

BRIEF REPORT

Possible Association between Serum Matrix Metalloproteinase-9 (MMP-9) Levels and Relapse in Depressed Patients following Electroconvulsive Therapy (ECT)

Chiyo Shibasaki, Kei Itagaki, Hiromi Abe, Naoto Kajitani, Mami Okada-Tsuchioka, Minoru Takebayashi

Division of Psychiatry and Neuroscience, Institute for Clinical Research, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan (Drs Shibasaki, Itagaki, Abe, Kajitani, Okada-Tsuchioka, and Takebayashi); Department of Psychiatry and Neurosciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan (Dr Shibasaki); Department of Psychiatry, NHO Kure Medical Center and Chugoku Cancer Center, Kure, Japan (Drs Itagaki and Takebayashi).

Correspondence: Minoru Takebayashi, MD, PhD, Department of Psychiatry, NHO Kure Medical Center and Chugoku Cancer Center, 3-1 Aoyama, Kure, Hiroshima 737-0023, Japan (mtakebayashi@kure-nh.go.jp).

Abstract

Background: Matrix metalloproteinases are involved in neuroinflammatory processes, which could underlie depression. Serum levels of MMP-9 and MMP-2 in depressed patients are significantly altered following electroconvulsive therapy, but an association between altered matrix metalloproteinases after successful ECT and possible relapse has yet to be investigated.

Methods: Serum was obtained twice, before and immediately after a course of electroconvulsive therapy, from 38 depressed patients. Serum was also collected, once, from two groups of age- and gender-matched healthy controls, 40 volunteers in each group. Possible associations between levels of matrix metalloproteinases and relapse during a 1-year follow-up period were analyzed.

Results: Excluding patients who did not respond to electroconvulsive therapy and patients lost to follow-up, data from 28 patients were evaluated. Eighteen of the patients (64.3%) relapsed within 1 year. In the group that did not relapse, serum levels of MMP-9 were significantly decreased after a course of electroconvulsive therapy, but not in the group that relapsed. No association between MMP-2 and relapse was observed.

Conclusion: The degree of change in serum MMP-9 change could be associated with relapse following electroconvulsive therapy in depressed patients.

Keywords: MMP-9, mood disorders, electroconvulsive therapy, relapse indicator

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent proteases that are involved not only in the degradation and remodeling of

the extracellular matrix but also in processing bioactive molecules, including cell surface receptors, neurotrophic factors,

Received: April 12, 2017; Revised: August 29, 2017; Accepted: September 14, 2017

© The Author(s) 2017. Published by Oxford University Press on behalf of CINP.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

chemokines, and cytokines (Kim and Joh, 2012). Gelatinases, including MMP-9 and MMP-2, are similar in structure and can enzymatically process various substrates of the extracellular matrix. These enzymes are also known to be involved in pathological processes such as cancer, neurodegenerative disorders, arthritis, and cardiovascular diseases (Sbardella et al., 2012). MMPs are involved in the pathogenesis of inflammatory diseases, including depression, as depression appears to be intimately linked to systemic inflammation (Maes et al., 2012; Bobińska et al., 2016a). Several studies have reported an association between depressive symptoms and state-dependent elevation in levels of inflammatory cytokines, such as interleukin-1 β , interleukin-6, and tumor necrosis factor- α (Felger and Lotrich, 2013; Rosenblat et al., 2014). Thus, inflammatory cytokine mediators, such as MMPs, could be pivotal in the clinical progression of depression (Bobińska et al., 2016a), which suggests that modulating these factors could lead to amelioration or remission of symptoms.

A previous study showed that there were significant associations between serum levels of MMPs and depressive symptoms (Shibasaki et al., 2016). Furthermore, serum levels of MMP-9 in depressive patients were decreased following a course of electroconvulsive therapy (ECT). Levels of MMP-2 in depressive patients were significantly lower than that of healthy controls, and low levels of MMP-2 were increased after a course of ECT (Shibasaki et al., 2016). The literature suggests that MMP-9 and MMP-2 could be related to depressive symptoms, and these symptoms appear to be sensitive to ECT.

