Alterations in the Kynurenine Pathway of Tryptophan Metabolism Are Associated With Depression in People Living With HIV

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Background: People living with HIV have increased risk of depression compared with uninfected controls. The determinants of this association are unclear. Alterations in kynurenine (Kyn) metabolism have been associated with depression in uninfected individuals, but whether they are involved in the development of depression in the context of HIV infection is unknown.

Methods: A total of 909 people living with HIV were recruited from the Copenhagen Comorbidity in HIV infection study. Information regarding demographics and depression was obtained from questionnaires. HIV-related variables and use of antidepressant medication were collected from patient records. Logistic regression models before and after adjustment for confounders were used to test our hypotheses.

Results: The prevalence of depression was 11%. Among traditional risk factors, only being unmarried was associated with greater odds of depression. Higher levels of quinolinic-to-kynurenic acid ratio ($P = 0.018$) and higher concentrations of quinolinic acid ($P = 0.048$) were found in individuals with depression than in those without. After adjusting for confounders, high levels of quinolinic-to-kynurenic acid ratio and high concentrations of quinolinic acid remained associated with depression [adjusted odds ratio 1.61 (1.01; 2.59) and adjusted odds ratio 1.68 (1.02; 2.77), respectively].

Conclusions: The results from this study suggest that alterations in the kynurenine pathway of tryptophan metabolism are associated with the presence of depression in the context of HIV infection.

Key Words: kynurenine, quinolinic acid, kynurenic acid, depression, HIV infection, inflammation

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INTRODUCTION

Depression is the most common psychiatric comorbidity among people living with HIV (PLWH),[1,2] with prevalence estimates ranging from 5% to 40%.[2–6] Depression, especially when untreated, is associated with lower quality of life and may act as a barrier to adherence to combination antiretroviral treatment, contribute to progression of HIV infection, and, consequently, lead to higher morbidity and mortality.[5–9] In PLWH, depression is mainly attributed to psychosocial and lifestyle factors,[2,10–12] but its full etiology is unclear.

Tryptophan (Trp) is an essential amino acid that is metabolized either to kynurenine (Kyn) and other metabolites by the Kyn pathway or serotonin through the methoxyindole pathway.[13,14] Alterations of the Kyn pathway of Trp metabolism are well described in PLWH.[15] The association between alterations in this metabolic pathway and depression has previously been suggested in the uninfected population.[16,17] Both serotonin depletion[14,15,18] and alterations of Kyn metabolites concentration, particularly, quinolinic acid (QA) and kynurenic acid (KynA), have been proposed to play a role in the development of depression and suicidality in the general population.[14,19] Little is known about the association between the Kyn pathway of Trp metabolism and depression in the context of HIV infection, with few previous studies reporting conflicting results.[3,20]

In this study, we aimed to investigate possible associations between alterations in the Kyn pathway of Trp metabolism and the presence of depression in a predominantly well-treated PLWH population. Furthermore, we identified traditional and HIV-related risk factors associated with depression.

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METHODS

Study Populations

PLWH were recruited among participants in the Copenhagen Comorbidity in HIV infection (COCOMO) study. The COCOMO study is a longitudinal, observational, and noninterventional cohort study with the aim of assessing the burden of non-AIDS comorbidity in PLWH. Participants were enrolled from outpatient clinics at departments of infectious diseases at University Hospital Copenhagen Rigshospitalet and Hvidovre University Hospital. Inclusion criteria were participants aged 18 years or younger and a positive HIV test. Between March 2015 and December 2016, 1099 PLWH, equivalent to >40% of all PLWH living in the greater Copenhagen area, were included. Recruitment and data collection have previously been described in detail.[21] From April 2017 to December 2018, 949 PLWH from the COCOMO study cohort were included in a 2-year follow-up program that included a depression questionnaire [Major Depression Inventory (MDI)]. All participants with data available from depression questionnaires from the 2-year follow-up were included in this study.

Ethical approval was obtained by the Local Ethics Committee of Copenhagen (COCOMO: H-8-2014-004) and the Danish Data Protection Agency. Oral and written informed consent was obtained from all participants.

Data Collection

Information about smoking, alcohol, drug use, demographics, medication, and depression was collected using structured questionnaires collected at baseline (demographics and lifestyle-related factors) and at the 2-year follow-up (MDI questionnaire). Information regarding HIV infection and use of antidepressant medication was obtained by review of the medical charts at baseline and at 2-year follow-up. Median (interquartile range) time interval between baseline and 2-year follow-up was 2.3 years (2.1–2.4). At baseline, fasting venous blood samples were collected in ethylenediaminetetraacetic acid tubes and centrifuged. Plasma samples were stored at −80°C.

