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Bipolar Disorder and Aggression

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Abstract

Here, I present a review on aggression in bipolar disorder, based on questionnaire-assessed violence, violent crimes, and suicide. Additionally, the anti-aggressive effects of lithium used in medical drug formulations, and those in drinking water were discussed. clinical genetics and pathophysiology of aggression were reviewed and therapeutic coping was also proposed. Usually, symptoms of bipolar disorder are investigated in the viewpoint of mood, activity, and thought and there has been minimal investigation on aggression associated with bipolar disorder. Aggression in bipolar disorder is often directed towards others (violent crime in its serious from) and against oneself (suicide in its worst form). These are serious problems that cannot be overlooked. Although aggression in bipolar disorder and in schizophrenia is commonly attributed to the accompanying substance abuse, aggression in bipolar disorder, but not schizophrenia, has been revealed to be at least partially derived from the expression of a specific gene exclusively associated with bipolar disorder. This is important because the findings suggest that aggression may be attributed to bipolar disorder itself, and lithium may be an effective treatment for aggression as well as bipolar disorder. In any case, it is important to treat bipolar disorder with considerable attention to aggression.

Keywords: bipolar disorder, aggression, violence, suicide, lithium

Introduction

First, I would like to introduce a female case of aggression in my patient with bipolar disorder. episodes. At work, where she had been working without any particular problem, she suddenly got into an argument with her boss over a parking space and resigned a few days later. A few days after that, at home, she suddenly argued with her mother about her father's Buddhist memorial service, and, not wanting to live with her, she moved into a hotel and looked for an apartment. In addition, she suddenly argued with the hospital receptionist about a change in her appointment to see the doctor. In all of these incidents, there was no clear manic episode, but rather an impulsive outburst of aggression. Moreover, the aggression in this patient was verbal aggression, not physical aggression such as violence. In other words, aggression in bipolar disorder, even at the level of verbal aggression, can lead to obstacles in work, life, and treatment. Until now, symptoms of bipolar disorder have often been examined in terms of mood, activity, and thinking, but rarely in terms of aggression.

In this paper, I review the literature on the relationship between bipolar disorder and aggression, and refer to pharmacotherapy for aggression. This paper is based on a previous report in Japanese (19) and has been revised based on lectures given at the symposium and other literature.

I. Questionnaire-based survey

Ballester et al. (1,2) conducted a cross-sectional study and another longitudinal study to determine whether patients with bipolar disorder are more prone to aggression than patients with other mental disorders. In the cross-sectional study (1), aggression was measured using the Aggression Questionnaire (AQ) in 255 bipolar patients, 85 non-bipolar patients (depression, mood dysregulation, etc.), and 84 healthy subjects. Just in case, the AQ usually refers to the Autism Spectrum Quotient, but here it refers to a measure of aggression. The AQ contains 34 questions on five subscales (physical aggression, verbal aggression, anger, hostility, and indirect aggression).

For example, physical aggression includes the statement: "If someone provokes me, I will hit him/her", verbal aggression includes the statement: "If someone annoys me, I will tell him/her exactly what I think", and anger includes the statement: "Sometimes I feel like I am about to explode". Hostility is related to social alienation and paranoia, and includes the statement: "When people are nice to me, I think about what they want from me". Indirect aggression includes the statement: "When I get frustrated

because of someone, I ignore that person". Each statement is scored from one point if it does not apply to you at all to five points if it applies to you completely. The higher the total score, the higher the aggression. The results of the AQ showed that bipolar patients had significantly higher total scores and subscale scores than non-bipolar patients and healthy controls. This result did not change after adjusting for patient background.

