Dementia and Cognitive Impairment Prevalence in Patients with End Stage Chronic Kidney Disease: An Underdiagnosed Condition That Should Not Be Missed

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Received Date: 12 November; Accepted Date: 19 November; Published Date: 26 November, 2018

Abbreviation list
- MMSE: Minimental state examination
- CKD: Chronic kidney disease
- SBIs: Silent brain infarctions

Abstract

Introduction: Dementia and cognitive impairment are progressive conditions correlated to aging and chronic diseases both of which prevalence and incidence are increasing as world population gets older. These are conditions commonly underdiagnosed in elderly population suffering from end stage chronic kidney disease.

Methods: Cross-sectional, descriptive and observational study in which 158 patients from two private hemodialysis centers in Puebla, México were included. All of them ≥ 60 years old, with end stage chronic kidney disease. Folstein’s minimental test (MMSE) was applied to every patient.

Results: 13 (8.22%) patients had no alterations, 54 (34.1%) of the patients results suggested cognitive impairment, 83 (52.53%) patients presented compatible diagnosis for cognitive impairment and 8 (5.0%) patients with confirmed dementia. It was found that 63 (69.23%) patients from the 100% of patients with positive MMSE were female and 28 (30.7%) male; 73 (80.2%) of them had hypertension and diabetes mellitus as comorbidities and 18 (19.74%) presented hypertension as single comorbidity, 16 (17.5%) patients with cognitive impairment diagnosis had a previous history of stroke. A prevalence of 60.33% was found.

Conclusions: It is essential to perform a cognitive screening test in every patient on his first geriatric evaluation. Patients with CKD can suffer from dementia and different stages of cognitive impairment that are overshadowed by the baseline kidney pathology. It is important to anticipate the possibility for this condition and establish action measures for early diagnosis and progression delay measures to improve the patient’s functionality in spite of their chronic disease state.

Keywords: Cognitive impairment; chronic kidney disease; comorbidity; dementia; MMSE; prevalence
Introduction

Mexican clinical practice guidelines define cognitive impairment as a clinical syndrome characterized by the loss or impairment of mental capacity on the different functions and neurophysiological structure that enables memory, orientation, calculation, comprehension, judgment, visual recognition, conduct and overall personality of a person [1]. As a neurologic disorder the acquired lack of cognitive and emotional abilities becomes severe enough to interfere with the social or occupational functionality of the patient or in some cases both [1,9]. The diagnostic criteria based on the Mexican guidelines are summarized on table 1 (See table 1). This guideline dictates that first contact physicians on the first level of attention must identify the neurophysiachiatric symptoms associated to this condition [1].

### Diagnostic criteria of cognitive impairment and dementia

- Acquired memory deterioration
- One or more of the following:
  - Aphasia
  - Apraxia
  - Agnosia
  - Altered executive function
- Cognitive impairment severe enough to interfere in laboral, social or personal plan.
- Gradual beginning and progressive course
- Cognitive impairment mustn’t appear exclusively in a delirium course

<table>
<thead>
<tr>
<th><strong>Table 1:</strong> Diagnostic criteria for cognitive impairment and dementia by the Mexican clinical practice guidelines</th>
</tr>
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</table>
| It is known that patients with chronic kidney disease (CKD) over 65 years old are significantly more likely to develop dementia or cognitive impairment [14], Miwa & cols mention that the presence of CKD and mild CKD was associated with an increased risk of acquiring Alzheimer’s disease, CKD per se can be considered as a marker of an individual’s vulnerability to develop dementia and therefore could be a potential therapeutic target for prevention of such disease [11,12,14,20]. In México the overall prevalence of cognitive impairment in population over 65 years old is around 8% [1]. The most frequent type of dementia in the world as it is also in Mexico is Alzheimer’s disease, which has an insidious onset and slow progression and a 10-year survival rate from the time of diagnosis. The second most frequent cause of dementia in Mexico is vascular dementia, conventionally associated with stroke and hypertensive disease [1-12]. Recommendations for diagnosis of mild cognitive impairment in American guidelines stipulate the need for early diagnosis due to Alzheimer’s disease high prevalence in population at risk [20].

