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Cognitive disorders in patients with chronic kidney disease: specificities of clinical assessment

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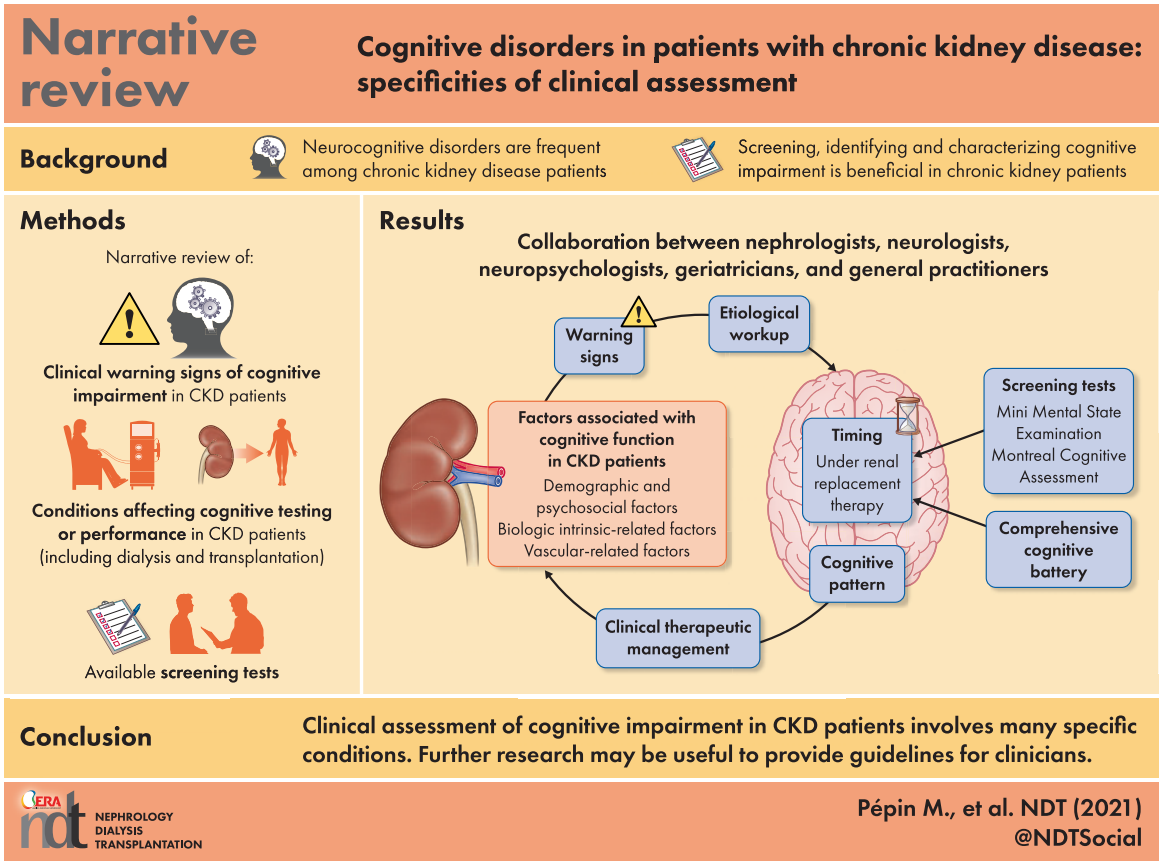
ABSTRACT

Neurocognitive disorders are frequent among chronic kidney disease (CKD) patients. Identifying and characterizing cognitive impairment (CI) can help to assess the ability of adherence to CKD risk reduction strategy, identify potentially reversible causes of cognitive decline, modify pharmacotherapy, educate the patient and caregiver and provide appropriate patient and caregiver support. Numerous factors are associated with the development and progression of CI in CKD patients and various conditions can influence the results of cognitive assessment in these patients. Here we review clinical warning signs that should lead to cognitive screening; conditions frequent in CKD at risk to interfere with cognitive testing or performance, including specificities of cognitive assessment in dialysis patients or after kidney transplantation; and available tests for screening and observed cognitive patterns in CKD patients.

