Journal of Affective Disorders Reports 12 (2023) 100578

Contents lists available at ScienceDirect

Journal of Affective Disorders Reports

journal homepage: www.sciencedirect.com/journal/journal-of-affective-disorders-reports

Research Paper

The effect of electroconvulsive therapy (ECT) on serum kynurenine pathway metabolites in late-life depression

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ARTICLE INFO

Keywords:
Kynurenine
Tryptophan
Neopterin
Inflammation
Depression treatment
Somatic comorbidity

ABSTRACT

Background: Depression is reportedly associated with alterations in kynurenine pathway metabolites (kynurenines). Several kynurenines are involved in glutamate signaling, and some have potentially neurotoxic effects while others are considered neuroprotective. The pathway is upregulated under inflammatory conditions, which is associated with depression. Modulation of kynurenine metabolism has been investigated as a potential mechanism in electroconvulsive therapy (ECT), an effective treatment for major depressive disorder, particularly in late-life depression. However, results have been inconclusive. Here we aimed to investigate changes in tryptophan and kynurenines in older patients treated with ECT.

Methods: We analyzed levels of tryptophan, eight kynurenine pathway metabolites and the inflammation marker neopterin in serum samples collected at baseline and after a full ECT series for 48 patients with late-life depression from the Dutch MODECT study.

Results: There were no significant changes in the concentration of single metabolites after ECT, but a significant reduction in the ratio of kynurenic acid to 3-hydroxykynurenine (KA/HK). Analyses of change in kynurenines after ECT in remitters and non-remitters revealed no clear patterns or link to the therapeutic effect of ECT. There was considerable covariation between neopterin and several kynurenines.

Limitations: Variations in diet and serum collection timing may have impacted the results.

Conclusions: This study did not show consistent changes in the kynurenine pathway activation or balance between neuroactive metabolites after ECT. Still, changes in kynurenines were strongly related to changes in neopterin concentrations. This demonstrates the importance of considering inflammation when investigating the effect of ECT on the kynurenine pathway.

1. Introduction

The kynurenine pathway of tryptophan (Trp) metabolism (Fig. 1) has been implicated in the pathophysiology of depression (O'Farrell and Harkin, 2017; Savitz, 2020). This pathway includes several neuroactive metabolites, most notably the N-methyl-D-aspartate receptor (NMDAr) antagonist kynurenic acid (KA), considered neuroprotective (Foster et al., 1984), and the NMDAr agonist quinolinic acid (QA) and the free radical generator 3-hydroxykynurenine (HK). The latter two metabolites are considered neurotoxic (Guillemin, 2012; Okuda et al., 1998). The

Abbreviations: AA, anthranilic acid; ECT, electroconvulsive therapy; HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; IFN-γ, interferon gamma; KA, kynurenic acid; KTR, kynurenine-tryptophan-ratio; Kyn, kynurenine; MD, major depression; NMDAr, N-methyl-D-aspartate receptor; Pic, picolinic acid; PLP, pyridoxal 5′-phosphate; QA, quinolinic acid; Trp, tryptophan; XA, xanthurenic acid.

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https://doi.org/10.1016/j.jadr.2023.100578
Received 23 August 2022; Received in revised form 27 February 2023; Accepted 18 March 2023
Available online 21 March 2023