In another longitudinal study, Ballester et al. (2) also followed the three groups (bipolar patients, non-bipolar patients, and healthy subjects) for two or four years. The results showed that bipolar patients still had significantly higher levels of aggression as measured by the AQ compared to non-bipolar patients and healthy controls. The subtype of bipolar disorder (type I and II) and the polarity and severity of mood episodes at the time of observation were not related to aggression. In addition, psychotic symptoms were not related to aggression. However, patients in some mood episodes at the time of the study had significantly higher aggression than those in normal mood. These two studies (1,2), which observed the same patients cross-sectionally and longitudinally, suggest that bipolar patients are more aggressive than depressed patients, and that aggression is even higher when they are in some mood episodes.

Dervic et al. (3) compared patient background and impulsivity and aggression in 685 patients with depressive episodes. The patients included 455 patients with depression, 151 patients with bipolar I disorder, and 79 patients with bipolar II disorder. As a result of investigating the aggression of these patients, impulsivity, aggression, and hostility were greater in patients with bipolar I and II disorders than in patients with depression. Patients with bipolar I disorder showed greater impulsivity and aggression than patients with bipolar II disorder, but less hostility. Cluster A and B personality disorders, alcohol and substance use disorders, and anxiety disorders were more common in bipolar I and II patients than in depressed patients. In addition, more patients with bipolar I disorder were unemployed than those with depression. Although this study concluded that patients with bipolar disorder were more likely to be aggressive and impulsive than those with depression, it did not correct for comorbidities. Thus, the possibility that aggression and impulsivity were more prevalent in bipolar disorder due to comorbid personality and substance use disorders cannot be ruled out.

II. Violent crime (aggression toward others)

Fazel et al. (4) used a national database of Sweden to collect cases of people aged 15 years and older who were convicted of violent crimes (i.e., killings of others, assaults, robberies, arson, sexual offenses, and threats and intimidation) between January 1, 1973, and December 31, 2004. The results showed that the percentage of people convicted of violent crimes was higher among bipolar patients (8.4%) than among the general population (3.5%), and among their peers without the disorder (6.2%). After adjusting for age, sex, income, marital status, and immigration status, patients with bipolar disorder were 2.3 times (95% CI 2.0-2.6) as likely to commit violent crimes as the general population, and 1.6 times (95% CI 1.2-2.1) as likely to commit violent crimes as their unaffected peers. The odds ratio was 1.6 times (95% CI 1.2-2.1) higher than that of unaffected peers.

The odds ratio for violent crime increased to 6.4-fold (95% CI 5.1-8.1) when bipolar disorder was combined with substance abuse compared to the general population, and decreased to 1.3-fold (95% CI 1.0-1.5) when bipolar disorder was not combined with substance abuse compared to the general population. Surprisingly, in subgroup analyses, the odds ratio for mood episodes resulting in this violent crime was not significantly different between manic and depressive episodes, at 1.2 times (95% CI 0.8-1.9), nor between manic, hypomanic, or mixed episodes and depressive episodes, at 1.1 times (95% CI 0.0-1.5). The odds ratio for depressive episodes compared to manic, hypomanic, or mixed episodes was 1.1 (95% CI 0.7-1.7), and the odds ratio for depressive episodes compared to those with and without psychotic symptoms was 0.8 (95% CI 0.4-1.4). By gender, violent crimes occurred in 226 of 1,635 (13.8%) male patients with bipolar disorder, but only in 88 of 2,108 (4.2%) female patients. However, the odds ratio was 4.1 times (95% CI 3.0-5.5) for female bipolar patients compared to the general female population, and 1.9 times (95% CI 1.6-2.3) for male bipolar patients compared to the general male population. The odds ratio was 1.9 times (95% CI 1.6-2.3) for female bipolar patients. The results were not directly related to mood, as they did not depend on the type of mood episode.

In addition, Fazel et al. (4) collected eight similar studies and performed a meta-analysis along with their own study. They found that overall, bipolar patients had a 4.1-fold (95% CI 2.9-5.8) increased odds ratio for violence compared to the general population. These results suggest that bipolar

disorder may increase violent crime. However, since the odds ratio decreased to 6.4-fold in the presence of substance abuse and 1.3-fold in the absence of substance abuse, it is more likely that involvement in substance abuse is linked to violent crime.