Kynurenine, Tryptophan, and Kynurenine Metabolites

Plasma samples were used for the quantification of Trp, Kyn, KynA, and QA concentrations. Analyses were performed at Bevital (Bergen, Norway) using liquid chromatography–tandem mass spectrometry as previously described.[22,23] Kynurenine-to-tryptophan ratio (KTR) was defined as the ratio of Kyn to Trp and was used as a measure of IDO-1 activation. The neurotoxic ratio was defined as the ratio between quinolinic acid and kynurenic acid (QA/KynA), as previously described.[17]

Outcomes Definition

Depression was defined as a diagnosis of depression according to the MDI (2 or 3 core symptoms with a score ≥4 plus at least 2 minor symptoms with a score ≥3) and/or current use of antidepressive medications (tricyclic antidepressants, selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, monoamine oxidase inhibitors, melatonin agonist, or atypical antidepressant). MDI questionnaires were used to score depression and were scored according to relevant guidelines.[24] MDI is a self-rating inventory developed to measure *DSM-IV* and *ICD-10* diagnoses of depression by the patients' self-reported symptoms. It is characterized by a sensitivity of 0.86–0.92 and specificity of 0.82–0.86 when compared with the Schedule for Clinical Assessment in Neuropsychiatry index.[24] According to WHO guidelines, abdominal obesity was defined as waist-to-hip ratio ≥0.90 for men and ≥0.85 for women.

Statistical Analyses

Continuous variables were reported as mean and SD and categorical variables as frequency and percentage. Differences in biomarkers of the Kyn pathway between PLWH with and without depression were assessed with the Mann–Whitney U test for continuous data and the χ^2 and Fisher exact test for categorical data.

The association between depression and traditional and HIV-specific factors (viral load <50 copies/mL, CD4 cells nadir <200, exposure to efavirenz, and previous AIDS defining event) were tested using univariable and multivariable logistic regression analyses, respectively. Multivariable models were adjusted for a priori defined confounders: age, sex, geographical origin, marital status, educational level, and high alcohol intake. HIV-related factors were added to this model one at a time.

Possible associations between depression and the Kyn pathway of Trp metabolism were tested by logistic regression models, before and after adjusting for age, sex, abdominal obesity, and smoking status. In sensitivity analyses, the models were further adjusted for high-sensitivity c-reactive protein.

High levels and concentrations of each ratio or metabolite were defined as the highest quartile and compared with the rest of the study population (first, second, and third quartiles). In a similar manner, low concentrations of Trp and KynA were defined as the lowest quartile and compared with the rest of the study population (second, third, and fourth quartiles).

A P value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 3.6.1.

RESULTS

Study Population

A total of 909 PLWH were included from the COCOMO study. Study participants' demographics and clinical characteristics are depicted in Table 1. The prevalence of depression was 11% (n = 100) (Table 2), and 80 (8.8%) individuals reported current use of antidepressant treatment. Among those without use of antidepressant treatment, 809 had "no depression" according to MDI questionnaire, 5 (0.6%) "mild depression," 9 (1.1%) "moderate depression," and 6 (0.7%) "severe depression."

TABLE 1. Characteristics of People Living With HIV

	PLWH n = 909
Age, mean (SD)	50.8 (11.3)
Sex, male, n (%)	777 (85.5)
Geographic origin, European, n (%)	758 (85.0)
Marriage status, unmarried, n (%)	420 (49.3)
High alcohol intake, yes, n (%)	205 (25.3)
Low education level, yes, n (%)	418 (48.9)
Current smoker, yes, n (%)	246 (27.1)
Depression, yes, n (%)	100 (11.0)
Current exposure to antidepressive medications, yes, n (%)	80 (8.8)
HIV transmission mode	
Heterosexual	198 (22.0)
IDU	10 (1.1)
MSM	648 (71.9)
Other	45 (5.0)
CD4, mean (SD)	713.7 (281.5)
CD4 nadir <200 cells, yes, n (%)	360 (40.5)
Current cART, yes, n (%)	896 (98.8)
Viral load < 50 copies, yes, n (%)	865 (95.7)
Current use of efavirenz, yes, n (%)	233 (25.6)
Kynurenine, μmol/L, median (IQR)	1.6 (1.4–1.8)
Tryptophan, μmol/L, median (IQR)	62.4 (55.0–70.8)
Kyn-to-Trp ratio, median (IQR)	25.3 (21.4–29.9)
Quinolinic acid, nmol/L, median (IQR)	383 (308.0–475.5)
Kynurenic acid, nmol/L, median (IQR)	48 (37.3–59.9)
QA-to-KynA ratio, median (IQR)	80.3 (64.8–105.5)

High alcohol intake was defined as ≥14 units/week in male participants and ≥7 units/week in female participants.

