

Assessment of the Cognitive State in Hemodialysis Patients – Relation to the Potential Risk Factors for Abnormalities

J. Popovic¹, V. Popovic², N. Dimkovic¹, Z. Paunic³ and T. Damjanovic¹

¹Centre for Renal Diseases, Zvezdara University Hospital, ²Institute for Psychiatry, Clinical Centre of Serbia, ³Clinic of Nephrology, Military Medical Academy, Belgrade, Serbia

Abstract

Background. A risk for cognitive impairment is suggested in long term maintenance haemodialysis (HD). The aim of the study was to analyze and compare the cognitive state of HD patients at baseline and after two years, considering the potential risk factors.

Methods. The sample consisted of 7 females and 14 males, mean age 53.7 ± 9.9 years, range 32-69, with mean HD duration of 90.7 months. They were non-diabetics, free of intercurrent complications, with normal hepatic function, without vascular disease and history of psychiatric disorders. The cognitive state was assessed at baseline and after two years via Mini-Mental State Examination (MMSE). Following potential risk factors were observed: hypertension, dyslipidemia, common carotid arteries intima media thickness, anemia, erythropoietin (EPO) therapy, smoking, adequacy of HD and education.

Results. Prevalence of scores suggesting cognitive impairment was found in 9.5% of patients at baseline (none at re-test). During two year interval change in MMSE score did not indicate cognitive deterioration. Performance was significantly better at the re-test (28.7 ± 1.6 vs. 27.7 ± 1.7 ; $p=0.004$) followed by significant increase in hematocrit (Hct) (33.5 ± 4.3 vs. 26.6 ± 4.3 ; $p \leq 0.01$) and hemoglobin (Hb) concentration (10.8 ± 1.3 vs. 9.4 ± 1.6 ; $p \leq 0.01$). Hb concentration of <10 g/dl significantly correlated to lower baseline MMSE score. Correction of anemia was especially beneficial to patients aged > 55 years and to subjects with the University level education. Other risk factors were not significantly associated to the cognitive function.

Conclusions. MMSE represents a practical test to track the changes in patient's cognitive state. Anemia proved to be an important factor in cognitive functioning of HD patients (especially in those aged over 55 years). This population should be routinely screened for a cognitive impairment in the future.

Key words: cognitive function, hemodialysis, risk factors

Introduction

Uremia is associated with alterations in cognitive functions (orientation, attention, immediate and delayed memory...) (1). Many of its neuropsychiatric accompanying manifestations including cognitive deficits, are improved upon the initiation of dialysis. Studies found nondialyzed uremic patients more cognitively impaired compared with dialysis population and identified latter to have a greater cognitive deficit than

controls, with 2-7- fold higher prevalence of the cognitive impairment and dementia than the general population (2-6). Age, diabetes, hypertension, hyperlipidaemia and smoking in general population and so called uremia related factors (anemia and dialysis adequacy) are risk factors for cognitive impairment. There are a few recent detailed studies of cognitive function in increased dialysis adequacy settings. Pliskin et al (7) did not show impairments in dialyzed patients in comparison to controls (chronically ill), finding the explanation in dramatic improvements in dialysis adequacy. Nevertheless, there is a risk for cognitive impairment and cognitive function disturbances in patients on maintenance haemodialysis even in adequately dialyzed subjects. Deficit could be subtle showing wide individual variations.

The aim of the study was to analyze and compare cognitive state of HD patients at baseline and after two years. Potential risk factors for abnormalities in cognitive testing as demographic characteristics, hypertension, dyslipidemia, diabetes, anemia, psychiatric illness, smoking, education level, adequacy of HD, along with the significant laboratory findings and clinical factors were taken into consideration in the process of analysis.

Patients and Methods

Twenty-one non-diabetic stable HD patients on a thrice-weekly schedule, free of intercurrent complications, with normal hepatic function, without vascular disease and history of psychiatric disorders, were enrolled. Their demographic characteristics are listed in table 1.