Recently, Volavka (22) has compiled a review of the various literature on violence in schizophrenia and bipolar disorder and found that 12.2% of bipolar patients, 8.2% of alcohol abusers, and 10.9% of drug abusers exhibited aggression that required police intervention. The lifetime prevalence of aggressive behavior in healthy individuals aged 15 and older was 0.66%, compared with 25.3% in bipolar I disorder and 13.6% in bipolar II disorder. Because these figures are likely influenced by comorbidity, when uncomplicated bipolar patients were included, the lifetime prevalence of aggressive behavior decreased to 2.5% in bipolar I disorder and 5.1% in bipolar II disorder. Incidentally, the lifetime prevalence of aggressive behavior was 7.2% in uncomplicated alcoholics and 11.3% in uncomplicated substance abusers. Bipolar disorder is often associated with alcoholism, substance abuse, paranoid personality disorder, and antisocial personality disorder, which may increase the risk of aggression.

Although the risk of violence is significantly higher in both schizophrenia and bipolar disorder than in the general population, it is higher in bipolar disorder than in schizophrenia, and most violence in bipolar patients occurs during manic episodes, which are more severe when complicated by substance abuse (22). While the aforementioned studies by Ballester et al. (1,2) and Fazel et al. (4) reported that aggression and violent crimes were not associated with manic episodes, the fact that the review by Volavka (22) clearly states that violence is common in manic episodes suggests that the former picks up aggression associated with impulsivity, while the latter picks up aggression associated with mania. It is possible that the former picks up aggression associated with impulsivity and the latter picks up aggression associated with manic episodes.

III. Effects of drugs on suicide-related behaviors (self-directed aggression)

Toffol et al. (21) used a national database to follow up 826 bipolar patients hospitalized for suicide attempts in Finland for a mean of 3.5 years. The study included readmissions, completed suicide attempts, and total mortality during that period, but we focus on suicide here. Analyses showed that the Cox hazard ratio for suicide was significantly lower with lithium at 0.37 (95% CI 0.16-0.88), but not with

antipsychotics at 0.78 (95% CI 0.43-1.40), antidepressants at 1.45 (95% CI 0.79-2.65), or valproate at 0.50 (95% CI 0.50-2.65). 0.50 (95% CI 0.24-1.08) for antidepressants, 0.91 (95% CI 0.51-1.63) for benzodiazepines, and no significant decrease was observed.

Recently, Song et al. (17) also followed up 51,535 bipolar patients in Sweden from 2005 to 2013 using a national database and found that the hazard ratio for suicide-related events in 21,129 patients treated with lithium was 0.86 (95% CI 0.78-0.95), a 14% of decrease, compared with 1.02 (95% CI 0.89-1.15) in patients treated with valproate. They found that the hazard ratio for suicide-related events was 0.86 (95% CI 0.78-0.95), a 14% of reduction, in 21,129 patients receiving lithium, compared with 1.02 (95% CI 0.89-1.15) in patients receiving valproate. These results suggest that lithium has a stronger suicidal effect than valproate. Oddly, in the subgroup analysis, the anti-suicidal effect was observed only in bipolar II disorder, but not in bipolar I disorder. Terao et al. (20) thought that the reason for this was the mixed state and wrote the following letter, where if Song et al. (16) used the DSM-IV-TR for diagnosis, all patients with mixed episodes would have bipolar I disorder. In the first place, the mixed state has a high suicide rate and is difficult to respond to lithium, which may explain the lack of anti-suicidal effect of lithium in bipolar I disorder. So, Terao et al. (20) asked the question: "What would be the result if we fairly assigned mixed status to bipolar I and II using the "mixed characteristics" of DSM-5? Song et al's answer (11) was that they actually tried to reanalyze the data that way, but unfortunately the result did not change.

