia in a male patient with a history of brain injury and known primary thyroid dysfunction.

The patient

Mr. R was a 38-year-old, single, Hispanic male with a *DSM-IV* diagnosis of bipolar mood disorder due to hypoxic brain injury and coma after a motor vehicle accident 20 years before admission. One year after the accident, a right thalamotomy reduced muscular hypertonia and restored his ability to walk unassisted. The current psychiatric hospitalization was his fourth for behavioral symptoms secondary to his organic disorder, including labile mood, inappropriate social behaviors, and impulsivity.

Mr. R's neurologic deficits included residual stiffness of his right side, an antalgic gait, and a neurogenic bladder. He had been clinically and chemically euthyroid on .075 mg of levothyroxine daily, with normal TSH and serum T₄.

Risperidone 2.5 mg twice a day was prescribed for an episode of increased irritability, hypersexuality, pressured speech, and disorganized, paranoid thinking—evidence of re-

current hypomania. On day 12 of risperidone treatment, Mr. R complained of galactorrhea. His serum prolactin level on day 13 was 48.2 ng/mL (reference range of 1.4 ng/mL to 24.2 ng/mL). He remained clinically euthyroid. On examination, pendulous breasts with bilateral milky, white discharge were noted. He did not complain of breast tenderness.

Risperidone was stopped on day 14. After a ten-day washout period, Mr. R's prolactin level on day 24 had returned to normal (9.6 ng/mL) (see Figure 1). He remained psychiatrically symptomatic, and olanzapine was started on day 29.

By day 37 Mr. R's breast size had decreased by 50 percent, and no discharge was noted 23 days after risperidone was stopped. By day 87 breast size had decreased by 75 percent, and no discharge was noted. On olanzapine 5 mg daily, with valproic acid levels in the therapeutic range of 77 µg/mL, his serum prolactin level remained in the normal range on day 42 (4.7 ng/mL) and on day 54 (10.5 ng/mL). His continuing hypomanic symptoms required a further increase in the dosage of valproic acid to reach an effective level above 90 µg/mL for this patient. From day 12 through discharge at day 294, his weight varied between 190 pounds and 194 pounds.

A thyroid-releasing hormone (TRH) stimulation test is usually performed to investigate hyporesponsiveness of the anterior pituitary (16–18). An elevation of the thyroid-stimulating hormone (TSH) to two to three times baseline is considered a normal re-

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sponse. TRH is also known to stimulate prolactin secretion. To determine whether Mr. R had an increased sensitivity to TRH because of his primary hypothyroidism, 400 µg of TRH was administered as a challenge test on day 87 (Figure 1), and TSH and prolactin levels were obtained. The patient had continued on olanzapine with normal prolactin levels ranging from 4.7 ng/mL (day 42), to 10.5 ng/mL (day 54), to 6.9 ng/mL (day 86).

After the administration of TRH on day 87, Mr. R's TSH increased eightfold from his baseline level to 9.90 µIU/mL (reference range of .38 µIU/mL to 4.70 µIU/mL). His prolactin level transiently increased sixfold from his baseline level of 6.7 ng/mL to 40.1 ng/mL with this trial.

The free T4 remained normal at 1.1 ng/dL (reference range of .7 to 1.8 ng/dL). Follicle-stimulating hormone (FSH) (2.1 mIU/mL), luteinizing hormone (LH) (4.5 ng/dL), and testosterone level (374 ng/dL) (reference range of 1 to 8 mIU/mL for FSH, 2 to 12 mIU/mL for LH, and 286 to 1,510 ng/dL for testosterone) were all normal, indicating no anterior pituitary abnormality. The source of Mr. R's thyroid dysfunction was known to be only in his thyroid gland (primary hypothyroidism).

Mr. R continued on olanzapine 5 mg daily and valproic acid 1,500 mg daily for the remainder of his hospitalization, with valproic acid levels averaging 98 µg/mL (reference range of 50 µg/mL to 125 µg/mL). Monitoring of prolactin levels, anterior pituitary hormone levels (FSH, LH, ACTH, and TSH), and testosterone levels indicated that all remained normal for the remainder of his hospitalization. Liver function and renal function tests were all within normal limits throughout his hospitalization.

At discharge on day 294, Mr. R's prolactin level was normal at 12.2 ng/mL, his TSH was normal at 1.62 µIU/mL, his FSH was normal at 2.3 mIU/mL, his LH was normal at 5.3 mIU/mL, and his testosterone was normal at 695 ng/dL.