ECT is a highly effective acute treatment for severe depressive symptoms (Heijnen et al., 2010). However, there is a high rate of relapse of patients who respond to an acute course of ECT (Kellner et al., 2006; Itagaki et al., 2017). The prevention of relapse is an important clinical issue, and clarification of potential predictors associated with relapse after ECT are needed. Some clinical factors that suggest likelihood to relapse following ECT have been suggested, including greater frequency of depressive episodes, symptom resistance to medication, residual symptoms, female gender, psychosis, and comorbid conditions (Nordenskjöld et al., 2011; Medda et al., 2013). Biological markers, objective measures of physiological functioning, could be used to compare and contrast the efficacy of therapeutics. Potential biological markers that could be used to predict relapse after ECT, such as the dexamethasone suppression test, thyrotropin-releasing hormone stimulation, and rapid eye movement sleep latency, have been suggested, but all have, thus far, proven inconclusive (Grunhaus et al., 1994; Bourgon and Kellner, 2000). The current study proposes that peripheral inflammatory markers could be used to predict the potential for relapse after ECT. Serum levels of MMP-9 and MMP-2 were measured before and after ECT in depressed patients.

Methods

Subjects

The current study was a prospective study performed in a hospital setting at the Department of Psychiatry of the National Hospital Organization (NHO) Kure Medical Center. Data were collected between January 2011 and August 2016. Thirty-eight patients with depressive symptoms scheduled to receive acute ECT, based on eligibility guidelines of the American Psychiatric Association, participated in the study. Patients on maintenance ECT were not included in the current study. ECT is often prescribed when a patient exhibits episodes of severe major

depression, psychosis, and catatonia or has shown insufficient improvement with prescribed pharmacotherapy (American Psychiatric Association, 2001). The patients in the current study were diagnosed as having mood disorder, either a major depressive disorder or bipolar disorder, with a current episode of major depression according to the criteria of the DSM-IV-TR. No patient was diagnosed with either Axis I or Axis II disorders. Exclusion criteria were past or present history of substance abuse, substance dependence, significant neurological illness, or any other significant medical illness. After procedures were fully explained, written informed consent was obtained from all subjects prior to participation. The current study was approved by the Ethics Committee of NHO Kure Medical Center.

The current study employed 2 separate control groups of a total of 80 healthy volunteers. In control group 1, 40 healthy volunteers (14 men and 26 women, mean age \pm SD: 54.2 \pm 13.9 years) with no history or current mental disorder were recruited. While the volume of serum obtained from control group 1 was sufficient to assay for MMP-9, it was insufficient to assay for MMP-2. Thus, MMP-2 was measured from serum obtained from a second control group (control group 2) consisting of 40 healthy volunteers (17 men and 23 women: 57.6 \pm 12.9 years).

Clinical Assessments

Clinical symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D) prior to the first ECT session (Pre-ECT) and the day after the final ECT session (Post-ECT) by the same psychiatrist. Responders to ECT were defined as demonstrating a 50% decrease in HAM-D score.

Relapse was considered to have occurred when a patient had Clinical Global Impressions Improvement Scale scores ≥ 6 after ECT and/or required hospitalization for exacerbation of psychiatric symptoms. After the acute course of ECT, all patients received standard pharmacotherapy, such as antidepressants or mood stabilizers, for major depressive disorder or bipolar disorder according to clinical guidelines of the Japanese Society of Mood Disorders.

ECT Treatment Procedures

ECT was performed according to previously established protocols (Shibasaki et al., 2015). Anesthesia was induced with i.v. thiamylal sodium and suxamethonium chloride. The ECT device used was the Thymatron System IV brief pulse square wave apparatus (Somatics Inc). Bilateral frontal-temporal electrodes were used, since the majority of patients demonstrated life-threatening or treatment-resistant depressive illness. Only one adequate seizure was required for each session, which was defined as an electroencephalographic seizure lasting more than 25 seconds with a high-amplitude, regular slow wave and postictal suppression. According to American Psychiatric Association guidelines, responsiveness to treatment was based on changes in the targeted symptoms. While the typical ECT course in patients with major depression is between 6 and 12 treatments, some patients manifest complete remission after only a few treatments (American Psychiatric Association, 2001). We continued ECT until the patient was asymptomatic or the primary care psychiatrist determined that the patient had obtained the maximum benefit within 3 to 15 sessions.

