Psychiatr. Pol. 2017; 51(3): 455–468
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/61584

Blood serum concentrations of kynurenic acid in patients diagnosed with recurrent depressive disorder, depression in bipolar disorder, and schizoaffective disorder treated with electroconvulsive therapy

Marcin Olajossy[1], Bartosz Olajossy[2], Sebastian Wnuk[2], Emilia Potembska[3], Ewa Urbańska[2]

[1] 2nd Department of Psychiatry and Psychiatric Rehabilitation, Medical University of Lublin
[2] Chair and Department of Experimental and Clinical Pharmacology, Laboratory of Cellular and Molecular Pharmacology
[3] Department of Psychiatric Nursing, Medical University of Lublin

Summary

Aim. The aim of the present study was to compare blood serum kynurenic acid (KYNA) concentrations measured before ECT and after 1, 6 and 12 electroconvulsive treatment (ECT) sessions in patients with diagnoses of recurrent depressive disorder (RDD), depression in bipolar disorder (DBD) and schizoaffective disorder (SAD).

Subjects and methods. The study group comprised of 50 patients with ICD-10 diagnoses of RDD, DBD and SAD. Blood serum KYNA concentrations were determined and clinical assessment was performed using the MADRS and the GAF scale.

Results. Significant differences were found in blood serum KYNA levels between RDD, DBD and SAD patients treated with electroconvulsive therapy and healthy controls: 1) KYNA concentrations in DBD patients measured before ECT and after 12 ECT sessions were significantly lower than in the control group; 2) KYNA concentrations in the serum of RDD patients measured before ECT and after one and 12 ECT sessions were significantly lower than in the control group, while those measured after 6 ECT sessions did not differ significantly from KYNA concentrations in healthy controls; 3) higher pre-treatment blood serum concentrations of KYNA in DBD patients correlated with a higher number of illness phases and poorer general functioning before treatment; 4) significant relationships were found between higher blood serum concentrations of KYNA in RDD patients after 1 ECT session and male gender, and between higher KYNA concentrations after 6 ECT sessions and increased depression and poorer functioning before treatment in those patients.

Conclusions. Results show that KYNA concentrations in all diagnostic groups were lower before ECT (not statistically significant for the SAD group) and that there were no significant changes in those concentrations (compared with the baseline) during ECT.

Key words: kynurenic acid, depression, electroconvulsive therapy

Introduction

In the last decade, there has been growing interest in the role of the glutamatergic system in the pathophysiology of mental diseases. Numerous studies [1–3] confirm that this system plays an important role in the pathophysiology of depression. Research on the role of the glutamatergic system in the pathogenesis of depression has been spurred by Trullas and Skolnick's [4] seminal discovery of antidepressant properties of the NMDA receptor antagonist – ketamine. Later studies showed that patients with depression had significantly higher blood serum and cerebrospinal fluid (CSF) levels of glutamate than healthy subjects [5]. Hashimoto et al. [6], in a *postmortem* study, found increased levels of glutamate in the frontal cortex of patients with bipolar disorder (BD) and major depression. Clinical studies conducted in the recent years have shown that administration of single doses of ketamine results in very rapid reduction of depressive symptoms [7–9]. By blocking NMDA receptors, ketamine unlocks the translation of the Brain Derived Neurotrophic Factor (BDNF) leading to an increase in the concentration of this factor [10]. However, the use of ketamine is limited due to its psychomimetic effects [10].

Kynurenic acid (KYNA) is an endogenous substance which modulates neurotransmission in the glutamatergic system [11]. It has been observed that depression is associated with reduced synthesis of the neuroprotective KYNA, an NMDA receptor antagonist; this decrease is accompanied by an increase in the synthesis of the neurotoxic quinolinic acid, which stimulates NMDA receptors [12]. It has been found in an animal model study that increased concentrations of quinolinic acid and 3-hydroxykynurenine are associated with increased anxiety [13], which is one of the symptoms of depressive disorders. Olson et al. [14] revealed that men with bipolar disorder (BD) in euthymia had higher CSF concentrations of KYNA than healthy controls.

The glutamate hypothesis of schizophrenia assumes that this disease involves insufficient glutamatergic stimulation, which leads indirectly (via insufficient stimulation of GABA) to dopaminergic overstimulation in the mesolimbic system, or directly (without the mediation of GABA) to insufficient stimulation in the mesocortical system [15]. Increased interest in the action of glutamate is also related to the psychomimetic properties of phencyclidine, a non-competitive inhibitor of the NMDA receptor [16]. Administered to healthy subjects, phencyclidine induces psychotic symptoms which resemble an acute episode of schizophrenia [16]. Baran et al. [17] have observed increased KYNA levels in the frontal cortex of patients with HIV-1 infection. Atlas et al. [18] have additionally found that acute psychotic symptoms in patients with HIV are accompanied by a nearly twofold increase in KYNA levels in the CSF, whereas in patients without psychotic symptoms, no such increase in KYNA has been observed. The authors believe that the occurrence of psychotic symptoms is caused by NMDA receptor hypofunction caused by an increase in KYNA [18].