Keywords: chronic kidney disease, clinical assessment, cognitive impairment, cognitive screening test, comprehensive battery

GRAPHICAL ABSTRACT



INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem with a high global incidence and prevalence, with important multisystemic complications leading to poor outcomes and high-cost treatments [1]. According to Kidney Disease: Improving Global Outcomes, CKD is defined as abnormalities of kidney structure or function present for >3 months with implications for health. The following criteria determine the diagnosis: decreased glomerular filtration rate (GFR; <60 mL/min/1.73 m^2) or evidence of kidney damage such as albuminuria, tubular disorders, urine sediment abnormalities, structural deviations detected by histology or by imaging methods or a history of kidney transplantation. The reduction of GFR and increased albuminuria have a crucial role in the development of complications of CKD, and for this reason the disease is classified in five stages based on the GFR and risk levels are subclassified according to albuminuria levels [1]. CKD stages are associated with all-cause death, cardiovascular death, anaemia and bone and mineral disorders, among other complications [2]. The prevalence of CKD and cognitive impairment (CI) both increase with age. Cognitive changes occur early in CKD, when GFR decreases to <60 mL/min/1.73 m^2 or even before [3, 4].

The latest version of the Diagnostic and Statistical Manual of Mental Disorders defined neurocognitive disorder (NCD) as primarily cognitive disorders, acquired and progressive [5]. Deterioration can affect one of the following six cognitive domains: complex attention, executive function, learning and memory, language, perceptual motor and social cognition. In mild NCD [corresponding to the state usually called 'mild cognitive impairment' (MCI)], the individual remains functionally independent, while in major NCD (subsumes the entity called 'dementia'), CI is severe enough to compromise social and/or occupational functioning [6]. Cognitively impaired CKD patients often exhibit executive dysfunction that would be expected in vascular NCD, but CKD patients are also at higher risk of Alzheimer's disease and mortality compared with the general population [7]. CI is associated with adverse outcomes and financial and social costs, including caregiver burden. CKD patients [especially when under renal replacement therapy (RRT)] could benefit from cognitive screening. Identifying CI in patients with CKD can help to assess the ability to adhere to a CKD risk reduction strategy, identify potentially reversible causes of dementia, modify pharmacotherapy, educate the patient and caregiver and provide appropriate patient and caregiver support. The potential benefits of screening likely outweigh the possible risks associated with identification, such as negative reaction to the diagnosis or stigma resulting from a diagnosis of dementia. We aim to review the specificities of clinical assessment for cognitive disorders in CKD patients: clinical warning signs that should lead to cognitive screening;

conditions frequent in CKD that may interfere with cognitive testing or performance, including specificities of cognitive assessment in dialysis patients or after kidney transplantation; and available tests for cognitive screening and observed cognitive patterns in CKD patients.

Warning signs of cognitive decline in CKD patients

Neurological complications frequently become clinically evident in advanced stages of the disease, therefore early detection and management of these conditions could reduce their impact at later stages [8]. Of interest, subjective cognitive complaints are not highly correlated with the presence of objective CI in end-stage renal disease (ESRD), highlighting the importance of periodic screening for early identification of CI that may lead to targeted interventions and timely discussions with the patient and his/her family [4, 9, 10]. Nephrologists and other clinicians may rely on their clinical judgement to obtain appropriate diagnoses. Of note, a previous study reported that mental impairment among haemodialysis (HD) patients was poorly recognized by healthcare providers/HD technicians, even though they reported spending an average of 47 min with each patient during each of the twice- or thrice-weekly treatments [11].

History taking and physical examination in conjunction with neuropsychological testing can accurately identify cognitive declines. Caregivers and family often notice cognitive deficits before they are apparent to clinicians. Therefore history taking from both the patient and caregiver/family is important for accurate reports on the onset, duration and severity of cognitive and behavioural deficits, the presence of functional impairments and other symptoms (e.g. sleep disturbance, depression, etc.) or other events including unexplained falls or confusion about medication [10, 12]. Of note, caregiver-reported sleep disturbances are frequently associated with early stages of dementia and might be considered as warning signs of cognitive deterioration [13]. The examiner should look for focal neurological deficits such as tremors, bradykinesia or rigidity suggestive of previous stroke and signs of parkinsonism [10].

Assessment of functionality in everyday activities and mobility performance metrics such as the gait speed assessment could also offer hints of cognitive decline. For instance, mobility performance metrics that involved multifaceted coordination between different parts of neuropsychology, such as cumulated posture duration and postural transition, could assist in discriminating those with and without CI [14]. CI suspicion may lead to a global and comprehensive patient assessment, especially screening for factors affecting cognitive performance. Older CKD patients might benefit from a nephrology-tailored comprehensive geriatric assessment including a cognitive assessment [15].