Antidepressant and antipsychotic pharmacotherapy received before ECT were continued in principle during ECT. The clinical psychiatrist could change the type and dosage of their medication on a case-by-case basis. Mood stabilizers were

withdrawn prior to the first ECT session but restarted after ECT. The use of benzodiazepines was permitted during the study period. Patients underwent standard supportive psychotherapy during the study period.

MMP Assay

Venous blood samples were taken during the morning (between 7:00 and 8:00 AM) before the first ECT session (Pre-ECT) and the day after the final ECT session (Post-ECT). From healthy controls, blood samples were collected only once. Blood samples were drawn into anticoagulant-free tubes, kept at room temperature for 1 h, and serum was separated by centrifugation at 3000 rpm for 15 minutes at 4°C. Serum samples were stored at -80°C until assay. Serum levels of MMP-2 and MMP-9 were measured using ELISA (Quantikine ELISA, R&D Systems) according to the manufacturer's instructions.

Statistical Analysis

The data are shown as the mean \pm SD. The normal distribution of data was tested by Shapiro-Wilk and the Kolmogorov-Smirnov tests (supplementary Table 1), and statistical analysis was performed with nonparametric tests. The Mann-Whitney *U* test was used to determine significant differences among groups in clinical and laboratory values. A chi-squared test was used for categorical variables. The Wilcoxon signed-rank test was used to determine whether differences in clinical and laboratory values between Pre-ECT and Post-ECT were significant. Statistical significance was defined as $P < .05$. Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Japan Corporation).

Results

The final sample included 28 patients. Of the initial 38 patients, 10 were excluded for the following reasons: 3 patients did not recover from their depressive episode following ECT, 5 had moved from the area, and 2 patients were lost to follow-up. Among the remaining 28 patients (18 women and 10 men, mean age 59.6 ± 14.3 years) who were regularly followed for more than 1 year, 18 patients relapsed (64.3%) and the mean period to relapse was 21.2 ± 12.3 weeks. Of these, 4 relapsed within 3 months, 9 between 3 and 6 months, and 5 between 6 months to 1 year after ECT.

The baseline clinical characteristics of the 28 patients who completed the study are shown in Table 1. Baseline characteristics were compared with relapsed and nonrelapsed patients, and there were no significant differences between the groups in terms of gender, age, age at onset, diagnosis of major depressive disorder or bipolar disorder, HAMD score, or number of ECT sessions.

Levels of serum MMP-9 were compared between patients before ECT and healthy controls from control group 1. There was no significant difference in mean serum MMP-9 levels between the patients at Pre-ECT and healthy controls (537.1 ± 244.5 ng/mL vs 481.5 ± 216.9 ng/mL, $P = .334$). Over the course of ECT, a statistically significant decrease in serum MMP-9 (415.5 ± 162.8 ng/mL at Post-ECT, $P = .008$) was observed in these patients.

Levels of serum MMP-2 were compared between patients before ECT and healthy controls from control group 2. The mean serum MMP-2 level of patients before ECT was significantly lower than that of healthy controls (186.1 ± 36.1 ng/mL vs 235.5 ± 56.8 ng/mL, $P < .001$). There was a tendency of increased

serum MMP-2 over the course of ECT in patients (206.3 ± 53.3 ng/mL Post-ECT, $P = .055$). Additionally, serum levels of MMPs were not significantly different between patients with major depressive disorder and bipolar disorder (supplementary Table 2).

