Neurological, psychological, and cognitive disorders in patients with chronic kidney disease on conservative and replacement therapy

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Abstract
Chronic kidney disease (CKD) is a highly prevalent condition in the world. Neurological, psychological, and cognitive disorders, related to CKD, could contribute to the morbidity, mortality, and poor quality of life of these patients. The aim of this study was to assess the neurological, psychological, and cognitive imbalance in patients with CKD on conservative and replacement therapy. Seventy-four clinically stable patients affected by CKD on conservative therapy, replacement therapy (hemodialysis (HD), peritoneal dialysis (PD)), or with kidney transplantation (KT) and 25 healthy controls (HC), matched for age and sex were enrolled. Clinical, laboratory, and instrumental examinations, as renal function, inflammation and mineral metabolism indexes, electroencephalogram (EEG), psychological (MMPI-2, Sat P), and cognitive tests (neuropsychological tests, NPZ5) were carried out.

The results showed a significant differences in the absolute and relative power of delta band and relative power of theta band of EEG (P < 0.001, 0.016, 0.001, P = 0.051), a positive correlation between relative power of delta band and C-reactive protein (CRP) (P < 0.001) and a negative correlation between estimated glomerular filtration rate (eGFR) (P < 0.001) and 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) (P < 0.001), in all the samples. Qualitative analysis of EEG showed alterations of Grade 2 (according to Parsons–Smith classification) in patients on conservative therapy, and Grade 2–3 in KT patients. The scales of MMPI-2 hysteria and paranoia, are significantly correlated with creatinine, eGFR, serum nitrogen, CRP, 1,25-(OH)2D3, intact parathyroid hormone (iPTH), phosphorus, and cynical and hysterical personality, are correlated with higher relative power of delta (P = 0.016) and theta band (P = 0.016). Moreover, all NPZ5 scores showed a significant difference between the means of nephropathic patients and the means of the HC, and a positive correlation with eGFR, serum nitrogen, CRP, iPTH, and vitamin D.

In CKD patients, simple and noninvasive instruments, as EEG, and cognitive-psychological tests, should be performed and careful and constant monitoring of renal risk factors, probably involved in neuropsychological complications (inflammation, disorders of mineral metabolism, electrolyte disorders, etc.), should be carried out. Early identification and adequate therapy of neuropsychological, and cognitive disorders, might enable a better quality of life and a major compliance with a probable reduction in the healthcare costs.

Abbreviations: 1,25-(OH)2D3 = 1,25-dihydroxyvitamin D3, BMI = body mass index, CAPHES = Health Examination Survey study, CKD = chronic kidney disease, CRP = C-reactive protein, Cyn = cynicism, DST = digit span test, EEG = electroencephalogram, eGFR = estimated glomerular filtration rate, ESV = erythrocyte sedimentation velocity, GCs = guanidino compounds, GPT = Grooved Pegboard Test, HC = healthy controls, HD = hemodialysis, HDL = high-density lipoprotein, Hy = hysteria, iPTH = parathormone, KDOQI = Kidney Disease Outcomes Quality Initiative, KT = kidney transplantation, LDL = low-density lipoprotein, MDRD = Modification of Diet in Renal Disease, MMPI-2 = Minnesota multiphasic personality inventory, NHANES = National Health and Nutrition Examination Survey III, NPZ5 = neuropsychological test, Pa = paranoia, PD = peritoneal dialysis, Pd = psychopathic deviate, RAVL = Rey auditory verbal learning test, SAT-P = satisfaction profile, SDMT = symbol digit modalities test, TMTT = trail-making test.

Keywords: chronic kidney disease, hemodialysis, kidney transplantation, peritoneal dialysis, quality of life
1. Introduction
Chronic kidney disease (CKD) is a highly prevalent condition and its prevalence is growing in the world. Epidemiological data derived from cardiovascular risk in renal patients of the Health Examination Survey study (CARHES) showed a prevalence of CKD in Italy of 7.5% for men and 6.5% for women, and the National Health and Nutrition Examination Survey III (NHANES III) showed that CKD is estimated at about 10% of the world population. The CKD is a clinical condition that can progress to the end-stage renal disease, with high cardiovascular morbidity and mortality, that is not fully explained by traditional risk factors, but partially explained by risk factors associated with CKD (mineral metabolism disorders, metabolic acidosis, endothelial dysfunction, inflammation, oxidative stress, etc.). Even the neurological complications related to CKD, greatly contribute to the morbidity, mortality, and poor quality of life of these patients. Neurological complications are characterized by cognitive impairment, anxiety, fatigue, apathy, clumsiness, irritability, sleep disturbances, and impaired concentration. Moreover the patient may become emotionally labile, more obviously forgetful and sluggish, make perceptual errors, and develop sleep inversion until sleep myoclonus. These patients may manifest, also, peripheral neuropathy, leading to weakness and disability, but currently these clinical manifestations are avoided by early replacement therapy. Cognitive decline is significantly associated with CKD, regardless of age and other potential confounding factors. Elia and Elia and Kurella Tamura and Wadley showed early appearance of global cognitive deficit in CKD, which progressively increases with worsening renal function, independently from other traditional risk factors. Furthermore, another fundamental aspect that has been considered in recent years is related to psychological problems, that may appear along with neurological and cognitive disorders and that significantly reduce the quality of life of these patients.