IV. Prevention of Tap Water Lithium and Aggression

Incidentally, ordinary tap water also contains lithium, although at much lower concentrations than the lithium preparations used as therapeutic agents. It was Schrauzer et al. (14) in Texas, who first found that suicide rates and crime rates were lower in areas with high lithium concentrations in tap water. Based on this previous study, Ohgami et al. (12) hypothesized that lithium has a suicide prevention effect, and examined the correlation between the concentrations of lithium in tap water and the Standardized Mortality Ratio (SMR) of suicide rates in 18 municipalities in Oita Prefecture, and found that there was a significant negative correlation. In addition, Kapusta et al. (9) measured the lithium concentrations in tap water at 6,460 locations in 99 Austrian provinces and examined the correlation with suicide rate and SMR of suicide. The results showed that the tap water lithium

concentrations had a significant negative correlation with the SMR of suicide, even after adjusting for socioeconomic and medical factors. These findings suggest that even a small amount of lithium in tap water may exert a suicide prevention effect. However, a study by Kabacs et al. (7) in the eastern part of the United Kingdom did not find a significant correlation between the lithium concentrations of lithium in tap water and the SMR of suicide.

Since the results were not consistent, Ishii et al. (5) measured the concentrations of lithium in tap water throughout Kyushu and examined the correlation with suicide while adjusting for various factors. They conducted a multiple regression analysis, weighted by population, and found a significant negative correlation between lithium concentrations in tap water and the SMR of suicide for the total population and males. In addition, Shiotsuki et al. (15) re-examined the relationship between lithium concentrations in tap water and suicide by analyzing data from Hokkaido (all 35 cities) and Kyushu (all 118 cities), which have very different climatic conditions, at the same time adjusting for climatic condition. The results showed that the SMR of suicide and the lithium concentrations of lithium in tap water were significantly negatively correlated in the total population and males, and were significant in males even after adjusting for the four weather conditions. No correlation was found among females.

Kugimiya et al. (10) measured lithium concentrations in the tap water of all 47 prefectures, including 23 wards in Tokyo and 785 cities in other prefectures. The suicide rate was calculated by averaging the SMRs of suicide in 808 cities and wards over a 7-year period from 2010 to 2016. The analysis showed that the SMR of suicide is still significantly negatively correlated with the lithium concentrations of lithium in tap water among a total population and males when adjusted for related factors. In a review by Ishii et al. (6) in 2018, 9 of 12 papers showed a significant negative correlation between tap water lithium concentrations and suicide rate, but none showed a positive correlation. The remaining three papers did not find any association; however, the range of tap water lithium concentrations in the target area was narrow, and this narrow range may have made it difficult to find a significant correlation. Regarding gender differences, four papers showed a significant negative correlation in males but not in females, and three papers showed a significant negative correlation in females but not in males.

Up to this point,

epidemiological studies have examined the relationship between lithium concentrations in tap water and suicide rate, but not directly the relationship between blood lithium concentrations and suicide rate. Therefore, we have to ask what will happen to those who drink mineral water instead of tap water, what will be the effect of the small amount of lithium contained in vegetables and cereals, and if it is possible that the psychological effect of even a small amount of lithium is due to long-term intake, what will happen to those who move from other places? These are just some of the questions that have been raised in epidemiological studies. These were due to the limitations of epidemiological studies, and if the blood lithium concentrations could be measured, all lithium ingested from mineral water, vegetables, and cereals would be reflected in the blood lithium concentrations, which would solve the problem. However, the problem of duration of consumption remains unresolved. In addition, patients taking lithium as a therapeutic drug have much higher blood lithium concentrations, so patients taking lithium should be excluded from clinical studies on the effects of trace amounts of lithium.