Numerous studies confirm that patients with schizophrenia have increased concentrations of KYNA [19, 20]. Miller et al. [21], in a *postmortem* study, found increased concentrations of kynurenine in the anterior cingulate cortex of patients with schizophrenia and BD with psychotic features, but not in the brains of patients with depres-

sion. In schizophrenia and BD, an increase in the concentration of 2,3-dioxygenase is associated with an increase in the concentration of kynurenine; no such relationship has been observed in major depression [21]. This finding allowed the authors to conclude that schizophrenia and BD involved upregulation of the kynurenine pathway [21]. It has also been shown that increasing of the endogenous concentration of KYNA through administration of a KYNA precursor or a kynurenine 3-hydroxylase inhibitor enhances, similarly as in schizophrenia, the activity of neurons in the ventral cap [22].

On the basis of literature data, it is hypothesized that excessively high concentrations of KYNA can cause the development of psychotic disorders due to excessive blocking of the NMDA receptor, while too low concentrations of KYNA and weak blocking of the NMDA receptor by KYNA lead to overactivity of the glutamatergic system, which is observed in depression.

The aim of the present study was to compare blood serum concentrations of KYNA in patients diagnosed with recurrent depressive disorder (RDD), depression in bipolar disorder (DBD) and schizoaffective disorder (SAD) determined before treatment and after 1st, 6th and 12th ECT session.

Study group

The study group comprised of 50 patients (30 women and 20 men) with ICD-10 diagnoses of major depression with or without psychotic features in the course of recurrent depressive disorder (RDD), depression in bipolar disorder (DBD) and schizoaffective disorder (SAD). The subjects were inpatients of the Department of Psychiatry of the Medical University of Lublin.

RDD group consisted of 32 patients (19 women and 13 men). The mean age of RDD patients was 49.41 (*SD* = 12.73) years; the duration of symptoms was 11.69 (*SD* = 8.95) years; the mean number of phases of the illness was 4.53 (*SD* = 2.91); and the mean duration of the current phase of depression was 4.95 (*SD* = 3.23) months.

DBD group included 11 subjects (7 women and 4 men). The mean age of DBD patients was 44.73 (*SD* = 13.83) years; the duration of symptoms was 10.91 (*SD* = 4.97) years; the mean number of phases of the illness was 5.82 (*SD* = 2.68); and the mean duration of the current phase of depression was 6.45 (*SD* = 6.21) months.

SAD group consisted of 7 patients (4 women and 3 men). The mean age of SAD patients was 33.29 (*SD* = 8.56) years; the duration of symptoms was 4.43 (*SD* = 3.05) years; the mean number of phases of the illness was 3.71 (*SD* = 1.38); and the mean duration of the current phase of depression was 3.86 (*SD* = 2.48) months.

The control group consisted of 48 (25 women and 23 men) age-matched healthy subjects. The study was approved by the Clinical Research Ethics Committee of the Medical University of Lublin, Poland (decision KE-0254/3/2006).

Research methods

The ECT procedure

Patients were referred for ECT in accordance with relevant procedures after they had given their informed consent, had undergone an ECG, an EEG and laboratory tests to assess their physical state, and had been consulted by a neurologist and an internist. In accordance with the accepted principles, all patients referred for ECT were discontinued from all drugs that significantly affected the seizure threshold – this excluded the use of barbiturates, benzodiazepines, lithium and other mood-stabilizing drugs. The majority of the patients received antidepressants; most often, they were treated with a monotherapy of SSRIs, as this method is considered to be both safe and effective [23]. This procedure was mostly a continuation of existing treatment. Recruitment of a so-called pure group of patients who receive ECT alone is difficult and may raise ethical objections.

The therapeutic procedures for the application of ECT did not deviate from the standards recommended in Poland [23]. Bilateral ECT was performed using a Spectrum 500Q device in the fronto-temporal position, at suggested stimulus doses. Anesthetic premedication was used, namely, general anesthesia and muscle relaxation (injections of thiopental, succinylcholine and atropine). During premedication and after ECT, the patients were oxygenated. The treatment included 12 ECT sessions, two sessions per week.

Laboratory tests

Material for laboratory tests

All patients enrolled in the study gave their informed consent to venous blood sampling. Blood was collected four times: before ECT and after the first, sixth and twelfth ECT session.