Conditions affecting cognitive assessment in CKD patients

Numerous factors can affect the results of cognitive assessment and cause deviations from the 'norm' in the psychometric definition. These factors should be considered when interpreting results in patients with CKD.

Demographic and psychosocial factors . Demographic factors such as lower education status, gender and age are key factors affecting the results of cognitive testing in the general population. Advancing age, a lower educational level and female gender are associated with poorer performance [15]. However, the impact of such factors on cognitive testing among CKD patients is limited [16]. Psychosocial factors including social support, socio-economic care and access to healthcare were also found to influence cognitive functioning in the general population. Similarly, data are limited regarding such factors and CI in this patient population. Of note, marital status, religious activity and employment were found to influence psychosocial adjustment to dialysis treatment and the risk for developing depression among dialysis patients [17].

Drug-related factors, sleep and depression. Multiple medications are required in CKD patients and the optimal dosing of several medications is unclear, therefore these patients could be more susceptible to potential adverse drug effects and interactions between medications [18]. Some medications are associated with CI in CKD patients, such as H1-receptor antagonists and opioids, probably because of their anticholinergic effect [19]. If possible, unnecessary or ineffective medications with central nervous system activity should be discontinued [19]. In addition, sleep disturbances are often underdiagnosed and undertreated in CKD patients, which can impact cognitive function (e.g. memory and concentration), leading to excessive daytime fatigue and sleepiness, impairing cognitive abilities directly [20]. Sleep-disordered breathing (sleep apnoea) was also found to affect cognitive testing in CKD patients [21]. Lastly, depression was found to be highly prevalent in dialysis patients compared with the general population, with most studies estimating that 20–30% of such individuals are depressed [22, 23]. Even though depression is relatively common in patients with all stages of CKD, it remains significantly underdiagnosed [20, 24]. Depression may influence the results of cognitive testing and hence assessment of depression and anxiety should be part of all neuropsychological evaluations [25].

Factors associated with impaired cognitive performance

Biologic intrinsic-related factors. Anaemia has been linked with cognitive deficiency in both CKD and the elderly [26]. This might be due to a decreased blood haemoglobin concentration that leads to reduced oxygen delivery to the brain, with a detrimental effect on brain metabolism, or could be because once the blood haemoglobin concentration declines, cerebral blood flow increases from normal to high levels, resulting in increased distribution of uraemic toxins to the brain. Of interest, early small-scale studies have shown cognitive improvement with the treatment of anaemia in CKD patients; however, it remains undetermined whether this is because of the improvement in the blood count or due to an independent effect of supplementation with erythropoiesis-stimulating agents (ESAs) [27]. This observation was not confirmed in more recent large-scale studies, where ESAs have not shown the expected beneficial clinical cognitive effects in CKD patients. Also, putative neurotoxins, including parathyroid hormone and by-products

of nitrogen metabolism, have also been mentioned as possible mediating factors of CI in CKD, but the underlying mechanisms are not well understood [28]. Interestingly, recent findings on the role of the glymphatic system, which clears the brain of protein waste products, primarily during sleep, offer pathophysiological hypotheses in CKD patients [13]. The link between uraemic toxins and cognitive disorders is described in detail in a parallel article in this supplement (Liabeuf *et al.*, NDT 2021). Evidence data about albuminuria as a risk factor for CI and dementia are also detailed in another article in this supplement (Hafez *et al.* NDT 2021).

Amino acids. Amino acids have a multifaceted physiological significance in addition to being the main building material in protein synthesis. Plasma levels of homocysteine, cysteine and cysteine sulfinic acid are elevated in uraemia and the percentages of protein-bound homocysteine and cysteine are higher in uraemic dialysis patients than in conservatively treated patients. Elevated homocysteine levels have been associated with impairment and decline on tests of cognitive function. Hyperhomocysteinaemia and low taurine levels are probably involved in the pathogenesis of concomitant cardiovascular and cerebrovascular diseases in patients with CKD. Supplementation with vitamin B (combinations containing B6, B12 and folic acid) in the Homocysteine Study to some extent corrected hyperhomocysteinaemia but had no effect on cognitive function [29]. The lack of a positive effect can be attributed to comorbidities [29]. Increased amounts of aspartate may contribute to ageing-related CI by facilitating excitotoxicity [30].