Table 1. Characteristics of study participants

| | |
|-----------------------------|-----------------|
| Age (years \pm SD) | 55.7 \pm 9.9 |
| Age range (years) | 32 - 69 |
| Sex (M / F) | 14 / 7 |
| HD length (months \pm SD) | 90.7 \pm 96.0 |
| Smoking (yes / no) | 8 / 13 |
| Hypertension (yes / no) | 15 / 6 |

The cognitive state of HD patients was assessed before HD sessions via Mini-Mental State Examination (MMSE) at baseline and after two years. MMSE is the most widely used cognitive test (8). It is an important screening tool for the cognitive impairment. A broad range of cognitive functions are tested with following tasks included: orientation, registration, recall, attention, calculation, language manipulation and constructional praxis. The scale easily reveals the changes in cognitive functioning (9), it is useful for follow-up of cognitive state in longer periods of time, and

its test-retest reliability is high. The total maximal score is 30 points. Scores between 28 and 30 do not support the diagnosis of dementia. Performance of 25 and less suggests cognitive impairment and a score of less than 20 indicates definite impairment (10). Some investigators have suggested a cutoff score of 26 or 27 in symptomatic populations, thus making results between 25 and 27 points borderline (11).

Important laboratorial findings were analyzed at both points: anemia parameters – hemoglobin concentration (Hb) and hematocrit (Hct), glucose and triglycerides levels. Classic atherogenic risk factors (smoking, hypercholesterolemia), adequacy of HD (Kt/V), common carotid arteries intima media thickness (IMT), presence of hypertension, erythropoietin (EPO) therapy and the education level (primary school, high school, vocational school and university) were also evaluated.

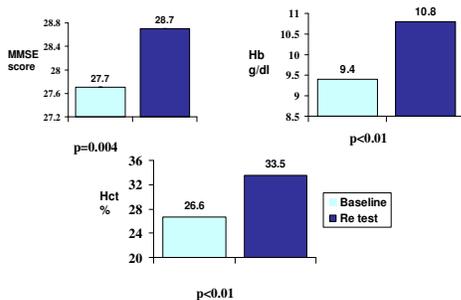
Results were presented as mean ± standard deviation (SD). Statistical analysis was performed using t-test, one-way analysis of variance (ANOVA), Chi-square analysis, Fisher Exact test and Wilcoxon’s signed ranks test. Logistic regression was performed with the improvement of cognitive state as a dependent variable (binary outcome) and all variables with difference of at least 0.1 at previous tests as the independent variables. P value of <0.05 was considered statistically significant.

The statistical program SPSS for Windows (Release 11.5.0, SPSS Inc., Chicago, IL, USA 2002) was used for data analysis.

Results

Overall mean MMSE score did not indicate cognitive impairment at both, baseline and the re-test. Performance was better after two years with a mean increase of 1 point (28.7 ± 1.6 vs. 27.7 ± 1.7) (Fig 1).

Figure 1. MMSE score, hemoglobin and hematocrit levels at baseline and after two years



Scores indicating definite impairment were not observed. In two patients (9.5%) at baseline (none at the re-test) results suggesting cognitive impairment were found. Prevalence of borderline score occurred in 28.6% and 23.8% at baseline and after two years, respectively. Interestingly, the patients (both at test and the re-test) scored fewer points than maximum in the first part of the questionnaire, especially in the fields of attention and calculation as well as with the recall. Only two patients reached the maximal score at baseline. Performance was significantly better at the re-test (9 out of 21, p=0.032). As for the second part of the questionnaire (language

manipulation and constructional praxis being prominent features) the situation was quite opposite. Only one patient (at baseline) scored less than maximum.

Anemia and MMSE

A prominent change in laboratory results occurred in anemia parameters at the re-test in comparison to the baseline. Significantly higher Hct (33.5 ± 4.3 vs. 26.6 ± 4.3; p=0.000) and Hb levels (10.8 ± 1.3 vs. 9.4 ± 1.6; p=0.004) were observed (Fig 1).

The group with improved levels of Hb and Hct, had significantly better MMSE performance after two years (Z=-2.871; p=0.004).

Hb concentration of <10 g/dl highly significantly correlated to the lower baseline MMSE score (27.0 ± 1.8 vs. 28.9 ± 0.6; p=0.01), but not to the MMSE at re-test (28.3 ± 1.7 vs. 28.8 ± 1.6) mainly due to the small number of subjects (only 4 patients). Similar situation was observed with Hct of less than 27%. It correlated significantly to the baseline MMSE (27.1 ± 1.8 vs. 28.6 ± 1.1; p=0.047). After two years only two patients presented with Hct < 27%. Insignificant correlation with MMSE at that time was established (28.0 ± 2.8 vs. 28.7 ± 1.5; p=0.539).