5.0 ml samples of native blood were drawn from the median cubital vein before the first ECT and half an hour after the first, sixth and twelfth (final) ECT. After collecting, the blood was centrifuged for 15 minutes at 3500 rpm, and then the supernatant was collected and frozen at −72°C.

The content of KYNA in serum was assessed at the Department of Experimental and Clinical Pharmacology of the Medical University of Lublin, using a Varian Pro Star 210 liquid chromatograph (California, USA). The chemical reagents used during the chromatographic evaluation of KYNA content in the test samples were from Baker B.V. (Deventer, the Netherlands). The supernatant was frozen using an Innova U-101 ultra low temperature lab freezer.

The material for analysis was prepared using a modified method by Turski et al. [11]. This method is based on the assumption that at appropriate pH values, KYNA is retained and then washed off into an ion exchange layer. Owing to this process, KYNA concentrations increase to values that can be detected during further analysis.

Equivalent volumes of serum were mixed with 8% perchloric acid, stirred and centrifuged for 20 min at 4°C at 12 000 rpm. The following chemical reagents were used: Dowex 50-W, double-distilled water and 0.1 N hydrochloric acid. Pasteur columns, 0.5 cm in diameter, were filled with 0.3 ml of a 50% Dowex suspension in double-distilled water (v/v), and then with 1 ml of 0.1 N hydrochloric acid. 1 ml of undiluted samples was added to the Pasteur columns thus prepared. Then the columns were washed once again with 1 ml of 0.1 N hydrochloric acid and 1 ml of double-distilled water. Samples were deproteinized using Millipore syringe filters.

Clinical rating scales

The severity of depressive disorders was assessed on the Montgomery–Åsberg Depression Rating Scale (MADRS) [24]. MADRS is a seven-point scale for assessing depression, in particular the so-called endogenous type. It shows good agreement with other psychometric instruments for depression rating and is often used in clinical trials which test the effectiveness of treatment. Severity of depression according to the MADRS score is as follows: 0–11 – no depressive symptoms, 12–19 – mild depression, 20–28 – moderate depression, 29–43 – severe depression, 44–60 – very severe depression. The subjects' social, occupational and psychological functioning was assessed using the Global Assessment of Functioning (GAF) scale [25].

Improvement of mental state was defined as a 30% reduction in symptoms on MADRS, as rated after 12 ECT sessions.

Statistical tests

The results were analyzed statistically using STATISTICA 10.0PL software. Because the measurements were characterized by high skewness, results were presented as median, a measure of central tendency. Equality of distribution for each variable within normal distribution groups was tested using the Lilliefors' version of the Kolmogorov–Smirnov test as well as the Shapiro–Wilk test. Because the test variables did not have a normal distribution, non-parametric tests were used for further analysis. These tests are resistant to deviations from the assumptions of normality of distribution and heterogeneity of variance in the compared groups. Pairs of independent groups were compared using the Mann–Whitney *U* test. Three independent groups were compared using the Kruskal–Wallis ANOVA followed by multiple *post hoc* comparisons. Friedman's ANOVA with *post hoc* tests (Wilcoxon signed rank tests) was used to show differences among more than two dependent variables. The relationships among variables were determined by calculating Spearman's correlation coefficient.

Results

In the first stage of the study, the Mann–Whitney *U* test was used to compare blood serum concentrations of KYNA determined before treatment and after 1, 6 and

12 ECT sessions in SAD (Table 1), DBD (Table 2) and RDD patients (Table 3) with blood serum KYNA concentrations of healthy controls.

Table 1. **Comparison of blood serum KYNA concentrations between SAD patients and controls**

KYNA concentration	Median		Z	p
	SAD	Control Group		
Before treatment	0.16	0.20	-1.31	0.19
After 1st ECT	0.13	0.20	-1.45	0.15
After 6th ECT	0.12	0.20	-1.27	0.21
After 12th ECT	0.16	0.20	-0.85	0.39

Table 2. **Comparison of blood serum KYNA concentrations between DBD patients and controls**

KYNA concentration	Median		Z	p
	DBD	Control Group		
Before treatment	0.12	0.20	-2.44	0.02
After 1st ECT	0.15	0.20	-1.60	0.11
After 6th ECT	0.17	0.20	-1.50	0.13
After 12th ECT	0.11	0.20	-1.99	0.05

Table 3. **Comparison of blood serum KYNA concentrations between RDD patients and controls**

KYNA concentration	Median		Z	p
	RDD	Control Group		
Before treatment	0.15	0.20	-2.21	0.03
After 1st ECT	0.15	0.20	-2.65	0.01
After 6th ECT	0.18	0.20	-1.52	0.13
After 12th ECT	0.17	0.20	-2.18	0.03

KYNA concentrations in SAD patients did not differ significantly from those in the control group. In DBD patients, KYNA concentrations before treatment and after 12 ECTs (post-treatment) were significantly lower than in the control group, while those determined after one and six ECTs did not differ from KYNA concentrations in healthy controls. Blood serum concentrations of KYNA in RDD patients before treatment and after 1 and 12 ECTs were significantly lower than in the control group.

