General Hospital Psychiatry 50 (2018) 76–82

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

Differences in the association of inflammation and tryptophan with depressive symptoms between white and non-white chronic dialysis patients

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ARTICLE INFO

Keywords:
Chronic dialysis patients
Depressive symptoms
Inflammatory markers
Racial differences
Tryptophan degradation

ABSTRACT

Objective: Possibly, different biochemical parameters are involved in the development of depressive symptoms in white and non-white dialysis patients. We examined whether the association between inflammation and depressive symptoms and between tryptophan and depressive symptoms differs between white and non-white dialysis patients and whether the association between inflammation and depressive symptoms is mediated by tryptophan degradation along the kynurenine pathway in both groups.

Method: Depressive symptoms were measured with the BDI-II. HsCRP, IL-1β, IL-6, IL-10, and TNFα and tryptophan and its degradation products kynurenine and 3-hydroxykynurenine were measured in 270 white and 220 non-white patients.

Results: The presence of depressive symptoms was significantly higher in non-white patients (51%) than in white patients (37%) ($P < 0.01$). Among white patients, HsCRP was significantly associated with depressive symptoms ($\beta = 0.6$ (95% CI: 0.1–1.2)). Among non-white patients, significant associations with depressive symptoms were found for both HsCRP ($\beta = 1.0$ (95% CI: 0.1–2.0)) and IL-6 ($\beta = 2.6$ (95% CI: 0.8–4.4)). Tryptophan levels were only significantly associated with depressive symptoms in non-white patients ($\beta = -0.3$ (95% CI: -0.4–-0.1)). Tryptophan degradation along the kynurenine pathway did not mediate the association between inflammatory markers and depressive symptoms in either group.

Conclusion: Our results indicate that for white and non-white dialysis patients different biochemical parameters are associated with depressive symptoms.

1. Introduction

The incidence rate of chronic dialysis treatment is 352 per million per year in the United States. It is known that Black Americans have a 3.7-fold higher incidence of end-stage renal disease compared to white Americans [1]. Racial differences have also been found in the prevalence of depressive symptoms in chronic dialysis patients, with a higher prevalence in black dialysis patients (30%) than in white patients (23%) [2]. This difference could be explained by social factors [3], but it may also involve biochemical markers (e.g. inflammatory markers and tryptophan (TRP)). It is not clear whether racial differences exist among chronic dialysis patients regarding the associations between inflammatory markers and depressive symptoms and between TRP and its degradation products (e.g. kynurenine (KYN)) and depressive symptoms.

Dialysis patients are known for a chronic inflammatory state [4,5], which has often been linked to a higher presence of depressive symptoms [6]. In general population studies, indications have been found for racial differences regarding concentrations of inflammatory markers [7,8] and for the association between inflammatory markers and depressive symptoms [9,10]. For example, higher CRP levels were found in black subjects than in white subjects [8]. Also, one study found significant associations between depressive symptoms and CRP in white women [10] and another study found stronger associations in non-Hispanic whites compared to non-Hispanic blacks and Hispanics [9].

Besides high inflammatory markers, dialysis patients also have been

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http://dx.doi.org/10.1016/j.genhosppsych.2017.10.003
Received 24 August 2017; Received in revised form 9 October 2017; Accepted 11 October 2017

found to have low TRP and high TRP degradation products [11,12]. Both low TRP and degradation products of TRP have been linked to depression in the general population and other medical settings [11–13]. Examining racial differences in the association of inflammatory markers and TRP with depressive symptoms may help to clarify the differences in the prevalence of depressive symptoms between ethnic groups, but may also be important for adapting future treatment to different ethnic groups.

Inflammatory markers are linked to TRP and its degradation products through the inducible enzyme indoleamine 2,3-dioxygenase (IDO). IDO expression is induced by pro- inflammatory cytokines and degrades TRP into KYN [14,15] (Supplementary Fig. 1). As TRP is a precursor of the neurotransmitter serotonin (5-HT), degradation of TRP into KYN reduces the availability of TRP for the conversion to 5-HT [16]. A low concentration of 5-HT increases the susceptibility to develop depressive symptoms [17,18]. Degradation products of KYN, in particular quinolinic acid (QA) and 3-hydroxykynurenine (3-OH-KYN), are potentially neurotoxic and may additionally contribute to the development of depressive symptoms [19]. Therefore, TRP degradation along the kynurenine pathway is one of the presumed mechanisms linking inflammation and depression [20].

The aims of this study were as follows: 1) To determine whether the association between inflammatory markers and depressive symptoms differs between white and non-white chronic dialysis patients; 2) to determine whether the association between TRP/TRP degradation products and depressive symptoms differs between white and non-white chronic dialysis patients; and 3) to determine whether TRP degradation along the KYN pathway explains the association between inflammatory markers and depressive symptoms in both white and non-white patients. In addition, we were interested in examining whether there were differences in the concentrations of TRP and TRP degradation products between white and non-white chronic dialysis patients.