2. Aim of the study
The aim of this study was to assess the neurological, psychological, and cognitive disorders in patients with CKD (Stage 4/5 Kidney Disease Outcomes Quality Initiative (KDOQI)), in conservative and replacement therapy (hemodialysis (HD), peritoneal dialysis (PD), or with kidney transplantation (KT)) and the correlation with risk factors associated with renal disease.

3. Materials and methods
The study protocol was approved by the Clinical Research Ethics Committee of University Hospital “Policlinico Umberto I” of Rome, Sapienza University of Rome, Italy with protocol number 807/12. The study conforms to the principles outlined in the Declaration of Helsinki and we obtained a written consent from each patient before the enrollment.

3.1. Study design and subjects
We performed an observational study on 99 clinically stable patients, enrolled from December 2013 to March 2015, at the University Hospital “Policlinico Umberto I” of Rome, Sapienza University of Rome, Italy. The study included 22 patients with CKD on conservative therapy (eGFR ≤ 30 mL/min, stage 4/5 KDOQI), 15 patients on HD, 16 patients on PD, 21 patients with KT (from at least 36 months with eGFR ≥60 mL/min, in the absence of acute renal failure, without proteinuria or renal infections), and 25 healthy controls (HC) matched for age and sex. Statins, antihypertensive, antplatelet therapies, and/or therapies with calcium, calcitriol, and phosphate binders were continued in all patients included in the study. We excluded patients with heart failure, liver insufficiency, chronic obstructive pulmonary disease, cerebrovascular disease, degenerative neurological or psychiatric diseases, acute myocardial infarction, and acute coronary syndrome within 3 months before the study. Patients who refused to give consent and patients with missing data were not enrolled.

eGFR was calculated with the abbreviated Modification of Diet in Renal Disease (MDRD) formula, as defined by Levey et al. Clinical, laboratory, and instrumental examinations, and neuropsychological tests were carried out. Clinical and instrumental examinations of HD patients were performed during the middle of the week, after HD treatment, while PD patients were examined before the first replacement of the morning with an empty peritoneum at routine visits.

3.2. Anthropometric assessments
Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index (BMI) was calculated by the formula: [weight (kg)/height (m²)].

3.3. Laboratory measurements
Blood was drawn in the morning after an overnight fast of at least 12 hours. In all patients, the levels of fasting plasma glucose (mg/dL), total serum cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein (HDL) (mg/dL), serum creatinine (mg/dL), hemoglobin (g/dL), nitrogen (mg/dL), serum uric acid (mg/dL), serum calcium (mg/dL), phosphate (mg/dL), serum electrolytes (mEq/L), C-reactive protein (CRP) (mg/L), and erythrocyte sedimentation velocity (ESV) (mm/H) were measured using standard automated techniques. Serum albumin (g/dL) was determined by bromocresol purple method. Parathormone (pg/mL) was measured using a 2-site assay that measures “intact” hormone (iPTH). 1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3) (ng/mL) was measured by radioimmunoassay. Low-density lipoprotein (LDL)-cholesterol (mg/dL) was calculated using the Friedewald equation: LDL = total cholesterol – HDL – (triglycerides/5). We have evaluated routine and microscopy urinalysis and albuminuria in 24-hour urine in KT patients and calculated urea-based dialysis adequacy Kt/V (K, dialyzer clearance of urea, t, dialysis time, V, volume of distribution of urea), in particular weekly standard Kt/V (sdtKt/V) in dialysis patients. We have also assessed plasma ammonia, hemogasanalysis, and plasma concentration of immunosuppressive drugs to exclude other forms of metabolic encephalopathy or brain damage related to drug toxicity according to standard outpatient protocols. Plasma ammonia was performed using venous blood samples with ethylene diamine tetraacetic acid and to maintain the cold chain, samples were quickly delivered to the laboratory on ice. Plasma ammonia was measured by an enzymatic method using glutamate dehydrogenase (Ammonia NH3L, Cobas, Roche Diagnostics, Inc., Tokyo, Japan). Hemogasanalysis was performed using a blood gas analyzer (Nova Phox Plus C, Bollate (Mi), Italy).