Low education level was defined as education <3 years.

cART, combination antiretroviral treatment; KynA, kynurenic acid; IDU, intravenous drug user; IQR, interquartile range; MSM, male to male sex; QA, quinolinic acid.

Traditional and HIV-Specific Factors Associated With the Presence of Depression

In unadjusted analyses, being unmarried [odds ratio, OR: 2.28 (1.44; 3.61)] and current smoking [OR 1.60 (1.04; 2.49)] were associated with depression. After adjusting for relevant confounders, being unmarried remained associated with excess risk of depression [adjusted odds ratio (aOR): 2.07 (1.25–3.42)]. No other traditional factors were found to be associated with depression (Table 2). Among HIV-specific factors, current exposure to efavirenz was associated with lower risk of depression, both before and after adjusting for confounders (Table 2). No differences in several HIV-specific factors or metabolic comorbidities were found between PLWH with and without depression (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B631).

Kynurenine Pathway of Tryptophan Metabolism and Depression

Higher levels of quinolinic-to-kynurenic acid ratio (QKA) [102.1 (70.4) vs. 89.2 (46.8), $P = 0.018$] and higher concentrations of QA [457.8 (247.9) vs. 415.4 (188.5) nmol/L, $P = 0.048$] were found in individuals with depression. By contrast, no differences in levels of KTR [27.6 (9.8) vs. 26.4 (7.5), P value 0.188] and concentrations of Kyn [1.7 (0.6) vs. 1.6 (0.6) μmol/L, P value 0.578] and KynA [50.9 (24.9) vs. 50.8 (20.3) nmol/L, P-value 0.967] were found between PLWH with and without depression. In multivariable logistic regression analyses, high levels of QKA and QA remained associated with the presence of depression [aOR 1.61 (1.01–2.59), P value 0.047 and aOR: 1.68 (1.02–2.77), P value 0.042, respectively] (Table 2). The association between depression and high QA [high QA, aOR 1.72 (1.02–2.88)] and high QKA [aOR 1.54 (0.94–2.52)] was consistent in sensitivity analyses after further adjustment for sensitivity c-reactive protein, without, however, reaching statistical significance in the latter. These associations were consistent in further sensitivity analyses after exclusion of individuals with depression but not those on current antidepressive treatment (data not shown). Differences in Kyn metabolites in male and female participants are presented in Supplemental Digital Content (Table 2, http://links.lww.com/QAI/B631).

DISCUSSION

In this study, we described that alterations in the balance between QA and KynA production are associated with the presence of depression in PLWH. The association between alterations in the Kyn pathway of Trp metabolism and HIV infection is well described.[15,25] Trp is metabolized into Kyn through IDO-1, whose activity is enhanced in PLWH.[15] Kyn is further metabolized by kynurenine aminotransferase and kynurenine monooxygenase (KMO), resulting in either KynA or, alternatively, 3-hydroxykynurenine and, eventually, QA. Alterations in Kyn metabolism have been associated with depression in the uninfected population.[26] Reduction in Kyn and KynA together with increased QA and QA/KynA ratio has been the most consistently reported findings.[16,17] KynA and QA are antagonistic and agonistic to the NMDA receptor, respectively, and alterations in glutamatergic functions are known to be involved in the pathogenesis of depression.[17] Thus, alterations in concentrations of these Kyn metabolites may lead to glutamatergic dysfunction and, consequently, depression, as reviewed in a previous study.[27] In this study, we described higher levels of QA and QA/KynA ratio in PLWH with depression than the levels in those without. These findings are in line with previous studies in uninfected individuals[16,17] and may suggest increased activity of KMO to play a role in the pathogenesis of depression. In the central nervous system, KMO is mainly expressed in the macrophages of the microglia. Interestingly, increased microglial macrophage activity measured by positron emission tomography has been described in individuals with depression.[28] Previous results from our group reported a close association between QA and QA/KynA with markers of systemic inflammation.[25] In the light of the existing literature and the findings presented in this study, we hypothesize that the presence of a close relation between macrophage-driven inflammation and depression in the context of HIV infection may be partly mediated by alterations in the Kyn pathway of Trp metabolism.

