Psychiatric Patients with Antipsychotic Drug-Induced Hyperprolactinemia and Menstruation Disorders

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Note

Treatment with antipsychotic drugs has been associated with hyperprolactinemia. The same antipsychotic drugs have also been associated with side effects such as menstruation disorders. The aim of this study was to evaluate the prevalence of hyperprolactinemia and menstruation disorders in women undergoing antipsychotic treatment. We performed a retrospective chart review study of psychiatric patients who underwent laboratory testing for serum prolactin (PRL) level between March 2011 and March 2015 in Ehime University Hospital. Patients presenting with and without menstruation disorders were evaluated to determine if they presented concomitant hyperprolactinemia. Patients with menstrual disorders had a significant increase in serum PRL level with a mean of approximately 90 ng/mL. Those with menstrual disorders presented increased PRL levels by 2-fold that of patients without menstrual disorder. However, there was no significant difference in the equivalent dose of chlorpromazine between these two groups. Additionally, about 70% of patients with menstrual disorders received risperidone treatment. The receiver operating characteristic curve showed that the optimal cutoff point of serum PRL level associated with the development of menstrual disorders was 60 ng/mL. Based on these results, we concluded that patients with menstrual disorders presented increased serum PRL, and that most of them underwent treatment with risperidone.

Key words prolactin; antipsychotic drug; menstruation

Atypical antipsychotics are recommended as first-line treatments for individuals with schizophrenia. These drugs not only improve symptoms, such as auditory or visual hallucinations, but compared with typical antipsychotics, they are associated with fewer side effects, such as sleepiness, weight gain, and tremors. However, antipsychotic drugs are also known to influence the hypothalamo-hypophysial axis and induce variable degrees of hyperprolactinemia. Hyperprolactinemia is a recognized adverse side effect of antipsychotic drugs. It can be acute or chronic, and it can be associated with sexual dysfunction, menstrual irregularities, amenorrhea, galactorrhea and osteoporosis. The proportion of premenopausal women who develop hyperprolactinemia during treatment with antipsychotic drugs can be as high as 48 to 93%. Despite such high prevalence, in most cases, hyperprolactinemia is asymptomatic. However, some patients present clinical symptoms along with severe disease. Additionally, the condition and its management strategies are scarcely mentioned in psychiatric nursing journals or textbooks. Therefore, hyperprolactinemia induced by antipsychotic drugs may be less successfully managed. This could be potentially harmful to patients and affect their QOL. In clinical practice, serum prolactin (PRL) levels are helpful in the early detection of adverse side effects induced by antipsychotic drugs. Hyperprolactinemia is the presence of abnormally high levels of PRL in serum. Normal PRL levels are less than 25 ng/mL for women and less than 20 ng/mL for men. However, if patients receiving antipsychotic therapy develop hyperprolactinemia (>25 ng/mL), it is very difficult to discontinue medication at once, because of therapeutic efficacy. It remains unclear what cutoff level of PRL concentration causes menstrual disorders. Therefore, the relationship between serum PRL and adverse side effects, such as menstrual irregularities, needs further investigation.

The purpose of this study was to evaluate the prevalence of hyperprolactinemia in women with psychiatric disorders receiving antipsychotic treatment.

PATIENTS AND METHODS

Ethical Approval of the Study Protocol This study was conducted in accordance with the guidelines for the care of human study participants adopted by the Ethics Committee of Ehime University Hospital (approval number: 16020009), the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the principles of the Helsinki Declaration.

Research Data and Patient Characteristics This retrospective study was carried out at Ehime University Hospital using data from electronic medical records dated between March 2011 and March 2015. We excluded the medical records of pregnant women, nursing women, as well as women with hypothyroidism or hypophysyal adenoma. Patients who underwent serum PRL monitoring after administration of psy-

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Psychiatric drugs were enrolled in this study. Patient characteristics (age [under 55 years], sex [only women]) and necessary research data (serum PRL and prescription history) were collected from the medical records of 83 patients with psychiatric disorders (Table 1). The antipsychotic drugs prescribed in this study were chlorpromazine, haloperidol, levomepromazine, risperidone, paliperidone, quetiapine, olanzapine, blonanserin, aripiprazole and clozapine. We used the equation described by Woods to calculate the equivalent dose of chlorpromazine for the dose of the other psychiatric drugs. The antipsychotic drug dosages used were then compared by chlorpromazine equivalent dosages.

**Statistical Analyses** The data are shown as means and standard deviation. The statistical significance of the differences resulting from comparisons of patients with or without menstrual disorders was evaluated using the Mann–Whitney U test or Fisher’s exact test after checking for normal distribution using the Kolmogorov–Smirnov test. Receiver operating characteristic (ROC) curves were calculated, and the area under the curve (AUC) was calculated to evaluate the optimal cutoff point of serum PRL level to induce menstrual disorders. The optimal cutoff value was calculated using the following formula: \((1 - \text{sensitivity})^2 + (1 - \text{specificity})^2\) with the ROC curve. A value of \(p<0.05\) was considered significant. Statistical analyses were performed using Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

**RESULTS**

**Relation of Serum PRL and Menstrual Disorders** The changes in serum PRL level in the antipsychotic drug treatment group were compared between patients with or without menstrual disorders (Fig. 1). A total of 83 women were included in this study. Patients with and without menstrual disorder had a mean age (range) of 32 (15–44) and 37 (15–44) years, respectively. The mean age of women with menstrual disorder was significantly less than that of patients without menstrual disorders \((p<0.05)\). The mean PRL serum level was significantly higher in patients with menstrual disorders compared with those without menstrual disorder \((89.3\pm36.9 \text{ vs. } 42.5\pm54.5; 95\% \text{ confidence interval} (CI): 46.8 [19.3–74.3], p<0.001)\) (Fig. 1A). However, patients with menstrual disorder showed no significant difference in chlorpromazine equivalent dose (mg/d) compared with patients without menstrual disorder \((401.6\pm387.6 \text{ vs. } 495.8\pm419.7; 95\% \text{ CI: } 94.2 [-124.7–313.2], p=0.36)\) (Fig. 1B).