After 6 ECTs, however, they reached a level that did not differ significantly from that in the control group.

The three groups of patients described in this study differed in the dynamics of changes in KYNA concentration during ECT, as shown graphically in Diagram 1

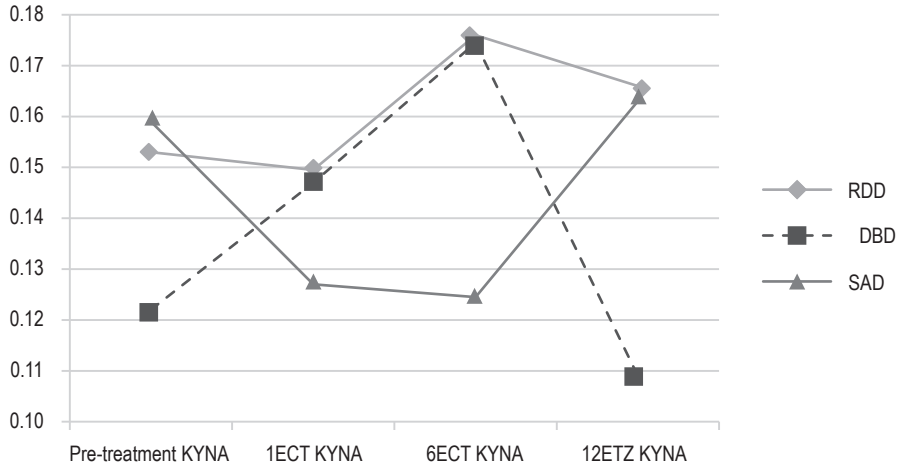

Diagram 1. **Comparison of blood plasma KYNA concentrations among RDD, DBD and SAD patients**

To answer the question whether pre-treatment blood serum concentrations of KYNA in patients diagnosed with RDD, DBD and SAD differed significantly from those determined after 1, 6 and 12 ECT sessions, the results were analyzed using Friedman's ANOVA and Kendall's coefficient of concordance. In patients with SAD, KYNA concentrations determined in the blood serum after 1 and 6 ECT sessions were lower than the baseline, and after 12 ECT sessions they reached the pre-treatment level. These changes, however, were not statistically significant ($\chi^2 = 0.66$; $df = 3$; $p = 0.88$). KYNA concentrations in patients diagnosed with DBD after 1 and 6 ECT sessions were higher than the baseline and after 12 ECT sessions they decreased to a level below the baseline. The changes in KYNA concentration in this group of patients (DBD) were also statistically insignificant ($\chi^2 = 0.33$, $df = 3$, $p = 0.95$). KYNA concentrations in the serum of patients diagnosed with RDD decreased slightly after the first ECT, then reached a level higher than the baseline after 6 ECT sessions to finally decrease after 12 ECT sessions to a level slightly higher than the baseline. Also in this group of patients, the changes in the concentration of KYNA during ECT were not statistically significant ($\chi^2 = 1.41$, $df = 3$, $p = 0.70$).

In summary, pre-treatment and post-treatment blood serum KYNA concentrations in SAD and RDD patients were comparable and were, at the same time, higher than KYNA concentrations in the serum of patients with DBD. After 1 and 6 ECT sessions,

KYNA concentrations in DBD and RDD patients increased to a similar level, while in SAD patients these concentrations decreased.

To find out whether and what relationships existed between blood serum KYNA concentrations in RDD, DBD and SAD patients, on the one hand, versus sociodemographic variables (gender, age and number of illness phases) and patients' scores on the used clinical scales (MADRS and GAF), on the other hand, Spearman's rho correlation coefficients were calculated (Table 4).

Table 4. **Spearman's rho correlation coefficient between patients' KYNA concentrations and demographic and clinical data**

		Spearman's rho	p
RDD	KYNA after 1st ECT & gender	0.35	0.05
	KYNA after 6th ECT session & pre-treatment MADRS	0.35	0.05
	KYNA after 6th ECT session & pre-treatment GAF	-0.34	0.05
DBD	Pre-treatment KYNA & number of phases	0.64	0.04
	Pre-treatment KYNA & pre-treatment GAF	-0.67	0.03
SAD	KYNA after 1st ECT & gender	0.93	0.003
	KYNA after 12th ECT session & gender	0.83	0.04

In SAD patients, higher blood serum concentrations of KYNA after 1 ECT correlated with older age, and higher KYNA concentrations after 12 ECT sessions were associated with male gender. Higher pre-treatment blood serum concentrations of KYNA in DBD patients correlated with a higher number of illness phases and poorer general functioning before treatment. These results show that there are significant relationships between higher blood serum concentrations of KYNA in RDD patients after 1 ECT session and male gender, and between higher KYNA concentrations after 6 ECT sessions and increased depression and poorer functioning before treatment.