Discussion

This is the first report of risperidone-induced galactorrhea and gynecomastia resulting from elevated serum pro-

lactin in a male patient who had normal testosterone levels and known primary hypothyroidism. The elevation of serum prolactin in this male patient was lower (48.2 ng/mL) than the levels previously reported in two female patients (83.5 ng/mL and 261 ng/mL) treated with risperidone who were premenopausal and amenorrheic (6). Although these two women complained of breast tenderness, our male patient did not.

In a recent report of galactorrhea in two female patients treated with risperidone, one with hypothyroidism receiving 3 mg twice a day developed galactorrhea and amenorrhea. This patient's serum prolactin level was 261 µg/mL. In the same study, a second, nonhypothyroid female patient treated with 2 mg of risperidone at bedtime had an elevated prolactin level of only 83.6 µg/mL, which was associated with breast tenderness and galactorrhea (19). Galactorrhea without breast tenderness in this hypothyroid male patient with a prolactin level of 48.2 ng/mL may reflect the sensitivity of his breast tissue to the elevated prolactin levels.

In a larger study that used data from four randomized double-blind clinical trials of risperidone, among the 215 females who received 2 to 16 mg per day of risperidone, the mean endpoint prolactin levels ranged from 24 to 60 ng/mL (20). Among the 372 males who received 2 to 16 mg per day of risperidone, the mean endpoint prolactin levels ranged from 38 to 86 ng/mL. In both males and females, the mean endpoint plasma prolactin levels were 10 mg per day higher for patients receiving risperidone than for patients on haloperidol. Thyroid status of these patients was not determined.

Our patient treated for 14 days with risperidone had elevated prolactin levels equivalent to those of both males and females treated with risperidone who participated in these clinical trials. Further, the TRH challenge test in our hypothyroid male patient resulted in an elevated prolactin level (40.1 ng/mL), exceeding the levels for males treated for six weeks with higher doses of risperidone (16 mg per day), which would be consistent with increased sensitiv-

ity to TRH due to his primary hypothyroidism.

A recent report described a study of prolactin levels among males in a state hospital population that was triggered by identification of an elevated prolactin level of 82 ng/mL at discharge in a male patient with a diagnosis of paranoid schizophrenia who had been treated with 12 mg risperidone per day over a 20-month period (21). Prolactin levels among 29 males in the same hospital were compared; 12 were on risperidone and 15 on traditional antipsychotics, such as haloperidol and fluphenazine. After 25 weeks of treatment, prolactin levels were higher among patients on risperidone (range of 17.8 ng/mL to 87.5 ng/mL) than among those on traditional antipsychotics (range of 27.4 ng/mL to 62.2 ng/mL) (21).

Our male patient with primary hypothyroidism had a prolactin level of 48.2 ng/mL after only two weeks of risperidone. A nonhypothyroid male treated with 5 mg of risperidone twice a day reported loss of libido and an almost total inability to obtain an erection (22). His serum prolactin level was 66 mg/mL, and his testosterone level was low (5.3 nmol/L; reference range, 8 to 29 nmol/L).

The hypothesized increased sensitivity to TRH of this patient with primary hypothyroidism was confirmed with the TRH challenge test, which produced an eightfold increase in the baseline TSH level and a transient elevation of the serum prolactin level by six times the baseline level. In a patient with normal thyroid function, the TSH and prolactin levels would be expected to increase no more than two or three times the baseline level, as found in recent studies of nonhypothyroid males (21). None of these males were found to have gynecomastia or galactorrhea associated with their elevated prolactin levels.

The findings of our study contrasted with the literature that describes compromise of anterior pituitary function due to trauma, which affects, to varying degrees, growth hormone, the gonadotropins (FSH and LH), thyrotropin (TSH), ACTH, and prolactin (10–15). This patient with hypoxic brain injury and surgical thalamotomy had no abnormality of the

anterior pituitary function. His hormonal dysfunction was only in his primary hypothyroidism.

Conclusions

Our data suggest that male patients with primary hypothyroidism (5) may be particularly sensitive to a neuroleptic-induced elevation of prolactin levels (16–18). Close monitoring of serum prolactin levels in the first three months of the initiation of risperidone for males with primary hypothyroidism is suggested.

A second population to be closely assessed would be patients with a history of head injury for whom the clinician suspects anterior pituitary dysfunction. Close monitoring of anterior pituitary function may be helpful in the clinical management of such patients.

Further studies of prolactin levels in euthyroid and hypothyroid males with mental disorders treated with risperidone and other atypical neuroleptics may provide additional guidelines for monitoring the use of atypical antipsychotics in these patients. ♦

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