While patients who relapsed showed decreased mean serum MMP-9, the decrease was less than that of the group that did not relapse (relapse group $= -60.7 \pm 174.1$ ng/mL; nonrelapse group $= -213.3 \pm 215.1$ ng/mL; $P = .021$, see Table 2). In patients who relapsed, mean serum MMP-9 did not change during the course of ECT (Pre-ECT vs Post-ECT, $P = .327$). However, mean serum MMP-9 significantly decreased over the course of ECT treatment in patients who did not relapse ($P = .007$, supplementary Figure 1). There were no significant differences in mean serum levels of MMP-9 between the 2 groups of patients at Pre-ECT or Post-ECT. Mean serum levels of MMP-2 at Pre-ECT and Post-ECT were not significantly different, and the magnitude of change of serum MMP-2 over the course of treatment was not significantly different between patients who relapsed and patients who did not relapse (Table 2).

Discussion

A previous study showed that circulating levels of MMP-9 in depressed patients are different compared with that of healthy controls (Domenici et al., 2010; Bobińska et al., 2016b), and a positive correlation was observed between serum levels of MMP-9 and HAMD scores (Yoshida et al., 2012; Shibasaki et al., 2016). The current study confirms previous findings that serum levels of MMP-9 declined during ECT (Shibasaki et al., 2016) and further demonstrates an association between serum levels of MMPs and a higher risk of relapse after a course of ECT in depressed patients. In the current study, depressed patients who did not relapse showed significantly decreased Post-ECT MMP-9 serum levels compared with Pre-ECT levels. By contrast, in patients who relapsed, Post-ECT serum levels of MMP-9 were not significantly altered compared with Pre-ECT levels. The current findings suggest that MMP-9 levels could be used as an indicator of the likelihood of relapse in depressed patients after successful ECT.

Table 1. Clinical Characteristic of Relapsed vs. Nonrelapsed Depressed Patients after ECT

	Relapsed n = 18	Nonrelapsed n = 10	P
Gender			.724
Female	12 (66.7%)	6 (60.0%)	
Male	6 (33.3%)	4 (40.0%)	
Age (y)	58.6 ± 12.8	61.4 ± 17.3	.549
Age at onset (y)	49.9 ± 11.5	55.4 ± 20.2	.337
Diagnosis			.569
Major depressive disorder	11 (61.1%)	5 (50.0%)	
Bipolar disorder	7 (38.9%)	5 (50.0%)	
HAMD score at Pre-ECT	21.7 ± 7.4	22.0 ± 8.5	.885
HAMD score at Post-ECT	4.9 ± 1.8	3.9 ± 2.0	.115
Reduction of HAMD score	16.8 ± 7.6	18.1 ± 8.6	.648
Number of ECT (sessions)	9.8 ± 3.2	10.2 ± 1.8	.825
IMI equivalence at Pre-ECT	163.2 ± 109.3	153.8 ± 149.1	.869
IMI equivalence at Post-ECT	153.5 ± 90.9	108.8 ± 150.5	.175

Abbreviations: ECT, electroconvulsive therapy; HAMD, Hamilton Rating Score for depression; IMI, imipramine.

Data show the mean \pm SD or percent (%).

P values of the chi-square test and the Mann-Whitney *U* test are reported.

Table 2. Serum Levels of MMP-9 and MMP-2 of Relapsed and Nonrelapsed Depressed Patients after ECT

	Relapsed n = 18	Nonrelapsed n = 10	Control n = 40	P
MMP-9 (ng/mL)				
At Pre-ECT or baseline	513.5 ± 241.5 ^{ns}	579.5 ± 257.1 ^{**}	481.5 ± 216.9	.424 ^b
At Post-ECT	[452.8 ± 158.1]	[348.2 ± 156.3]		.093 ^a
Magnitude of change from Pre-ECT to Post-ECT	-60.7 ± 174.1	-231.3 ± 215.1		.021 ^{a*}
MMP-2 (ng/mL)				
At Pre-ECT or baseline	185.4 ± 39.0	187.5 ± 32.1	235.5 ± 56.8	.001 ^b
At Post-ECT	207.4 ± 62.5	204.5 ± 33.8		.415 ^a
Magnitude of change from Pre-ECT to Post-ECT	22.0 ± 52.9	17.0 ± 35.4		.811 ^a

Abbreviation: ECT, electroconvulsive therapy; ns, not significant.

Data show the mean ± SD.

^aP values of the Mann-Whitney U test.