Discussion

The results obtained in the present study show that there are significant differences between pre-treatment and post-treatment blood serum concentrations of KYNA in DBD and RDD patients, on the one hand, and KYNA concentrations in the blood plasma of healthy people, on the other hand. Serum concentrations of KYNA in BDB patients before and after treatment were significantly lower than the concentrations of KYNA in the control group; they increased during treatment (after 1 and 6 ECT sessions), but did not differ significantly from KYNA levels in healthy individuals. The results obtained in this work are consistent with a previous study by Olajossy [26], who observed significantly lower concentrations of KYNA in patients with depression in BD. Myint et al. [27] have pointed out that the path of changes in the metabolism of tryptophan and kynurenine in response to treatment in BD goes in two directions. These researchers showed, by calculating the KYNA to kynurenine ratio, how much of the

antagonist went to a specific metabolic pathway. They found that this ratio was lower in patients with major depression in the course of BD. According to Myint et al. [27], BD can be associated with a weakening of the neuroprotective factor. In this present study, KYNA concentrations in the serum of RDD patients before and after treatment and after one ECT were also significantly lower than the concentrations of KYNA in healthy individuals. KYNA concentrations determined after 6 ECT sessions were also the highest in this group of patients, but they did not differ significantly from the levels of KYNA in the control group. These results fully correspond with literature data, which show that patients with depression have significantly lower blood plasma levels of KYNA compared to healthy individuals [26–29]. Pre-treatment, mid-treatment and post-treatment KYNA concentrations in the blood plasma of patients with depression in the course of schizoaffective disorder did not differ significantly from KYNA levels in healthy subjects, but it should be noted that mid-treatment KYNA concentrations were lower than both the baseline and post-treatment KYNA levels.

Considering these results, it seems important to analyze the dynamics of changes in KYNA concentrations in the blood plasma of patients from the studied groups. The reduction in KYNA concentration after 6 ECT sessions was greater in DBD patients than in RDD patients. These results may provide a clue as to the selection of the optimal number of ECT sessions and type of treatment for patients suffering from different disorders.

The analyses conducted in this paper show that higher pre-treatment concentrations of KYNA in the blood plasma of DBD patients correlate with a larger number of phases of the illness and poorer general functioning before treatment, and higher concentrations of KYNA in RDD patients after 6 ECT sessions correlate with increased depression and poorer functioning of the subjects prior to treatment.

A review of the literature data regarding KYNA concentrations in various psychiatric disorders shows that a study should be conducted on KYNA concentrations in euthymia and mania in bipolar disorder with and without psychotic features, as well as in other disease entities in which psychotic features are observed. The present findings combined with the results reported in the literature suggest that, in the future, KYNA could become a marker of various mental disorders.

The study examined the effects of ECT on KYNA concentrations in SAD patients, where there were no significant differences in baseline values between the test group and the control group, as differences between the groups could emerge in the course of successive ECT sessions. Undoubtedly, it would be useful to know the nature and dynamics of these changes. A major difficulty is drawing a blood samples from the patients after each ECT session, because patients with depressive disorders irrespective of their typology may regard each subsequent diagnostic procedure that does not brings them to the wellbeing as burdensome and stressful, which can have the impact on their health. At this point it is difficult to skip the ethical and methodological problems (frequency of using the clinical scales) related to this procedure. Moreover, the measurement error must be taken into account. The authors found no significant differences in KYNA concentrations between the group of SAD patients before ECT and the control group, which does not mean that there were no real differences. An analysis of

the power of the test showed that it had a statistical power of 0.075 (1-β = 0.075). The probability of finding statistically significant differences of at least 0.20 in a population is 7.5/100. We have no grounds for claiming that there are no differences, because this could only be stated if no statistical differences were found and the power of the test was high, i.e., 1-β > 0.80. Therefore, our study has a developmental and hypothesis-generating character and requires recruitment of a larger cohort of patients. The value of the study is that it points to the need for further research on larger patient samples. The correlation method presented in Table 4 highlights correlations for which statistical significance was observed. Because of the multiplicity of described parameters for the different treatment groups, presented data may cast the impression of a certain selectivity of the media. A valuable direction of the continuation of this research could be a statement of changes in KYNA concentration with the severity of symptoms depending on the number of ECT sessions. This may be a chance for reference a changes in the KYNA concentration to the clinical status of patients and to evaluate KYNA as a biomarker of the illness.