3.4. Blood pressure measurements
Clinic blood pressure measurements were made three times after 10 minutes of rest in a seated position using a standard automatic
3.5. Electroencephalogram (EEG)

Electroencephalogram (EEG) recordings were performed by a digital apparatus (Micromed, Treviso, Italy) and sampled at a rate of 256/second. According to the International 10-20 System,[15] the following scalp electrodes were applied: Fp2, Fp1, F8, F7, F4, F3, C4, C3, T4, T3, P4, P3, O2, and O1. Baseline EEG tracings were recorded for 20 minutes, with eyes closed. Tracings of patients and control subjects were blindly inspected offline by 2 neurophysiologists who assessed the general organization of the EEG background activity and the prevalence and type of abnormalities. The severity of EEG changes was classified according to a modification of the Parson–Smith qualitative classification as: Grade 1 (normal EEG), Grade 2 (distinctive features of encephalopathy), and Grade 3 (signs of severe encephalopathy).[16] For the quantitative analysis, 20 artifact-free epochs each lasting 4 seconds, were randomly selected from each baseline recording. According to a procedure described elsewhere,[16,17] on these tracing epochs and from the mean values of all electrodes, the absolute (microV2) and relative (%) power in the various frequency bands (delta = 1-3.5 Hz, theta = 4-7.5 Hz, alpha = 8-12.5 Hz, beta1 = 13-19.5 Hz, and beta2 = 20-29 Hz) were calculated.[18] Main dominant frequency and median frequency were also calculated.

3.6. Neurological, psychological, and cognitive tests

All individuals completed a standardized battery of neuropsychological tests:

3.6.1. Minnesota multiphasic personality inventory (MMPI-2). The Minnesota multiphasic personality inventory-2 (MMPI-2): a standardized psychometric test of adult personality and psychopathology. MMPI-2 consists of 567 items. MMPI-2 includes 8 validity, 10 clinical, 16 additional, and 15 content categories: Factor I (Psychological functioning), Factor II (Physical functioning), Factor III (work), Factor IV (sleep/diet/free time), and Factor V (Social functioning). The questionnaire consists of 32 items, measured on a visual analog scale: the level of agreement with a statement is indicated by marking a position along a continuous line (10 cm) between 2 end-points (totally satisfied/totally dissatisfied).[20] The score range is 0 to 100, 0 = total dissatisfaction and 100 complete satisfaction.

3.6.2. Satisfaction profile (SAT-P). It is a test that provides both qualitative and quantitative self-satisfaction assessment within the health-related quality of life; the SAT-P is a self-report scale widely used in the healthcare context. The scale defines satisfaction as the result of a cognitive process that compares real with ideal expectations. Level of satisfaction is linked to the gap between real and ideal expectations. The SAT-P assesses subjective satisfaction in the preceding month using 5 macro-categories: Factor I (Psychological functioning), Factor II (Physical functioning), Factor III (work), Factor IV (sleep/diet/free time), and Factor V (Social functioning). The questionnaire

3.6.3. Neuropsychological test (NPZ5). Neurocognitive testing was administered by a designated investigator at each study site who had completed standardized training to administer the test procedures. Five domains were assessed as follows:

- Rey auditory verbal learning test (RAVL) (List A and List B) evaluates different functions: short-term auditory-verbal memory, rate of learning, learning strategies, retroactive and proactive interference, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval.
- Trail-making test (TMT) (Parts A and B) is a neuropsychological test of visual attention and change task used in clinical settings for the evaluation of cognitive deficits.
- Digit span test (DST) (forward and backward) is used to measure working memory’s number storage capacity.
- Symbol digit modalities test (SDMT) (90 and 120 seconds) is widely used because it is easy to administer, reliable, and evaluates information processing speed, including attention and visual scanning.
- Grooved Pegboard Test (GPT) (with dominant hand and with nondominant hand) is a manipulative dexterity test and it requires complete visual and motor coordination.[21]

