Association between depression in chronic phase and future clinical outcome of patients with schizophrenia

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Acknowledgments

Conflict of Interests

Contributors

Y. Yamada, M. Takaki, M. Fujiwara, S. Sakamoto, Y. Okahisa, and N. Yamada participated in the design of the study, supervised the project, and contributed intellectually to the interpretation of the data. M. Takaki and S. Sakamoto investigated patient clinical records. Y. Yamauchi and S. Takao interpreted the statistical analyses. M. Takaki, M. Fujiwara, and S. Sakamoto revised critically. All authors contributed to and have approved the final manuscript.

Running title: Depression and clinical outcome in schizophrenia

Abstract

Rationale

Depression in schizophrenia is an important symptom. We investigated whether depression and suicidal symptoms in the chronic phase are related to remote future clinical outcomes in patients with schizophrenia and whether psychotropics improved clinical outcomes.

Objectives

The subjects included 462 outpatients of working age (15 to 64 years old) with schizophrenia treated at Okayama University Hospital from January 2010 to December 2011. We investigated the relationship between the Clinical Global Impression Severity score at the last visit (average 19.2 years) and the existence of previous depression, suicidal ideas, and suicide attempts. We adjusted by several possible confounders including medical history using multiple regression analysis or logistic regression analysis.

Results

Of 462 patients, 168 (36.4%) presented with depression two years after schizophrenia onset. A history of suicidal ideas and attempts was related to worse clinical outcome. In males, a history of depression was related to worse clinical outcome, but not

in females. Lithium carbonate was related to better clinical outcome in all schizophrenia patients with depression, especially in males. Treatment with antidepressants was related to better clinical outcome only in males.

Conclusions

A history of depression or suicidal symptoms in the chronic phase predicted the future worse clinical outcome in patients with schizophrenia. The administration of lithium carbonate or antidepressants might be recommended, especially to male schizophrenia patients with depression.

Keywords: Schizophrenia, depression, suicide, lithium carbonate, antidepressants, multiple regression analysis, logistic regression analysis

Introduction

Depression in schizophrenia is an important symptom, and its prevalence is reported to be about 25% on average (Buckley et al. 2009). The coexistence of depression in patients with schizophrenia increases social difficulties and the risk of suicide (Conley et al. 2007; Schennach-Wolff et al. 2011). A previous history of suicide attempts also increases the risk of suicide (Hawton et al. 2005). The life-time mortality risk due to suicide among patients with schizophrenia is about 5% (Palmer et al. 2010) and has increased recently (Oakley et al. 2018).

The prevalence rates of depression in patients with schizophrenia range from 7% (Hirsch and Jolley 1989) to 83% (Hafner et al. 2005) due to differences in the definition and method of evalutation of depression (Schennach-Wolff et al. 2011), including various etiologies of depression, such as pure symptoms of schizophrenia, antipsychotic side effects, social hardship, and drug abuse or withdrawal (Lehman et al. 2004). Depression in schizophrenia emerges in all stages, e.g., the prodromal stage, first episode, acute stage, post-psychotic depression, and chronic stage (Siris et al. 2001). Depression in the acute phase of schizophrenia is related to a relatively good response to treatment and prognosis (Kay and Lindenmayer 1987; Oosthuizen et al. 2002). On the other hand, depression in the chronic phase of schizophrenia is related to a relatively poor prognosis, a high frequency of relapse and suicide (Johnson 1988; Hirsch and Jolley 1989; Cohen et al.

1990), and a low quality of life (Delahanty et al. 2001; Tomotake et al. 2006; Strauss et al. 2012; Suttajit and Pilakanta 2013). However, no study of the relationship between a history of depression in the chronic phase of schizophrenia and remote future clinical outcomes measured on a clinical scale has been reported. In addition, though the research on depression in patients with schizophrenia should be careful to avoid several confounders, such as background of patients, clinical course, social hardship, and medical histories of various types of psychotropics, there are not enough studies considering these elements.