In the literature, there are a number of discrepancies regarding the content of KYNA in different CNS structures as well as the cerebrospinal fluid (CSF) and plasma both in animals and in humans. The lowest reported CSF concentrations of KYNA were 0.5±1.1 pmol/l [30], but some researchers also found concentrations that were several times higher, up to 4.09±0.14 pmol/l [31]. Similarly, plasma KYNA concentrations described in the literature ranged from 3.91±1.84 nM [32] to 59.6±20.5 nM [33]. There are also a number of reports on changes in the content of KYNA in the course of CNS diseases, in the structures of the brain, CSF and blood serum. Of course, data on CNS concentrations mainly come from experimental studies and should be extrapolated to corresponding disorders in humans with caution. A similar caution should be exercised in interpreting the results obtained from *postmortem* examinations. As it is known, KYNA production is modulated by a number of factors such as pH and the content of ions, glucose or other components [34, 35]. One must agree that often there is no mutual dependence between plasma and CNS concentrations of KYNA. What is more, CSF concentrations of KYNA also differ from them. One example of this lack of correlation are the trends of changes in KYNA concentrations in patients with schizophrenia, where increases in serum concentrations of KYNA have been reported to be accompanied by both no changes in CSF concentrations and increased CSF KYNA concentrations [20, 36–37]. An additional problem is the fact that the passage of both tryptophan and kynurenine is subject to many peripheral regulatory processes such as peripheral changes in the concentrations of branched-chain and aromatic amino acids, competing for the same LAT (large neutral amino acid transporters) of the BBB (blood brain barrier), which strongly influence the peripheral metabolism of tryptophan [38].

The aim of our study was to search for a parameter which could be a useful practical tool for monitoring the effectiveness of treatment. We do agree that determination of KYNA concentrations in the brain tissue or CSF would be a much better way of monitoring them, but not from the point of view of clinical practice. In our opinion, it would be extremely difficult to require patients to agree to have their CSF collected for KYNA determination, because the sampling procedure may involve the risk of

complications ranging from post-puncture syndrome through infectious complications to cerebellar tonsillar herniation into the foramen magnum. The risk associated with the repetition of this procedure in the patients and the exposure of controls to it was the decisive factor in eliminating CSF from our study. The easy availability of peripheral blood and ease of sampling as well as the small burden that blood sampling imposes on patients make the content of various substances in blood serum a basic clinically useful parameter. Of course, interpretation of the results requires that the influence of other diseases and medication, gender, age and even the patient's diet is excluded. However, along the same lines, even the simple and routinely used blood count tests are burdened with a high error resulting from the impact of a number of interfering factors. It seems that at the present stage of knowledge about the role of KYNA in the etiopathogenesis of various diseases, it is more meaningful to study the dynamics and trends of changes in KYNA concentrations in a given person undergoing a specific procedure than to study absolute values of KYNA. Similarly, it would be difficult to relate the obtained results to the concentrations occurring in healthy controls, the more so that this would entail ethical dilemmas associated with the application of a given treatment in healthy subjects.

Conclusions

1. Pre-treatment and post-treatment KYNA concentrations in DBD patients were significantly lower than in the control group.
2. KYNA concentrations in the serum of RDD patients measured before ECT and after one and twelve ECT sessions were significantly lower than in the control group, while those measured after the sixth ECT session did not differ significantly from KYNA concentrations in healthy controls.
3. In SAD patients, higher blood serum concentrations of KYNA after one ECT session correlated with older age, and higher KYNA concentrations after twelve ECT sessions were associated with male gender.
4. Higher pre-treatment blood serum concentrations of KYNA in DBD patients correlated with a higher number of illness phases and poorer general functioning before treatment.
5. Significant relationships were found between higher blood serum concentrations of KYNA in RDD patients after one ECT session and male gender, and between higher KYNA concentrations after six ECT sessions and increased depression and poorer functioning before treatment.