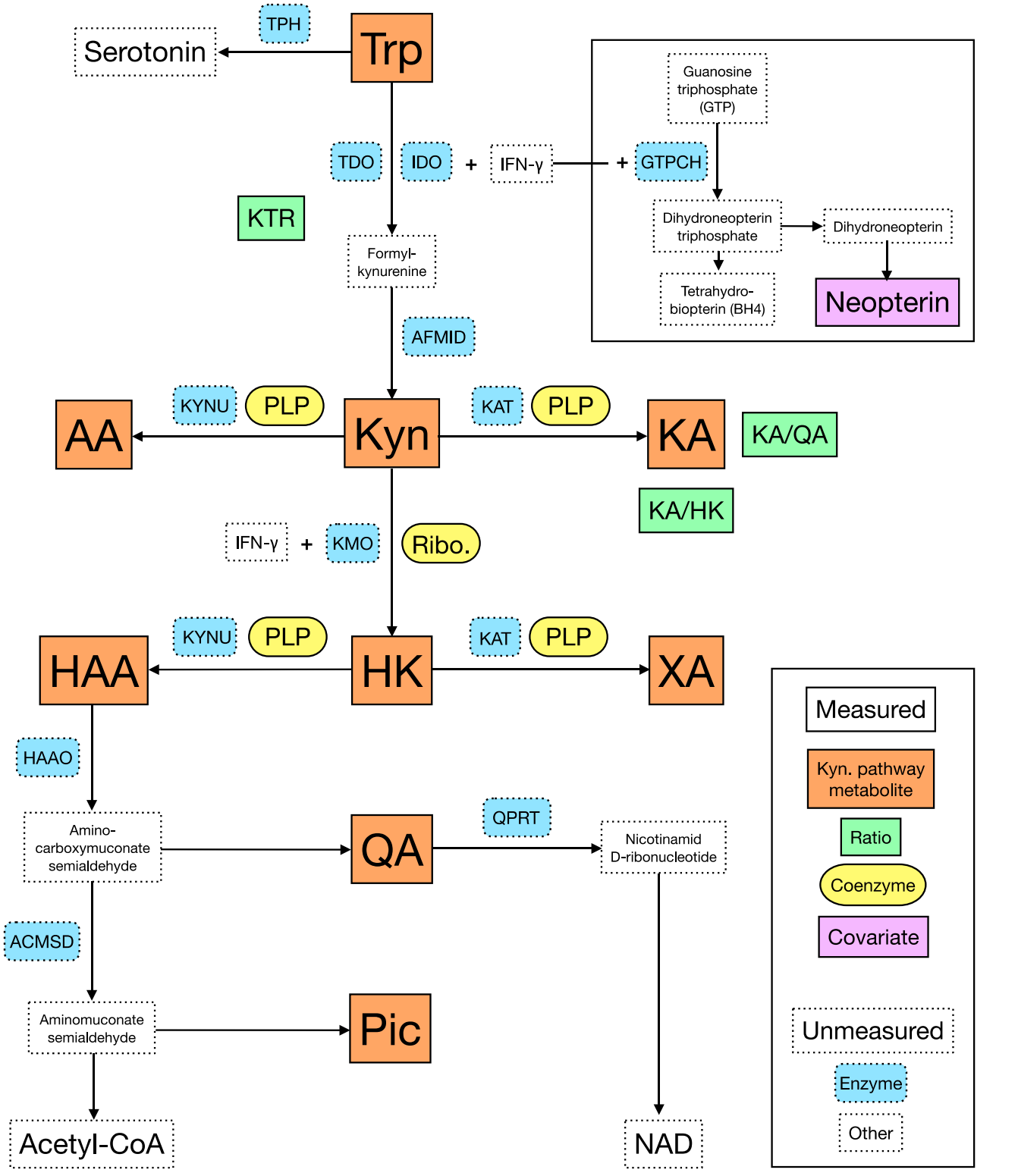

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Fig. 1. The kynurenine pathway of tryptophan metabolism. Kynurenine (Kyn) formation from tryptophan (Trp) is dependent on one of two enzymes, tryptophan 2,3-dioxygenase (TDO) in the liver, and indole 2,3-dioxygenase (IDO) in other tissues. Kyn is converted to kynurenic acid (KA) by kynurenine aminotransferase (KAT), to anthranilic acid (AA) by kynureninase (KYNU), or to 3-hydroxykynurenine (HK) by kynurenine 3-monooxygenase (KMO). KAT and KYNU are dependent on the coenzyme pyridoxal 5′-phosphate (PLP), an active form of vitamin B6, while KMO is dependent on flavin adenine dinucleotide (FAD), derived from riboflavin (vitamin B2). HK can be metabolized further to xanthurenic acid (XA) by KAT, or down the main branch to 3-hydryxyanthranilic acid (HAA) by KYNU. From HAA, the pathway leads to the production of nicotinamide adenine dinucleotide (NAD) via quinolinic acid (QA) or to aminomuconate semialdehyde which yields picolinic acid (Pic) or acetyl-coenzyme A (Acetyl-CoA). KA is an antagonist of the N-methyl-D-aspartate receptor (NMDAr) and is considered to be neuroprotective.[3] In contrast, QA is known to exert neurotoxic effects by stimulation of the NMDAr and through generation of free radicals.[4] While TDO activity is regulated mainly by Trp availability and by glucocorticoids, IDO and KMO can be induced by pro-inflammatory cytokines, especially interferon gamma (INF-γ).[19] The inflammatory marker neopterin is produced by macrophages upon stimulation with INF-γ and is correlated with increased metabolism through the kynurenine pathway measured as increased kynurenine to tryptophan ratio (KTR).[41] The ratios of KA to two metabolites of the main pathway branch, HK (KA/HK) and QA (KA/QA), are measures of the relative KA availability and represents the balance between neuroprotective and neurotoxic effects. Abbreviations: ACMSD, aminocarboxymuconate semialdehyde decarboxylase; AFMID, arylformamidase; GTPCH, GTP cyclohydrolase 1; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; TPH, tryptophan hydroxylase; QPRT, quinolinate phosphoribosyltransferase.

ratios between pathway metabolites, such as that of KA to QA (KA/QA), may reflect the balance between different neuroactive effects. It has been hypothesized that imbalance between neuroactive metabolites of the kynurenine pathway may contribute to neuronal toxicity and loss of neuronal tissue in depression (Maes et al., 2011; Muller and Schwarz, 2007; Myint and Kim, 2003; Savitz, 2020; Wichers et al., 2005). A recent meta-analysis of 59 studies supports this hypothesis by confirming that patients with major depression have lower levels of Trp, kynurenine (Kyn) and KA as well as lower ratios KA/Trp, KA/HK and KA/QA compared to healthy controls (Marx et al., 2020). Likewise, late-life depression has been associated with lower levels of Trp, Kyn and KA, and an increased Kyn to Trp ratio (KTR) compared to healthy older controls (Wu et al., 2018).

Electroconvulsive therapy (ECT) is a treatment option for severe or treatment-resistant depression with a relatively rapid effect and high response rate, especially in older patients (van Diermen et al., 2018). Hypothetically, successful treatment with ECT could be accompanied by normalized levels of KA, HK, QA, and other kynurenine pathway metabolites and ratios, that have been shown to be affected in depression. Several studies have investigated this possibility and show varying results (reviewed in Aarsland et al., 2022, Giron et al., 2022). In accordance with this hypothesis, Schwieler and colleagues reported a reduction in plasma Trp, Kyn and QA as well as reduced QA/KA after ECT, interpreted as a normalization of the imbalance between neuroprotective KA and neurotoxic QA (Schwieler et al., 2016). Similarly, increased KA was found by Guloksuz and collegues, along with increased KTR, KA/Kyn and KA/HK, taken as a sign of a strengthened neuroprotective effect (Guloksuz et al., 2015). In contrast, KA/HK decreased after ECT in another study (Yilmaz et al. (2022), and Ryan and colleagues found increased concentration of Trp and Kyn after an ECT series, with no significant increase in KA or reduction in QA (Ryan et al., 2020). A fifth study, from Allen and colleagues, found no significant changes in tryptophan kynurenine metabolites or ratios after ECT (Allen et al., 2018). In a previous study, we found a post treatment increase in 3-hydroxyanthranilic acid (HAA) and picolinic acid (Pic), in addition to an increased concentration of the inflammatory marker neopterin in adults with major depression after ECT series (Aarsland et al., 2019). These results could indicate a general stimulation of the kynurenine pathway in conjunction with an inflammatory response to ECT.

Inflammation plays an important role in the regulation of the kynurenine pathway (Hunt et al., 2020; Muller and Schwarz, 2007). As illustrated in Fig. 1, enzymes in the first and second steps of the main kynurenine pathway branch, responsible for the conversion of Trp to Kyn and Kyn to HK, are both induced by pro inflammatory cytokines, especially interferon gamma (IFN-γ) (Mandi and Vecsei, 2012). IFN-γ also stimulates macrophages to produce neopterin, an established inflammatory marker that often correlates strongly with KTR (Fuchs et al., 1991; Maes et al., 1994). Chronic low-grade inflammation is associated with depression, as shown in several meta-analyses (Kohler et al., 2017; Smith et al., 2018). Furthermore, a recent analysis of data from the UK Biobank showed that patients with depression had significantly higher levels of CRP than those without depression, independent of genetic, health and psychosocial factors (Pitharouli et al., 2021). Modulation of immune system activity is a potential effect of ECT (Yrondi et al., 2018). Summaries of studies on ECT and inflammation markers have suggested that single sessions increase inflammation, while full treatments series may reduce inflammation (Yrondi et al., 2018). Thus, inflammation constitutes a shared factor in the relationship between kynurenine metabolism, depression and ECT.

The natural aging process as well as many somatic pathological conditions are also associated both with changes in the kynurenine pathway (Badawy, 2017b; Savitz, 2020; Theofylaktopoulou et al., 2013) and with increased inflammatory activity (Franceschi et al., 2000; Pawelec, 2018). Higher age is associated with lower levels of Trp, and higher levels of most kynurenine pathway metabolites as well as higher KTR (Theofylaktopoulou et al., 2013). Importantly, the efficacy of ECT also increases with age, with especially high response rates in older patients (Kessler et al., 2018; van Diermen et al., 2018). Some studies suggest that kynurenine pathway modulation could be especially relevant in depressed patients with an inflammatory profile (Milaneschi et al., 2021) who possibly also benefit more from ECT (Carlier et al., 2019, 2021). Inflammation, age, and somatic disorders are therefore all relevant for the status of the kynurenine pathway in patients with late-life depression, and for changes in kynurenine pathway metabolite concentrations in conjunction with an ECT series.