3.7. Statistical analysis

Data management and analysis were performed using IBM SPSS Statistics 17 for Windows software and a probability value of P < 0.05 was considered to be statistically significant. All continuous variables that follow a normal distribution were expressed as mean (±standard deviation), and not normal variables were expressed as median (IQR). Categorical variables were expressed as number (percentage). Student t test or the Mann–Whitney U test (two-tailed) or ANOVA were performed to determine the differences between groups. The Chi-square test was used to compare categorical variables. The Spearman or Pearson correlation was used to determine the correlation bivariate relationship and the strength of association between variables. The groups were compared using Chi-square test, Kruskal–Wallis test, or analysis of variance. Variance inflation factor (VIF) was used to quantify the severity of multicollinearity in an ordinary least squares regression analysis. No problem of multicollinearity was identified.

4. Results

Table 1 shows the patient’s characteristics. In summary, there were no significant differences between the groups, except for values of creatinine (mg/dL) (P < 0.001), MDRD (mL/min) (P < 0.001), serum nitrogen (mg/dL) (P < 0.001), uric acid (mg/dL) (P < 0.001), potassium (mEq/L) (P < 0.001), phosphorus (mEq/L) (P < 0.001), hemoglobin (g/L) (P < 0.001), CRP (mg/L) (P < 0.001), ESV (mm/H) (P < 0.001), iPTH (pg/mL) (P < 0.001), 1,25-(OH)2D3 (ng/mL) (P < 0.001) (Table 1). The patients were receiving adequate dose of dialysis, as measured by weekly standard Kt/V (dtKt/V), that was >2 in all dialysis patients. The dosage of immunosuppressive therapy in patients with KT was in the therapeutic range in all patients (data not shown).
4.1. EEG analysis

The quantitative analysis of EEG data showed a significant difference between CKD patients and HC, of the relative and absolute power of delta band (P < 0.001, P = 0.008) (Table 2), more evident in PD patients (Fig. 1), of the relative power of theta band (P = 0.051), more evident in HD patients (P = 0.019) and of the relative and absolute power of Beta1 band (P = 0.012, P = 0.022) (Table 2). The qualitative analysis of EEG data, showed more regular and stable EEG, on conservative therapy and KT patients, most represented Grade 1 scale Parsons-Smith (Fig. 2), respect to HD and PD patients (greater Grade 2 and 3 scale Parsons-Smith). However, also in conservative therapy patients, EEG showed a lower percentage of Grade 2 and even Grade 3 on KT patients, respect to HC (Fig. 2). Bivariate analysis showed a negative correlation between relative power of delta band and 1,25-(OH)2D3 (Fig. 3), MDRD value (Fig. 4), and the TMT of NPZ5 score (r = 0.235, P = 0.043), and a positive correlation with CRP value (Fig. 5) and ESV (r = 0.418, P < 0.001) in all the samples.

EEG and MMPI-2 data analysis have showed that higher relative power of delta band, positively correlates with the content scale, Cyn (cynicism) (r = 0.276, P = 0.016) (Table 3), and an increased relative power of theta band, positively correlated with Hy (hysteria) (r = 0.277, P = 0.016), SC2 (emotional alienation) (r = 0.302, P = 0.008), SC4 (depressive tendency and apathy) (r = 0.226, P = 0.051), Fam (family problems) (r = 0.248, P = 0.032), D (depression) (r = 0.239, P = 0.039), and Gf (gender female; the perception of sexual role; r = −0.346, P = 0.035), while negatively correlated with Gm (gender male; r = 0.244, P = 0.002) (Table 3).

4.2. MMPI-2, SAT-P, and NPZ5 test analysis

Analysis of variance of MMPI-2, showed a difference between CKD patients and HC, in all baseline clinical scale D (depression) (Fig. 6), in particular, the HD and PD groups showed a significant difference of averages when compared with HC (P < 0.001, P < 0.001) (Fig. 6). The scale Hy of MMPI-2 showed a positive

