Original Paper

Evaluation of Mental Disorders Using Proton Magnetic Resonance Spectroscopy in Dialysis and Predialysis Patients

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Key Words

Chronic kidney disease • Mental disorders • Proton magnetic resonance spectroscopy • Dialysis • Brain

Abstract

Background/Aims: Psychological complications are prevalent in patients with chronic kidney disease (CKD). This study aimed to investigate mental disorders in stage 4-5 CKD patients, to detect metabolite concentrations in the brain by proton magnetic resonance spectroscopy (¹H-MRS) and to compare the effects of different dialysis therapies on mental disorders in end-stage renal disease (ESRD). **Methods:** The sample population was made up of predialysis (13), hemodialysis (HD) (13), and peritoneal dialysis (PD) patients (12). We collected the baseline data of patients' age, sex, hemoglobin (Hb) and parathyroid hormone (PTH) levels. The predialysis patients served as the control group. The psychological status of the three groups was assessed using three psychological scales. ¹H-MRS was used to evaluate the relative metabolite concentrations in the bilateral amygdala, hippocampus and unilateral anterior cingulate cortex (ACC). **Results:** The psychological status was better in HD patients than in predialysis and PD patients. ¹H-MRS alterations were predominantly found in the ACC. Choline-containing compounds relative to creatine (Cho/Cr), myo-inositol relative to creatine (MI/Cr) and glutamate and glutamine relative to creatine (Glx/Cr) in the ACC were higher in HD patients. ¹H-MRS results were correlated with the baseline data and the scores of psychological scales. **Conclusions:** CKD patients showed different types of mental disorders as well as metabolite disturbances in the brain. The metabolite concentrations correlated with the psychological status which was better in HD than in predialytic and PD patients.

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Introduction

Chronic kidney disease (CKD) is a highly prevalent disease with an about 10% morbidity rate worldwide [1]. The psychological complications associated with CKD contribute greatly to a poor quality of life, cardiovascular diseases, and increased mortality rate. Previous studies reported associations between poor mental health and cardiac death in dialysis patients [2, 3]. Psychological complications related to CKD are characterized by depression, anxiety, cognitive impairment, fatigue, impaired concentration, memory decline and sleep disturbances. However, these manifestations are usually ignored by clinicians. Depression is one of the most widely acknowledged psychological disorders among CKD patients [4, 5]. About 28% of predialysis patients suffer from major depression and the morbidity is also high in dialysis patients [6]. Another common problem is anxiety, which is inversely proportional to the quality of life [7]. Clinical variables such as age, residual renal function, comorbidities and uremic symptoms are identified to be closely related to anxiety in CKD patients [8]. However, little is understood about the relationship between psychological complications and alterations of metabolites concentrations in specific regions of the brain. Emerging evidence has shown that structural and metabolic alterations in specific brain regions are related to emotional and mental modulation. Increased activation of limbic and paralimbic areas, such as the ACC, hippocampus and amygdala, has been proved to be associated with major depressive disorder [9, 10]. Neurobiological experiment has demonstrated an excessive activity of the ACC in obsessive compulsive disorder (OCD) patients when making conflicting options [11]. The reward/avoidance circuitry of the basal ganglia and the fear circuitry of the amygdala both play a role in the development of social anxiety disorder [12, 13]. The ACC, as a part of cortical regions, is included in the reward/avoidance basal ganglia circuitry [14]. Hippocampus is known to be involved in mnemonic processes. The dorsal hippocampus has spatial navigational functions and the ventral hippocampus is associated with anxiety and context fear learning [15, 16]. Taken together, we chose unilateral ACC, bilateral amygdala, and hippocampus as the major brain regions for this study. Proton magnetic resonance spectroscopy (^1H -MRS), a noninvasive and quantitative technique that utilizes magnetic resonance and chemical shift to determine concentrations of chemicals and macromolecules, has been increasingly applied to investigate metabolites in specific regions of the brain *in vivo* [17, 18]. ^1H -MRS has been used to evaluate metabolites such as N-acetyl Aspartate (NAA), choline-containing compounds (Cho), creatine (Cr), myo-inositol (MI), glutamate and glutamine (Glx) in psychological disorders including depression, anxiety and OCD. Previous studies detected a decreased level of Glx in the anterior brain regions in acute depressed patients [19, 20], a decreased MI/Cr ratio in the left orbitofrontal region and an increased concentration of Cho in the left and right thalamic nuclei of OCD patients [21, 22]. However, research on the application of ^1H -MRS to assess psychological dysfunctions in CKD patients is limited. Therefore, our study aimed to explore the neuropsychological complications in CKD patients with the method of ^1H -MRS.