Vascular-related factors. Large prospective studies have indicated several vascular factors, including older age, hypertension, diabetes mellitus and dyslipidaemia, as risk factors for dementia in the general population [31]. Dialysis and CKD populations share most of these same risk factors for CI. Despite there is greater prevalence of traditional vascular risk factors [e.g. hypertension, diabetes mellitus, hyperlipidaemia, cigarette smoking, atrial fibrillation (AF) and myocardial infarction] and cardiovascular disease (CVD) among CKD patients, studies to date have failed to establish a direct link between any of these factors and the presence of cognitive dysfunction in patients with CKD [11, 28, 32, 33]. This implies that other factors may be implicated in the occurrence of CI.

A possible role has been suggested for novel vascular risk factors such as elevated levels of inflammatory mediators, which have been observed in CKD patients, highlighting the possibility of an association between inflammatory markers and all-cause dementia, as reported in the general population [34, 35]. Likewise, elevated levels of prostaglandin D2 synthase, a mediator of inflammation, could induce neural apoptosis in dialysis patients [36]. Higher C-reactive protein levels were also reported in dialysis patients [37] and have been linked to CI in the general population [38].

The significance of silent cerebrovascular disease is highlighted by studies that showed an association between CI and silent brain infarction, which was most commonly attributable to subcortical lacunar infarcts in the general population [39]. Silent brain infarction has been shown to be an independent risk factor for future cerebral and vascular morbidity and incident dementia in both CKD/dialysis patients and the general population [39–41]. Previous magnetic resonance imaging studies have indicated that clinically silent white matter hyperintensities of presumed vascular origin appear in $\geq$50% of patients with CKD [41, 42] and relate to deficits in the cognitive domains of executive function and processing speed, suggesting a subcortical, vascular pattern of CI. Notably, established risk factors for white matter disease in CKD include advanced age, hypertension and smoking [41]. Other lesions may be involved besides lacunar infarcts and white matter hyperintensities, such as brain microbleeds or atrophy related to cerebral small vessel disease.

Cardiac arrhythmias. CVDs frequently occur in CKD patients [43]. CKD is combined with haemodynamic changes, which might further contribute to the negative changes in cardiac structure. In particular, it has been reported that 50% of all patients affected by CKD Stages 4 and 5 have CVD and cardiovascular mortality accounts for almost 50% of all deaths in CKD patients (Stages 4 and 5) compared with 26% of age-matched healthy control subjects [43]. Focusing on myocardial alterations, left ventricular hypertrophy (LVH) is present in almost 30% of CKD patients, a prevalence that increases up to 70–80% in CKD Stage 5 patients [44]. LVH was associated with incident dementia due to the strong association with increased systemic blood pressure, followed by impaired ventricular filling, left ventricular diastolic dysfunction, whole body hypoperfusion as well as myocardial structural changes such as a dilated atrial chamber, with an enhanced probability to develop AF [45]. Such negative cardiac structural changes are often associated with a high ventricular rate [46], which again is responsible for brain hypoperfusion and sudden death. Among the cardiac arrhythmias, AF is most common, estimated to occur in 44% of CKD (Stages 3–5) patients [47]. AF is one of the treatable cognitive risk factors in CKD. Direct evidence of the strong relationship between AF and cognitive decline is also provided by the evidence that anticoagulation and ablation, but not anti-aggregation, are helpful therapeutic tools for treating AF and preventing cognitive decline [48].

Pulse wave velocity. Arterial stiffness can cause microvascular damage in the brain due to an increased impact of pulsatility on the microvasculature, which possibly alters brain structure or cognitive functioning. Several studies in CKD patients have shown an association between increased pulse wave velocity and CI (global cognition or executive dysfunction), pointing to the role of large artery damage in this complex process [49].

Specificities of cognitive assessment for patients under RRT

Dialysis. One important aspect for clinicians and researchers involved in cognitive testing of patients with CKD is the timing: when, during the day, should a cognitive test be administered? This question is especially crucial for HD patients. There is a theoretical risk that administering tests during the dialysis session may lead to altered performance due to the lack of privacy,

the ongoing extracorporeal treatment (with modifications in electrolyte and water content of the plasma), the forced immobilization, the psychologically stressful situation and the effect of accumulated toxins. Furthermore, these variables make comparisons with a control population more difficult, as non-HD control subjects are tested in completely different conditions.

To empirically test this problem, Murray *et al.* [50] observed that the Mini–Mental State Examination (MMSE) score was reduced by 1 point (4%) when administered before HD compared with the score achieved 1 h after treatment or the day after [50]. This result has been known since the 1970s and confirmed several times [51]. Unsurprisingly, the lower MMSE scores do not improve during the first hour of HD [50, 52]. Likewise, imaging studies [53] and electroencephalogram (EEG) records [54] have shown variations in brain activity according to the timing of the dialysis session.