CKD is related to an accelerated and active vascular calcification process, it has been estimated that approximately half of the patients with advanced CKD stages have SBIs (silent brain infarctions) associated with an increased risk for stroke, cognitive decline, and incident dementia [15,26] and because of that, it should be considered a matter of urgent necessity to determine the prevalence of dementia in this group of patients.

Several clinical trials establish that patients with CKD are at an increased risk of cognitive decline and dementia, particularly cognitive decline associated to an underlying vascular component. Also, an inflammatory process is implicated in many vascular diseases and more so, inflammation may be playing the role of both the cause and the consequence of CKD [11-16].

To determine the prevalence of dementia in this group of patients could improve impact of preventive and therapeutic measures for enhancing quality of life and the delay of the cognitive impairment progression in order to have functional elderly individuals throughout society in spite of their chronic disease states.

Methods

We performed a descriptive, observational, cross-sectional study on which 286 patients were included, analyzing data from clinical files since August 2015 to 2018 from two private hemodialysis units in Puebla, México. From a total of 286 patients, 158 patients qualified within inclusion criteria which were defined as follows; to be ≥ 60 years old, with end stage chronic disease diagnosis for at least 6 months, receiving hemodialysis treatment, and with a 6 month follow up with a Folstein’s minimental test applied by a trained psychologist to each patient individually in the hemodialysis unit. The study included 83 patients from “Beneficencia Española de Puebla” and 75 patients from “Centro MEDICI Puebla”. Exclusion criteria included pre-existing neuropsychiatric disease such as psychosis or schizophrenia previous to the beginning of the study, change of hemodialysis unit, recent hospitalization <2months, presence of delirium during hospitalization, lack of follow up by minimental test and death.

We sought to determine the prevalence of dementia and cognitive impairment in a group of patients with end stage CKD and its relation with age, sex, level of education, nutritional status and associated comorbidities. The minimental test was modified due to the level of education of the patients and prevalence was determined at dint of WinEpi working with an Epidemiology calculator, supported with the last Cochrane systematic reviews from 2016 that reports MMSE sensibility and specificity of 85% and 90% respectively [16]. The study was conducted from August 2015 to August 2018. Descriptive statistic was used, involving central and dispersion tendency measures; range, average, median, mode, standard deviation, proportion and percentages.
Results

From a total of 286 patients, 158 were eligible by inclusion criteria, a general characteristics table was made for reference data (See Table 2). We based the prevalence of dementia and cognitive impairment in spite of follow up as day “0” August the 31st collecting the minimental tests applied from August 2015 to the cut-off date in 2018, results are presented in table 3 (See. Table 3).

Table 2: General Characteristics of the study sample.

### General Characteristics of the study sample

<table>
<thead>
<tr>
<th>Total N</th>
<th>286</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who fulfill inclusion criteria</td>
<td>158</td>
</tr>
<tr>
<td>Sex F: M (%)</td>
<td>F 112 (70.88%); M 46 (29.11%)</td>
</tr>
<tr>
<td>Average age</td>
<td>62.3± 12.6</td>
</tr>
<tr>
<td>Average weight</td>
<td></td>
</tr>
<tr>
<td>- low weight (IMC &lt;18.5)</td>
<td>77 (48.7%)</td>
</tr>
<tr>
<td>- normal weight (IMC 18.5-24.9)</td>
<td>25 (15.8%)</td>
</tr>
<tr>
<td>- overweight (IMC 25-29.9)</td>
<td>54 (34.1%)</td>
</tr>
<tr>
<td>- obesity (IMC ≥ 30)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Study level</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>74 (46.8%)</td>
</tr>
<tr>
<td>Junior high</td>
<td>32 (20.2%)</td>
</tr>
<tr>
<td>High school</td>
<td>27 (17.08%)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>19 (12.02%)</td>
</tr>
<tr>
<td>Master’s degree</td>
<td>5 (3.1%)</td>
</tr>
<tr>
<td>Doctorate</td>
<td>1 (0.63%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>123 (77.8%)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>141 (89.24%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>32 (20.2%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>16 (10.1%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (0.63%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (1.26%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (2.53%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (1.89%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (0.63%)</td>
</tr>
</tbody>
</table>

Table 3: Minimetal results: Dementia or cognitive impairment diagnosis by Folstein’s minimental test.