To our knowledge, no previous studies have been published on kynurenine pathway metabolite changes after ECT in older patients with depression, a population where ECT is especially effective. In this study therefore, we aimed to investigate changes after ECT in kynurenine pathway metabolites in patients with late-life depression, and to investigate the role of inflammation and somatic disorders in this context.

2. Material and methods

This study was carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in the study. The MODECT study was approved by the Medical Ethical Committee of the Amsterdam UMC, location VUmc. The current study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics North (REK Nord 2018/721).

2.1. Patients

The participants in this study ($n = 48$) were recruited as part of Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) study (Dols et al., 2017). They were patients aged 55 years or older, diagnosed with unipolar depression and referred to ECT at GGZ inGeest, Amsterdam, in the period between January 1, 2011, and December 31, 2013. All patients were diagnosed by psychiatrists and the diagnosis confirmed with the Mini International Neuropsychiatric Interview (MINI). Patients with schizoaffective disorder, bipolar disorder or major neurologic illness were excluded. Previous treatment resistance was

defined as at least two failed trials of antidepressants in adequate doses. Montgomery and Åsberg Depression Scale (MADRS) was used to assess severity of depression before treatment, weekly during treatment, and after the completed ECT series. A post treatment MADRS score below 10 was considered as remission. Comorbid somatic disorders and medication use were assessed using a semi-structured interview, and baseline serum concentration of kidney function marker creatinine was measured for all patients. Psychotropic medication was either discontinued at least one week before ECT or kept unchanged from six weeks before ECT until the end of the ECT series.

2.2. ECT

Patients received brief-pulse (0.5–1.0 ms) right unilateral ECT twice a week, administered with the Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA) (maximum energy 200%, 1008 mC). Treatment response was evaluated weekly, and the treatment was concluded when the patient reached a MADRS score of less than 10 at two consecutive ratings. The treatment was switched to bilateral ECT if the clinical condition worsened or if there was no clinical improvement after six unilateral sessions. If there was no further improvement during the last two weeks of treatment after a minimum of six unilateral and six bilateral sessions, treatment was discontinued.

2.3. Blood sampling and analyses

Two venous blood samples were collected for each patient, one at baseline and one after the completed ECT series (median = 5 days, IQR = 5.25). For 37 of the patients, the baseline blood sample was collected before the treatment series (median = 5 days, IQR = 4), but for 11 patients it was collected after the first ECT (median = −5 days, IQR = 4). Blood was drawn between 7.30 and 9.30 A.M. after an overnight fast. Serum concentrations were measured for tryptophan (Trp) and the eight kynurenine pathway metabolites kynurenine (Kyn), kynurenic acid (KA), 3-hydroxykynurenine (HK), xanthurenic acid (XA), anthranilic acid (AA), 3-hydroxyanthranilic acid (HAA), quinolinic acid (QA) and picolinic acid (Pic). In addition, levels of riboflavin (vitamin B2), pyridoxal 5′-phosphate (PLP, vitamin B6), the nicotine metabolite cotinine and the inflammatory marker neopterin were measured. All serum analyses were performed by Bevital (www.bevital.no) in Bergen, Norway, using liquid chromatography/tandem mass spectrometry (Midttun et al., 2009).

2.4. Statistical analyses

Statistical analyses were done using RStudio version 1.2.1335 RStudio (Team, 2018) with packages *ggplot2, reshape2, tidyverse* and *ggsignif*. Three ratios of metabolite concentrations were calculated: KTR (1000*[Kyn]/[Trp]); KA/HK (10*[KA]/[HK]) and KA/QA (100*[KA]/[QA]). The main analyses of changes in serum concentrations from before to after treatment were performed using paired Wilcoxon signed-rank test (wilcox.test, paired=TRUE) for all patients with complete biochemical data. Percentage change for metabolite and ratio levels were calculated as 100*([post] – [pre])/[pre] for each individual to use as the primary measure of change. To control for the effect of variation in the collection time of the baseline blood samples, we also performed this analysis without the 11 patients for whom the baseline blood sample was collected after the first ECT. Additional subgroup analyses were performed with patients split in dichotomous groups by three variables: remission status, neopterin change after ECT, and diagnosis of somatic disease. Remission groups consisted of remitters and non-remitters. Neopterin change groups were created with patients with increased neopterin after ECT in one group, and those with reduced neopterin after ECT in the other. Somatic disease groups were defined as patients with no diagnosis of somatic disease in one group, and those with one or more such diagnoses in the other. Linear regression with natural logarithm transformed biochemical variables as outcome were used to compare baseline concentrations between patients with and without diagnoses of somatic disease. The linear regressions were adjusted for sex, age, smoking status, and serum creatinine concentration, all four possible confounders selected a priori. Like in the main analyses, Paired Wilcoxon signed rank test was used to investigate change after ECT in each of the six groups. Unadjusted Spearman correlation analyses was performed to investigate the relationship between kynurenine pathway metabolites, neopterin and baseline serum creatinine. Here, change in kynurenine pathway metabolites and neopterin was calculated as [post] – [pre]. The relationship between change in neopterin and change in QA was also investigated using a linear regression model (RStudio, ggplot2, geom_smooth with the lm() function) for all patients and in remission and somatic disease groups. Because of extreme neopterin values, one participant was excluded from all correlation analyses. Due to the tight relationship between the investigated kynurenine pathway metabolites, correction for multiple testing was not applied.

3. Results

3.1. Clinical data

MADRS decreased from a median of 32.5 (IQR = 13.5) to 6.5 (IQR = 11.75) after the full treatment series (Fig. 2). Age, sex, time of blood sample collection, number of ECT sessions, depression characteristics, data on medication, and somatic disorders for all patients as well as remitters and non-remitters are shown in Table 1. Corresponding data on subgroups of patients based on neopterin change and somatic comorbidity are available in Supplementary Table 1.

3.2. Changes in tryptophan and kynurenine pathway metabolites in all patients after ECT

Serum levels for kynurenine pathway metabolites and ratios, riboflavin, PLP and neopterin at baseline and after ECT together with results from paired Wilcoxon signed-rank tests on all patients (n = 48) are shown in Fig. 2 and listed in Supplementary Table 2. We observed a significant reduction in KA/HK (median = −16.1%, IQR = 29.2, p = 0.02) after the ECT series, whereas the levels of other kynurenine pathway metabolites or ratios were unchanged in the patient group as a whole. We also compared metabolite levels after excluding the 11 patients who had baseline blood samples collected after the first ECT. The overall changes in the metabolites and ratios did not diverge from analyses of the full set (data not shown). Similar trends were present, with the same reduction in KA/HK being closest to the significance threshold (p = 0.07).

3.3. Subgroups based on remission status

Thirty patients were classified as remitters and 18 as non-remitters. Performing paired Wilcoxon signed-rank tests for remitters and non-remitters separately, there were increased post treatment levels of HK, XA and HAA in remitters, and reduced QA concentrations after ECT in non-remitters, see Table 2 and Fig. 2.