Subjects not treated with EPO therapy at baseline had significantly lower performance on MMSE in comparison to the score of patients on EPO (27.0 ± 1.8 vs. 28.9 ± 0.6; p=0.01). Subsequently, EPO was also initiated in this group and MMSE at the re-test showed insignificant difference (28.3 ± 1.8 vs. 29.3 ± 0.7; p=0.185). At the same time their Hb (8.3) and Hct (23.7) increased to 11.1 and 34.3 respectively.

When influence of EPO dose on MMSE performance was analyzed insignificant correlation was obtained.

Gender

Female patients were slightly younger, less educated, longer on HD, with somewhat lower Hb and Hct at baseline but higher at the re-test. Their cognitive performance was better at both tested points in comparison to males. All the differences were statistically insignificant (Table 2).

Table 2. Important data observed with respect to gender

| Characteristics | Male | Female | p |
|---------------------------|-------------|---------------|-------|
| Number | 14 | 7 | |
| Age (years ± SD) | 54.1 ± 10.9 | 53.0 ± 8.2 | 0.823 |
| HD duration (months ± SD) | 76.4 ± 51.1 | 119.6 ± 153.2 | 0.344 |
| MMSE 1 | 27.4 ± 1.8 | 28.4 ± 1.4 | 0.182 |
| MMSE 2 | 28.4 ± 1.7 | 29.1 ± 1.2 | 0.335 |
| Hb 1 | 9.5 ± 1.7 | 9.1 ± 1.4 | 0.549 |
| Hb 2 | 10.6 ± 1.2 | 11.3 ± 1.6 | 0.246 |
| Hct 1 | 26.8 ± 4.7 | 26.1 ± 3.9 | 0.723 |
| Hct 2 | 32.7 ± 3.7 | 35.2 ± 5.2 | 0.226 |

1 = baseline, 2 = re-test.

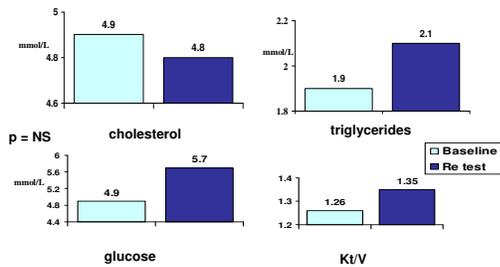
Age

Score obtained for patients over 65 years was insignificantly lower (p=0.218). With cutoff age of 55 years, significantly lower baseline performance was observed for patients over 55 years (26.8 ± 1.6 vs. 28.6 ± 1.4; p=0.015).

Duration of HD

The length of HD did not play significant role in the cognitive state testing results. Still, with the cutoff of 36 months (at baseline) higher scores in the group dialyzed less than 36 months almost reached statistical significance (29.3 ± 0.6 vs. 27.4 ± 1.7; p=0.075).

Education



If analyzed separately, patients with University level had lower score at baseline against other three education categories (26.0 ± 2.0 vs. 28.0 ± 1.5 , none with maximal score in the first part of the questionnaire). The difference was on the borderline of significance ($p=0.058$). Their performance was better at re-test (achievement of maximal 30 points, all three of them with maximal score of 21 in the first part, still with an insignificant difference from the baseline, $p=0.1$ Fisher's Exact test).

Other parameters

| | B | Wald | P | R ² | OR | 95,0% C.I.for OR | |
|---------------|--------|-------|------|----------------|--------|------------------|---------|
| | | | | | | Lower | Upper |
| Step 1(a) | | | | | | | |
| EPO | 1,711 | 1,505 | ,220 | | 5,532 | ,360 | 85,067 |
| Hgb < 10g/dl | 1,046 | ,838 | ,360 | | 2,845 | ,303 | 26,691 |
| Age >55 years | 2,484 | 3,880 | ,049 | 0,330 | 11,995 | 1,012 | 142,123 |
| Constant | -2,605 | | | | | | |

a Variable(s) entered on step 1: Age >55y.

In this model of logistic regression, correction of anemia (Hb cutoff concentration of 10 g/dl) was most important for the improvement of the cognitive state in patients with age over 55 years (the only statistically significant variable in the logistic regression model, $p=0.049$). This score difference could explain about 71% of all differences at tested points.

