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Gray matter volume and white matter lesions in chronic kidney disease: exploring the association with depressive symptoms

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ABSTRACT

Objective: Chronic kidney disease (CKD) is associated with structural brain damage and with a high prevalence of depression. We therefore investigated structural brain alterations in both gray and white matter in CKD patients, focusing on depression-related (frontal–subcortical) regions.
Method: This cross-sectional MRI study in 24 CKD patients and 24 age- and sex-matched controls first tested whether CKD was associated with regionally lower gray matter (GM) volumes and more severe white matter lesions (WMLs). In exploratory subanalyses, we examined whether differences were more pronounced in CKD patients with depressive symptoms.
Results: CKD patients showed lower global GM volume ($P = .04$) and more severe WMLs ($P = .04$) compared to controls. In addition, we found substantial clusters of lower GM in the bilateral orbitofrontal-cortex for CKD patients, which were however nonsignificant after proper multiple-comparison correction. In exploratory analyses for depressed CKD patients, reduced GM clusters were mainly detected within the frontal lobe. WML severity was unrelated to depression.
Conclusion: CKD was characterized by differences in brain structure. Although subthreshold, lower GM volumes were observed in depression-related brain areas and were more pronounced for depressed patients. There is a need for replication in larger and longitudinal studies to investigate whether WMLs and regional GM reductions may render CKD patients more susceptible for depression.

1. Introduction

Depression is common in patients with chronic kidney disease (CKD). More than a quarter of patients with CKD have elevated depressive symptoms, which is as much as 40% in the most advanced stage of CKD (Stage 5) [1]. CKD is associated with a high burden of somatic symptoms, disability and reduced quality of life [2,3], predisposing patients to depression [4].

CKD is also an established risk factor for cerebrovascular disease and subclinical brain changes visualized on MRI, such as white matter lesions (WMLs), reduced white matter (WM) integrity, gray matter (GM) atrophy and hypo-perfusion [5–7]. These abnormalities can be caused by toxic processes and ischemia resulting from a range of underlying processes associated with CKD, such as chronic hypertension, uremia, inflammation and vascular calcification [8–10]. Furthermore, hemodialysis (HD) treatment can alter tissue hydration and/or perfusion, which could have additional damaging effects on the brain [10,11]. Brain alterations associated with CKD may be partly responsible for the high prevalence of depression in patients with CKD [6,7,12,13].

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The vascular depression hypothesis proposes that disruption of frontal–subcortical networks, due to cerebrovascular disease, may lead to depressive symptoms [14,15]. A late age at onset of depression, the presence of cardiovascular risk factors and cerebrovascular abnormalities are proposed characteristics of this vascular depression subtype. Some recent meta-analyses including longitudinal and cross-sectional studies in the elderly and in patients with a recent stroke showed that the presence of WMLs was associated with depressive symptoms [16,17]. In addition, reduced GM volumes within the frontal and limbic areas are suggested to play a role in the pathophysiology of depression later in life [18].

Although both depression and structural brain alterations are common in patients with CKD, very few studies have evaluated whether brain changes in patients with CKD are related to depressive symptoms. Nevertheless, some studies that focused on perfusion — using single photon emission computed tomography — in patients with CKD Stages 4 and 5 (no dialysis), observed perfusion changes in depression-related brain areas [e.g., the orbitofrontal cortex (OFC)], which were associated with depressive symptoms [19]. To our knowledge, no studies so far focused on the relation between brain structure and depression in the context of CKD. Volumetric neuroimaging studies in CKD patients most consistently reported lower GM volumes in structures within the frontal and temporal lobes, such as in the hippocampus, OFC and the cingulate cortex [5,12,20,21]. Interestingly, these regions have also been found to be reduced in depressed patients [18]. Abnormalities in these regions may therefore play a role in the association between CKD and depression. Of note, CKD has been associated with diffusely reduced GM volumes, including regions that have not specifically been associated with depression as well [12]. As much as 30–70% of CKD patients are reported to have WMLs [22–24]. Some studies suggested that lesion severity (number and size) and lesion localization (frontal–subcortical) are of importance in the association between WMLs and depression in late life [25–27]. To date, none of the existing studies that reported on the presence and severity of WMLs in CKD patients examined the localization of WMLs [22–24,28,29].

The aim of the present study was to compare GM volumes and the presence and severity of WMLs in patients with CKD to persons without CKD. We specifically examined whether depression-related areas (i.e., frontal–subcortical) were affected. We hypothesize that differences will be more pronounced in patients with depressive symptoms; this was examined in exploratory subanalyses.