### Table 1: Patients' characteristics.

|        | CKD (n = 22) | HD (n = 15) | PD (n = 16) | KT (n = 21) | HC (n = 25) | P   |
|--------|--------------|-------------|-------------|-------------|-------------|-----|
| Male, n (%) | 12 (54.5) | 6 (40) | 10 (62.5) | 8 (38.0) | 8 (32.0) | n.s. |
| Age, y | 67 ± 15.2 | 53 ± 14.1 | 67 ± 10.7 | 56.9 ± 9.9 | 57.8 ± 11.2 | n.s. |
| BMI, kg/m² | 23.8 ± 2.0 | 23.5 ± 3.4 | 23 ± 2.4 | 23.5 ± 1.6 | 23.2 ± 2.5 | n.s. |
| SBP, mm Hg | 133.2 ± 13 | 127.7 ± 17.8 | 136.7 ± 11 | 130.7 ± 17.8 | 127.3 ± 128 | n.s. |
| DBP, mm Hg | 79 ± 9.8 | 76.3 ± 7 | 82 ± 9.7 | 77.9 ± 11 | 77.5 ± 6.6 | n.s. |
| Serum creatinine, mg/dL | 2.5 ± 0.8 | 9.6 ± 1.4 | 7.3 ± 3.2 | 1.4 ± 0.4 | 1 ± 0.16 | <0.001 |
| MDRD, mL/min/1.73m² | 25.3 ± 9.1 | 5.2 ± 1 | 8.2 ± 3.8 | 49.4 ± 17 | 72.3 ± 15.3 | <0.001 |
| Serum nitrogen, mg/dL | 92.9 ± 29.6 | 156.7 ± 31.9 | 135.6 ± 36.5 | 57.0 ± 29.0 | 37.7 ± 4.9 | <0.001 |
| Serum uric acid, mg/dL | 6.3 ± 1.4 | 5.8 ± 0.85 | 4.7 ± 1.2 | 6.6 ± 1.5 | 5.5 ± 0.8 | <0.001 |
| Sodium, mEq/L | 140.5 ± 2.8 | 141.1 ± 2.9 | 143.0 ± 3.2 | 140.0 ± 3.7 | 139.8 ± 1.6 | <0.001 |
| Potassium, mEq/L | 4.9 ± 0.4 | 5.7 ± 1 | 4.68 ± 0.6 | 4.3 ± 0.5 | 3.8 ± 0.3 | <0.001 |
| Calcium, mg/dl | 8.6 ± 1.7 | 9.0 ± 0.84 | 8.8 ± 0.67 | 9.3 ± 1.0 | 8.8 ± 0.2 | n.s. |
| Phosphorus, mg/dl | 4 ± 0.9 | 5.0 ± 0.85 | 4.8 ± 1.0 | 3.4 ± 0.8 | 3.6 ± 0.3 | <0.001 |
| Serum albumin, g/dl | 4.9 ± 0.6 | 4.2 ± 0.29 | 3.9 ± 0.4 | 3.8 ± 0.4 | 4.3 ± 0.5 | n.s. |
| Serum glucose, mg/dl | 105.8 ± 28.6 | 90.2 ± 17 | 90.5 ± 37.2 | 93.2 ± 12 | 87.4 ± 9.9 | n.s. |
| Ammonium, µmol/L | 42.8 ± 8.5 | 46.0 ± 5.3 | 46.0 ± 5.8 | 44.0 ± 6.8 | 44.9 ± 5.9 | n.s. |
| Hemoglobin, g/dl | 12.0 ± 1.4 | 11.27 ± 1.37 | 12.0 ± 1.0 | 13.0 ± 1.4 | 13.9 ± 0.7 | <0.001 |
| CRP, mg/L | 10.4 ± 10.3 | 12.75 ± 7.9 | 15.4 ± 5.4 | 3.3 ± 2.6 | 2.0 ± 1.6 | <0.001 |
| ESV, mm/h | 4.7 ± 28.4 | 44.7 ± 30 | 70.3 ± 28.3 | 44.7 ± 20.5 | 17.8 ± 8.6 | <0.001 |
| iPTH, pg/mL | 174.2 ± 78.4 | 247.8 ± 232.4 | 330.7 ± 175.7 | 126.5 ± 67.3 | 53.0 ± 9.8 | <0.001 |
| 1,25-(OH)2D3, ng/mL | 15.2 ± 10.0 | 14.87 ± 2.8 | 9.3 ± 6.8 | 12.7 ± 7.9 | 29.0 ± 9.2 | <0.001 |

Data are shown as mean ± standard deviation or number (%).
1.25-(OH)2D3 = 1,25-dihydroxyvitamin D3, BMI = body mass index, CKD = chronic kidney disease, CRP = C-reactive protein, DBP = diastolic blood pressure, ESV = erythrocyte sedimentation velocity, HC = healthy controls, HD = hemodialysis, iPTH = intact parathyroid hormone, KT = kidney transplant, MDRD = Modification of Diet in Renal Disease, n.s. = not significant, PD = peritoneal dialysis, SBP = systolic blood pressure.