3.4. Subgroups based on neopterin changes after ECT

After ECT, 25 patients had increased neopterin concentrations. For the other 23 patients neopterin concentrations were reduced. In paired Wilcoxon signed-rank tests, patients who had increased neopterin after ECT also had significantly increased HK (median = 20.6%, p = 0.03) and KTR (median = 8.06%, p = 0.04) and reduced levels of PLP (median = −23.1%, p = 0.02) and KA/HK (median = −17.2%, p = 0.01) after ECT (Fig. 3, Supplementary Table 3). Patients with reduced neopterin after ECT had significantly reduced levels of AA (median = −6.64%, p =

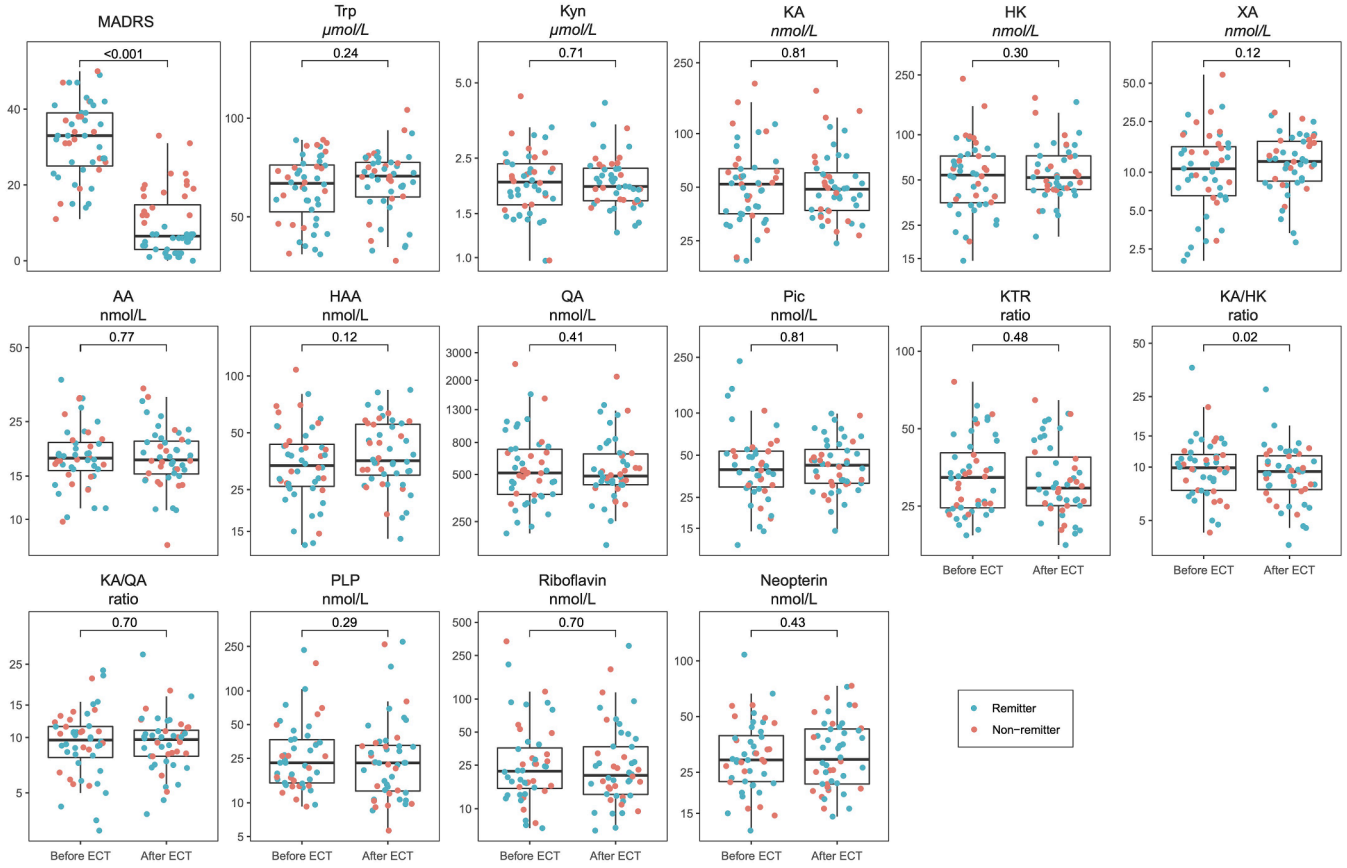

Fig. 2. MADRS scores and levels of kynurenine pathway metabolites, ratios, and coenzymes and neopterin at baseline and after ECT treatment for all patients (n = 48). P values from paired Wilcoxon signed-rank analyses of change after ECT are shown for each variable. Except for MADRS, the y-axes display serum measures logarithmically, providing a better visual resolution for lower values of metabolites with a large concentration spread, like QA, PLP and riboflavin. The middle horizontal line of the box indicates the median of the data (Q2), while the bottom and top horizontal lines indicate first and third quartile (Q1 and Q3). The bottom and top whiskers are calculated as Q1 – (1.5 x IQR) and Q3 + (1.5 x IQR). Abbreviations: MADRS, Montgomery and Åsberg Depression Rating Scale; Trp, tryptophan; Kyn, kynurenine; KA, kynurenic acid; HK, 3-hydroxykynurenine; XA, xanthurenic acid; AA, anthranilic acid; HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; Pic, picolinic acid; KTR, kynurenine-tryptophan-ratio; PLP, pyridoxal 5′phosphate.

0.03), QA (median = −15.0%, p = 0.002) and KTR (median = −12.4%, p = 0.005) and increased concentration of Trp (median = 6.78%, p = 0.048) after ECT (Fig. 3, Supplementary Table 3).

In unadjusted Spearman correlation analyses, change in neopterin after ECT was significantly correlated with change in HK (rho 0.33, p = 0.02), AA (rho = 0.40, p = 0.01), QA (rho = 0.47, p = 0.0009), and KTR (rho = 0.37, p = 0.01). Changes in neopterin was also significantly and positively correlated with change in change in KTR (rho = 0.56, p = 0.02) in non-remitters. Linear regression analyses in 47 patients, showed positive relationship between change in neopterin and change in QA after ECT in the whole patient group, in remitters, and in patients with and without somatic comorbidity (Fig. 4).

3.5. Subgroups based on diagnoses of somatic disease

Among the patients, 35.4% had a history of heart or vessel disease, 33.3% a history of hypertension, 22.9% a cancer diagnosis and 6.2% diabetes (Table 1). Eleven patients had none of these somatic conditions, while 37 had one or more. Patients with one or more diagnoses of somatic disease had significantly higher Trp (1.19 times, p = 0.03), Kyn (1.41 times, p = 0.0001), KA (1.38 times, p = 0.02), HK (1.66 times, p = 0.001), AA (1.24 times, p = 0.04), HAA (1.56 times, p = 0.01), QA (1.39 times, p = 0.01) and Pic (1.56 times, p = 0.04) at baseline than those without somatic disease (Supplementary Table 4). Patients without diagnosis of somatic disease had significant increase in Trp (median = 10.2%, p = 0.002), HK (median = 15.6%, p = 0.02) and HAA (median = 31.6%, p = 0.01) concentrations after ECT (Supplementary Table 4). There were no other significant changes in any metabolites or ratios after ECT in either somatic disease group.