2. Material and methods

2.1. Participants

MRI data of 24 patients with CKD Stages 4 and 5 (mean age, 59 years; 21% female), and 24 age- and sex-matched control participants (mean age, 57 years; 29% female) were derived from the Depression In the Picture (DIP) study. CKD patients were recruited at the University Medical Center Groningen, Martini Hospital Groningen and Dialysis Center Groningen. Healthy control participants were recruited by means of advertisements at public places and in local newspapers.

Participants of the DIP study had to be older than 18 years. CKD patients had to be in Stage 4 or 5 (glomerular filtration rate <30 mL/min/1.73 m^2), either predialysis or receiving HD or peritoneal dialysis (Stage 5D). General exclusion criteria were MRI incompatibility, cerebrovascular accidents (CVA) and past or current psychiatric diagnoses other than depressive and anxiety disorders, as these potentially confound results. Specific exclusion criteria for the control group were a diagnosis of CKD or cardiovascular disease (myocardial infarction, heart failure, CVA, serious stenosis of a major vessel); Beck Depression Inventory (BDI) score ≥ 10; and past or current diagnosis of depressive or anxiety disorder. Furthermore, depressed CKD patients with concrete suicidal plans and currently nondepressed CKD patients with a history of depressive or anxiety disorders were excluded. The study protocol was approved by the local Medical Ethics Committee, and all participants gave written informed consent before entering the study.

2.2. Measurements

All participants were assessed for depressive symptoms using the Beck depression inventory-II (BDI-II), which consists of 21 items [30]. When CKD patients had at least mild symptoms of depression (BDI>13), they were considered to have elevated depressive symptoms ($N=10$) [31]. The reason for setting different BDI thresholds for CKD and healthy controls is that CKD patients generally have higher BDI scores due to somatic symptoms. Excluding patients with a BDI≥10 may therefore result in a selection bias towards relatively healthy patients in the nondepressed group. Further, 13 is the upper limit for a low depression score according to the BDI-II manual, and thus, this is a natural way to split the total sample of CKD patients in two halves. In addition, psychiatric diagnoses were established using the semistructured psychiatric interview Mini-Schedules for Clinical Assessment in Neuropsychiatry according to the *Diagnostic and Statistical Manual of mental disorders, fourth edition* (*DSM-IV*) criteria [32], administered by trained interviewers. Demographic variables and the presence of hypertension and diabetes were assessed by a self-report inventory. For CKD patients, presence of hypertension and diabetes and laboratory values were also obtained from medical records.

2.3. Data acquisition

Participants underwent an MRI scan in a 3-Tesla MRI scanner, with a SENSE 32-channel head coil (Philips Intera, Best, NL, USA). A three-dimensional gradient-echo T1-weighted sequence was used to acquire anatomical images (170 slices; TR = 9 ms; TE = 3.6 ms; matrix = 256×231; voxel size = 1×1×1 mm; scan duration = 4:11 min). In addition, T2-weighted FLAIR scans were used (180 slices; TR = 8000 ms; TE = 355 ms; matrix = 256×255; voxel size = 1×1×1 mm; scan duration = 4:56 min).

2.4. Data preprocessing voxel based morphometry (VBM) analyses

Statistical Parametric Mapping software (SPM12), implemented in Matlab 7.8.0, was used to preprocess and analyze the MRI data. First, the images were manually reoriented to the anterior commissure. Then, the standard segmentation option in SPM12, with the "light clean-up" setting, was used to segment the images into GM, WM, cerebrospinal fluid, skull and soft tissue outside the brain. Diffeomorphic Anatomical Registration Trough Exponentiated Lie (DARTEL) algebra was used for normalization and modulation of the images. All individual deformation fields were registered to a DARTEL template, created based on the deformation fields produced during the segmentation procedure. After this, they obtained deformed images were used to generate smoothed, spatially normalized and Jacobian-scaled gray and white images in Montreal Neurological Institute (MNI) space. To increase the signal-to-noise ratio, the GM and WM images were smoothed using an 8-mm full-width-half-maximum Gaussian kernel. Voxels were resampled into 1.5×1.5×1.5 mm.

2.5. WMLs rating scale

Periventricular and subcortical WMLs (scWML) were counted if visible as hyperintense on T2-weighted images and isointense on T1-weighted images. We used the same scoring method as de Groot et al. used previously [33]. When the WML was adjacent to the lateral ventricle, it was considered as periventricular, otherwise as subcortical. Periventricular WMLs (pvWML) were scored for three separate regions: adjacent to the frontal horns (frontal caps); lateral walls (bands); and occipital horns (occipital caps). The severity for each region was determined based on a scale ranging from 0 to 3 (0 = *none*; 1 = *pencil thin*;