Medical treatment of depression in schizophrenia is still controversial (Hasan et al. 2015). Antipsychotics are known to induce a subjective dysphoria, like depression, called neuroleptic dysphoria (Voruganti and Awad 2004). Neuroleptic dysphoria is induced by the blockade of dopamine D2 receptors in the nucleus accumbens (Mizrahi et al. 2007) and is related to poor clinical outcome (Bartko et al. 1987). Reduction of antipsychotics is reported to reduce depression in schizophrenia (Hogarty et al. 1995). Second generation antipsychotics (SGAs), like clozapine, olanzapine, and quetiapine, are reported to be better than first generation antipsychotics for treatment of depression in schizophrenia (Leucht et al. 2009), but inverse findings also are reported (Addington et al. 2011; Riedel et al. 2012; Rybakowski et al. 2012). Reduction of antipsychotics and

SGAs for depression in schizophrenia has only a weak grade 3 recommendation in the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines (Hasan et al. 2015). Further, addition of lithium carbonate had limited positive evidence in a controlled study (Leucht et al. 2004) and a grade 2 recommendation in the WFSBP Guidelines (Hasan et al. 2015). Addition of antidepressants is not automatically recommended (Whitehead et al. 2003; Leucht et al. 2013; Moazen-Zadeh et al. 2020), with also only weak evidence from an uncontrolled study (Terevnikov et al. 2011) and a grade 3 recommendation in the WFSBP Guidelines (Hasan et al. 2015).

Therefore, we investigated whether a history of depression and suicidal symptoms in the chronic phase is related to a remote future clinical outcome and whether various types of psychotropics improve clinical outcomes in patients with schizophrenia after adjusting for many susceptibility confounders.

Materials and methods

Subjects

This study is a historical cohort study. The subjects were 543 outpatients with schizophrenia treated at Okayama University Hospital from January 2010 to December 2011 (study entry period). The diagnosis of schizophrenia was based on the criteria of the

International Statistical Classification of Diseases and Related Health Problems, 10th Revision. This study was approved by the research ethics committee of Okayama University Hospital. We carefully protected patient personal information.

Assessment

To assess the clinical outcomes of patients with schizophrenia, we investigated the severity of illness according to the Clinical Global Impression Severity scale (7 point Likert scale; 1 point: normal, not at all ill to 7 points: the most extremely ill) (Busner and Targum 2007) at the last visit between January 2010 and December 2011. We also investigated the existence of depression and suicidal ideas and attempts during the period between two years after schizophrenia onset and the last visit during the study entry period in previous clinical records. Depression was defined as "patients complained of depressive feelings, and the psychiatrists in charge mentioned the existence of depression for more than two weeks two years after the schizophrenia onset" in the clinical record. In this study, we excluded depression during the first two years after the onset of schizophrenia because we aimed to investigate the impact of depression in the chronic phase of the disease. The rationale for the 2-year period was that a large number of reports defining the "early course of schizophrenia" as cases within two years of onset (Newton

et al. 2018). To assess social outcomes of patients with schizophrenia, we investigated

their social adjustment. "Social adjustment" was defined as functioning as a member of

society, including employment. "Social maladjustment" was defined as being

unemployed, a housewife, or student (Sakamoto et al. 2016). If there was a history of

schizophrenia in first-degree relatives, the information was obtained from all available

clinical records. The physician in charge and a trained senior psychiatrist assessed all

clinical records. The assessment of Clinical Global Impression - Severity (CGI-S) was

made independently, and the two scores were averaged. The two raters were blind to each

other's assessments.

Statistical analysis

We first estimated crude and adjusted odds ratios (ORs) and 95% confidence

intervals (CIs) of sex, family history of schizophrenia, early onset of depression, suicidal

ideation, and suicide attempts by using logistic regression models on a relative scale.

Adjusted variables were age and sex for model 1, and early onset (under 20 years old)

and a family history of schizophrenia in model 2 in addition to model 1 variables. When

we estimated ORs for sex, family history, and early onset, these variables were omitted

from adjusted models. At the same time, we also evaluated absolute changes of CGI-S

and estimated beta coefficients by using regression models for the same variables (sex, family history, and early onset) used the previous analysis. Then, we estimated crude and adjusted beta coefficients for CGI-S change of depression and suicidal history (ideas and attempts). Finally, we restricted participants to depression cases (n=168), suicidal ideas (n=76), and suicidal attempts (n=38) and repeated the same multiple regression analyses separated by sex and estimated betas for CGI-S change due to lithium carbonate and antidepressants. In all multiple regression models, we adjusted the following possible confounders: Model 1: sex, age; Model 2: sex, age, onset under 20 years old, family history of schizophrenia, recent employment; Model 3: sex, age, onset under 20 years old, family history of schizophrenia, recent employment, history of administration of typical antipsychotics, antidepressants, lithium carbonate, and anti-epileptics as mood stabilizers, and over 1000 mg chlorpromazine-equivalent dose (CP) (Inada and Inagaki 2015) of previous antipsychotics. All statistical analyses were conducted by using STATA 14/SE for Windows (Stata Corp., College Station, TX, USA).