This timing parameter seems less problematic regarding cognitive testing in peritoneal dialysis (PD), due to it being an at-home treatment and the frequent dialytic exchanges (often on the order of two to three per day, every day). Indeed, one major difference between HD and PD is the intermittent nature of the HD treatment compared with the almost continuous PD treatment. An EEG study confirmed that PD brain activity is more stable compared with the great changes occurring before and after HD (with better EEG after HD) [54]. Therefore, studies adopt an off-dialysis timing (with an interval of at least 2 h from the last session) [55]. New methods of HD (such as nocturnal HD or the use of a cooled dialysate) are expected to reduce the burden of sessions on neurocognitive function and quality of life.

These data suggest that the cognitive performance in HD patients is not stable and may constantly decrease as a function of the elapsed time from the last dialysis session. This may greatly impinge on interpretation of the results. Therefore we recommend testing patients at least 1 h after the HD session, particularly if a control group without HD is used. The testing time for PD should be the same as for the general population. We also recommend establishing appropriate timing in research studies in case patients with CKD are included.

Kidney transplantation. Cognitive function has been shown to improve after kidney transplantation, specifically in psychomotor speed, attention, visual planning, learning and memory and abstract thinking [56]. Nevertheless, CI remains more frequent in kidney transplant (KT) patients than in the general population and is associated with frailty measured using the physical frailty phenotype developed [57, 58]. Frail KT recipients are at a higher risk of immunosuppression intolerance and mortality than non-frail patients [58]. Post-KT frailty and cognitive performance are likely dynamic. On the one hand, frailty initially worsens in the first month post-KT, but then improves by 3 months post-KT; on the other hand, cognitive performance, assessed by the modified MMSE (3MSE), tends to improve in the first 3 months post-KT [57, 58]. More research is needed to differentiate if post-KT issues, like wound healing, immunosuppression and infections, may affect the reversal of frailty and CI after KT.

Of note, in animal models, stress and corticosteroids are associated with memory impairment and both reversible and irreversible changes in the hippocampus. Clinical studies observed that exposure to exogenous corticosteroids can change mood and declarative memory, but a negative effect on cognition was modest [59]. Psychopathological signs frequently observed indicate that corticosteroids may also induce functional disorder of additional brain regions (e.g. frontal and temporal lobes), which are important for cognitive and emotional processing [60]. In order to minimize the impact of high-dose steroids and operative procedures on cognition, we recommend performing an assessment at least 1 month after transplantation.

Perceived and measured cognition in KT patients differs. In 157 KT patients assessed by trained medical personnel, perceived cognition scores weakly correlated with Montreal Cognitive Assessment (MoCA) scores [61]. Therefore, as in other CKD patients, efficient cognitive screening in KT patients relies on objective screening tests. However, it is still not fully clear which screening tool should be used. Recent studies observed discrepancies in the prevalence of CI in KT patients, probably because the tests were different (MoCA, DemTect tool) [62].

Calcineurin inhibitors (CNIs) have a known side effect of neurotoxicity [63]. A small study observed that attention and working memory were impaired in KT patients treated with sirolimus or tacrolimus, while performance of cyclosporine-treated subjects was similar to healthy volunteer controls. Long-term effects of CNI on cognition and physiopathology are not well understood [63]. Further studies may establish the optimal timing for cognitive assessment after KT and identify an optimal screening test in this specific population.

Screening tests

Today, most scientific societies, including nephrology, recommend cognitive assessment in individuals with cognitive complaints and in individuals whose caregivers notice symptoms that may indicate the presence of CI, especially when there are difficulties in daily functioning. Various screening tests are commonly used in daily clinical practice to assess cognitive status [64] (see Table 1).

There is no consensus on which screening instrument should be used to identify NCD (major or mild) in people with CKD. Rather, the screening methods used reflect the availability of tests in a given language or the habits of the examinees.