Regarding the prevalence of dementia or cognitive impairment in our settled group, we divided the results as presented in table 3 (See table 3). It was found that 13 (8.22%) patients had no alterations or underlying disease, 54 (34.1%) of the patients results suggested cognitive impairment; with this result it could be predictable that in the near future the patient will progress to dementia, though it is necessary to carry out probability trials for confirmation of this hypothesis. On the other hand, 83 (52.53%) patients presented a MMSE compatible with diagnosis for cognitive impairment which demonstrates that there is a very important underdiagnosed issue in more than half of the patients included in the study with no secondary interventions due to the diagnosis of CKD. Also, in 8 (5.0%) patients dementia was diagnosed thus, confirming the same underdiagnose issue in this type of patients. No action measures were taken. Applying the Cochrane 2016 sensibility and specificity for the diagnosis of dementia and cognitive impairment, our study reported a real prevalence of 60.33%.

No epidemiological association mesures were performed for statistical analysis. We globalize diagnosed patients together not only for cognitive impairment diagnosis but also for dementia diagnosis with a total of 91 patients (57.59%) of the general total. A general characteristics chart was made for reference data. (See table 2.) It was found that 63 (69.23%) patients from the 100% patients with positive MMSE were female and 28 (30.7%) male, suggesting greater prevalence in women, 73 (80.2%) of them had hypertension and diabetes mellitus as concomitant comorbidities and 18(19.74%) hypertension as a single comorbidity, from this sample 16 (17.5%) patients with cognitive impairment diagnosis had stroke history which probably could explain a vascular dementia and the consequent presence of positive MMSE.

Regarding to the education level, 25 (27.47%) patients with dementia diagnosis had elementary school as greater education level, 27 (29.6%) patients had junior high level, 20 (21.9%) patients with high school level, 19(20.8%) with bachelor’s degree, whereby it’s necessary to perform further studies to evaluate the impact of study level in the development of cognitive impairment. Concerning IMC from the total of patients with positive MMSE for cognitive impairment and dementia 64(70.3%) patients had low weight, 9(9.8%) patients normal weight, 17(18.6%) with overweight and one (1.09%) with obesity. The average age of the study sample was 63± 12.6 years old; from the 91 (57.59%) patients who presented positive MMSE, the average age for diagnosis was 65±3 years old.

All patients with cognitive impairment suspicion, diagnosed cognitive impairment or dementia were referred for neuropsychiatric evaluation and management.
Discussion

The miniminal status test (MMST) is a study designed with the purpose of evaluating the psychological and mental capability of the elderly patient in order to obtain certain information regarding the patient’s cognitive capability or impairment and his or her functionality in our society. This screening test was developed by Folstein et.al in 1975 [17]. Among the aspects evaluated, the following are involved: temporal (5 points) and spatial (5 points), fixation capacity (3 points), attention and calculation (5 points) memory (3 points), nomination (2 points), repetition (1 point) and compression (3 points), reading (1 point), writing (1 point) and drawing (1 point). The normal and pathological scores are listed in table 3 (See table 3). Every evaluation test has its limitations for application and interpretation, for example MMSE has a “ceiling” effect on subjects with high education level and sensory deficit; therefore, depending on the context, it’s necessary to elucidate not only the result of the test from the score obtained, but also each one of the aspects affected individually.

Individuals at all stages of chronic kidney disease (CKD) may have a greater risk of developing dementia and cognitive impairment than those without CKD. It should be noted that cognitive impairment in CKD is not limited to patients with stage 5 CKD (14, 31). In this study we learned that almost half of the patients had a certain level of cognitive impairment and that if it had not been detected and referred to a neuropsychiatry specialist, disease could have progressed and led to serious negative consequences on the quality of life of the patients. This shows the great importance of recognizing the imminent risk in this group of patients and must be considered a red flag for first contact physicians and it must change the way a clinical evaluators approach on mental health preventive medicine.