In unadjusted Spearman correlation analyses for all patients, baseline serum creatinine was significantly correlated to baseline Kyn (rho = 0.43, p = 0.003), KA (rho = 0.46, p = 0.001), HK (rho = 0.43, p = 0.003), QA (rho 0.54, $p < 0.001$) and KTR (rho = 0.54, $p < 0.001$), and post treatment concentrations of Kyn (rho = 0.54, $p < 0.001$), KA (rho = 0.50, $p < 0.001$), HK (rho = 0.56, $p < 0.001$), QA (rho = 0.59, $p < 0.001$) and KTR (rho = 0.59, $p < 0.001$), but not to change in these metabolites (data not shown).

4. Discussion

In this study of 48 patients with late-life depression treated with ECT we analyzed changes in kynurenine pathway metabolites and ratios. We found no significant changes in any of the metabolites after ECT, only reduced level of KA/HK. The most notable changes in kynurenine pathway metabolites were in two subgroups of patients with opposite neopterin change after ECT, illustrating the importance of including inflammation markers in investigation of changes in kynurenine pathway metabolism.

Hypothetically, successful treatment with ECT could be accompanied by normalized levels of KA, HK, QA and other kynurenine pathway metabolites and ratios that have been shown to be affected in depression (Marx et al., 2020; Myint and Kim, 2003). Several studies have measured

Table 1
Clinical characteristics for all patients and for remitters and non-remitters.

	All patients ($n = 48$)			Remitters ($n = 30$)			Non-remitters ($n = 18$)		
	median	(IQR)	range	median	(IQR)	range	median	(IQR)	range
Age (years)	73	(12.3)	55 - 92	74.5	(14)	57 - 92	69	(11.8)	55 - 82
Baseline MADRS [a]	32.5	(13.5)	11 - 50	33	(16)	14 - 49	31.5	(11.5)	11 - 50
Number of ECT sessions [b]	10	(8)	4 - 29	9	(3.75)	4 - 28	14	(9.75)	4 - 29
Days from from baseline blood sample to first ECT [c]	2	(5)	−12 - 30	2	(4.75)	−12 - 11	3	(7)	−5 - 30
Days from last ECT to blood sample [d]	5	(5.25)	−9 - 16	4	(5)	−9 - 16	5.5	(3.25)	1 - 13
Number of previous episodes	2	(4)	0 - 16	2	(3)	0 - 16	3	(4)	0 - 15
Age at onset of depression (years)	57	(24)	18 - 87	57.5	(24)	18 - 87	50.5	(21)	23 - 77
Length of index episode (weeks)	6	(12.5)	1 - 144	4	(11)	1 - 144	12	(18)	2 - 84
Baseline serum creatinine (μmol/L)	78.5	(23.8)	52 - 197	76.5	(21)	61 - 135	79.5	(32)	52 - 197
	n	(%)		n	(%)		n	(%)	
Female	30	(62.5)		17	(56.7)		13	(72.2)	
Non-smoker	38	(79.2)		23	(76.7)		15	(83.3)	
Never alcohol [e]	31	(72.1)		18	(69.2)		13	(76.5)	
Late onset of depression [f]	26	(54.2)		18	(60.0)		8	(44.4)	
MDD with psychotic features	25	(52.1)		17	(56.7)		8	(44.4)	
Previous treatment resistance [h]	25	(52.1)		15	(50.0)		10	(55.6)	
No medication	27	(56.2)		0	(0.00)		10	(55.6)	
Antidepressants	15	(31.2)		9	(30.0)		6	(33.3)	
Only antidepressants	13	(27.1)		7	(23.3)		6	(33.3)	
Antipsychotics	6	(12.5)		4	(13.3)		2	(11.1)	
Only antipsychotics	6	(12.5)		4	(13.3)		2	(11.1)	
Heart and vessel	17	(35.4)		11	(36.7)		6	(33.3)	
Hypertension	16	(33.3)		12	(40.0)		4	(22.2)	
Diabetes	3	(6.2)		2	(6.70)		1	(5.60)	
Stroke	4	(8.3)		4	(13.3)		0	(0.00)	
Cancer	11	(22.9)		5	(16.7)		6	(33.3)	
Migrain	0	(0.0)		0	(0.0)		0	(0.0)	
Parkinson's disease	0	(0.0)		0	(0.0)		0	(0.0)	
Neurological disorder	0	(0.0)		0	(0.0)		0	(0.0)	

[a] For one patient, MADRS could not be collected at baseline, and was replaced by MADRS at two weeks into the treatment series.
[b] Number of ECT sessions in the current treatment series.
[c] For eleven patients, the baseline blood sample was collected after the first ECT, indicated by a negative number of days for this variable.
[d] For one patient, the post ECT blood sample was collected before the last ECT session (nine days). This patient received a total of 14 ECT sessions over seven weeks.
[e] Data on alcohol consumption was missing for five patients.
[f] First depressive episode at 55 years or older.
[h] Previous treatment resistance was defined as at least two failed trials of antidepressants in adquate doses. Abbreviations: IQR, inter quartile range; MADRS, Montgomery and Åsberg Depression Scale; MDD, major depression disorder.

Table 2
Baseline serum metabolite concentrations and effect of ECT on metabolites according to remission status.

	Remitters ($n = 30$)							Non-remitters ($n = 18$)						
	Before ECT		After ECT		% change			Before ECT		After ECT		% change		
Variable	Median	(IQR)	Median	(IQR)	Median	(IQR)	p	Median	(IQR)	Median	(IQR)	Median	(IQR)	p
Trp, μmol/L	61.1	(21.0)	65.8	(16.3)	5.32	(25.9)	0.20	67.5	(18.6)	67.7	(15.4)	−0.04	(35.2)	0.74
Kyn, μmol/L	1.87	(0.76)	1.96	(0.57)	2.16	(16.0)	0.50	2.13	(0.67)	1.89	(0.68)	−3.98	(19.2)	0.20
KA, nmol/L	46.2	(24.0)	46.7	(20.8)	13.7	(39.2)	0.39	56.9	(24.6)	50.4	(31.5)	−4.34	(39.2)	0.15
HK, nmol/L	48.6	(31.7)	49.8	(30.0)	15.9	(51.7)	**0.02**	59.8	(52.1)	53.3	(24.3)	−3.31	(33.2)	0.20
XA, nmol/L	9.16	(7.61)	11.6	(8.37)	22.8	(92.1)	**0.04**	14.4	(11.0)	14.1	(6.65)	−0.45	(56.3)	1.00
AA, nmol/L	18.2	(4.08)	18.1	(5.30)	1.28	(25.0)	0.81	17.4	(5.57)	16.8	(5.33)	−5.41	(18.9)	0.38
HAA, nmol/L	30.0	(16.1)	34.9	(23.5)	21.9	(57.1)	**0.01**	41.2	(26.3)	40.4	(24.2)	−10.4	(69.8)	0.61
QA, nmol/L	451	(404)	482	(298)	0.09	(34.4)	0.57	522	(194)	499	(99.0)	−9.26	(15.1)	**0.03**
Pic, nmol/L	37.8	(22.5)	43.6	(31.2)	19.9	(68.6)	0.29	43.7	(22.2)	38.6	(14.3)	−19.0	(49.3)	0.33
KTR, ratio	32.4	(20.4)	30.0	(18.9)	1.93	(25.6)	0.84	31.6	(11.0)	28.7	(8.99)	−4.15	(20.0)	0.39
KA/HK, ratio	10.2	(3.55)	9.55	(4.03)	−14.7	(33.4)	0.06	9.79	(4.25)	9.03	(3.88)	−16.5	(27.2)	0.23
KA/QA, ratio	9.13	(3.25)	9.74	(3.30)	−0.80	(40.8)	0.90	10.7	(3.73)	9.74	(3.15)	−4.68	(27.8)	0.67
PLP, nmol/L	23.5	(20.8)	22.8	(20.4)	−19.0	(51.8)	0.40	18.8	(17.5)	21.2	(21.2)	−14.3	(44.1)	0.50
Riboflavin, nmol/L	20.6	(19.2)	21.0	(28.5)	1.54	(67.7)	0.54	25.5	(28.7)	18.8	(13.0)	−9.48	(52.3)	0.16
Neopterin, nmol/L	29.1	(16.7)	33.9	(18.9)	3.72	(34.4)	0.42	30.4	(18.2)	25.7	(24.6)	0.51	(47.4)	0.77