Kanehisa et al. (8) examined the relationship between lithium and suicide-related behaviors in 199 patients at the Advanced Emergency Center of Oita University. There were 31 patients with suicide attempts, 21 patients with intentional self-harm, and 147 patients with normal accidents or injuries (control group). All of these patients were not taking lithium as a drug, and their bodies were thought to have trace amounts of lithium ingested from food and water. When these patients visited the emergency room, blood samples were taken to measure the lithium concentrations in their blood. The median blood lithium concentrations among the three groups (suicide attempt group, intentional self-injury group, and control group) were 0.00058 mEq/L in the suicide attempt group, 0.00072 mEq/L in the intentional self-injury group, and 0.00072 mEq/L in the control group. Log-transformed analysis of variance showed that there was a significant difference between the three groups, and a post-test showed that the suicide attempt group had a significantly lower blood lithium level than the control group. Furthermore, when the three groups were compared using multinomial logistic analysis with the control group as the reference group while adjusting for age and sex, the log-transformed blood lithium concentrations was significantly lower in the suicide attempt group than in the reference group (odds ratio 0.23, 95% CI 0.06-0.88). The association was

significant only in males.

Therefore, lithium in drinking water may be inversely associated with suicide probably in males.

V. Clinical Genetics

Sariaslan et al. (13) used a sample of 3,332,101 individuals born between 1958 and 1989 in Sweden using the National Database and identified 923,259 twins, plus 10,265 schizophrenic, 12,627 bipolar, and 2,425,703 healthy subjects. The lifetime rates of substance abuse and violent crime in these subjects were 29.3% and 23.2% for schizophrenia, 26.7% and 10.9% for bipolar disorder, and 3.2% and 3.1% for the normal subjects, respectively. Thus, violent crime was twice as common in schizophrenic patients as in bipolar patients. A multivariate quantitative genetic model, using data from monozygotic and dizygotic twins and their peers, showed that patients with schizophrenia (r=0.32) were more likely to commit violent crimes than those with bipolar disorder (r=0.23), and that most of the association between schizophrenia and violent crime (51-67%) was explained by genetic effects associated with substance abuse. In the case of schizophrenia, the involvement of genetic influences not associated with substance abuse, such as the influence of disease-specific genes for schizophrenia, was ruled out. On the other hand, in bipolar disorder, the influence of disease-specific genes for bipolar disorder explained 21% of the association between bipolar disorder and violent crime.

Thus, bipolar disorder, unlike schizophrenia, is likely to be influenced by disease-specific genes that increase the risk of violence. This is quite significant, and suggests that treatment of bipolar disorder itself may lead to the treatment of aggression and violence.

VI. Pathophysiology of aggression and violence and lithium

Siever (16) summarized a review on the pathophysiology of aggression and violence and proposed that aggression occurs when there is an imbalance between bottom-up drives, which originate in the limbic system, such as the amygdala and insula, and top-down control, which originates in the orbitofrontal cortex and anterior cingulate gyrus. In other words, the bottom-up drive generates emotions that lead to aggressive behavior, while the top-down control serves to compensate for such behavior by examining it in a social context and predicting rewards and punishments. If this interaction does not go well, aggression is revealed. The authors hypothesized that valproate and gabapentin contribute to the calming of

the bottom-up drive by suppressing limbic excitation.

Terao (18) suggested that lithium increases the volume of the prefrontal cortex and the anterior cingulate gyrus, and also increases the volume of the hippocampus, which may potently suppress aggression by enhancing top-down control and suppressing the bottom-up drive(18).

Conclusion

Based on what I have said so far, clinically, the therapeutic response to aggression in bipolar disorder is to listen to the patient's arguments as calmly as possible, explain the therapist's thoughts in an easy-to-understand manner, and try to clear up any misunderstandings. In terms of pharmacotherapy, lithium is basically administered, and the dose is increased while monitoring the change in aggression, sometimes up to 1.0 mEq/L.

Conflicts of interest: I have received lecture fees from Mochida Pharmaceutical Co.