References

1. Hashimoto K. *The role of glutamate on the action of antidepressants*. Prog. Neuro-Psychoph. 2011; 35(7): 1558–1568. doi:10.1016/j.pnpbp.2010.06.013.
2. Sanacora G, Treccani G, Popoli M. *Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders*. Neuropharmacology 2012; 62(1): 63–77. doi:10.1016/j.neuropharm.2011.07.036.
3. Tokita K, Yamaji T, Hashimoto K. *Roles of glutamate signaling in preclinical and/or mechanistic models of depression*. Pharmacol. Biochem. Beh. 2012; 100(4): 688–704. doi:10.1016/j.pbb.2011.04.016.
4. Trullas R, Skolnick P. *Functional antagonists at the NMDA receptor complex exhibit antidepressant actions*. Eur. J. Pharmacol. 1990; 185(1): 1–10. doi:10.1016/0014-2999(90)90204-J.
5. Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. *Increased cerebrospinal fluid glutamine levels in depressed patients*. Biol. Psychiat. 2000; 47(7): 586–593. doi:10.1016/S0006-3223(99)00284-X.
6. Hashimoto K, Sawa A, Iyo M. *Increased levels of glutamate in brains from patients with mood disorders*. Biol. Psychiat. 2007; 62(11): 1310–1316. doi:10.1016/j.biopsych.2007.03.017.
7. Rybakowski JK, Permoda-Osip A, Skibinska M, Adamski R, Bartkowska-Sniatkowska A. *Single ketamine infusion in bipolar depression resistant to antidepressants: are neurotrophins involved?* Hum. Psychopharm. Clin. 2013; 28(1): 87–90. doi:10.1002/hup.2271.
8. Price RB, Nock MK, Charney DS, Mathew SJ. *Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression*. Biol. Psychiat. 2009; 66(5): 522–526. doi:10.1016/j.biopsych.2009.04.029.
9. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA et al. *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression*. Arch. Gen. Psychiat. 2006; 63(8): 856–864. doi:10.1001/archpsyc.63.8.856.
10. Kavalali ET, Monteggia LM. *Synaptic mechanisms underlying rapid antidepressant action of ketamine*. Am. J. Psychiat. 2012; 169(11): 1150–1156. doi.org/10.1176/appi.ajp.2012.12040531.
11. Turski WA, Nakamura M, Todd WP, Carpenter BK, Whetsell WO Jr, Schwarcz R. *Identification and quantification of kynurenic acid in human brain tissue*. Brain Res. 1988; 454(1–2): 164–169. doi:10.1016/0006-8993(88)90815-3.
12. Müller N, Schwarz MJ. *A psychoneuroimmunological perspective to Emil Kraepelins dichotomy: schizophrenia and major depression as inflammatory CNS disorders*. Eur. Arch. Psych. Clin. N. 2008; 258(Suppl. 2): 977–106. doi:10.1007/s00406-008-2012-3.
13. Lapin IP. *Neurokynurenines (NEKY) as common neurochemical links of stress and anxiety*. Adv. Exp. Med. Biol. 2003; 527: 121–125. doi:10.1007/978-1-4615-0135-0_14.
14. Olsson SK, Samuelsson M, Saetre P, Lindström L, Jönsson EG, Nordin C et al. *Elevated levels of kynurenic acid in the cerebrospinal fluid of patients with bipolar disorder*. J. Psychiatr. Neurosci. 2010; 35(3): 195–199. doi:10.1503/jpn.090180.
15. Wciórka J. *Psychozy schizofreniczne*. In: Pużyński S, Rybakowski J, Wciórka J. ed. *Psychiatria kliniczna*. Wroclaw: Elsevier Urban & Partner; 2011.
16. Javitt DC, Zukin SR. *Recent advances in the phencyclidine model of schizophrenia*. Am. J. Psychiat. 1991; 148(10): 1301–1308. doi:org/10.1176/ajp.148.10.1301.
17. Baran H, Hainfellner JA, Kepplinger B, Mazal PR, Schmid H, Budka H. *Kynurenic acid metabolism in the brain of HIV-1 infected patients*. J. Neural. Transm. 2000; 107(10): 1127–1138. doi:10.1007/s007020070026.