Results

Clinical characteristics of patients with schizophrenia

A flow chart of the selection of subjects is shown in Supplemental Figure 1.

Because this study investigated the relationship between a history of depression and suicidal symptoms only in the chronic phase and remote future clinical outcomes during working age (from 15 to 64 years old), 8 patients with a history of less than two years from the onset of schizophrenia, 68 patients not between 15 to 64 years old, and 5 patients with deficient clinical records were excluded. Finally, 462 patients with schizophrenia were included.

Backgrounds of the subjects included in the analyses are shown in Supplemental Table 1. The average duration of treatment was about 19.2 years. Of 462 patients, 168 (36.4%) also met diagnosis criteria of depression two years after of the onset of schizophrenia. In addition, 76 of 168 patients had suicidal ideas, and 38 patients executed suicidal attempts. One-hundred twenty-seven patients (27.5%) had early onset, were less 20 years old, males had earlier onset than females. 49 patients (10.6%) had a family history of schizophrenia, 133 patients (28.9%) were recently employed, and more were male than female.

The medical histories indicated that typical antipsychotics were administered to 242 patients (52.4%), of which 124 had been administered previously but were stopped, and 118 were administered continuously. Recently administered atypical antipsychotics were aripiprazole (n=71), blonanserin (n=31), olanzapine (n=69), perospirone (n=25),

quetiapine (n=33), and risperidone (n=101); 16 patients were not treated with any antipsychotic. Forty-nine patients (10.6%) were recently treated with a high dosage of antipsychotics (over CP 1000 mg/day). Patients with depression (30/168, 17.9%) were less frequently treated with typical antipsychotics than those without depression (88/294, 29.9%) (chi-square test, P=0.0026), and a dose over CP 1000 mg was administered to only three patients with depression (1.8%).

Lithium carbonate was administered to 25 patients (5.4%), two of which had been administered previously but were stopped, and 23 were administered continuously. Twenty-seven patients (5.8%) recently were treated with anti-epileptics as mood stabilizers, valproic acid (n=23), lamotrigine (n=3), and carbamazepine (n=1).

Antidepressants were administered to 75 patients (16.2%), of which 18 had been administered previously but were stopped, and 57 were administered continuously: selective serotonin reuptake inhibitors (SSRIs) (n=30); paroxetine (n=16), fluvoxamine (n=10), sertraline (n=3), escitalopram (n=1), serotonin and norepinephrine reuptake inhibitors (SNRI) (n=4); milnacipran (n=2), duloxetine (n=2), tricyclic antidepressants (n=19); amoxapine (n=10), clomipramine (n=7), amitriptyline (n=2); tetracyclic antidepressants (n=12): trazodone (n=9), setiptiline (n=2), mianserin (n=1); and noradrenergic and specific serotonergic antidepressant (NaSSA); and mirtazapine (n=6).

Relationship between depression or suicidal symptoms in chronic phase and background of patients with schizophrenia (Table 1)

Females were more likely than males to have depression in the chronic phase even after adjusting for possible confounders (odds ratio (OR): 1.575, 95%CI: 1.061, 2.338, P=0.024), but suicidal ideas (OR: 1.68, 95%CI: 0.984, 2.870, P=0.058). A family history of schizophrenia was more often related to suicidal ideas in the chronic phase even after adjusting for possible confounders (OR: 2.019, 95%CI: 1.012, 4.030, P=0.046) than lack of a family history of schizophrenia. On the other hand, early onset of schizophrenia was not related to depression or suicidal ideas and attempts in the chronic phase.

Relationship between future clinical outcome and background of patients with schizophrenia (Table 2)

Females had better clinical outcomes than males even after adjusting for possible confounders including medical history (beta=-0.31, 95% CI: -0.509, -0.111, P=0.002). A family history of schizophrenia was related to worse clinical outcomes than no family history of schizophrenia, even after adjusting for possible confounders including medical history (beta=0.44, 95% CI: 0.129, 0.752, P=0.006). Early onset of schizophrenia was

related to worse clinical outcome than the lack of early onset of schizophrenia even after adjusting for possible confounders including medical history (beta=0.366, 95% CI: 0.133, 0.600, P<0.001).

