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Cognitive Impairment in Chronic Kidney Disease-Prevalence, Mechanisms and Consequences

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Abstract

In ageing populations, chronic kidney disease (CKD) gets an increasing health problem worldwide. While current therapy of CKD mostly focusses on kidney function and cardiovascular comorbidity, cognition, which crucially influences adherence to CKD therapy, is often neglected. Prevalence of cognitive impairment is high in CKD, ranging from 17% to 87%, depending on CKD severity and cognitive domain affected. In contrast to Alzheimer's disease patients, which often show impairment in memory function, CKD patients present with a broader spectrum of cognitive deficits, namely impairment in executive function, information processing, language and visuoconstruction which is usually mild in early CKD stages but advances with CKD progression and progression of comorbidities. Mechanisms underlying cognitive impairment in CKD are discussed and conclusions are derived how cognitive impairment may be prevented in CKD and, if cognitive deficits are present, how cognitive impairment may be taken into consideration in patient management.

Keywords: Chronic kidney disease; Cognitive impairment; Cerebral microangiopathy; Cerebral small vessel disease; Vascular risk factors; Dialysis

Introduction

Due to consistently low birth rates and increasing life expectancy in industrialized countries [1], age-related diseases like chronic kidney disease (CKD) get an increasing health problem worldwide [2,3]. CKD is linked to age-related renal function decline which is accelerated in comorbid conditions like hypertension, diabetes and obesity [4,5]. Regarding consequences of CKD, most studies concentrate on cardiovascular morbidity and mortality [6], while cognitive function, which is an important determinant of adherence to CKD therapy, is often overlooked [7]. Cognitive impairment in CKD is getting an increasingly relevant topic for healthcare systems, since CKD prevalence worldwide is estimated to be about 12% [8] and cognitive impairment to affect 17% to 87% of CKD patients, depending on CKD severity [7,9-15].

Prevalence of Chronic Kidney Disease

CKD is diagnosed by indicators of kidney damage as well as indicators of decreased kidney function. Kidney damage is revealed by imaging or proteinuria that is mostly assessed by albumin to creatinine ratio (ACR) while kidney function is evaluated by glomerular filtration rate (GFR). GFR is usually estimated (eGFR) using serum creatinine concentrations by means of different equations of which the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16] should be preferred over the Modification of Diet in Renal Disease (MDRD) equation [17] according to current recommendations by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline for evaluation, classification, and stratification of chronic kidney disease [18]. In specific cases, GFR should additionally be estimated from serum cystatin to confirm CKD diagnosis [18]. Based on eGFR and ACR, severity of CKD is classified according to stages [18]. Stratified by stages, global prevalence of CKD is 3.5% for stage 1 (eGFR>90 ml/min/1.73 m^2+ACR>30), 3.9% for stage 2 (eGFR 60–89+ACR>30), 7.6% for stage 3 (eGFR 30–59), 0.4% for stage 4 (eGFR 29–15) and 0.1% for stage 5 (eGFR<15) [8]. Consequently, healthcare systems are mostly affected by the rather mild CKD stage 3, which due to an increase in CKD prevalence of 0.4% per year from the age of 30 years [8] is further highly prevalent in elderly people with about 35% of people over 70 years suffering from CKD stage 3 [19]. Stage 3 represents an important cutoff for CKD patient care since these patients should be included in a CKD register and monitored at least once per year [18]. Early stages of CKD like stage 3 are often asymptomatic and thus not diagnosed early enough for prevention or delay of progression to more severe stages [5]. Interestingly, patients with early stages of CKD already show cognitive impairment [20]. Depending on CKD stage, CKD is frequently associated with prevalence of cognitive impairment in different domains including executive function, information processing speed, memory and language, which range from 17% to 87% [7,9-15].

Prevalence of Cognitive Impairment in Chronic Kidney Disease

Cross-sectional studies are able to evaluate the prevalence of cognitive impairment in CKD. However, it is also of high clinical relevance to understand mutual links between CKD and cognitive impairment to develop strategies that allow us to prevent or delay cognitive decline. For that purpose, longitudinal studies are needed. So far, the majority of longitudinal studies reported decline in cognitive performance in CKD patients [21]. Unfortunately, in most of the previously published longitudinal studies, the association between CKD and cognitive performance over time was not the primary focus, thus participants were recruited outside hospital environments and only partly suffered from CKD. Further, mostly short screening tools like the Mini-Mental State Examination (MMSE) test or telephone interviews were used to assess cognitive performance which does not allow evaluating mild cognitive deficits and different domains. In addition, there is a problem with the selection of an adequate control group to evaluate cognitive