4.1. EEG analysis

4.2. MMPI-2, SAT-P, and NPZ5 test analysis
correlation with Pa (paranoia) \( r=0.407, P<0.001 \), D \( r=0.615, P<0.001 \), Pd (psychopathic deviate) \( r=0.56, P<0.001 \) scales, and with hypochondria \( r=0.791, P<0.001 \) (Table 3). Moreover, Hy scale showed a positive correlation with Factor I (psychological functioning), Factor II (physical functioning), and Factor IV (sleep/diet/free time) \( r=-0.079, P=0.008, r=-0.309, P=0.007, r=0.309, P=0.007 \), respectively, of SAT-P and with TMT \( r=-0.241, P=0.037 \) and SDMT \( r=0.298, P=0.009 \) of NPZ5 score, as well as with creatinine, MDRD, serum nitrogen, CRP, iPTH, phosphorus \( r=0.554, P<0.001; r=0.374, P=0.001; r=0.381, P=0.001; r=-0.318, P=0.005; r=-0.255, P=0.027; r=0.246, P=0.033; r=-0.301, P=0.009 \), respectively), such as the scale Pd (psychopathic deviate) \( r=-0.402, P<0.001; r=0.332, P<0.001; r=-0.488, P<0.001; r=-0.447, P<0.001; r=0.331, P=0.004; r=-0.283, P=0.014 \), respectively). The scale Pd of MMPI-2, showed also a significant correlation with RAVL, DST, SDMT, and TMT tests, of NPZ5 score \( r=0.271, P=0.019; r=0.270, P=0.019; r=0.318, P=0.005; r=-0.283, P=0.014 \), respectively) (Table 3), while the TRT (negative treatment indicators), an alternative scale of MMPI-2, that indicate negative attitudes of the subject towards health treatments, showed a negative correlation with factor IV of SAT-P \( r=-0.327, P=0.004 \), that indicate sleep/diet/free time and with SDMT (90–120 seconds) of NPZ5 \( r=-0.304, P=0.008; r=-0.311, P=0.007 \), that assesses attention, visual scanning, and information processing speed (data not shown). Moreover, the subscale D2 (psychomotor retardation) showed a positive correlation with DST and SDMT \( r=0.289, P=0.12; r=0.262, P=0.23, \)

**Figure 1.** Bar charts with error bars. The mean value of relative power of delta band (% was significantly higher in patients on peritoneal dialysis (PD), compared with control group (51.5±12.3 vs 23.9±14.3, *P*<0.001). Boxes represent means; error bars indicate the 95% of CI (confidence interval). CKD=chronic kidney disease, HC=healthy controls, HD=hemodialysis, KT=kidney transplantation, PD=peritoneal dialysis, ReDelt=relative power of delta band.

**Figure 2.** EEG visual analysis classification according to the Parsons–Smith grading. Grade 1: normal EEG, Grade 2: distinctive features of encephalopathy, Grade 3: signs of severe encephalopathy. CKD=chronic kidney disease, HC=healthy controls, HD=hemodialysis, KT=kidney transplantation, PD=peritoneal dialysis.

**Figure 3.** Linear regression plot. 1,25-(OH)2D3 (ng/mL) vs ReDelt (%) in overall population. Negative correlation was found between the 2 parameters \( r=−0.820, P<0.001 \). 1,25-(OH)2D3=1,25-dihydroxyvitamin D3 ng/mL, ReDelt=relative power of delta band.