Relationship between history of depression or suicidal symptoms in chronic phase and future clinical outcome of patients with schizophrenia (Table 3)

Histories of suicidal ideas (beta=0.309, 95% CI: 0.0305, 0.587, P=0.03) and attempts (beta=0.467, 95% CI: 0.103, 0.831, P=0.012) were related to worse clinical outcomes even after adjusting by possible confounders, including medical history versus no history. A history of depression was not insignificant (beta=0.212, 95% CI: -0.0341, 0.457, P=0.091). A history of depression (beta=0.362, 95% CI: 0.0260, 0.698, P=0.035), suicidal ideas (beta=0.598, 95% CI: 0.192, 1.004, P=0.004), and attempts (beta=1.079, 95% CI: 0.488, 1.670, P<0.001) were related to worse clinical outcome in males, but not in females.

Relationship between lithium carbonate (Table 4) or antidepressants (Table 5) and future clinical outcome of patients with schizophrenia

A history of administration of lithium carbonate was related to better clinical

outcome than no administration of lithium carbonate in all schizophrenia patients with

depression (beta=-0.617, 95% CI: -1.130, -0.103, P=0.019). A history of administration

of lithium carbonate was related to better clinical outcome than no administration of

lithium carbonate in schizophrenia patients with depression after adjusting by possible

confounders including medical history (beta=-1.893, 95% CI: -3.101, -0.684, P=0.003)

in males, but not in females (beta=-0.374, 95% CI: -0.930, -0.181, P=0.184).

A history of administration of antidepressants was not related to clinical outcome

in all schizophrenia patients with depression or suicidal history. However, a history of

administration of antidepressants was related to better clinical outcome than no

administration of antidepressants in schizophrenia patients with depression after adjusting

by possible confounders including medical history (beta=-0.7, 95% CI: -1.293, -0.107,

P=0.022) in males, but not in females (beta=0.172, 95% CI: -0.190, 0.535, P=0.348).

A history of administration of typical antipsychotics and anti-epileptics was not

related to clinical outcome of all schizophrenia patients with depression or suicidal history

after adjusting by possible confounders including medical history.

Discussion

This is the first study to show a relationship between the remote future (average

19.2 years) clinical outcome (CGI-S) and a history of depression or suicidal symptoms in patients with schizophrenia after adjusting for many susceptibility confounders including medical history. In addition, there is only one Japanese study that showed the relationship between recent depressive symptoms and quality life in patients with schizophrenia, even unadjusted by confounders (Tomotake et al. 2006). Depression and suicidal symptoms in the chronic phase are related to remote future worse clinical outcome, and a history of lithium carbonate or antidepressant administration is related to a better clinical outcome, especially of male schizophrenia patients with depression.

Though male sex, early onset, and a family history of schizophrenia are relatively well known to be related to poor outcomes (Murray and Van Os 1998; Lauronen et al. 2007; Clemmensen et al. 2012; Lang et al. 2013; Käkelä et al. 2014), almost all were shown only by a crude model. Our results also supported the same tendency, and this tendency increased after adjusting by susceptible confounders. On the other hand, only a family history of schizophrenia was related to suicidal ideas, and female sex was related to depression and nominally to suicide ideas and attempts. Female patients with schizophrenia are reported to have depressive symptoms more frequently than males (Delahanty et al. 2001), and male patients with schizophrenia are reported to have higher suicide risk than female patients with schizophrenia (Hor and Taylor 2010). The reason

may be that patients who accomplished suicide were not included in our retrospective study, and sex differences become insignificant in schizophrenia patients with suicide attempt. To our knowledge, there is no previous report about the relationship between depression or suicidal symptoms in the chronic phase and a family history of schizophrenia, and we should be more careful to anticipate the suicide of schizophrenia patients with a family history of schizophrenia.

In this study, a history of suicidal ideas and attempts in patients with schizophrenia was related to a remote future clinical outcome, but depression was insignificant in the total sample and relevant only in males. The first reason for the difference is the difference in methods of evaluation of depression, e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM) (Delahanty et al. 2001), Calgary Depression Scale for Schizophrenia (CDSS) (Tomotake et al. 2006), and depression cited in clinical records (this study). Underdiagnosis of depression possibly induces the opposite results (Delahanty et al. 2001). The second reason is different outcome measures, e.g., high frequency of relapse (Johnson 1988; Hirsch and Jolley 1989) and suicide (Cohen et al. 1990), Lehman Quality of Life Interview (Delahanty et al. 2001), Schizophrenia quality life scale (Tomotake et al. 2006), psychological well-being scale (Strauss et al. 2012), World Health Organization Quality of Life-Brief (Suttajit and

Pilakanta 2013), and CGI-S (this study). The third reason is the difference in the evaluation period of depression and outcome, e.g., a history of depression related to a future clinical outcome (this study) or a recent depression related to a recent clinical outcome (Delahanty et al. 2001).