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performance in CKD because most studies used healthy control subjects or norm values from healthy subjects published in literature. Since CKD patients often suffer from comorbidities like hypertension and diabetes [4,5], this procedure could overestimate cognitive impairment caused by CKD due to the confounding influence of CKD-associated risk factors and comorbidities on cognition. To overcome this problem, the New Tools for the Prevention of Cardiovascular Disease in Chronic Kidney Disease (NT^{CVD}) study compared well-controlled CKD patients recruited in a dedicated university department of nephrology with control patients without CKD but with similar vascular risk profile in cognitive performance assessed with a standardized comprehensive test battery comprising 10 neuropsychological tests at baseline and two-year follow-up [22]. In the cross-sectional analysis based on 119 CKD patients stages 3-5 (including 35 on hemodialysis) and 54 control patients, 19% of CKD patients showed impairment in memory, 26% in information processing, 38% in executive functions, 35% in language and 39% in visuoconstruction, defined by test scores more than one standard deviation below the mean of the control group. Patients on hemodialysis only showed significantly poorer results than CKD patients without hemodialysis in the language domain. In the summary score of all tests, about one third of all CKD patients showed impaired performance. Based on published norm values (T-scores), the summary score of CKD patients was only about half a standard deviation below that of the control group. This difference reached significance for both CKD patients with and without hemodialysis but demonstrates that cognitive impairment in CKD is rather mild. Multivariable regression analyses showed that high patient age, high HbA1c and high fibrinogen in blood were associated with cognitive impairment, suggesting an influence of disturbed glucose control and inflammation [20]. In the longitudinal course, cognitive performance remained rather stable in CKD patients with only higher age predicting cognitive decline. Also markers of kidney function and vascular risk remained stable during the two-year follow-up in CKD patients and controls, indicating that dedicated medical care with tight risk factor control might prevent cognitive decline in CKD patients [22].

In line with this, Davey et al. [23] could not show an association between baseline eGFR as indicator of kidney function and change in cognitive function also assessed with a comprehensive neuropsychological test battery at baseline and 5-years follow-up, but between decreases in eGFR and decreases in cognitive performance, with about 37% of CKD patients experiencing a clinically relevant deterioration of eGFR defined by >3 mL/min/1.73 m^2/year, which was twice the frequency observed in the NT^{CVD} cohort. Also in accordance with this finding of high relevance of tight control of kidney function and CKD-associated risk factors and diseases for the prevention of progression of cognitive deficits is the positive effect of dialysis and transplantation therapy on cognition [24]. For hemodialysis patients it is important to consider the timing of neuropsychological examination. In general it has been shown that patients with hemodialysis show more severe cognitive deficits than patients without hemodialysis [11], but there are high inter- and intra-hemodialysis session fluctuations [25,26]. Williams et al. [25] for example examined cognition 1, 24 and 67 h after the last hemodialysis session in 20 CKD patients receiving hemodialysis three times a week and in 10 patients on continuous ambulatory peritoneal dialysis (CAPD) and observed greatest impairment 67 h post-dialysis in hemodialysis patients while performance remained stable in CAPD patients, which the authors attributed to increasing accumulation of toxic uremic metabolites in the period between the hemodialysis sessions [25]. Within one session, there was a significant improvement from immediately before dialysis to upon completion time in hemodialysis patients while there was no significant change in the CAPD group [26]. However, kidney transplantation is the therapy of choice in end-stage renal disease and should usually be preferred over hemodialysis because cognition mostly improves after successful kidney transplantation compared with previous adequate hemodialysis [24]. In the increasing number of elderly patients desiring kidney transplantation, the benefits of improved cognitive outcomes after transplantation due to partly reversion of underlying mechanisms have to be traded off against the risk of surgery as well as side-effects or complications of immunosuppressive medication [27].

Mechanisms of Cognitive Impairment in Chronic Kidney Diseases

Although the exact pathomechanisms of cognitive impairment in CKD are still not completely clear, mixed cerebrovascular disease including overt ischemic or hemorrhagic stroke [28], as well as subclinical alterations like cerebral microbleeds [29], white matter lesions, and atrophy [30] has been suggested to play an important role [31]. In patients receiving hemodialysis, additional mechanisms contributing to cerebrovascular disease have been put forward including rapid changes in blood pressure, microembolization and dialysis disequilibrium [32]. In a recent review, van Sandwijk et al. [27] developed a comprehensive model of pathophysiolocial pathways contributing to cognitive impairment in CKD. According to this model, uremic toxins, hyperparathyroidism and Klotho deficiency lead to chronic inflammation, endothelial dysfunction and vascular calcification, which results in cerebrovascular disease. In addition to vascular pathology, also Alzheimer pathology should not be neglected. Various vascular risk factors which are highly prevalent in CKD like hypertension are not only associated with vascular dementia, but also Alzheimer's disease [33]. Furthermore, it has already been shown that cystatin C, which co-localizes with β-amyloid in brains of Alzheimer's disease patients, was associated with cognitive impairment and cognitive decline in a large elderly community-dwelling cohort as well as in a CKD cohort [34,35]. Since CKD prevalence and cognitive impairment increase with age, but often are not diagnosed in the early stages, the above-mentioned NT^{CVD} study also analyzed the association between plasma β-amyloid and cognitive impairment as well as cognitive decline during two-year follow-up in CKD patients with different CKD stages and controls matched for vascular risk factors based on the idea that successful Aβ elimination, which is compromised in Alzheimer's disease [36], requires not only Aβ efflux from the brain into the blood, but also peripheral Aβ clearance from the blood e.g. via kidneys [37]. In line with previous findings, plasma levels of Aβ40 and Aβ42 increased with increasing stage of CKD at baseline [38] and total plasma baseline plasma Aβ showed a tendency towards significant association with baseline cognition when adjusted for age while it was significantly associated with cognitive decline from baseline to the two-year follow-up [39].