In clinical practice, two main screening tests of CI are used, the MMSE and, more recently, the MoCA. As in other diseases [65], the superiority of the MoCA, which also assesses executive functions, and is especially sensitive to brain dysfunction compared with the MMSE, has been examined in several studies in CKD patients. Focusing on the few studies using a comprehensive neuropsychological battery as a gold standard and receiver operating characteristics curve analysis, the area under the curve (AUC) did not significantly differ across tests [66, 67]. This indicates that the sensitivity of both screening tests does not differ greatly, although the small to moderate sample sizes require careful conclusion. From our point of view, the important conclusion from these studies is that the sensitivity of both

Table 1. Examples of psychometric tests used in CKD patients

Examples of tests	Details of test	Function assessed	Use in CKD
Global cognition			
MMSE	30-point test (orientation, attention and calculation, memory, language and visuospatial abilities)	Screening of global CI	Yes
MoCA	30-point test (visuospatial abilities, executive functions, memory, attention, language, abstract reasoning and orientation)	Screening of global CI (including executive functions)	Yes
CDT	Non-verbal test. The patient is asked to draw a clock face and mark the hours and then draw the hands to indicate a particular time	Executive functions, visuospatial and visuoconstructional functioning	Yes
Language			
Boston Naming Test	Name objects shown in 60 black-and-white line drawings. Items are ordered according to their ability to be named, which is correlated with their frequency	Confrontation naming	Yes
Visuospatial and constructive abilities			
Cancellation test	Lines, circles, letters bells or stars are drawn in random positions on a sheet of paper (A4) and presented to patient, who is asked to cancel or cross out the target	Visual neglect, response inhibition, motor perseveration and attention	Yes
Judgement of line orientation	30-item test in which the patient is asked to match two angled lines to a set of 11 lines that are arranged in a semicircle and separated 18 degrees from each other	Visuospatial perception	Yes
Rey–Osterrieth complex figure test (copying)	Patient is asked to copy a complex geometrical figure	Complex visuospatial constructional ability	Yes
Wechsler Adult Intelligence Scale (WAIS) block design	Timed subtest of the WAIS. Identical blocks with surfaces of solid red, surfaces of solid white and surfaces that are half-red and half-white are presented to the patient. The patient is asked, using an increasing number of blocks, to replicate a pattern that the test administrator presents to the patient	Visuospatial and organizational abilities and processing speed	Yes
Episodic memory			
Verbal memory			
Free and Cued Selective Recall Test (FCRST)	The test is based on 12 pictorial stimuli. The patient is asked to identify pictured items (e.g. grapes and vest) in response to category cues (fruit and clothing). In the test phase, subjects are asked to recall the items they learned (free recall). The category cues are used to prompt recall of items not retrieved by free recall	Memory (includes assessment of retrieval processes)	Yes
California Verbal Learning Test	Patient is asked to recall List A (16 words) $\geq$5 times. List B (interference, 16 words) is administered after List A for one trial. Short-delay free recall and cued recall are administrated after List B. A long delay follows the short-delay recalls, followed by non-verbal testing	Memory (includes assessment of proactive interference)	Yes
Visuospatial memory			
Baddeley Door Test	The patient views photographs of 12 doors for 3 s each. Immediately thereafter, the patient tries to identify the door from the study list among 12 arrays of 4 doors each	Visual memory	Yes
Rey-Osterrieth Complex Figure Test (3 min recall)	The patient is asked to reproduce from memory the complex geometric figure he copied after a short delay (3 min) and then a long delay (30 min)	Visual memory	Yes
Executive functions and action speed			
TMT	Part A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. In Part B the patient must alternate between numbers and letters (1-A-2-B-3-C)	Visuomotor speed, visual attention (TMT Part A) and task switching (TMT Part B)	Yes
The Stroop Colour and Word Test	First, the subject is required to read names of colours printed in black ink. Second, the subject names different colour patches. Third, he/she is required to name the colour of the ink instead of reading the word (colour words are printed in an inconsistent colour ink)	Inhibition of cognitive interference	Yes
Semantic and literal fluency	The patient is given 1 min to produce as many words as possible within a semantic category or starting with a given letter	Lexico-semantic knowledge, lexical retrieval ability and executive control ability	Yes

Continued

Table 1. Continued

Examples of tests	Details of test	Function assessed	Use in CKD
WAIS Digit Symbol Substitution subtest	Timed subtest of the WAIS. The test involves a key consisting of numbers (1–9), each paired with a unique symbol. Below the key is a series of numbers (1–9) in random order. The subject is then allowed 90 s to fill in the corresponding symbol for each number	Processing speed, working memory, visuospatial processing and attention	Yes
Wisconsin Card Sorting Test	The subject is given a set of four stimulus cards, each different from the other in terms of colour, shape or number. The participant is asked to accurately sort every response card with one of four stimulus cards but not how to match. The administrator provides simple feedback (right or wrong) based on a predetermined rule	Abstract reasoning, mental flexibility and problem solving	Yes
Inventory of the Behavioural Dysexecutive Syndrome	Structured interview of an individual assessing changes relative to previous behaviour in 12 domains	Behavioural disorders (apathy, impulsivity, psychomotor instability, anosognosia etc.)	Yes