As mentioned before, Patients with CKD show a high prevalence of stroke and vascular dementia, perhaps an image follow up by computed CT could also be considered a preventive measure for detecting SBIs (silent brain infarcts) and as a secondary preventive action to reduce the consequent cognitive impairment as the incidence of cerebral microbleeds is higher in patients undergoing hemodialysis and also in patients with a moderate decrease in renal function; as Bugnicourt & cols mention, faster eGFR decline (>4mL/min per 1.73m² during the first 4-year period of follow-up) in their trial was associated with overall cognitive decline and incident dementia with a vascular component [15]. It’s evident that there is a vascular component in cognitive impairment/dementia manifestations in patients with end stage chronic kidney disease. Just like in our settled group of study, Tamura & Cols allude to the intensity of systemic inflammation, as indicated by elevations in multiple markers of inflammation, including interleukin- 1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), appears to increase as kidney function declines. CKD is more strongly associated with vascular dementia than Alzheimer’s disease [34]. Lower eGFR is a risk factor for both ischemic and hemorrhagic stroke and consequently increases dementia prevalence. Also, direct neuronal toxicity from uremic toxins seems to be another cause of cognitive decline in patients with CKD. Further trials must be realized to implement action measures for preventing complications.

As first contact physicians we must be aware that cognitive impairment might already be present in the early stages of CKD as the mineral and bone disorder of metabolism of calcium, phosphate, parathyroid hormone, and fibroblast growth factor-23 contributes to the acceleration of vascular calcifications. Alterations in vitamin D metabolism are one of the key features of CKD mineral and bone disorder. Vitamin D deficiency has been shown to contribute to depression and memory disorders [31-33]. Realization of screening tests as MMSE could contribute to the early diagnosis in other to diminish complications.

Each characteristic of cognitive and mental function followed a unique pattern of decline, such is the case of language as it continued to worsen and in other patients plateaued or only became difficult at a certain point in the communication process.

Further studies must be realized to determine association measures regarding sex, age, nutritional status, and associated comorbidities to determine its impact in the cognitive impairment or dementia presentation in patients with end stage chronic kidney disease.

It was demonstrated that in more than half of our study sample there was a suspicion of cognitive impairment, cognitive impairment per se and dementia and that all of these were under-diagnosed or miss-diagnosed previous to the screening intervention of this study.

Conclusions

Half of the patients in our study, ages 65 and older were diagnosed from CKD. The most prevalent underlying diseases leading to CKD are diabetes and hypertension. Impairment in cognitive function is a common finding in patients with CKD. The prevalence of cognitive impairment among patients with CKD, which occurs independently of the general age-related decrease in performance, increases remarkably. Our group of patients with end stage chronic kidney disease presented a prevalence of 60.33% for cognitive impairment.

It is essential to perform a cognitive screening in every patient in his first geriatric evaluation, thus we must consider as first contact physicians that any patient over 60 years old needs this screening [19]. Prevalence of a disease is defined as the proportion of individuals of a certain population that present the pathology at a specific moment in time and we should consider the very high prevalence of mental impairment on this type of patients at the moment of first evaluation and not under-diagnose or miss-diagnose this condition, also we should be aware that patients with CKD suffer from dementia and different levels of cognitive impairment that is sometimes overshadowed by the baseline kidney pathology.

As more guidelines for a correct medical practice and preventive medicine are emerging, we have the opportunity to be pioneers in this matter and have the responsibility to identify population at risk, whereby the age curve around the world is changing every day, life quality improves, longevity increases and dementia and cognitive impairment become a more serious public health issue that added to the already increased risk of dementia and cognitive impairment in patients with end stage chronic kidney disease predisposes to a decline in quality of life in elderly population. All of this might be preventable or slowed down as mentioned before in order to have more society functional patients regardless of disease or associated comorbidities, as is the case in patients with end stage chronic kidney disease.

We found as the main limitation of this study that it was difficult to determine and establish causal relations that dictate a temporary sequence in which the cause is given first and the effect after. Also, there is a survival bias possibility. The MMSE is not the only screening test for cognitive impairment or dementia in the elderly as the simple act of raising awareness, which is an important action carried out by health professionals and also the basis of the first steps to take in order to develop action plans in our patients. We must recognize suggestive symptomatology in the elderly with end stage chronic kidney disease who present to the hemodialysis unit for treatment in order to refer promptly to the specialist needed (neurology or psychiatry) for a comprehensive management of this patient group and not only to treat the baseline kidney disease in a systematic way.

Funding: This work was performed in Hospital Beneficencia Española de Puebla; no funding was needed for this work.

Acknowledgements: none

References


Volume 2018 , Issue 01