Combination therapy with lithium has positive evidence for the treatment of depression in patients with schizophrenia (Terao et al. 1995; Leucht et al. 2004), but the opposite suggestion is also reported (Lehman et al. 2004). Combination therapy with antidepressants has also some positive evidence (Whitehead et al. 2003; Terevnikov et al. 2011; Moazen-Zadeh et al. 2020). In this study, a history of administration of lithium carbonate was related to better clinical outcome, especially in male schizophrenia patients with depression, and a history of administration of antidepressants was related to better clinical outcome only in males. Though there is no study of sex differences in depression in patients with schizophrenia, many studies of depression are reported. Depression is two-fold higher, and anxiety, somatic symptoms, reported symptoms in self-ratings, comorbidity of abuse and dependence, and thyroid disease are more common in females than in males (LeGates et al. 2019; Rubinow and Schmidt 2019). Tricyclic antidepressants are less effective, but SSRIs are effective in females (Rubinow and Schmidt 2019). This may be due to the difference of sex hormones (LeGates et al. 2019) and synaptic

transmission (Rubinow and Schmidt 2019). In this study, SSRIs were most frequently administered, but the results were controversial. The mechanisms of pure depression and depression in patients with schizophrenia may be different, and antipsychotics may change sex hormones and synaptic transmission. In addition, because thyroid system function is commonly disturbed in females and lithium carbonate impairs thyroid metabolic pathways (Bauer et al. 2013), lithium carbonate might be preferable for males rather than females.

There are several limitations to be noted in this study. First, the sample size is not large enough to achieve significant results on the effectiveness of lithium carbonate and antidepressants to treat depression in patients with schizophrenia. Second, we used only CGI-S as the clinical scale, not the Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, patients' QOL scale, or a functional scale. Third, a history of electroconvulsive therapy (ECT) was not examined, though it is sometimes reported to be effective for depression and suicidal behavior in patients with schizophrenia (Leucht et al. 2013). Fourth, the duration of untreated illness was not established, though it is also reported to be related to the outcome in patients with schizophrenia (Murru and Carpiniello 2018). In addition, other susceptibility covariants, such as a history of chronic somatic diseases and family living together were not checked. Fifth, clozapine is reported

to prevent suicide (Griffiths et al. 2014) by patients with schizophrenia. However, because clozapine was approved only in June 2009 in Japan (Yada et al. 2021) and not administered in this study, the effectiveness of lithium carbonate and antidepressants to treat depression in patients with schizophrenia may be investigated separately. Sixth, depression in this study was not defined by CDSS or structured diagnostic interviews. Lastly, this study is a historical cohort study in a solely observational setting (real clinical practice). Patients who committed suicide before the observation period from January 2010 to December 2011 were excluded. As a future study, we need to confirm the results with prospective/interventional research using a large sample.

Conclusion

A history of depression or suicidal symptoms in the chronic phase is important because these symptoms may predict remote future worse clinical outcomes in patients with schizophrenia. We should always take care in the existence of these symptoms, and the administration of lithium carbonate or antidepressants might be recommended, especially to male schizophrenia patients with depression.

Supplemental figure legends

Supplemental figure 1: A flow chart of the selection of subjects

      The subjects included 543 outpatients with schizophrenia treated at Okayama University Hospital from January 2010 to December 2011. Because this study investigated the relationship between a history of depressive and suicidal symptoms only in the chronic phase and future clinical outcomes during working age (from 15 to 64 years old), 8 patients with less than 2 years since the onset of schizophrenia, 68 patients not between 15 and 64 years old, and 3 patients with deficient clinical records were excluded. Finally, 462 patients with schizophrenia were included. Of 462 patients, 168 (36.2%) also met diagnosis criteria of depression for at least 3 months 2 years after the onset. In addition, 92 of 168 patients had suicidal ideas, and 38 patients attempted suicide.

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