18. Atlas A, Gisslén M, Nordin C, Lindström L, Schwieler L. *Acute psychotic symptoms in HIV-1 infected patients are associated with increased levels of kynurenic acid in cerebrospinal fluid*. Brain Behav. Immun. 2007; 21(1): 86–91. doi:10.1016/j.bbi.2006.02.005.
19. Erhardt S, Blennow K, Nordin C, Skogh E, Lindström LH, Engberg G. *Kynurenic acid levels are elevated in the cerebrospinal fluid of patients with schizophrenia*. Neurosci. Lett. 2001; 313(1–2): 96–98. doi:10.1016/S0304-3940(01)02242-X.
20. Nilsson LK, Linderholm KR, Engberg G, Paulson L, Blennow K, Lindström LH et al. *Elevated levels of kynurenic acid in the cerebrospinal fluid of male patients with schizophrenia.* Schizophr. Res. 2005; 80(2–3): 315–322. doi:10.1016/j.schres.2005.07.013.
21. Miller CL, Llenos IC, Dulay JR, Weis S. *Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder*. Brain Res. 2006; 1073-1074: 25–37. doi:10.1016/j.brainres.2005.12.056.
22. Erhardt S, Olsson SK, Engberg G. *Pharmacological manipulation of kynurenic acid: potential in the treatment of psychiatric disorders*. CNS Drugs. 2009; 23(2): 91–101. doi:10.2165/00023210-200923020-00001.
23. Zyss T. *Elektrowstrząsy: wprowadzenie do bioelektrycznej natury zaburzeń depresyjnych*. Warsaw: Elmico; 2009.
24. Montgomery SA, Åsberg M. *A new depression scale designed to be sensitive to change*. Brit. J. Psychiat. 1979; 134(4): 382–389. doi:10.1192/bjp.134.4.382.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC; 1995.
26. Olajossy M. *Poziom kwasu kynureninowego w surowicy chorych na depresję leczonych elektrycznie*. Habilitation thesis. Lublin: Medical University of Lublin; 2010.
27. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. *Kynurenine pathway in major depression: evidence of impaired neuroprotection*. J. Affect. Disord. 2007; 98(1–2): 143–151. doi:10.1016/j.jad.2006.07.013.
28. Olajossy M, Olajossy B, Potembska E, Skoczeń N, Wnuk S, Urbańska E. *Stężenie kwasu kynureninowego i wybranych cytokin podczas leczenia przeciwdepresyjnego*. Neuropsychiatria i Neuropsychologia 2014; 9(2): 1–7.
29. Maes M, Gałecki P, Verkerk R, Rief W. *Somatization, but not depression, is characterized by disorders in the tryptophan catabolite (TRYCAT) pathway, indicating increased indoleamine 2,3-dioxygenase and lowered kynurenine aminotransferase activity*. Neuroendocrinol. Lett. 2011; 32(3): 264–273.
30. Rejdak K, Bartosik-Psujek H, Dobosz B, Kocki T, Grieb P, Giovannoni G et al. *Decreased level of kynurenic acid in cerebrospinal fluid of relapsing-onset multiple sclerosis patients*. Neurosci. Lett. 2002; 331(1): 63–65. doi:10.1016/S0304-3940(02)00710-3.
31. Kepplinger B, Baran H, Kainz A, Ferraz-Leite H, Newcombe J, Kalina P. *Age-related increase of kynurenic acid in human cerebrospinal fluid – IgG and beta2-microglobulin changes*. Neurosignals 2005; 14(3): 126–135. doi:10.1159/000086295.
32. Urbańska EM, Luchowski P, Luchowska E, Pniewski J, Woźniak R, Chodakowska-Zebrowska M et al. *Serum kynurenic acid positively correlates with cardiovascular disease risk factor, homocysteine: a study in stroke patients*. Pharmacol. Rep. 2006; 58: 507–511.
33. Iłżecka J, Kocki T, Stelmasiak Z, Turski WA. *Endogenous protectant kynurenic acid in amyotrophic lateral sclerosis*. Acta Neurol. Scand. 2003; 107(6): 412–418. doi:10.1034/j.1600-0404.2003.00076.x.
34. Chmiel-Perzyńska I, Perzyński A, Wielosz M, Urbańska EM. *Hyperglycemia enhances the inhibitory effect of mitochondrial toxins and D,L-homocysteine on the brain production of kynurenic acid*. Pharmacol. Rep. 2007; 59: 268–273.

35. Urbańska EM, Chmiel-Perzyńska I, Perzyński A, Derkacz M, Owe-Larsson B. *Endogenous Kynurenic Acid and Neurotoxicity*. In: Kostrzewa RM. ed. *Handbook of Neurotoxicity*. New York: Springer Science+Business Media; 2014: 421–453. doi:10.1007/978-1-4614-5836-4_92.
36. Heyes MP, Brew BJ, Saito K, Quearry BJ, Price RW, Lee K et al. *Inter-relationships between quinolinic acid, neuroactive kynurenines, neopterin and 2 – microglobulin in cerebrospinal fluid and serum of HIV-1-infected patients*. J. Neuroimmunol. 1992; 40(1): 71–80. doi:10.1016/0165-5728(92)90214-6.
37. Ravikumar A, Deepadevi KV, Arun P, Manojkumar V, Kurup PA. *Tryptophan and tyrosine catabolic pattern in neuropsychiatric disorders*. Neurol. India 2000; 48(3): 231–238.
38. Sekine A, Okamoto M, Kanatani Y, Sano M, Shibata K, Fukuwatari T. *Amino acids inhibit kynurenic acid formation via suppression of kynurenine uptake or kynurenic acid synthesis in rat brain in vitro*. SpringerPlus. 2015; 4: 48. doi:10.1186/s40064-015-0826-9.

Address: Marcin Olajossy
2nd Department of Psychiatry and Psychiatric Rehabilitation
Chair of Psychiatry
Medical University of Lublin
20-439 Lublin, Głuska Street 1