Next, we focused on the rate of prescribed atypical antipsychotic drugs in patients receiving antipsychotic drugs to identify a relationship between menstrual disorder and type of drug. The proportion of atypical antipsychotic drugs used is shown in Table 2. The proportion of patients with menstrual disorders that received risperidone treatment was significantly higher than that in those without menstrual disorders, while the proportion of patients without menstrual disorders that received aripiprazole treatment was higher than that of patients with menstrual disorders.

**Association of Serum PRL Level with Menstrual Disorders**

![Fig. 1.](image-url) **Comparison of Serum Prolactin Levels (A) and Chlorpromazine Equivalent Dose (B) between Patients with and without Menstrual Disorders**

**Table 1. Background of Patients with and without Menstrual Disorders**

<table>
<thead>
<tr>
<th></th>
<th>No menstrual disorder</th>
<th>Menstrual disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td>Age</td>
<td>37 [15–44]</td>
<td>32 [15–44](^a)</td>
</tr>
<tr>
<td>Combination use (%)</td>
<td>8 (12)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Chlorpromazine equivalent dose (mg/d)</td>
<td>495.8±419.7</td>
<td>401.6±387.6</td>
</tr>
</tbody>
</table>

\(^a\) Rate of prescribed atypical antipsychotic following patients with menstrual disorder versus with no menstrual disorder: \(a p<0.05\). Combination use show the number of patients with over two drugs induced by hyperprolactinemia such as chlorpromazine, haloperidol, levomepromazine, risperidone, paliperidone, quetiapine, olanzapine, blonanserin, aripiprazole and clozapine.

**Table 2. The Proportion of Prescribed Atypical Antipsychotics between Patients with and without Menstrual Disorders**

<table>
<thead>
<tr>
<th></th>
<th>No menstrual disorder ((n=65))</th>
<th>Menstrual disorder ((n=18))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (%)</td>
<td>16 (25)</td>
<td>0 (0)(^a)</td>
</tr>
<tr>
<td>Risperidone (%)</td>
<td>15 (23)</td>
<td>12 (67)(^a)</td>
</tr>
<tr>
<td>Olanzapine (%)</td>
<td>19 (29)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Quetiapine (%)</td>
<td>11 (17)</td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

Rate of prescribed atypical antipsychotic following patients with menstrual disorder versus with no menstrual disorder: \(a p<0.05\); \(b p<0.01\).
antipsychotics. The introduction of atypical antipsychotics, which have a stronger 5-HT receptor affinity, and blood–brain disposition of these drugs, led to lower adverse side effects compared with typical antipsychotics. However, risperidone has a strong D2-blocking effect and a simultaneous effect on the 5-HT₂ receptors. Thus, patients with hyperprolactinemia were more likely to receive risperidone in our study. In contrast, Zhao et al. reported that adjunctive aripiprazole treatment in patients with schizophrenia who develop risperidone-induced hyperprolactinemia results in a significant reduction of serum PRL level. In a previous study, it was reported that at week 52, the median PRL had increased by 177% in the haloperidol group and decreased by 40% in the aripiprazole group. Interestingly, our results showed that the proportion of patients without menstrual disorders that received aripiprazole treatment was significantly higher than that of patients with menstrual disorders. Thus, our results seem to be consistent with those of previous research. These findings indicate that the increase in PRL induced by antipsychotics can be attributable to the drug type rather than the dose of antipsychotics. Bostwick et al. reported that if the effects of PRL are evident, the drug can be changed to another agent that is less likely to affect PRL levels.

Further research is needed to clarify the appropriate method for PRL monitoring. In the present study, using ROC curve analysis, we estimated that the cutoff value of PRL that can lead to adverse side effects induced by antipsychotic drugs, such as menstrual disorders, was 60 ng/mL. Additionally, the AUC (0.82) of the ROC curve had an acceptable accuracy.

The limitations of this study and details that we should consider in the future are as follows. This was a single-center study with a relatively small sample size. This study was retrospective in nature and we did not include a control group. Additionally, the previous treatments received by the patients were various and heterogeneous. Therefore, a large-scale prospective cohort validation study, including other factors associated with hyperprolactinemia, is necessary. Future large-scale prospective validation studies may determine whether the cutoff value of 60 ng/mL in serum PRL may be a useful indicator of menstrual disorders induced by antipsychotic treatment. Although further studies are required to clarify the involvement of hyperprolactinemia in the adverse effects induced by psychiatric treatment, our findings indicate that clinicians should monitor PRL in these patients based on the cutoff value of 60 ng/mL to improve early detection of adverse effects such as menstrual disorders.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

5) Kinon BJ, Gilmore JA, Liu H, Halbreich UM. Prevalence of hyper-