TABLE 2. Association of General, HIV-Related, and Kynurenine Metabolism–Related Factors With the Presence of Depression

	Unadjusted OR (95% CI)	*P*	aOR (95% CI)	*P*
Age, per yr	0.99 (0.97 to 1.01)	0.278	0.99 (0.97 to 1.02)	0.561*
Sex, male	0.88 (0.50 to 1.55)	0.656	1.21 (0.55 to 2.67)	0.631*
Geographical origin, European	1.07 (0.59 to 1.94)	0.828	1.12 (0.50 to 2.50)	0.778*
Marriage status, married	2.28 (1.44 to 3.61)	<0.001	2.07 (1.25 to 3.42)	0.004*
Alcohol intake, high	0.69 (0.39 to 1.22)	0.205	0.58 (0.31 to 1.07)	0.082*
Education level, low	1.22 (0.79 to 1.88)	0.375	1.21 (0.75 to 1.97)	0.434*
Smoking status, current	1.60 (1.04 to 2.49)	0.034	1.54 (0.93 to 2.56)	0.095*
CD4 nadir, <200 cells	0.81 (0.52 to 1.26)	0.348	0.85 (0.50 to 1.45)	0.552*
Efavirenz, current	0.11 (0.04 to 0.29)	<0.001	0.14 (0.05 to 0.39)	<0.001*
Previous AIDS, yes	0.89 (0.51 to 1.57)	0.699	0.89 (0.46 to 1.73)	0.739*
Viral load, <50 copies	1.09 (0.38 to 3.14)	0.869	1.42 (0.32 to 6.24)	0.640*
High Kyn	1.18 (0.73; to 1.91)	0.495	1.25 (0.75 to 2.08)	0.396†
Low Trp	1.13 (0.71 to 1.79)	0.603	0.99 (0.61 to 1.61)	0.956†
High KTR	1.11 (0.68 to 1.81)	0.668	1.27 (0.76 to 2.13)	0.357†
High QA	1.49 (0.94 to 2.37)	0.091	1.68 (1.02 to 2.77)	0.042†
Low KynA	0.80 (0.47 to 1.34)	0.388	0.68 (0.39 to 1.17)	0.160†
High QKA	1.62 (1.02 to 2.56)	0.039	1.61 (1.01 to 2.59)	0.047†

High and low kynurenine concentrations were defined as having a concentration in the highest and lowest quartiles, respectively.
*Adjusted for age (in decades), sex, geographical origin, marital status, educational level, and high alcohol intake.
†Adjusted for age, sex, abdominal obesity, and current smoking.
CI, confidence interval.

The MDI questionnaire is used to screen for depression by general practitioners in Denmark,[24,29] where the prevalence of depression has been reported to be 2.3% in the general population.[30] The results presented in this study suggest that depression may be up to 5 times more prevalent among PLWH than that in the general population, as previously described,[31] even in the context of well-treated individuals. However, because a control population was not present in this study, conclusions regarding possible differences in the prevalence of depression between PLWH and uninfected individuals cannot be drawn.

The determinants of depression in the context of HIV infection are not fully understood. Both traditional and HIV-specific risk factors have been proposed to be involved.[2,6] In this study, only being unmarried was strongly associated with depression, as previously reported.[2] Efavirenz has been previously described to be strongly associated with psychiatric illnesses.[6] We observed an inverse association between current treatment with efavirenz and the presence of depression. Although this finding may seem to be in contrast with previous literature, we deem it probable to be because of statistical confounding by indication. According to local guidelines, PLWH with a history of or risk factors for depression are not prescribed efavirenz as a part of their HIV treatment, thus resulting in very low prevalence of depression among the individuals using this medication.

This study had several limitations. The time interval between the collection of plasma samples and questionnaires regarding depression may have influenced the results. Second, although Kyn has been described to pass the brain–blood barrier, QA and KynA pass this barrier poorly.[32] Thus, it is unclear how peripheral concentrations of the latter metabolites may reflect those in the central nervous system. However, this is the first study to investigate the association between Kyn metabolites and depression in PLWH. Furthermore, the indication for antidepressive treatment was not explored, thus possibly resulting in individuals on antidepressive medications for reasons other than depression. Finally, no uninfected controls were included.

In conclusion, we presented data suggesting that higher concentrations of circulating QA and higher levels of QA/KynA are associated with the presence of depression in the context of HIV infection. One could speculate whether specific novel treatments targeting this pathway may reduce the burden of psychiatric comorbidities in well-treated PLWH.

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