Clinical Implications of Cognitive Impairment in Chronic Kidney Disease

To date, diagnosis of early stages of cognitive impairment in CKD is often missed by nephrologists and primary care physicians [31] because they mainly focus on optimizing cardiovascular and metabolic parameters. To overcome this problem and prevent or delay the development of more advanced stages of cognitive impairment in CKD, standardized screening protocols should be developed. The Mini-Mental State Examination (MMSE) test is currently the most widely used screening tool for cognitive impairment in the general population,

however it is not able to detect mild cognitive impairment and especially not impairment in executive function which is highly prevalent in CKD [40]. For the CKD context, further the Cognitive Capacity Screening Examination (CCSE) has been suggested to complement MMSE to evaluate cognitive function and the Kidney Disease Quality of Life (KDQOL) self-report instrument including a cognitive function subscale (KDQOL-CF) to additionally assess health-related quality of life [12]. To complement cognitive screening, magnetic resonance imaging could be useful to detect cerebrovascular disease as important determinant of cognitive impairment in CKD.

To date, the clinical relevance of cognitive impairment still remains to be determined but cognitive impairment could impact compliance with diet, fluid restriction, adherence to medication and dialysis schedules, ability to make complex decisions, and self-care behaviours [25]. Based on this idea, it was suggested to pitch patient education materials at a level of around the 5th grade (age 10-11 years), which however so far mostly is not realized [41]. Further testing is needed to determine adequate levels of patient information provided by caregivers.

Suggestions to prevent or delay the development of cognitive deficits in CKD concentrate on adequate management of CKD itself and vascular and nonvascular CKD-related risk factors like hypertension, diabetes, hypercholesterolemia, smoking, cardiovascular disease, hyperhomocysteinemia, inflammation, anemia and hyperparathyroidism as well as procedure-related risk factors [12,18]. As to procedure-related risks for cognitive impairment in CKD, different types of dialysis have been compared. Since hemodialysis is an intermittent treatment mostly applied 3 times a week in end-stage renal disease, fluid and uremic toxins have to be removed at a high rate leading to intradialytic hypotension and rapid osmotic changes. It has already been shown that dialysate cooling can reduce blood flow variability and partly protect against development of white matter lesions [42]. More frequent hemodialysis to avoid rapid fluid and osmotic changes however could not consistently show benefits for cognitive function [43,44], but peritoneal dialysis was in some studies associated with better cognitive outcomes compared to hemodialysis although selection bias has to be taken into account here [45]. The effect of diet (limiting phosphate intake, taking phosphate binders, limiting sodium and fluid intake) to avoid fluid and osmotic changes [18] on cognition in CKD has to our knowledge so far not systematically been investigated and also the effect of exercise still needs further investigation even though exercise is recommended in CKD patients [18,46]. For vitamin D supplementation, which is important for cognition [47] and bone mineral density [18], evidence is so far insufficient for a recommendation in CKD patients with vitamin D deficiency on a regular basis, either for skeletal or non-skeletal health outcomes [48, 49]. While vitamin D deficiency is a well-known risk factor for cognitive impairment in the general population and it has been hypothesized that this association is even stronger in CKD patients, studies in CKD patients are sparse [50]. So far, two studies reported an association of low vitamin D levels with cognitive impairment, one study recruiting hemodialysis patients [51] and the other peritoneal dialysis patients [52]. The only study which included patients with and without dialysis observed no significant association between vitamin D levels and cognitive function in multivariable models [53]. Special attention in the management of cognition in CKD is also paid to anemia, in hemodialysis as well as in predialysis stages of CKD. Anemia has been associated with cognitive impairment in CKD patients in some studies [54,55], and correction of anemia with erythropoietin treatment has been shown to improve cognition [56]. However, according to current guidelines for anemia management it has to be considered that diagnosis of iron deficiency anemia can be difficult using standard markers due to a complex inflammatory situation in CKD and that some patients fail to respond to erythropoietin treatment [57].

Importantly, patients with CKD progression are suggested to be treated in a multidisciplinary care setting including dietary counseling, advice about different renal replacement therapies and cardiovascular risks as well as psychological and social support [18]. In view of the high percentage of cognitive impairment, reduced quality of life and depression even in stable CKD patients [22,58], psychological screening should probably get integrated in clinical routine for CKD treatment.

Conclusion

Cognitive impairment in CKD is still widely neglected in clinical diagnostics and therapy despite its increasing prevalence in ageing populations. The prevalence of cognitive impairment in CKD is high and increases with increasing CKD severity. Adequate screening procedures able to detect early signs of cognitive impairment will have to be established and pathomechanisms of cognitive impairment will further have to be clarified, e.g., by brain imaging, blood and urinary assessments. Current clinical recommendations that largely focus on the control of CKD and its cardiovascular comorbidities should more systematically evaluate cognitive deficits and adapt patient counseling to cognitive function.

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