EVALUATION OF RENAL FUNCTION IN ALZHEIMER’S DISEASE AND GERIATRIC PATIENTS: RESULTS FROM A TURKISH TWO-CENTER STUDY

PROCENA BUBREŽNE FUNKCIJE U ALCHAJMEROVOJ BOLESTI I KOD GERIJATRIJSKIH PACIJENATA: REZULTATI TURSKE STUDIJE IZ DVA CENTRA

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Summary

Background: Alzheimer’s disease (AD) is a severe multifactorial neurodegenerative proteopathy associated with advanced age. Discrepancies in the renal function of these patients compared to geriatric patients with dementia have rarely been reported. In this study, we aimed to disclose the importance of associated renal changes for the pathogenesis of AD.

Methods: Patients with AD (n=107) and geriatric patients with dementia and without dementia (n=124) (231 patients in total) from Dokuz Eylul and Cukurova University Hospitals were enrolled in the study. We measured serum Na, K, Cl, Ca, BUN, creatinine, total protein levels and MDRD [eGFR] in all groups.

Results: From Izmir Center, the first study arm consisted of patients with AD dementia (n=74), and the second arm included geriatric patients with dementia (n=79). From Adana, 78 patients were recruited to the study, of which 33 were with AD and 45 were geriatric patients without dementia. When we analyzed comparatively the AD and geriatric dementia patients study arms, a statistically significant difference was observed both in the median age and in the renal function parameters. We observed a higher median age in the AD group compared to the geriatric dementia group. Moreover, the AD group had significantly lower serum Na and BUN levels, and higher serum Cl and creatinine levels compared to the geriatric dementia group.

Kratak sadržaj

Uvod: Alchajmerova bolest (AB) predstavlja tešku multifaktorijsku neurodegenerativnu proteopatiju koja je povezana sa starenjem. Dosad nije bilo mnogo izvještaja o razlikama u bubrežnoj funkciji kod obolelih od AB i kod gerijatrijskih pacijenata sa demencijom. U ovoj studiji, cilj je bio da se otkrije važnost povezanih promena bubrežne funkcije u patogenezi AB.

Metode: Studija je obuhvatila obolele od AB (n=107) i gerijatrijske pacijente sa demencijom i bez demencije (n=124) (ukupno 231 pacijent) iz bolnica Dokuz Eylul i Univerziteta Cukurova. U svim grupama, izmerili smo serumne nivoa Na, K, Cl, Ca, BUN, kreatinina, ukupnog proteina i MDRD (eGFR).

Rezultati: Iz centra Izmir, kao jednog od dva centra u kojima je studija sprovedena, uključeni su pacijenti sa demencijom AB (n=74) i gerijatrijski pacijenti sa demencijom (n=79). Iz centra Adana, u studiju je uključeno 78 pacijenata, od kojih je 33 imalo AB, dok su 45 bili gerijatrijski pacijenti bez demencije. Kada smo uporedo analizirali pacijente sa AD i gerijatrijskom demencijom, uočene su statistički značajne razlike kako u prosečnoj dobi (p<0,001) tako i u biohe-
Alzheimer’s disease, dementia, renal function

Introduction

The proportion of older people in the general population is steadily increasing worldwide in both developed and developing nations (1). However, a rapidly aging population also has important implications on healthcare and the age-related comorbidities including Alzheimer’s disease (AD) which is a very complex, progressive, irreversible neurodegenerative disease and is the most common type of dementia (2). This neurodegenerative disease has been associated with three main structural changes in the brain: diffuse loss of neurons, intracellular protein deposits termed neurofibrillary tangles, and extracellular protein deposits termed amyloid or senile plaques, surrounded by dystrophic neurites (3). It has been known that cortical atrophy, neuron degeneration, neuronal loss, accumulation of extracellular (amyloid β containing) plaques and accumulation of intracellular (tau) neurofibrillary tangles are the dominant factors behind the cognitive decline of patients with AD (4–8). During the aging process, biochemical events such as defective cell signaling, oxidative damage, and aberrant tau protein phosphorylation eventually drive cells to apoptosis which in turn may prelude to AD. AD finally reaches to episodic short-term memory deficits and progress to further decline and loss of general cognitive functioning during the late dementia stage (9). Although the exact mechanisms behind AD are still poorly understood and it is usually considered as a complex disease with environment-gene interactions, there are various proposed distinct and interrelated triggering factors such as aberrant phosphorylation of tau proteins that triggers apoptotic pathway and neuronal loss. In addition to accumulation of Aβ plaques, intrusions that disturb normal cellular function which are essential for elimination or reduction of oxidative stress, such as vitamin deficiencies, might have a key role in AD. Furthermore, the ε4 allele of Apolipoprotein E (ApoEε4) is the only known major risk factor for late onset AD in a variety of ethnic groups (9–15).