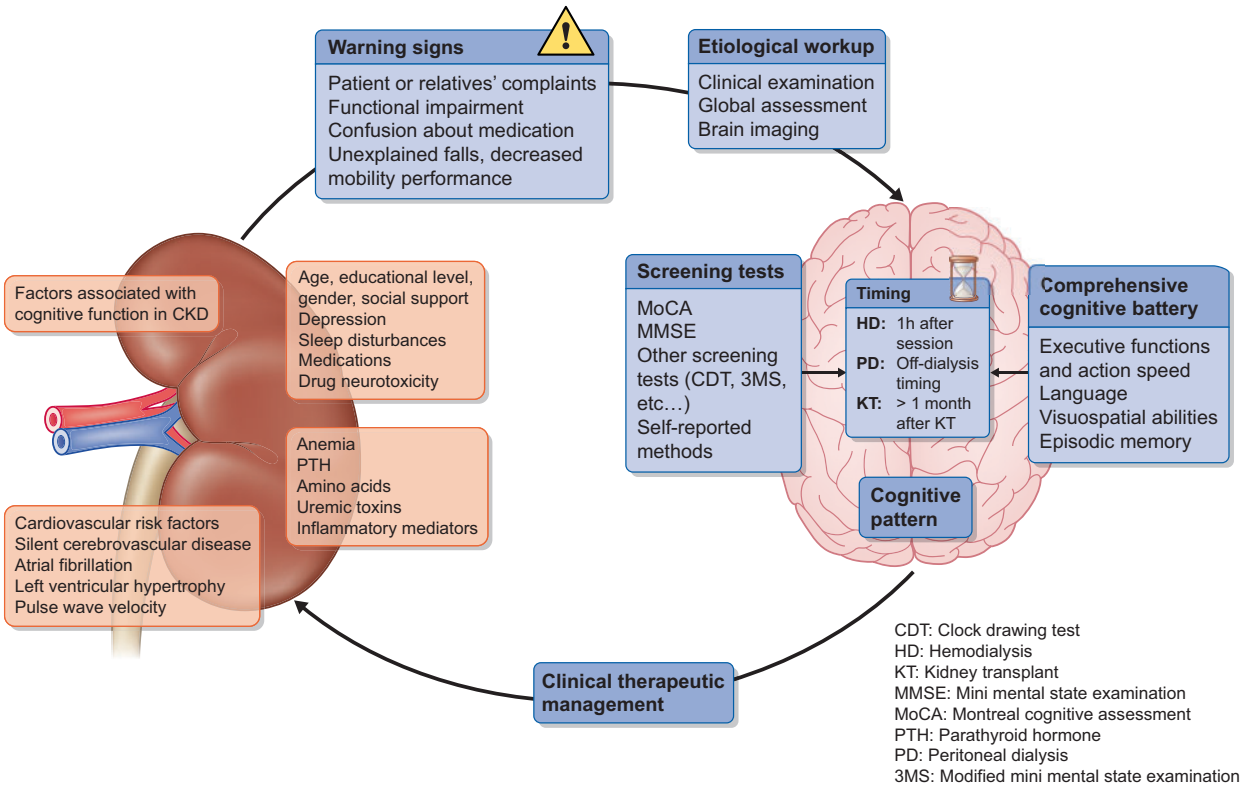


FIGURE 1: Integrating CKD in NCDs.

screening tests is usually <80%, which appears to be moderate [66–68].

Regarding other screening tests, the Clock Drawing Test (CDT), the digit span backward and the fist-edge-palm test showed similar performance in identifying MCI in this population when compared with the MoCA (≤24/30 patients) [69]. In a recently published study, Drew *et al.* [67] compared the predictive ability of MMSE, 3MSE, MoCA, Trail Making Test (TMT) Part B, Mini-Cog Test and the Digit Symbol Substitution Test performance for identifying severe CI among patients with HD. The MoCA had the highest overall predictive ability for severe CI (AUC 0.81). The score of ≤21/30 patients had a sensitivity of 86% and specificity of 55% for severe impairment, with a negative predictive value of 91%. The TMT Part B and Digit Symbol Substitution Test also performed reasonably well (AUCs 0.73 and 0.78, respectively). The other tests had lower predictive performances.