**Figure 4.** Linear regression plot. ReDelt (%) vs MDRD (mL/min/1.73 m²) in overall population. Negative correlation was found between the 2 parameters \( r=−0.617, P<0.001 \). MDRD=Modification Diet of Renal disease, ReDelt=relative power of delta band.
The neurological, psychological, and cognitive complications related to CKD, could contribute to the morbidity, and poor quality of life of these patients, but the prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The neurologic complications are better detected by pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. The prevalence, the pathogenesis, and the eventual therapy, remain currently unknown. 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patients and HC, in all baseline clinical scale D (depression), already present in conservative therapy and not completely disappear in KT patients, even if, only HD and PD patients, showed a significant difference respect to HC (Fig. 6). Lack of vitamin D has a high prevalence in patients with renal disease in which the traditional causes of deficits (lack of sunlight exposure, reduced dietary intake), combine with those of the CKD (reduced synthesis in the skin, urinary loss of vitamin D, and vitamin D metabolism) and in intestinal absorption of calcium, and thus to the reduction of Ca ionized circulating, in part to the absence of the negative feedback directly exercised by vitamin D on the VDR on parathyroid.[4,31] Others potential risk factors, could be the anemia, as reported in other studies[34] and confirmed in our study, with a significant difference of hemoglobin value (Table 1), and the hyperuricemia (Table 1), possible endothelial dysfunction index.[37] These alterations, could, at least partially, contribute to explain the early neuropsychological and cognitive decline in CKD, still poorly known.[18] In our study, the MMPI-2 scales, Hy and Pa, are significantly correlated with creatinine, MDRD, serum nitrogen, CRP, 1,25-(OH)2D3, iPTH, phosphorus;
moreover Hy and cyn are correlated with higher relative power of theta and delta band (Table 3). Moreover, Pd scale showed a significant correlation with Pa, Hy, depression scales, and all tests of NPZ5 score, but a negative correlation with creatinine, serum nitrogen, CRP, iPTH, and phosphorus, and a positive correlation with MDRD, 1,25-(OH)2D3 (Table 4) showing a possible and early, cognitive deficit in CKD patients on conservative therapy, and a noncomplete recovery in KT patients, also after 3 years from transplantation, associated with psychological disorders, that could jeopardize the quality of family, work, and social life.\[39\] The start of dialysis is an important change in a person’s life and determine stress for the permanently and continuously commitment and the many physical difficulties related to treatment, as well as the discomfort caused by dietary and fluid intake restrictions.\[40\] These aspects not only affect the personal habits but also the social and family relationships, modifying and/or resizing the patient’s role in the family and at work. The main causes of psychological distress in CKD patients could be, the fear of death, but especially the condition of dependence from healthcare, dialysis machine, transplanted organ and/or family, which could be associated with anxious and/or depression disorders. In the past, treating the psychological, relational, and behavioral aspects of dialysis patients was considered “secondary” to the need to keep the patient alive. Currently, dialysis patients have an important alternative to resignation, in fact, through multidisciplinary interventions (nephrological, neurological, and psychological), is possible reach advanced levels of adaptation, maintain good compliance, with effective control of fluid intake and of weight gain interdialytic, promoting significant improvements in the quality of life and survival, enabling a significant reduction in the healthcare costs worldwide.\[39,40\]

5.1. Limitations of the study

This study is a pivotal study, conducted in relatively small cohort of CKD patients; therefore, a larger population is requested to confirm our results. Also, all patients were on therapies with
Bold highlights the statistically significant values.

calcium, calcitriol, and phosphate binders and their treatments could have confounded the results. It seems that future large-scale studies are needed to clarify these differences.

6. Conclusions

The results of our study underscore the importance to employ simple and noninvasive instruments, as EEG, and cognitive- psychological tests, for early identification of patients at risk of developing neurological, psychological, and cognitive disorders. Could be important, also, carry out careful and constant monitoring of renal risk factors, probably involved in neuropsychological complications (inflammation, disorders of mineral metabolism, electrolyte disorders, etc.). Early identification and adequate therapy of neuropsychological, and cognitive disorders,