Materials and Methods

Subjects

We recruited 13 predialysis patients, 13 HD patients and 12 peritoneal dialysis (PD) patients with ages ranging from 27 to 74 years old, from the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, from July 2015 to September 2016, in this study. Inclusion criteria: (i) 18 to 80 years old inpatients; (ii) Dialysis age over one month or predialysis patients with stage 4-5 CKD; (iii) No cognition-interference factors (color blind, deaf, disabled upper limbs, or poor general condition); (iv) Written informed consent. Exclusion criteria: (i) Diagnosed with intracranial tumor; (ii) Diagnosed with non-atherosclerotic cerebrovascular disease (e.g. vasculitis); (iii) Diagnosed with metabolic encephalopathy such as hepatic encephalopathy and pulmonary encephalopathy; (iv) Diagnosed with

epilepsy requiring long-term medication; (v) Alcohol or other drugs addiction; (vi) Cardiac pacemakers, other electrodes or magnetic substances implanted or aneurysm clip *in vivo* or metal foreign bodies in the eye. The study protocol was approved by the Ethics Committee of Huazhong University of Science and Technology. All participants signed consents after detailed explanation of the study. Age, sex, hemoglobin (Hb, g/L), parathyroid hormone (PTH, pg/ml) were collected as the baseline data.

Psychological assessments

Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS) [23] and Symptom Checklist 90 (SCL 90) were used to assess the psychological status. According to Chinese norm, total score of SDS can be divided into 4 grades: normal (<53 points), mild depression (53-62 points), moderate depression (63-72 points) and severe depression (>72 points). Total score of SAS can be divided into 4 grades: normal (<50 points), mild anxiety (50-59 points), moderate anxiety (60-69 points) and severe anxiety (>70 points). Ten subscales of SCL 90 are F1 Somatization, F2 OCD, F3 Interpersonal sensitivity, F4 Depression, F5 Anxiety, F6 Hostility, F7 Phobophobia, F8 Paranoia, F9 Psychopathy, and F10 Others (sleeping and diet). A total score of SCL 90 over 160 points or numbers of positive factors over 43 or any subscale over 2 points is defined as positive.

MRS methodology

¹H-MRS was performed on a GE 750W 3.0T scanner with a 16-channel head-neck combined coil after the conventional magnetic resonance imaging examination. The patients laid flat on the examining table with their heads fixed during the scanning. Three-dimensional multi-voxel spectroscopy (Repetition time = 1000 ms, Echo time = 144 ms, Acquisition time = 8 min, voxel = 12 × 20 × 20 mm) was used for the bilateral amygdala and hippocampus. Single voxel spectroscopy (Repetition time = 1500 ms, Echo time = 35 ms, Acquisition time = 3 min, voxel = 20 × 20 × 20 mm) was used for the unilateral ACC. A rapid automated shimming method was conducted by the machine. After water suppression and tuning, ¹H-MRS spectra were obtained and directly analyzed by Functool 9.4.05 software in the GE Medical System.

Statistical analysis

All data were analyzed by IBM SPSS statistic 22.0. A two-sided probability value of $P < 0.05$ was considered as statistically significant. Analysis of variance (ANOVA) followed by Student-Newman-Keuls-q (SNK-q) test was used to analyze the differences between the three groups. Spearman's test was performed for correlation analysis.

Results

High prevalence of psychological disorders in CKD patients

Depression and anxiety were quite common in our CKD patients. The patients mainly suffered from mild to moderate depression or mild anxiety. The prevalence of depression in predialysis, HD and PD patients was 84.62%, 84.62%, and 83.33% (Fig. 1A, 1B, 1C), while the prevalence of anxiety was 15.38%, 15.38%, and 58.33% (Fig. 1D, 1E, 1F), respectively.

The total score of SDS ($P = 0.58$) and SAS ($P = 0.15$) was not statistically different between the predialysis, HD and PD

Table 1. Characteristics of all patients. HD = hemodialysis; PD = peritoneal dialysis; Hb = hemoglobin; PTH = parathyroid hormone. * $P < 0.05$ Predialysis patients vs. HD patients. ** $P < 0.05$ HD patients vs. PD patients.