References

1) Ballester, J., Goldstein, T., Goldstein, B., et al.: Is bipolar disorder specifically associated with aggression? Bipolar Disord, 14 (3); 283-290, 2012

2) Ballester, J., Goldstein, B., Goldstein, T.R., et al.: Prospective longitudinal course of aggression among adults with bipolar disorder. Bipolar Disord, 16 (3); 262-269, 2014

3) Dervic, K., Garcia-Amador, M., Sudol, K., et al.: Bipolar I and II versus unipolar depression: clinical differences and impulsivity/aggression traits. Eur Psychiatry, 30 (1); 106-113, 2015

4) Fazel, S., Lichtenstein, P., Grann, M., et al.: Bipolar disorder and violent crime: new evidence from population-based longitudinal studies and systematic review. Arch Gen Psychiatry, 67 (9); 931-938, 2010

5) Ishii, N., Terao, T., Araki, Y., et al.: Low risk of male suicide and lithium in drinking water. J Clin Psychiatry, 76 (3); 319-326, 2015

6) Ishii, N., Terao, T.: Trace lithium and mental health. J Neural Transm (Vienna), 125 (2); 223-227, 2018

7) Kabacs, N., Memon, A., Obinwa, T., et al.: Lithium in drinking water and suicide rates across the East of England. Br J Psychiatry, 198 (5); 406-407, 2011

8) Kanehisa, M., Terao, T., Shiotsuki, I., et al.: Serum lithium concentrations and suicide attempts: a case-controlled comparison in lithium therapy-naive individuals. Psychopharmacology (Berl), 234 (22); 3335-3342, 2017

9) Kapusta, N. D., Mossaheb, N., Etzersdorfer, E., et al.: Lithium in drinking water and suicide mortality. Br J Psychiatry, 198 (5); 346-350, 2011

10) Kugimiya T, Ishii N, Kohno K, et al.: Lithium in drinking water and suicide prevention: The largest nationwide epidemiological study from Japan. Bipolar Disord. 23(1): 33-40, 2021.

11) Landén, M., Song, J.: More efforts needed to clarify the effect of lithium in bipolar disorder: response to Terao et al. Am J Psychiatry, 175 (1); 80-81, 2018

12) Ohgami, H., Terao, T., Shiotsuki, I., et al.: Lithium concentrations in drinking water and risk of suicide. Br J Psychiatry, 194 (5); 464-465, 2009

13) Sariaslan, A., Larsson, H., Fazel, S.: Genetic and environmental determinants of violence risk in psychotic disorders: a multivariate quantitative genetic study of 1.8 million Swedish twins and siblings. Mol Psychiatry, 21 (9); 1251-1256, 2016

14) Schrauzer, G. N., Shrestha, K. P.: Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res, 25 (2); 105-113, 1990

15) Shiotsuki, I., Terao, T., Ishii, N., et al.: Trace lithium is inversely associated with male suicide after adjustment of climatic factors. J Affect Disord, 189; 282-286, 2016

16) Siever, L. J.: Neurobiology of aggression and violence. Am J Psychiatry, 165 (4); 429-442, 2008

17) Song, J., Sjölander, A., Joas, E., et al.: Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am J Psychiatry, 174 (8); 795-802, 2017

18) Terao, T.: Aggression, suicide, and lithium treatment. Am J Psychiatry, 165 (10); 1356-1357, 2008

19) Terao, T.: Bipolar disorders and aggression. Clinical Psychiatry, 46(9); 1135-1139, 2017 (in Japanese)

20) Terao, T., Kanehisa, M., Shiotsuki, I., et al.: Mixed features in bipolar I disorder and the effect of lithium on suicide. Am J Psychiatry, 175 (1); 80, 2018

21) Toffol, E., Hätönen, T., Tanskanen, A., et al.: Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: a nationwide registry-based prospective cohort study. J Affect Disord, 183; 159-165, 2015

22) Volavka, J.: Violence in schizophrenia and bipolar disorder. Psychiatr Danub, 25 (1); 24-33, 2013