Table 4

| Bivariate correlation between NPZ5 test score and others variables in overall population. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| RAFL: List A                    | RAWL: List B                    | TMT: Parts A, s                 | TMT: Parts B, s                 | GPT: DH, s                      | GPT: NDH, s                     |
| **r**                           | **r**                           | **r**                           | **r**                           | **r**                           | **r**                           |
| Creatinine, mg/dL               | Creatinine, mg/dL               | Creatinine, mg/dL               | Creatinine, mg/dL               | Creatinine, mg/dL               | Creatinine, mg/dL               |
| MDRD, mL/min/1.73 m²            | MDRD, mL/min/1.73 m²            | MDRD, mL/min/1.73 m²            | MDRD, mL/min/1.73 m²            | MDRD, mL/min/1.73 m²            | MDRD, mL/min/1.73 m²            |
| Serum nitrogen, mg/dL           | Serum nitrogen, mg/dL           | Serum nitrogen, mg/dL           | Serum nitrogen, mg/dL           | Serum nitrogen, mg/dL           | Serum nitrogen, mg/dL           |
| CRP, mg/mL                      | CRP, mg/mL                      | CRP, mg/mL                      | CRP, mg/mL                      | CRP, mg/mL                      | CRP, mg/mL                      |
| ESV, mm/h                       | ESV, mm/h                       | ESV, mm/h                       | ESV, mm/h                       | ESV, mm/h                       | ESV, mm/h                       |
| iPTH, pg/mL                     | iPTH, pg/mL                     | iPTH, pg/mL                     | iPTH, pg/mL                     | iPTH, pg/mL                     | iPTH, pg/mL                     |
| 1,25-(OH)2D3, ng/mL             | 1,25-(OH)2D3, ng/mL             | 1,25-(OH)2D3, ng/mL             | 1,25-(OH)2D3, ng/mL             | 1,25-(OH)2D3, ng/mL             | 1,25-(OH)2D3, ng/mL             |
| **P**                           | **P**                           | **P**                           | **P**                           | **P**                           | **P**                           |
| -0.549                          | -0.547                          | -0.527                          | -0.467                          | -0.292                          | -0.383                          |
| <0.001                          | <0.001                          | <0.001                          | <0.001                          | <0.001                          | <0.001                          |
| -0.409                          | -0.407                          | -0.428                          | -0.408                          | -0.337                          | -0.320                          |
| <0.001                          | <0.001                          | <0.001                          | <0.001                          | <0.001                          | <0.001                          |
| 0.134                           | -0.109                          | 0.237                           | 0.339                           | 0.199                           | 0.364                           |
| 0.252                           | 0.350                           | 0.040                           | 0.003                           | 0.086                           | 0.001                           |
| 0.227                           | -0.216                          | 0.244                           | 0.331                           | 0.108                           | 0.315                           |
| 0.050                           | 0.062                           | 0.035                           | 0.004                           | 0.358                           | 0.006                           |
| 0.001                           | <0.001                          | <0.001                          | <0.001                          | <0.001                          | <0.001                          |
| 0.172                           | -0.337                          | 0.187                           | 0.262                           | 0.116                           | 0.177                           |
| 0.141                           | 0.003                           | 0.108                           | 0.023                           | 0.321                           | 0.129                           |
| 0.076                           | -0.156                          | 0.049                           | 0.098                           | -0.061                          | 0.045                           |
| 0.515                           | 0.181                           | 0.679                           | 0.402                           | 0.605                           | 0.699                           |

1.25-(OH)2D3 = 1,25-dihydroxy vitamin D3 (ng/mL), CRP = C reactive protein, DST = digit span test, ESV = erythrocyte sedimentation velocity, GPT: DH = Grooved Pegboard Test dominant hand, GPT: NDH = Grooved Pegboard Test nondominant hand, iPTH = intact parathyroid hormone, MDRD = Modification of Diet in Renal Disease, NPZ5 = neuropsychologic z score for 5 tests, RAFL = Rey Auditory Verbal Learning test, SDMT = symbol digit modalities test, sec = seconds, TMT = Trail Making test.

Table 5

| Satisfaction profile analysis and comparison with healthy controls. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| CKD (n = 22)                                     | HD (n = 15)                                      | PD (n = 16)                                      | KT (n = 21)                                      |
| Factor I                                        | Factor I                                        | Factor I                                        | Factor I                                        |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.0031                                      | P = 0.045                                       | P = 0.001                                       |
| Factor II                                       | Factor II                                       | Factor II                                       | Factor II                                       |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.001                                       | P = 0.001                                       | P = 0.001                                       |
| Factor III                                      | Factor III                                      | Factor III                                      | Factor III                                      |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.17                                        | P = 0.014                                       | P = 0.77                                        |
| Factor IV                                       | Factor IV                                       | Factor IV                                       | Factor IV                                       |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.028                                       | P = 0.014                                       | P = 0.040                                       |
| Factor V                                        | Factor V                                        | Factor V                                        | Factor V                                        |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.52                                        | P = 0.014                                       | P = 0.001                                       |
| HC (n = 25): 69.42 ± 22.25                      | P = 0.001                                       | P = 0.001                                       | P = 0.001                                       |

Data are show as mean ± standard deviation.
Domains of satisfaction profile test—Factor I: psychological functioning, Factor II: physical functioning, Factor III: work, Factor IV: sleep/leisure/free time, Factor V: social functioning.
CKD = chronic kidney disease, HC = healthy controls, HD = hemodialysis, KT = kidney transplant, PD = peritoneal dialysis
Bold highlights the statistically significant values.
might enable a better quality of life and a major compliance with a probable reduction in the healthcare costs. For this purpose a multidisciplinary interventions could be recommended.

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