It is known that the pathophysiologic link between brain and kidney injury is strong and complex (16). Elimination of toxic, water-soluble nitrogenous compounds of protein and nucleotide metabolisms by urinary extraction are quintessential for normal neu-
of groups’ variances was checked by Levene’s test. When the parametric test assumptions were not met, in comparisons of two independent groups, Mann-Whitney U test was employed.

Data analyses were performed using the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago IL, USA). P values < 0.05 were considered as statistically significant. The results of statistical analysis were expressed as number of observations (n), mean±standard deviation (x±Sx), median and minimum–maximum values [M (min–max)].

**Ethics and Dissemination**

This study was approved by the Koc University Ethics Committee (2014.087.IRB3.063).

**Results**

In this study, we evaluated serum Na, K, Cl, Ca, BUN, creatinine, total protein levels and MDRD [eGFR] in AD and geriatric patients with dementia. We have selected our patients from two different geographic regions of Turkey; Izmir is from the Aegean region, and Adana is from the Mediterranean. We aimed to determine if there was a correlation between kidney disease and AD. Two hundred thirty-one female and male geriatric subjects were enrolled.

We evaluated the electrolyte panel, besides the glomerular and tubular function parameters, which is effective in a thorough assessment of renal function. These parameters act as an indicator of biological and/or pathologic processes, or pharmacologic responses to a therapeutic intervention and are routinely used for monitoring the effect of treatment on a known imbalance that is affecting bodily kidney function.

Reference ranges for the studied blood tests were as follows: serum sodium (Na): 136–145 mmol/L; serum potassium (K): 3.5–5.1 mmol/L; serum chloride (Cl): 98–107 mmol/L; serum calcium (Ca): 2.2–2.7 mmol/L; blood urea nitrogen (BUN): 2.9–8.2 (mmol/L); creatinine: 59.2–103.4 μmol/L; total protein: 66–83 g/L; MDRD [eGFR]: 90 mL/min.

From Izmir Center, 153 patients were recruited to the study, of which 95 were female and 58 were male. Furthermore, patients were assigned to two different arms; while the first study arm consisted of patients with AD (n=74), the second arm included geriatric patients with dementia (n=79). In the AD arm, 51 patients were female, and 23 patients were male.

The median age in the first arm in the AD arm was 76.16±6.54 years (66–91). Our evaluation of the electrolyte panel is shown in Figure 1. The mean Na level was 144.98±4.70 mmol/L (129–155). The mean K level was 3.51±0.22 mmol/L (3.01–3.98) (Figure 2). The mean Cl level was 105.68±6.08 (93–119) (not shown in the the Figure). The mean Ca level was 2.04±0.15 mmol/L (1.75–2.33) mmol/L (not shown in the Figure). The mean serum BUN level in AD patients was 5.59±1.09 (3.2–8.2) mmol/L (Figure 4). The mean serum BUN level in geriatric patients with dementia was 5.98±0.87 (3.53–8.1) mmol/L (Figure 4). The mean eGFR level in patients from Dokuz Eylul University with AD was 66.01±5.45 (55–77) (Figure 5). The mean eGFR level in geriatric patients from Dokuz Eylul University was 94.09±3.36 (88–99) (Figure 5). The mean serum total protein level in AD was 56.8±5.1 (50.1–64) g/L (Figure 6). The mean serum total protein level in geriatric patients from Izmir was 67.9±5.3 (60.6–75.3) g/L (Figure 6).
In the second arm (geriatric patients with dementia), the median age was 79.85±6.27 years (68–95). Analysis of biochemical parameters showed that the mean Na level was 136.13±4.09 mmol/L (125–148) (Figure 1), the mean K level was 3.88±0.15 mmol/L (3.65–4.75) (Figure 2), the mean Cl level was 103.59±3.98 mmol/L (93–110) (data not shown), and the mean Ca level was 2.32±0.1 mmol/L (1.9–2.5) mmol/L (data not shown).