2. Materials and methods

2.1. Study design

We analyzed data of the DIVERS study (Depression related factors in dialysis patients with Various Ethnicities and Races Study), an observational, prospective multiracial cohort study performed in chronic dialysis patients in four urban teaching hospitals and one university hospital in the Netherlands.

Patients were eligible for the DIVERS study if they were ≥ 18 years of age, underwent dialysis treatment (either hemodialysis or peritoneal dialysis) for at least 90 days, were able to complete a questionnaire in either Dutch or English, and had no cognitive impairments (e.g. dementia). Hemodialysis patients were approached for study participation during dialysis treatment, and peritoneal dialysis patients were approached during an outpatient appointment. Both prevalent and incident dialysis patients were included, respectively between June 2012 and December 2013 and between June 2012 and December 2014. All patients gave written informed consent before inclusion. The DIVERS study was approved by the medical ethical committees of all participating centers. The study was carried out in accordance with the Helsinki declaration of 1975, as revised in 2008.

The baseline assessment consisted of completion of a questionnaire and a blood sample, which was drawn before dialysis in hemodialysis patients and at a visit to the outpatient clinic in peritoneal dialysis patients. For the current analysis, patients were included in case of complete data on inflammatory markers (HsCRP, IL-1β, IL-6, IL-10, TNFα) and TRP degradation (TRP, KYN and 3-OH-KYN), and returned questionnaires.

2.2. Demographic and clinical characteristics

Data on socio-demographic characteristics were collected through a questionnaire: marital status, having children (yes/no), educational level, employment (yes/no), smoking (yes/no), alcohol use (yes/no), and ethnicity.

The following data were collected from electronic medical records: age, gender, dialysis modality, dialysis vintage (months on dialysis), Body Mass Index (BMI), primary kidney disease using the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) codes [21] (Diabetes Mellitus, Glomerulonephritis, Renal vascular disease, and other), comorbidities (classified according to the Davies comorbidity index [22], indicating no, intermediate or severe comorbidity), anti-depressant use (yes/no), and residual diuresis (indicating remaining glomerular filtration rate (GFR) and defined as a urine production of > 100 mL per day).

2.3. Race

Race was determined based on the country of birth of the patient's parents and classified into the categories white or non-white. All patients originating from European countries were considered whites. Patients were considered non-whites if they originated from Sub-Saharan Africa, North-Africa/Western Asia (including Morocco and Turkey), South Asia/South-East Asia, and South-America/Caribbean. Surinamese patients were classified according to the country of birth of their grandparents [23]. The use of country of birth as indicator of ethnicity is a standard approach in the Netherlands [23]. It is particularly useful in the Netherlands because most immigrants are first generation immigrants due to the short immigration history of the country (late 1970s and early 1980s) [23].

2.4. Depressive symptoms

Depressive symptoms were measured with the Beck Depression Inventory (BDI) [24]. The BDI consists of 21-items measuring symptoms of depression over the preceding two weeks. Items are scored on a 0–3 scale, and summed scores range from 0 to 63, with higher scores indicating more severe depressive symptoms. This questionnaire was validated in the ESRD population of one of the participating centers of this study [25]. A cut-off point of 13 was determined for the detection of depression, with a sensitivity of 0.75 and specificity of 0.90. We only used this cut-off point for descriptives (Table 1) to determine the prevalence of depressive symptoms in both white and non-white patients.

2.5. Inflammatory markers

We collected peripheral blood before dialysis in anticoagulant-free EDTA tubes. All samples were immediately centrifuged at 1200*g* for 10 min and serum was stored in aliquots at − 80 °C until analysis. The Department of Rheumatology & Clinical Immunology (University Medical Center Groningen, the Netherlands) determined pro-inflammatory cytokines (HsCRP, IL-1β, IL-6, and TNF-α) and the anti-inflammatory cytokine (IL-10) by using the Magnetic Luminex Screening or Performance assay (R & D Systems, Abingdon, UK) according to the manufacturer's instructions. Samples were measured using Luminex 100 System (Luminex, Austin, Tx, USA), and data were analyzed with StarStation software, version 2.3 (AppliedCytometry, Birmingham, UK).

2.6. Tryptophan and kynurenine

TRP, KYN and 3-OH-KYN concentrations were measured by the University Medical Center Groningen, the Netherlands (Department of Laboratory Medicine), using an automated online solid-phase extraction-liquid chromatographic-tandem mass spectrometric (XLC-MS/MS) method with deuterated internal standards, according to described methods [26]. We determined IDO-activity (tryptophan degradation) by calculating the KYN/TRP ratio × 10 [4] (Kyn/TRP ratio).