^bP values of Kruskal-Wallis test and Wilcoxon signed-rank test are reported.

*P<0.05, **P<0.01.

The mechanism by which ECT reduces serum levels of MMP-9 is unknown. A state of systemic inflammation has been proposed as the substrate of mood disorders, since circulating proinflammatory cytokines increase with the severity of mood disorders (Felger and Lotrich, 2013; Rosenblat et al., 2014) and cytokine levels decrease after an effective course of ECT (Hestad et al., 2003; Rotter et al., 2013). It is possible that the abnormal inflammatory state in depressed patients is normalized through ECT treatment (Shibasaki et al., 2016). Knockout of the MMP-9 gene reduced dendritic spine abnormalities and improved anxiety-related symptoms and poor socialization in a mouse psychiatric disorder model (Sidhu et al., 2014). Minocycline, which has inhibitory effects on MMP-9, decreased MMP-9 levels and appeared to attenuate clinical symptoms of psychiatric disorder (Dziembowska et al., 2013). Degradation of MMP-9 could improve depressive symptoms and suppress relapse by “calming” of the inflammatory state. Indirect support of this hypothesis is the finding that inflammatory cytokines, interleukin-1 α and monocyte chemoattractant protein-1, are associated with depression relapse within a year (Bond et al., 2016). In the current study, the difference in serum levels of MMP-9 between Pre-ECT and Post-ECT was significantly associated with the likelihood of relapse, rather than MMP-9 levels at either Pre-ECT or Post-ECT. An association may not be readily discernable at a given MMP-9 level, since MMP-9 levels have been shown to change in healthy subject for a variety of reasons, including psychosocial stress (Garvin et al., 2009). Further large-scale studies are needed to confirm whether alterations of MMP-9 serum levels can be used as a predictor of relapse in depressed patients.

During the 1-year follow-up period in the current study, 18 (64%) of the 28 treatment responders to ECT experienced a relapse. A recent meta-analysis of prospective studies in major depressive patients treated with ECT showed that the relapse rate after 12 months was 51.1% (Jelovac et al., 2013). A relapse rate of about 50% within 12 months during a mean follow-up period of 55.3 weeks with continuous pharmacotherapy for bipolar depression after a course of ECT has also been reported (Medda et al., 2013). Although previous results cannot be directly compared with each other because the definition of relapse and the severity of symptoms differ, the high relapse rate after responding to ECT for depressive symptom is a considerable problem. Therefore, finding a predictor of relapse after ECT will greatly aid in designing effective treatments for all depressed patients.

The current study focused on uncovering an association between MMPs and relapse following ECT in depressed patients. It is not known whether reduced levels of MMPs are observed after relapse with other treatments, such as pharmacotherapy and cognitive behavioral therapy. It would be important to determine if MMP-9 levels are associated with relapse in depressed patients after other types of treatments to see if altered MMP levels can be used as a general indicator of likelihood to relapse.

Some limitations of the current study should be mentioned. First, the relatively small sample size hampered identification of a significant association of MMP-9 levels and relapse. Second, the current study was designed as a naturalistic study. A variety of maintenance pharmacotherapies was allowed, because the medications were selected based on the clinical judgment of the attending psychiatrist and no attempt was made to standardize pharmacotherapeutic treatment. Third, other factors that could affect relapse rates, such as patient adherence to medication schedules, patient recognition of the severity of their own illness, adverse life events, level of social support, and premorbid psychosocial functioning were not collected. It is possible that these factors could somehow influence MMP levels—as mentioned earlier, MMP levels are modulated by a number of factors. Fourth, the effect of medications on serum MMPs levels is not well understood. In a past report, serum levels of MMP-9 in depressed patients with bipolar disorder were significantly higher than those of the controls, which remained elevated even following drug treatment (Rybakowski et al., 2013). ECT could have a greater influence on MMP-9 than medications. A future investigation could include drug-naïve patients to evaluate the effects of medications on MMP, at least before treatments. Fifth, it is unclear if peripheral concentrations of MMP reflect those in the brain. In an animal study, electroconvulsive seizure increases MMP-9 in the hippocampus (Girgenti et al., 2011). There are some reports that found no correlation between blood and cerebrospinal fluid concentrations of MMPs (Niebroj-Dobosz et al., 2010; Horstmann et al., 2017). Therefore, it is possible that the dynamics of MMPs in the brain are different from those in peripheral tissues. To overcome this issue, direct assessment of MMPs in cerebrospinal fluid from patients with mood disorders could be highly useful. Finally, because of the limited sample size, statistically significant increases in MMP-2 levels were not observed following ECT in the current study, in contrast to a previous finding (Shibasaki et al., 2016). In any case, in the current study, MMP-2 was not associated with relapse after ECT. Larger studies in the future could investigate the occurrence of relapse