Baseline data	Predialysis, n=13	HD, n=13	PD, n=12
Age			
Range	27-65	27-64	27-57
Mean	41.0 ± 11.9	51.1 ± 10.9	42.0 ± 11.4
Sex			
Female	7	5	6
Male	6	8	6
Hb (g/L)			
Range	66-126	63-128	81-110
Mean	88.9 ± 15.4*	107.2 ± 18.1	94.7 ± 9.2**
PTH (pg/ml)			
Range	52-862	2.7-1230	49.2-1304
Mean	295.2 ± 260.1	473.3 ± 363.2	501.5 ± 340.4

patients (data not shown). The positive rate of SCL 90 was 31.58%. The positive items of SCL 90 scale varied from F1 Somatization to F9 Psychopathy. There were significant differences between predialysis and HD patients in F2 OCD (1.76 ± 0.16 vs. 1.26 ± 0.07 , $P < 0.05$), F3 Interpersonal sensitivity (1.54 ± 0.16 vs. 1.18 ± 0.06 , $P < 0.05$), F5 Anxiety (1.56 ± 0.13 vs. 1.22 ± 0.04 , $P < 0.05$), F8 Paranoia (1.47 ± 0.14 vs. 1.09 ± 0.05 , $P < 0.05$) and F9 Psychopathy (1.53 ± 0.19 vs. 1.22 ± 0.06 , $P < 0.05$) (Fig. 2), suggesting a relatively less disordered psychological symptoms such as OCD, interpersonal sensitivity, anxiety, paranoia, and psychopathy in HD patients. SCL 90 results between HD and PD patients were not significantly different, although the mean score was lower in HD patients than in PD patients. In addition, the three groups didn't differ in age, sex, and PTH levels. The mean level of Hb was higher in HD patients than in predialysis and PD patients ($P < 0.05$, Table1). No correlations between the results of psychological scales and the baseline data (age, sex, Hb and PTH levels) were found (data not shown).

Fig. 1. Depression and anxiety are prevalent in CKD patients. Positive rates of SDS in predialysis patients (A), HD patients (B) and PD patients (C). Positive rates of SAS in predialysis patients (D), HD patients (E) and PD patients (F). HD = hemodialysis; PD = peritoneal dialysis; Data are shown as percentages.

Elevated ratios of Cho/Cr, MI/Cr and Glx/Cr in the ACC were found in HD patients

Differences of Cho/Cr in the ACC mainly existed between predialysis and HD patients (0.98 ± 0.06 vs. 1.14 ± 0.04 , $P < 0.05$), as well as between HD and PD patients (1.14 ± 0.041 vs. 0.98 ± 0.07 , $P < 0.05$) (Fig. 3A). Differences of MI/Cr in the ACC mainly existed between predialysis and HD patients (0.62 ± 0.02 vs. 0.68 ± 0.02 , $P < 0.05$), as well as between HD and PD patients (0.68 ± 0.02 vs. 0.60 ± 0.02 , $P < 0.05$) (Fig. 3B). Difference of Glx/Cr in the ACC was found between predialysis and HD patients (2.64 ± 0.10 vs. 2.94 ± 0.09 , $P < 0.05$) (Fig. 3C). In summary, these results suggested higher ratios of Cho/Cr, MI/Cr and Glx/Cr in the ACC in HD patients than in predialysis and PD patients.

Correlations between the relative concentrations of metabolites in the brain and the baseline data

MI/Cr in the right amygdala was positively correlated with age ($r = 0.350$, $P = 0.034$) (Fig. 4A). NAA/Cr in the left amygdala was positively correlated with Hb ($r = 0.359$, $P = 0.027$) (Fig. 4B). No correlations between ^1H -MRS results and sex or PTH were found (data not shown).

Correlations between the relative concentrations of metabolites in the brain and the scores of psychological scales

MI/Cr in the left amygdala was negatively correlated with SDS total score ($r = -0.370$, $P = 0.022$) (Fig. 5A). Cho/Cr in the right amygdala was positively correlated with F2 OCD ($r = 0.322$, $P = 0.048$), F5 Anxiety ($r = 0.381$, $P = 0.018$) and F9 Psychopathy ($r = 0.436$, $P = 0.006$) (Fig. 5B, 5C, 5D).

