



## A case of hyperprolactinemia and delusion of pregnancy during clozapine treatment

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### ABSTRACT

Clozapine (Clozaril, Novartis) is classified as a prolactin-sparing antipsychotic, so clozapine-induced hyperprolactinemia is rare. Herein, however, we present a case of severe hyperprolactinemia with delusion of pregnancy during the use of clozapine. We discuss various factors involved in the background of hyperprolactinemia and delusion of pregnancy. While clozapine-induced hyperprolactinemia is rare, the adverse events of this condition can be clinically important in the short- and long-term. In Japan, the measurement of prolactin levels is not a required item in the Clozaril Patient Monitoring Service (CPMS, Novartis), so the risk of hyperprolactinemia tends to be easily overlooked. We hope this case report will help to alert colleagues to the risk of hyperprolactinemia during clozapine use.

**Keywords:** *Clozapine, prolactin-sparing antipsychotic, hyperprolactinemia, delusion of pregnancy, CPMS, psychopharmacology*

Received November 5, 2020 / Accepted December 4, 2020 / Published January 14, 2021.

### Introduction

Clozapine (Clozaril, Novartis) is an antipsychotic drug prescribed for treatment-resistant schizophrenia [1]. Clozapine has multiple receptor affinities and exhibits multiple pharmacological actions; it therefore induces various side effects [2]. However, clozapine is classified as a prolactin-sparing antipsychotic [3], so hyperprolactinemia is a rare side effect during clozapine use. While a recent meta-analysis showed that clozapine has the lowest prolactin-elevating effect of any antipsychotic drug [4], we experienced a case of hyperprolactinemia with delusion of pregnancy during the use of clozapine. It is rare for clozapine to cause severe hyperprolactinemia, and there have been no previous

reports of clozapine-induced delusion of pregnancy. We obtained consent from the patient and her guardian to publish these features of her case, and the identity of the patient has been protected.

### Case Presentation

The patient was a 44-year-old woman with treatment-resistant schizophrenia.

After graduating from a junior college at age 20, she did not gain employment and lived alone. At age 26, hallucinations, paranoia, insomnia, and soliloquy appeared, with no cause. She experienced a delusion that “an earthquake was occurring.” She was detained by the police and referred for the first

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time to the psychiatric department of her local hospital. She was diagnosed with schizophrenia and appropriately treated with perospirone, quetiapine, and haloperidol. However, she did not recover and eventually required long-term hospitalization for at least 10 years. At age 42, she was transferred to another hospital and underwent electroconvulsive therapy, but this did not work. She returned to the previous hospital and was treated with a long-acting injection of paliperidone palmitate, which had little effect. At age 44, she was transferred to our hospital for the purpose of introducing her to clozapine.

During her first interview, her face was expressionless, and she spoke in a soliloquy during the interview. The content of her conversation was disorganized and immediately became derailed. She had a delusion of misidentification of her mother, and she repeatedly stated, while pointing at her mother, "this person is not a true mother." A blood test showed moderately high prolactin of 55.6 ng/ml. Irregular menstruation or galactorrhea was not clear. There were no other abnormalities from blood tests or computed tomography of her head.

After transferring to our hospital, clozapine was started and gradually increased. Initially, she had significant disorganized and delusional symptoms and walked around at night, loudly speaking in soliloquy, so she was kept in a quiet room. Two months after admission, clozapine was gradually increased to 300 mg, her psychotic symptoms gradually alleviated, and her isolation was lifted.

However, 4 months after admission and an increase to 400 mg clozapine, a delusion of pregnancy, genital itching, and uncomfortable sensations developed and she began refusing medication. We first thought clozapine-induced constipation and abdominal bloating might be causing the delusion of pregnancy, so we prescribed a laxative (sodium picosulfate) and her constipation was alleviated. However, her delusion continued. A blood test revealed severe hyperprolactinemia (117.1 ng/ml), suggesting the delusion of pregnancy was associated with this hyperprolactinemia; hence, we gradually decreased clozapine to 250 mg, and 6 mg/day aripiprazole was added to treat hyperprolactinemia. Although combining clozapine with other antipsychotic drugs is not recommended, we obtained consent from the patient and her mother for this. Her prolactin decreased to a moderate level (44.7 ng/ml), and the delusion of pregnancy and genital itching sensations

were alleviated. Thereafter, she continued mild soliloquys, and the delusion of pregnancy sometimes reappeared when her constipation worsened, but this was not so severe that she refused medication. Finally, her overall mental state improved, and she was discharged to return home after 6 months of hospitalization.

## Discussion

In this case, after increasing clozapine to 400 mg or more, a delusion of pregnancy and genital itching sensations occurred. At that time, the patient's prolactin levels were >100 ng/ml, and she was diagnosed with severe hyperprolactinemia.