Notes: Median and interquartile range (IQR) before and after ECT, percentage change and p-value from paired Wilcoxon signed-rank test are shown for remitters and non-remitters. p-values below the significance threshold 0.05 are marked in bold.
Abbreviations: Trp, tryptophan; Kyn, kynurenine; KA, kynurenic acid; HK, 3-hydroxykynurenine; XA, xanthurenic acid; AA, anthranilic acid; HAA, 3-hydroxyanthranilic acid; QA, quinolinic acid; Pic, picolinic acid; KTR, kynurenine-tryptophan-ratio; PLP, pyridoxal 5′phosphate.

kynurenine pathway metabolites in the context of ECT (Allen et al., 2018; Guloksuz et al., 2015; Ryan et al., 2020; Schwieler et al., 2016; Yilmaz et al., 2022; Aarsland et al., 2019). but the results have been inconsistent. Changes in the two first metabolites of the pathway, Trp-and Kyn, and their ratio KTR, provide information about the activation of the pathway. Trp-and Kyn were both increased after ECT in one study (Ryan et al., 2020). Increase in Kyn and KTR levels was also associated with reduced depression scores after ECT, and the authors concluded that ECT seemed to be activating the kynurenine pathway, at least in patients with unipolar depression (Ryan et al., 2020). In

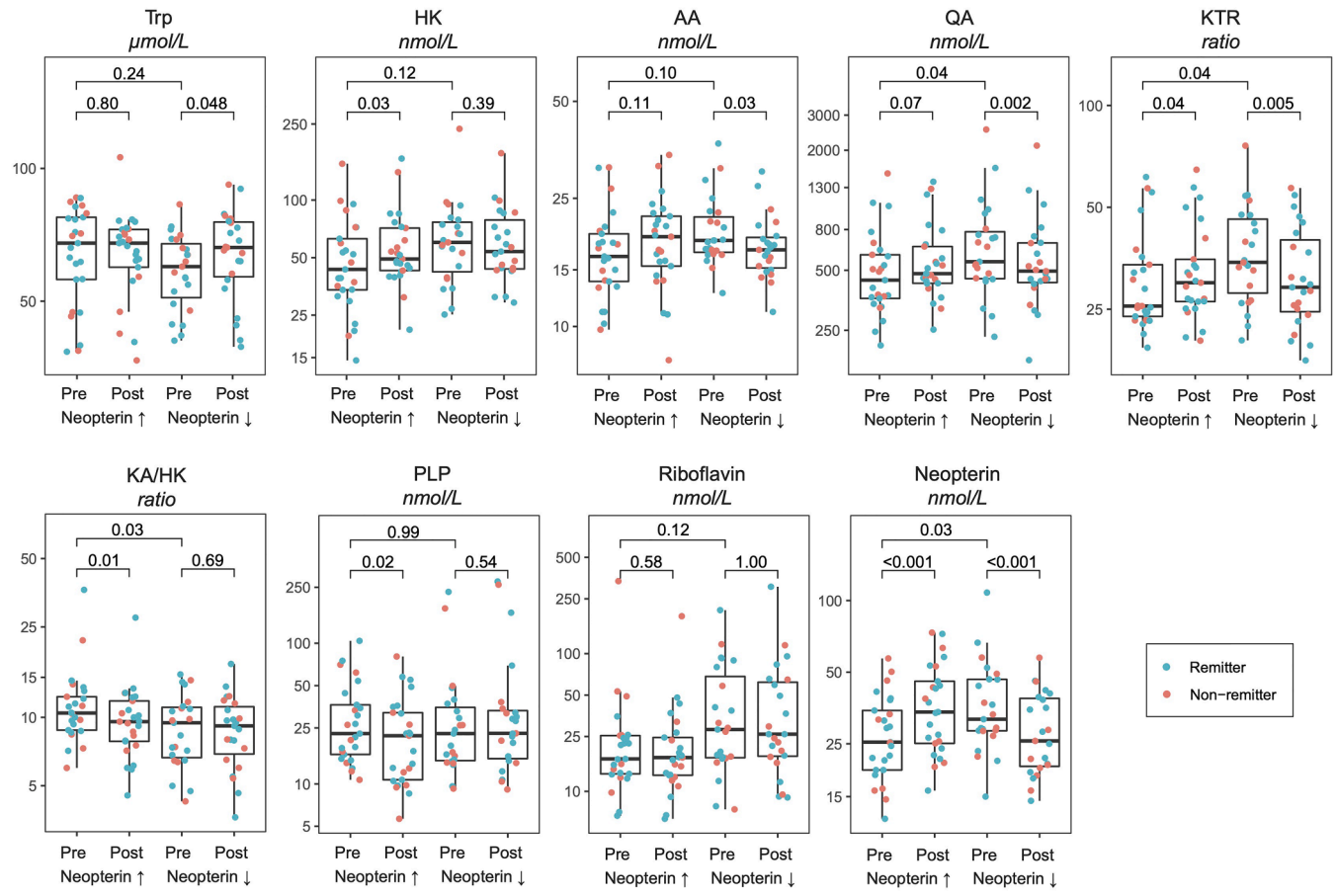

Fig. 3. Changes in selected biochemical variables after ECT in two groups of patients based on their change in neopterin concentration after treatment. Three p values are shown for each variable; two from paired Wilcoxon signed-rank tests of change after ECT in each group, and one from comparison of baseline values between the two groups by linear regression adjusted for sex, smoking status, and baseline serum creatinine. The y-axis serum measures are displayed on a logarithmic scale, providing a better visual resolution for lower values of metabolites with a large concentration spread, like QA, PLP and riboflavin. Abbreviations: Trp, tryptophan; HK, 3-hydroxykynurenine; AA, anthranilic acid; QA, quinolinic acid; KTR, kynurenine-tryptophan-ratio; PLP, pyridoxal 5′phosphate.