Fig. 2. Positive items of SCL 90 in CKD patients. Significant difference of F2 OCD (A), F3 Interpersonal sensitivity (B), F5 Anxiety (C), F8 Paranoia (D) and F9 Psychopathy (E) between predialysis and HD patients. HD = hemodialysis; OCD = obsessive compulsive disorder; PD = peritoneal dialysis; Data are presented as means $\pm$ SEM. * $P < 0.05$ Predialysis patients vs. HD patients.

Discussion

Psychological disorders with the symptoms of depression and anxiety are quite prevalent in CKD patients. Compared to HD patients, predialysis patients suffered more in OCD, interpersonal sensitivity, anxiety, paranoia, and psychopathy. These are consistent with a previous study showed that predialysis patients had high prevalences of depression and anxiety, which were associated with reduced quality of life [24]. Due to the transition state, the fears, uncertainties, and desperation experienced by predialysis patients may explain why they mostly suffer from the mental disorders. These results strongly suggest the necessity of strengthening human concern and psychological counsel to CKD patients, especially predialysis patients.

In our ^1H -MRS studies, we identified relatively higher levels of Cho/Cr, MI/Cr and Glx/Cr in the ACC in HD patients compared to predialysis and PD patients. Cho, as a cell membrane precursor and breakdown product, contributes to neural membrane synthesis and catabolism [25]. Increase of Cho peak in ^1H -MRS is attributed to accelerated turnover of

membrane phospholipids or neurodegeneration [26]. Our study may suggest an enhanced membrane turnover and cellular signal transduction in the ACC in HD patients. Similarly, MI/Cr in the ACC was elevated in HD patients, as was observed with Cho/Cr. MI, serving as an osmolyte involved in neuronal energy supply, is abundant in glial cells. MI and its related compounds play a significant role in intracellular second messenger transduction, as MI is a key metabolic precursor in the phosphoinositide second messenger cycle. Increased MI suggests glial cells proliferation while decreased MI suggests damage to glial cells or neurodegeneration [27]. Our study finds a better function of glial cells in the ACC in HD patients. Also, an ascending trend of Glx/Cr in the ACC in HD patients was found, implying that HD patients might have better functions of excitatory neurotransmitter than predialysis and PD patients in the ACC. Glx refers to glutamate and glutamine. Glutamate is one of the major excitatory neurotransmitters in the brain. Elevated level of Glx/Cr in HD patients may be associated with better glucose metabolism [28, 29], which helps to maintain a more stable environment for the brain.

Fig. 3. Elevated ratios of Cho/Cr, MI/Cr, Glx/Cr in the ACC are found in HD patients. Significant difference of Cho/Cr in the ACC between predialysis and HD patients, HD and PD patients (A). Significant difference of MI/Cr in the ACC between predialysis and HD patients, HD and PD patients (B). Significant difference of Glx/Cr in the ACC between predialysis and HD patients (C). ACC = anterior cingulate cortex; Cho = choline-containing compounds; Cr = creatinine; Glx = glutamate and glutamine; HD = hemodialysis; MI = myo-inositol; PD = peritoneal dialysis. Data are presented as means $\pm$ SEM. * $P < 0.05$ Predialysis patients vs. HD patients. # $P < 0.05$ HD patients vs. PD patients.

Fig. 4. Relative concentrations of metabolites in the brain are positively correlated with age and Hb. MI/Cr in the right amygdala is positively correlated with age (A). NAA/Cr in the left amygdala is positively correlated with Hb (B). Cr = creatinine; MI = myo-inositol; NAA = N-acetyl aspartate; Hb = hemoglobin.

Fig. 5. Relative concentrations of metabolites in the brain are correlated with the scores of psychological scales. MI/Cr in the left amygdala is negatively correlated with SDS total score (A). Cho/Cr in the right amygdala is positively correlated with F2 OCD (B), F5 Anxiety (C) and F9 Psychopathy (D). Cho = choline-containing compound; Cr = creatine; MI = myo-inositol; OCD = obsessive compulsive disorder; SDS = Self-rating Depression Scale.

Increasing evidence indicates that mental disorders, such as depression, are associated with dysfunction of the excitatory neurotransmitters glutamate [19].

Besides, MI/Cr in the right amygdala was positively correlated with age. Early study reported an increase of MI/Cr in mild cognitive impairment [30] and MI/Cr level was associated with dementia stages [31]. Accordingly, previous studies reported cognitive ability declined on an average rate of 0.04 standardized units per year [32]. Variables such as concentrations of brain metabolites, regional brain volume, and cortical thickness were associated with age-related decline of cognition [33, 34]. Based on these data, we conclude that elevated MI/Cr might be involved in aging-related cognition impairment.