after ECT in a more systematic manner and identify threshold levels of MMP-9 that best predict relapse following ECT.

Conclusion

The current study suggests that a greater magnitude in the decline of serum MMP-9 after ECT is related to a lower risk of relapse following ECT. The findings suggest that serum MMP-9 could be used to predict the likelihood of relapse following ECT in depressed patients.

Supplementary Material

Supplementary data are available at *International Journal of Neuropsychopharmacology* online.

Funding

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (grant nos. 15K09819, 16K18883, 16K19796).

Acknowledgments

We thank Dr. Aldric Hama for editorial assistance.

Statement of Interest

None.

References

- American Psychiatric Association (2001) The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association. Arlington, VA: American Psychiatric Association.
- Bobińska K, Szemraj J, Czarny P, Gałęcki P (2016a) Role of MMP-2, MMP-7, MMP-9 and TIMP-2 in the development of recurrent depressive disorder. *J Affect Disord* 205:119–129.
- Bobińska K, Szemraj J, Czarny P, Gałęcki P (2016b) Expression and Activity of metalloproteinases in depression. *Med Sci Monit* 22:1334–1341.
- Bond DJ, Andreazza AC, Hughes J, Dhanoa T, Torres JJ, Kozicky JM, Young LT, Lam RW, Yatham LN (2016) Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. *Psychoneuroendocrinology* 65:76–83.
- Bourgon LN, Kellner CH (2000) Relapse of depression after ECT: a review. *J ECT* 16:19–31.
- Domenici E, Willé DR, Tozzi F, Prokopenko I, Miller S, McKeown A, Brittain C, Rujescu D, Giegling I, Turck CW, Holsboer F, Bullmore ET, Middleton L, Merlo-Pich E, Alexander RC, Muglia P (2010) Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. *PLoS One* 5:e9166.
- Dziembowska M, Pretto DI, Janusz A, Kaczmarek L, Leigh MJ, Gabriel N, Durbin-Johnson B, Hagerman RJ, Tassone F (2013) High MMP-9 activity levels in fragile X syndrome are lowered by minocycline. *Am J Med Genet Part A* 161:1897–1903.
- Felger JC, Lotrich FE (2013) Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience* 246:199–229.
- Garvin P, Nilsson L, Carstensen J, Jonasson L, Kristenson M (2009) Plasma levels of matrix metalloproteinase-9 are independently associated with psychosocial factors in a middle-aged normal population. *Psychosom Med* 71:292–300.
- Girgenti MJ, Collier E, Sathyanesan M, Su XW, Newton SS (2011) Characterization of electroconvulsive seizure-induced TIMP-1 and MMP-9 in hippocampal vasculature. *Int J Neuropsychopharmacol* 14:535–544.
- Grunhaus L, Shipley JE, Eiser A, Remen A, Pande AC, Tandon R, Greden JF (1994) Sleep electroencephalographic studies after ECT. *Am J Geriatr Psychiatry* 2:39–51.
- Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW (2010) Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy. *J Clin Psychopharmacol* 30:616–619.
- Hestad KA, Tønseth S, Støen CD, Ueland T, Aukrust P (2003) Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. *J ECT* 19:183–188.
- Horstmann S, Budig L, Gardner H, Koziol J, Deuschle M, Schilling C, Wagner S (2017) Matrix metalloproteinases in peripheral blood and cerebrospinal fluid in patients with Alzheimer's disease. *Int Psychogeriatrics C Int Psychogeriatr Assoc* 226:966–972.
- Itagaki K, Takebayashi M, Shibasaki C, Kajitani N, Abe H, Okada-Tsuchioka M, Yamawaki S (2017) Factors associated with relapse after a response to electroconvulsive therapy in unipolar versus bipolar depression. *J Affect Disord* 208:113–119.
- Jelovac A, Kolshus E, McLoughlin DM (2013) Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology* 38:2467–2474.
- Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, Mueller M, Bernstein HJ, O'Connor K, Smith G, Biggs M, Bailine SH, Malur C, Yim E, McClintock S, Sampson S, Fink M (2006) Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression. *Arch Gen Psychiatry* 63:1635–1641.
- Kim Y-S, Joh T-H (2012) Matrix metalloproteinases, new insights into the understanding of neurodegenerative disorders. *Biomol Ther* 20:133–143.
- Maes M, Mihaylova I, Kubera M, Ringel K (2012) Activation of cell-mediated immunity in depression: association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. *Prog Neuro-Psychopharmacology Biol Psychiatry* 36:169–175.
- Medda P, Mauri M, Fratta S, Ciapponi B, Miniati M, Toni C, Dell'Osso L, Perugi G (2013) Long-term naturalistic follow-up of patients with bipolar depression and mixed state treated with electroconvulsive therapy. *J ECT* 29:179–188.
- Niebroj-Dobosz I, Janik P, Sokolowska B, Kwiecinski H (2010) Matrix metalloproteinases and their tissue inhibitors in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis. *Eur J Neurol* 17:226–231.
- Nordenskjöld A, von Knorring L, Engström I (2011) Predictors of time to relapse/recurrence after electroconvulsive therapy in patients with major depressive disorder: a population-based cohort study. *Depress Res Treat* 2011:470985.