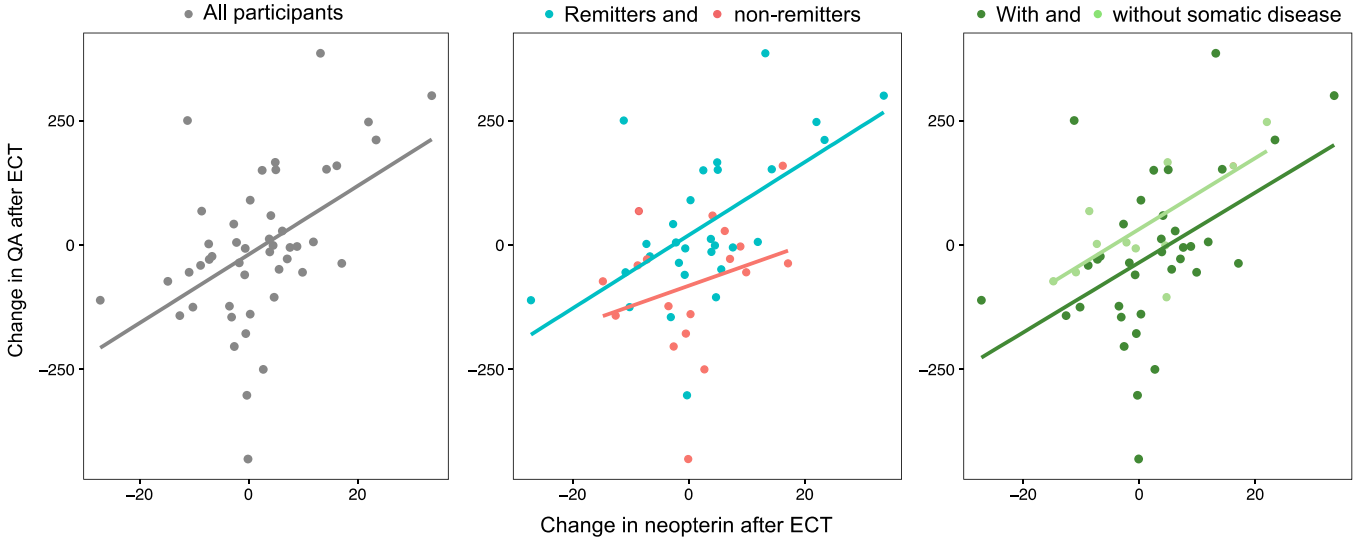

Fig. 4. The relationship between change (nmol/L) in neopterin and change (nmol/L) in QA after ECT in all patients ($n = 47$), in remitters ($n = 29$) and non-remitters ($n = 18$), and in patients with ($n = 36$) and without somatic comorbidity ($n = 11$). One patient was excluded from the analyses due to extreme values of neopterin. The dots show change for each patient. The lines show the relationship between the two change variables using a linear model for all patients ($\beta = 6.89$, $p < 0.001$), remitters ($\beta = 7.35$, $p = 0.001$), non-remitters ($\beta = 4.12$, $p = 0.26$), patients with no somatic diseases ($\beta = 7.03$, $p = 0.005$) and patients with one or more somatic diseases (7.13, $p = 0.01$).

contrast, Trp and Kyn were both reduced after ECT in another study (Schwieler et al., 2016), while in a third study KTR was increased after ECT without significant changes in Trp or Kyn (Guloksuz et al., 2015). In two other studies there were no changes in Trp, Kyn or KTR after ECT (Allen et al., 2018; Aarsland et al., 2019). Similarly, in the current study, Trp, Kyn and KTR all remained stable after ECT in the main analyses. There was therefore no apparent change in the activation of the pathway after treatment. This coincides with the conclusion of a recent meta-analyses that found moderate evidence for no effects of ECT on levels of TRP in eight studies (Giron et al., 2022), though the analysis only included plasma levels, and not serum TRP.

Regarding the relative concentrations of metabolites, two studies have found changes in markers indicating reduced neurotoxicity markers after ECT, with increased KA/QA in one (Schwieler et al., 2016), and increased KA and KA/HK in the other (Guloksuz et al., 2015). One other study did not find any such changes in ratios suggestive of reduced neurotoxicity (Allen et al., 2018). Furthermore, a fourth study found decreased KA/HK after ECT (Yilmaz et al., 2022), and another found that HK was significantly increased after ECT (Ryan et al., 2020), although not after correction for multiple testing. HK is a potentially neurotoxic metabolite (Okuda et al., 1998) on the main pathway branch that is produced from Kyn by kynurenine monooxygenase (KMO), a riboflavin dependent enzyme that can be induced by IFN-γ (Mandi and Vecsei, 2012) (Fig. 1). In the current study, like in the study of Yilmaz and collegues, we found an isolated reduction in KA/HK after ECT. Thus, we could not confirm a hypothesis of reduced neurotoxic markers after ECT when looking at the whole patient group.

We suspected, however, that changes in metabolite and ratio levels could be more prominent when analyzing remitters and non-remitters separately. After the ECT series, patients who remitted had significantly increased concentrations of HK, XA and HAA. XA and HAA are both formed directly from HK. The level of XA is dependent on kynurenine-aminotransferase (KAT) and its essential coenzyme PLP. Similar to KA, XA can inhibit glutamate transmission by blocking vesicular glutamate transportation and thereby reducing extracellular glutamate levels (Sathyasaikumar et al., 2017). HAA is formed by kynureninase (KYNU), which is also PLP dependent, and it is a metabolite on the main pathway branch and precursor of QA and Pic. The neuroactive effect of HAA seems to be context dependent, but it has been suggested to be neuroprotective under inflammatory conditions (Badawy, 2017a; Krause et al., 2011). In a previous study (Aarsland et al., 2019), we also found an increase in HAA after ECT, together with increase in the concentration of Pic which is also suggested to have neuroprotective effects (Brundin et al., 2016). These changes were accompanied by increased neopterin, a sign of increased inflammation after ECT. In the current study, there were no changes in the concentrations of riboflavin or PLP, and no increase in KTR or neopterin to suggest inflammation related increase in KMO activity and increased pathway flux in either remission group. The neurotoxic QA, downstream of HK and HAA, was stable in remitters after ECT, as were levels of KA. Non-remitters, on the other hand, had an isolated, significant reduction in the concentration of QA after ECT.

Like in the analyses of change in all patients, the findings from remitters do not immediately fit with the hypothesis of normalized kynurenine pathway metabolites after treatment. Rather, they suggest increased levels of metabolites in the main pathway branch leading up to QA. Still, there was no significant change in neopterin levels after ECT in the main analyses, nor in remitters or in non-remitters. There was, however, substantial variance between individuals in neopterin change following ECT, from a reduction of 69.7% to an increase of 33.6%. By creating two subgroups based on the direction of change in neopterin after ECT, we found several significant changes in kynurenine pathway metabolites and ratios in both groups.