Furthermore, we found a positive correlation between NAA/Cr in the left amygdala and Hb. NAA has been described as a neuronal marker. An increase of NAA in the left amygdala is considered as a functional enhancement and/or an increased density of neuronal cells [35] or improved osmolytic situations in the neuronal environment [36]. Anemia may affect the function of the brain by injuring neuronal cells. Former studies conducted in HD patients showed that anemia resulted in impaired cognition, and correction of renal anemia with erythropoietin improved not only the quality of life but also cognition and depression [37]. The underlying mechanism might be an enhanced delivery of oxygen to subcortical and frontotemporal brain structures, which are associated with mental disorders [38]. Previous studies found a significant decreased NAA concentration in the left amygdala and bilateral orbito-frontal cortex in the children with autism spectrum disorders, and the level of NAA was correlated with the social quotient of these autistic children. Further, oxygenated-Hb, measured by near-infrared spectroscopy machine, was significantly lower in the same areas of the brain. After imitation of emotional facial expression, the oxygenated-Hb level was elevated [39]. In summary, anemia in CKD patients may result in dysfunction or decreased density of neural cells because of decreased oxygen supply to the brain. In addition, the mean level of Hb was higher in HD patients than in predialysis and PD patients, which may be attributed to the normatively use of erythropoietin in HD patients.

Next, we found a negative correlation between MI/Cr in the left amygdala and depression. Similarly, a previous study discovered a relatively lower level of MI/Cr in the frontal white matter in acute depression [40]. Another study found elevated levels of MI and MI/Cr in the ACC in fully recovered depressed patients [41]. Lower MI/Cr may reflect dysfunction of glial cells in the left amygdala in CKD patients with mental disorders. Also, alteration of Cho concentrations in the brain may relate to psychological symptoms. Studies reported that Cho in the left thalamus was significantly correlated with social anxiety and its related symptoms [42]. Elevated levels of Cho were found in the ACC of patients with schizophrenia [43] and in the dorsolateral prefrontal cortex of patients with major depressive disorder [44]. Consistent with previous studies, Cho/Cr in the right amygdala was positively correlated with OCD, anxiety and psychopathy in our study, which might suggest a pathophysiological basis of changed Cho/Cr in the right amygdala in mental disorders of CKD patients.

It is noteworthy that our study didn't find a significant change of NAA in the amygdala, hippocampus and ACC in CKD patients with psychological disorders. Some studies reported no changes of NAA in depressed patients with antidepressant therapy for several weeks [45, 46], whereas others found an increase of NAA in the dorsolateral prefrontal cortex of the brain after therapy [47, 48]. Further studies with a wider range of brain structures and a larger sample size may be needed to obtain a definite answer about the changes of NAA in mental disorders. In addition, we didn't find any association between F4 Depression and changes of metabolites in the brain although depression is quite prevalent in CKD patients. The mean value of F4 Depression was 1.52 ± 0.55 whereas the point of a factor over 2 was considered as positive. The depressed symptom assessed by SCL 90 might be so slight that the changes of the metabolite could not be detected by ^1H -MRS.

Our study has several limitations: a relatively small sample size was the major limiting problem, as usually has occurred in previous studies. Another limitation was the lack of an age-matched healthy control. The use of the multiple-voxel method enabled accurate localization but limited findings in restricted regions. Also, to obtain a stable baseline, long Echo time in three-dimensional multi-voxel spectroscopy scanning was used, however, it may be inadequate to analyze the data of MI and Glx. In addition, this study could not provide a causal link between psychological symptoms and changes of metabolites. Finally, all the data were presented as the concentrations of metabolites relative to Cr, which were conventional but limited. It is possible that the absolute concentration of Cr was decreased or increased while the absolute concentrations of other metabolites were unchanged. Future studies may reference the concentrations of metabolites to tissue water to avoid the potential confounding effect of Cr.

Conclusion

The present study reported the psychological status of predialysis and dialysis patients by combining the psychological scales with ^1H -MRS technology to elucidate the pathological changes of metabolites in different regions of the brain. HD therapy showed benefits on patients' mental status. Further studies are required for larger samples clarifying the relationship between the mental status and the changes of metabolites in the brain of CKD patients.

Disclosure statement

The authors declare that there is no Disclosure Statements regarding the publication of this paper.

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