- Rosenblat JD, Cha DS, Mansur RB, McIntyre RS (2014) Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuro-Psychopharmacology Biol Psychiatry* 53:23–34.
- Rotter A, Biermann T, Stark C, Decker A, Demling J, Zimmermann R, Sperling W, Kornhuber J, Henkel A (2013) Changes of cytokine profiles during electroconvulsive therapy in patients with major depression. *J ECT* 29:162–169.
- Rybakowski JK, Remlinger-Molenda A, Czech-Kucharska A, Wojcicka M, Michalak M, Losy J (2013) Increased serum matrix metalloproteinase-9 (MMP-9) levels in young patients during bipolar depression. *J Affect Disord* 146:286–289.
- Sbardella D, Fasciglione GF, Gioia M, Ciaccio C, Tundo GR, Marini S, Coletta M (2012) Human matrix metalloproteinases: an ubiquitous class of enzymes involved in several pathological processes. *Mol Aspects Med* 33:119–208.
- Shibasaki C, Takebayashi M, Fujita Y, Yamawaki S (2015) Factors associated with the risk of relapse in schizophrenic patients after a response to electroconvulsive therapy: a retrospective study. *Neuropsychiatr Dis Treat* 11:67–73.
- Shibasaki C, Takebayashi M, Itagaki K, Abe H, Kajitani N, Okada-Tsuchioka M, Yamawaki S (2016) Altered serum levels of matrix metalloproteinase-2, -9 in response to electroconvulsive therapy for mood disorders. *Int J Neuropsychopharmacol* 19:pyw019.
- Sidhu H, Dansie LE, Hickmott PW, Ethell DW, Ethell IM (2014) Genetic removal of matrix metalloproteinase 9 rescues the symptoms of fragile X syndrome in a mouse model. *J Neurosci* 34:9867–9879.
- Yoshida T, Ishikawa M, Niitsu T, Nakazato M, Watanabe H, Shiraiishi T, Shiina A, Hashimoto T, Kanahara N, Hasegawa T, Enohara M, Kimura A, Iyo M, Hashimoto K (2012) Decreased Serum levels of mature brain-derived neurotrophic factor (BDNF), but not its precursor proBDNF, in patients with major depressive disorder. *PLoS One* 7:e42676.