KTR was significantly increased in patients with increased neopterin after ECT, and significantly reduced in those with reduced neopterin, in accordance with previous findings (Frick et al., 2004). Furthermore, patients with increased concentration of neopterin after ECT had significantly increased HK, and significantly reduced levels of PLP and KA/HK. As discussed above, PLP is an essential coenzyme for the conversion of HK to HAA, and, in general, a lack of this vitamer is associated with accumulation of HK (Theofylaktopoulou et al., 2014). Moreover, PLP is known to be reduced under inflammatory conditions (Ulvik et al., 2014). Thus, the pattern of increased neopterin and reduced PLP after ECT fits well with the increase in HK and reduction in KA/HK in this group (Ulvik et al., 2013). In the other group of neopterin change, reduction in neopterin was accompanied with increased Trp, and reduced AA and QA. This pattern is consistent with reduced activation through the pathway as was also reflected by the reduced level of KTR in this group. Additionally, in Spearman correlation analyses for 47 patients change in neopterin concentrations after ECT was strongly and positively correlated with changes in Kyn, HK, AA and QA.

All these changes are consistent with the role of neopterin as a marker of INF-γ activity which in turn induces activation of kynurenine pathway metabolism. Thus, it seems that inflammation is an important factor when assessing ECT-related changes in the kynurenine pathway in this material, even though neopterin was not significantly altered when looking at all participants together or grouped by remission status. A systematic review of inflammation in ECT suggests that there is an acute inflammatory response after ECT, but that a full treatment course is accompanied by reduced levels of inflammatory markers (Yrondi et al., 2018). In the current material, there seems to be large interindividual variation in neopterin changes after ECT, though the reason for this is unclear.

Somatic diseases are potential factors that could be associated both with inflammation and kynurenine changes. Somatic diseases could affect the levels kynurenine pathway metabolites, not only through increased inflammatory activity but also through altered nutritional status and organ function (Schrocksnadel et al., 2006; Strasser et al., 2017). In the current study diagnoses of heart or vessel disease, hypertension, cancer and diabetes, were registered, all of which are associated with inflammatory processes that may impact tryptophan metabolism (Cervenka et al., 2017; Strasser et al., 2017). Thirty-seven patients had one or more of these diagnoses, and had significantly higher baseline levels of Trp, Kyn, KA, HK, AA, HAA, QA and Pic compared to those without registered diagnosis of somatic disease. There was no baseline difference in neopterin concentrations between the two groups. After ECT, patients with no diagnosis of somatic disease had increased concentrations of Trp, HK and HAA, similar to the remitters discussed above. Patients with one or more such diagnoses had no significant changes in metabolites or ratios.

Kidney function is one factor that could be affecting the kynurenine pathway. In the current study there was substantial positive correlation between baseline serum creatinine and pre- and post-treatment concentrations of Kyn, HK, KA, QA and KTR. This is to be expected since kynurenine pathway metabolites are eliminated through the kidneys, thus potentially accumulating in the case of reduced kidney function (Pawlak et al., 2003). Importantly, there were no significant correlations of baseline creatinine to changes in these metabolites. This suggests that kidney function, although related to the absolute levels of kynurenine pathway metabolites, does not affect their potential for change in this material.

4.1. Strengths and limitations

We recently published a systematic review on changes in tryptophan and kynurneines after ECT, in which the current study is included (Aarsland et al., 2022). There, we discuss a wide range of factors that may affect the results, including patient characteristics, ECT delivery method, medication, and study design. A strength of the current study is that we included a large panel of metabolites and ratios, as well as coenzymes riboflavin and PLP, neopterin, cotinine and creatinine. We investigated these metabolites in a relatively homogenous group of

patients with age 55 years or higher. Furthermore, all psychotropic medication, some of which can affect tryptophan metabolism (Badawy, 2010), was either discontinued or kept stable during the whole treatment. On the other hand, we did not have information on nutritional status, physical activity, or body mass index, and could therefore not evaluate the possible effect of these factors. However, since this is a longitudinal study, the role of these factors should be of less importance than in cross sectional studies given that these traits are stable throughout the study. Although all patients were considered to have late life depression, about half of them had their first depressive episode before the age of 55 years (early onset). Differences in etiology, comorbidity and treatment efficacy between early and late onset depression could impact kynurenine metabolism. There was considerable variation in timing of blood sample collection at baseline, with 11 samples collected after the first ECT. However, from what we could see in sensitivity analyses without these 11 patients, this did not seem to have any significant effect on the direction or size of change in metabolites and ratios after ECT. The number of ECT sessions also varied between individuals, something that could bias the analyses of both kynurenines and inflammation markers. Ideally, the study should have included additional blood samples at a fixed number of ECT sessions (Aarsland et al., 2022). Neopterin was the only included measure of inflammation outside the kynurenine pathway, and a larger panel of inflammatory markers should preferably have been included. The sample size of the study was relatively low, especially when looking at subgroups of somatic disease. Furthermore, there was no available control group of healthy older adults, that could provide baseline control and inform on biological variation over time, nor a group of older patients with depression, treated with other treatment options than ECT to compare serum concentrations to before and after treatment. Such comparators could be very helpful when interpreting the kynurenine pathway metabolites in older patients with depression.

5. Conclusion

In this study of changes in kynurenine pathway metabolites after ECT, we did not find changes that suggest normalization of metabolite levels or ratios. On the contrary, reduced KA/HK in all patients and increased levels of HK and other metabolites in the main pathway branch in remitters, point to a reduction of the relative concentration of KA compared to neurotoxic HK and QA. The overall impression, however, is that large interindividual differences due to multiple uncontrolled sources of variance makes it difficult to isolate changes related to ECT and depression symptom relief. Inflammation is one such source of variability that could be related both to depression and the effect of ECT. When looking at patients with increased and reduced neopterin after ECT separately, we found more coherent changes in kynurenine pathway metabolites. Although effect modification by inflammation was expected, the substantial variation in neopterin change after ECT and close relationship to changes in kynurenine pathway metabolites illustrated the importance of including measures of inflammation and the need for further studies on the effect of ECT on tryptophan kynurenine metabolism.

Authors' contributions

This study was designed and executed by AD, UK, TIMA, JH, AU and PMU. AD contributed to data collection. AU and PMU were responsible for blood sample analyses. TIMA performed the formal analyses and writing - original draft. All authors read and approved the final manuscript.

Data availability

Individual deidentified participant data will be available at reasonable request.

Funding

This study was supported by Stiftelsen Kristian Gerhard Jebsen [SKJ-MED-02] and The Regional Health Authority of Western Norway [911986 and 912238]. The funding sources were not involved in study design, data collection, analyses or interpretation, writing or submission for publication.

Declaration of Competing Interest

Jan Haavik has received lecture honoraria as part of continuing medical education programs sponsored by Shire, Takeda, Medice and Biocodex. All other authors declare that they have no conflicts of interest.

Acknowledgments

We wish to thank all the patients how participated in this study. We also thank Leif Oltedal and Ketil Joachim Ødegaard for their contributions to the design and execution of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2023.100578.

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