Discussion

Only a few studies have focused their attention on the cognitive state in hemodialysis population. In the previous literature (2-4) dialysis patients had greater cognitive impairment than controls. In more recent era Sehgal et al (6) and Fazekas et al (12) also found a high prevalence of cognitive impairment in hemodialysis patients (MMSE score of 24 or less in 32% and 60% of patients respectively; 8% with severe cognitive impairment i.e. MMSE from 0 to 17). Their mean MMSE score (22.9) was significantly lower in comparison to healthy controls (27.9) (12). There is a discrepancy between the current study and findings previously cited. Subjects in present study at baseline and the re-test, achieved higher results in terms of mean MMSE

In the case of renal diagnoses, presence/absence of hypertension, adequacy of HD, smoking habits, IMT, cholesterol, triglycerides and glucose levels (Figure 2) the difference was insignificant between the two test periods.

Table 3. Multiple regression model with improvement in MMSE score as dependent variable and EPO therapy, Hgb < 10 g/dL, age over 55 years, HD > 36 months and University education as independent variables.

| | Observed | Predicted | | Percentage Correct |
|--------------------|----------|-----------------------------------|-----|--------------------|
| | | Age>55y. that improved MMSE score | | |
| | | No | Yes | |
| Age>55years | No | 8 | 3 | 72,7 |
| | Yes | 3 | 7 | 70,0 |
| Overall Percentage | | | | 71,4 |

In a multiple logistic regression model (Table 3) improvement of MMSE score was observed as a dependent variable and all variables with significance < 0.1 as independent ones (patients without EPO therapy, Hb concentration < 10 g/dL, patients older than 55 years, duration of HD treatment above 36 months and University level education).

score, i.e. 27.7 and 28.7 vs. 22.9, along with the lower prevalence of the cognitive impairment (9.5% vs. 32% and 60%). They were adequately dialyzed and similarly, when comparing well-dialyzed patients with chronically ill, Pliskin et al (7) did not find significant difference. In the study reported by Umans and Pliskin (13) attention and mental processing were not different in stable HD patients compared with age and education matched controls. Both studies involved a nonrandom selection of patients which could be the reason for difference from previous findings.

Deterioration in the cognitive function was not observed in the present study with over the time. It is otherwise suggested that during an interval of 1-4 years, a change of 4 or more points in MMSE score is needed to indicate substantial cognitive deterioration (14). In contrast, MMSE significantly improved after two years, along with the significant increments in Hb and Hct. Anemia is a potential nonvascular risk factor for abnormalities in cognitive testing in HD patients. Brain oxygen delivery decreases with decreased Hct and cerebral blood flow increases probably leading to both increased delivery of uremic toxins and intracranial pressure (15, 16). Anemia (Hb concentration < 10 g/dl) was associated

with a 25% increased risk of dementia (17). Reversal of anemia led to improved cognitive function. Patients not on EPO scored significantly less than the patients on EPO at baseline, and a better performance was demonstrated after the erythropoietin was introduced and anemia corrected. Significant improvement in cognitive function was also found in predialysis patients on EPO therapy with improvements in Hct levels (18), and the same occurred in HD population (19, 20) with the exception reported by Wolcott et al (21).

Several factors, including age, male gender and education were associated with MMSE scores, but only older age and lower education level were independently associated with < 24 points achievement on this test in multivariable analysis (6). In healthy population study (908 subjects deemed to be without cognitive impairment and given MMSE) the norms declined with advancing age, especially for the less educated women (22). In community sample (14) performance on the MMSE was influenced by age (over 59 years) and education, but not by sex. In the current study females performed insignificantly better on neuropsychological test. Patients over 55 years had worse score (significantly improved with the correction of anemia). Education did not represent an important factor for cognitive testing (subjects with University level benefited from the reversal of anemia).

The analysis of potential vascular risk factors (hypertension, dyslipidemia, smoking) for cognitive impairment revealed an insignificant difference.

Conclusion

Out of all potential risk factors for cognitive functioning analyzed, correction of anemia proved to be the most important. It led to an improvement in cognitive performance which was especially beneficial to patients over 55 years of age and the ones with the University level education. Results although obtained on a relatively small sample size, suggest a therapeutic approach for the future. With HD population ever growing older, the importance of recognition of even subtle changes in the cognitive state is mandatory.

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