Three main pathological conditions were considered for the delusion of pregnancy. First was the possibility her schizophrenia had worsened and a new delusional symptom had appeared. However, this was unlikely because of her good response to clozapine at that time. Second, the delusion of pregnancy was associated with her constipation. It is well known that delusions of pregnancy can be associated with constipation, and it has been reported that abdominal bloating can be delusionally interpreted, especially in patients with schizophrenia [5]. However, in this case, the delusion of pregnancy continued once her constipation improved. Third, unique symptoms, including genital itching sensations, were simultaneously observed with the delusion of pregnancy. So, we assumed the delusion of pregnancy was associated with hyperprolactinemia.

Symptoms of hyperprolactinemia include infertility (48%), headache (39%), abnormal menstrual cycle (29%), and lactation (24%) [6]. If prolactin levels are 100 ng/ml or more, hyperprolactinemia is classified as severe. In such cases, hypogonadism due to decreased estradiol secretion, amenorrhea, burning sensation, and vaginal dryness may occur [7]. It is possible that hyperprolactinemia causes delusions of pregnancy because some symptoms of hyperprolactinemia, such as amenorrhea, hypogonadism, and lactation, give the appearance of pregnancy-like physical sensations. There have been reports of delusions of pregnancy caused by antipsychotic-induced hyperprolactinemia [8]. However, in this case, amenorrhea, hypogonadism, or lactation in association with hyperprolactinemia were unclear, and the genital itching sensations were similar to the vaginal dryness observed in hyperprolactinemia. Therefore, it appears likely that clozapine-induced

hyperprolactinemia led to the delusion of pregnancy. Further support for this comes from the alleviation of genital itching sensations and delusions once the prolactin levels decreased after the addition of aripiprazole to her treatment. As one of the limitations, however, it cannot be ruled out that the combination of clozapine and aripiprazole might be directly effective for treating delusions.

Clozapine is classified as a prolactin-sparing antipsychotic [3]. There are various theories about why clozapine has fewer prolactin-elevating effects than other antipsychotics. One is the “fast dissociation hypothesis” ; if the D2 receptor dissociation rate of an antipsychotic is high, its D2 receptor blocking action is short and transient [9]. Another is the transmissibility of the antipsychotic through the blood-brain barrier (BBB). The pituitary gland is outside the BBB. Some atypical antipsychotics, such as quetiapine and olanzapine, can easily cross the BBB and therefore do not remain outside it and tend not to accumulate in the pituitary gland [10]. These antipsychotics are less likely to elevate prolactin.

In this case, it was unclear why clozapine caused hyperprolactinemia. There may be some individual differences in the susceptibility of pituitary D2 receptors, and this patient may have been especially susceptible to developing hyperprolactinemia. In fact, she already showed some hyperprolactinemia at the time of admission, suggesting her other antipsychotic drugs might also have caused hyperprolactinemia. However, it is noteworthy that her prolactin increased further after the change from paliperidone palmitate to clozapine. There are several other factors that can cause hyperprolactinemia. Stress, both physical and psychological, can cause an increase in serum prolactin concentration. As with all stimuli of prolactin secretion, women exhibit greater increases than men, presumably due to the effect of their higher serum estradiol concentrations on lactotroph cells [11]. In this case, she had been under chronic psychological stress resulting from treatment-resistant schizophrenia. When stressed, corticotropin releasing hormone is secreted by the paraventricular nucleus of the hypothalamus and can cause secretion of adrenocorticotropin from the anterior pituitary. At the same time, secretion of  $\beta$ -endorphin and prolactin from the anterior pituitary is promoted [12], forming part of the hypothalamic-pituitary-adrenal (HPA) axis cascade.

This was a successful case of clozapine treatment, but it became temporarily difficult to continue treatment due to rare adverse events. However, we were able to achieve a good outcome by investigating the cause and appropriately dealing with hyperprolactinemia and delusion of pregnancy.

Currently, in Japan, measurement of prolactin levels is not a required item in the Clozaril Patient Monitoring Service, so the risk of hyperprolactinemia may be easily overlooked. We hope this case report will help alert colleagues to the risk of hyperprolactinemia in cases of clozapine use.

### Author Contributions

KO, TY, SM, TR, EI, MD, and TS fulfill the criteria of authorship based on their substantial contributions to the conception and design or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; or the final approval of the version to be published. No one who fulfills these criteria has been excluded as an author. TY is the guarantor for the present manuscript; he accepts full responsibility for the finished article because he had access to all data and made the decision to submit the article for publication.

### CONFLICT OF INTEREST

Toshiyuki Someya has received research support or honoraria from Astellas Pharma Inc., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Mochida Pharmaceutical Co., Ltd., MSD K.K., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Shionogi Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd. The other authors have no conflicts of interest to disclose.

### ACKNOWLEDGEMENT

The authors would like to thank Enago ([www.enago.jp](http://www.enago.jp)) for the English language review.

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