The creatinine results of the patients with AD and geriatric patients with dementia are shown in Figure 3. The mean creatinine level in patients with AD was 91.05±5.3 (77.8–102.5) μmol/L (Figure 3). The mean creatinine level in geriatric patients was 99.0±5.3 (86.6–105.2) μmol/L (Figure 3).

Mean serum concentrations of these tests were in the normal range, but group values were statistically divergent from normal reference values. In addition, when two different study arms were compared, a statistically significant difference was observed both in the median age (p<0.001), as well as in biochemical parameters: Na (p<0.001), K (p<0.001), Cl (p<0.05), Ca (p<0.001), BUN (p<0.05), creatinine (p<0.001), MDRD [eGFR] (p<0.001) and total protein (p<0.001).

The mean Na and Cl levels were higher in the first arm, compared to the second arm; on the other hand, the mean K, Ca, BUN, creatinine, total protein and MDRD [eGFR] values were found to be lower.
From Adana Center (Cukurova University, Faculty of Medicine, Neurology Clinic), we evaluated clinical biochemical test results for renal function and in our study, we recruited patients over the age of 65 with previously diagnosed AD as well as geriatric patients without dementia to evaluate BUN and creatinine levels (in our evaluation, we used a Beckman Coulter DXI device according to the guidelines of the manufacturer).

From Adana Center, 78 patients were recruited to the study, of which 33 were with AD and 45 were geriatric patients with dementia. In the AD arm, 22 of the patients were male, whereas 11 of them were female, with a median age of 76.42±9.96 years (55–91). Evaluation of clinical biochemistry test results for discerning renal function was noted as follows: Na: 137.54±2.50 (132–141) mmol/L (Figure 7), K: 4.30±0.54 (3.30–5.40) mmol/L (Figure 8). The mean creatinine and BUN levels were 95.3±54.85 (40.66–323.54) μmol/L, 6.1±3.3 (2.5–15.4) mmol/L, respectively (Figure 9 and Figure 10). The mean Cl level was 108.57±2.68 (93–110) mmol/L (data not shown), and the mean Ca level was 2.1±0.1 (1.9–2.5) (data not shown) mmol/L. The mean MDRD [eGFR] level was 46.02±5.15 (55.0–77.0) mL/min (not shown in the Figure). Finally, the mean total protein level was 56.86±15.74 (15–72) g/L.

In the geriatric arm, 21 of the patients were male, and 24 were female, with a median age of 71.98±6.14 years (68–88). The median sodium level was 136.95±3.98 (125–145) mmol/L (Figure 7). The mean potassium level was 4.54±0.71...
The mean creatinine level was 78.11±28.66 (33.59–161.77) μmol/L (Figure 9), and the mean BUN level was 6.4±3.5 (2.6–22.1) mmol/L (Figure 10). The mean Cl level was 105.29±3.67 (93–110) mmol/L (data not shown), and the mean Ca level was 2.3±0.1 (1.9–2.5) mmol/L (data not shown). The mean eGFR level in patients from Adana with AD was 75.94±29.43 (13.11–148.57) mL/min (Figure 11). The mean eGFR level in geriatric patients from Adana was 89.92±32.84 (38.76–179.54) mL/min (Figure 11). The mean serum total protein level in patients from Adana with AD was 56.9±15.7 (15–72 g/L (Figure 12). The mean serum total protein level in geriatric patients without dementia from Adana was 63.6±8 (47–78) (Figure 12).

When we compared the age of the groups, the median age in the AD arm was significantly higher compared to the geriatric arm (p=0.004).

On the other hand, BUN, creatinine, sodium, potassium, chloride, calcium, total protein and MDRD eGFR levels did not show significant differences between the groups (p=0.96, p=0.259, p=0.220, p=0.215, p=0.84, p=0.46, p=0.27, p=0.25 respectively).

Urinary protein levels were omitted as they were found to be in normal ranges. In this study, we have used serum concentrations such as: creatinine, blood urea nitrogen (BUN), as well as electrolytes, to determine renal function.

Discussion

Renal disease is a risk factor for vascular diseases and for dementia, and renal insufficiency can in fact be a complication of AD as emerging evidence suggests that vascular mechanisms mediate the link between renal disease and dementia (1). We began our evaluation by first keeping in mind that healthy aging is a complex phenomenon with the interplay of many modifiable as well as heritable factors including but not limited to genetic and environmental factors, dietary habits, socioeconomic factors such as access to proper healthcare, degree of exposure to exogenous toxins etc. Multi-morbidity is common among older adults; however, for many aging-related diseases, population-based statistical data, including the statistics for U.S population that is commonly used as a model population, fell short in shedding light on how early these conditions begin to appear in life (21).

Definitive pathologies of AD are not well understood yet. It is usually proposed to be the sum of many factors such as genes, environment, lifestyle, and any kind of stress has a triggering effect in the occurrence of tangles and senile plaques. A previous population-based study has shown that individuals with decreased kidney function, as measured by low glomerular filtration rate, have smaller brain volume, smaller deep white matter volume, and more white matter lesions (1, 22–26). In addition, glomerular filtration rate is related to white matter lesions, subcortical atrophy, and to a lesser extent lacunar infarcts (24, 26). Therefore, poor kidney function is highly prevalent in the general elderly population (27–29). Electrolytes have enormous roles, such as modification of brain functions. In a previous study, it was demonstrated that exercise leads to increased serum calcium levels, and the calcium is transported to the brain. This in turn enhances brain dopamine synthesis through a calmodulin-dependent system, and increased dopamine levels regulate various brain functions (30). In addition, electrolytes are correlated with brain energy metabolism and it has been reported that a decline in cognitive functions may be miti-
gated by incorporating nutraceuticals in the diet (31). Dementia has been defined by Qui C as a clinical syn-
drome, which is characterized by a cluster of symp-
toms and signs manifested by difficulties in memory, dis-
turbances in language and other cognitive func-
tions, changes in behavior, and impairments in activi-
ties of daily living (24). Recent studies aimed at dis-
cerning a connection between cognitive brain
functions and renal function have proposed that there
is an observable decline in renal function in patients
with AD, which in turn can create a risk (1, 22).

In this study, we evaluated and presented a clini-
cal biochemistry panel of selected serum tests which
are widely used for monitoring kidney function. We
found that renal function, in fact, differed in geriatric
dementia and patients with AD. These results may be
correlated with the advanced age group of our patient
population. Also, although we observed significant
difference between patients with AD and geriatric
dementia patients’ results in Izmir Center, the same
statistical pattern did not emerge in patients recruited
from Adana Center. However, Adana Center also
included geriatric patients without clinical dementia
as a control group. This, in turn, can be attributed to
the geographical differences, including access to
healthcare and dietary habits.

Nonetheless, when we compared the study
arms of AD and geriatric patients, although the med-
ian age was found to be lower in Izmir Center, we did
not observe a significant difference between these
study arms for renal function in our selected serum
samples. However, the progressive decline of renal
function with aging is not inevitable and there is an
age-related decrease in glomerular filtration rate in
elderly people with diabetes, hypertension (33, 34).
Various researchers have proposed different ways to
define GFR (35). Therefore, it is essential in clinical
evaluations to include every variable and factor when
clinically examining an organ function or an enzyme
in all aspects of health (37–39).

Conclusion

From a public health perspective, Turkey still
lacks valuable statistical data for age-related diseases,
which are highly relevant in observing emerging com-
orbidity and clinical correlations when monitoring
such fragile populations. We examined the associ-
ations between AD and renal dysfunction in geriatric
patients as reflected by our selected serum routine
tests for normal renal function in a Turkish population
from two distinct geographical centers with palpable
differences in lifestyles including dietary habits. We
conclude that renal function differs significantly in
various age groups of AD and geriatric patients in our
population.

In order to discern valuable and practical data
that could later be translated to patient care, we pro-
posed that geriatric patients should be grouped by
age, per decades – i.e. 65–74 as the first group,
75–84 as the second group, 85–95 as the third
group and finally the fourth group of more than 95
years of age. We need further randomized, controlled
studies for this classification to recalculate new indica-
tors of aging based on the cutoff ages as stated above
between these groups.

Our study showed that age-associated decline in
renal function in elderly subjects and patients with AD
is correlated with co-occurrence even though our
findings are not conclusive that renal function is one
of the risk factors in AD due to limitations in our sam-
ple size.

Conflict of interest statement

The authors stated that they have no conflicts of
interest regarding the publication of this article.

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