Self-reported cognitive assessment methods (e.g. MAC-Q) are also available, but these are based primarily on observations of memory deficits and may not have sufficient diagnostic sensitivity in people with CKD. Despite some limitations, self-reported assessment of instrumental activities of daily living

remains useful in determining the cognitive function of a patient. In case it is not possible to examine the patient in person, it is advisable to use tools that allow for assessment by the caregiver. The AD8 scale or Informant Questionnaire on Cognitive Decline in the Elderly are recommended. Even if physicians do not frequently use these modalities in daily practice, they can be useful for epidemiologic studies. It is worth noting that most of these cognitive tests were developed and validated in the ageing population, affected by physiological decline in both brain and renal function.

From a practical point of view, we propose using one of the main screening tests (the MoCA or MMSE) with education- (both tests) and age-adjusted (MoCA) cut-offs computed using normative data from the population of the country. Future studies are required to identify an optimal screening test and cut-off for CKD patients.

Cognitive pattern in CKD patients

The diagnosis of mild NCD and mild dementia (which is the present targeted stage of diagnostics) requires comprehensive neuropsychological assessment performed by a neuropsychologist. In addition to a positive diagnosis, comprehensive assessment determines the cognitive pattern, which constitutes a central cue for the aetiological diagnosis. The choice of tests composing the battery is determined by the clinical context in order to improve sensitivity. It usually includes tests assessing instrumental functions (language, visuospatial and constructive abilities), episodic memory, action speed and executive functions assessed both at the cognitive (i.e. tests) and behavioural (i.e. semistructured heteroquestionnaires that include social cognition) levels. Such a battery is usually not used for diagnostic purposes in patients with clear impairment on screening tests (e.g. MMSE <18 or MoCA <14); it should be interpreted using country-related norms and specific procedures to improve diagnostic accuracy [70].

The pattern of CI in CKD is not definitely established. Berger *et al.* [4] systematically reviewed CI in CKD patients [estimated GFR (eGFR) <60 mL/min/1.73 m^2] without RRT, including 44 cross-sectional and cohort studies with 51 590 participants in the final meta-analysis. Cognitive domains were not assessed with the same frequency in the studies: attention and action speed (referred to as 'orientation and attention' in the article; 28 studies), global cognition (25 studies), memory (16 studies), executive functions (15 studies), construction and motor praxis (11 studies), language (9 studies), concept formation and reasoning (6 studies) and perception (1 study). CKD patients (eGFR <60 mL/min/1.73 m^2) performed worse than control groups in almost all cognitive domains except perception, construction and motor praxis. The study of Puy *et al.* [66] formally assessed test sensitivity in 40 patients and showed that four of the tests had a Cohen's d index ≥ 0.8: TMT Part B, Digit Symbol Substitution Test, literal fluency and the groupe de reflexion pour l'evaluation des fonctions eXécutives (GREFEX) inventory of the behavioural dysexecutive syndrome. This is accounted for by the cognitive pattern with prominent impairment of action speed (also called psychomotor speed or processing speed) and cognitive and behavioural executive functions. Anxiety and depression symptoms were also common [66].

Cognitive decline occurs early in CKD and its frequency has been observed with different rates across cognitive domains according to GFR decline in these cross-sectional studies [4]. Interestingly, in studies assessing cognitive function in HD patients, the frequency of every cognitive domain measurement has the same ranges as in patients without RRT, from the most frequent (with the most frequent test used): orientation and attention (with TMT Parts A and B), global cognition (MMSE), memory (Weschler Memory Scale), construction and motor (Clock and Grooved Peg Board), executive function (Stroop test), concept and reasoning (progressive matrices), language (Hopkins Verbal Learning Test) and perception (Haltstead–Reitan Neuropsychological Battery) [71]. Executive functions and orientation and attention are the most frequently affected domains in HD patients, even if their performance is poorer than controls in other domains [51, 71]. The cognitive pattern seems to be different in PD patients, with less impaired executive function [55].

These studies converge towards a prominent impairment of three neuropsychological domains (action speed, cognitive and behavioural executive functions) followed by impairment of language and episodic memory [4, 51, 66, 71]. Such a cognitive pattern is close to that of the two leading causes of CI, vascular CI and Alzheimer's disease. Based on this review, future research may establish test sensitivity and cognitive patterns in a large and representative population of CKD patients, including full aetiological workup.

CONCLUSION

Cognitive disorders are a frequent issue in patients with CKD. Clinical assessment of CI in this population involves many specific conditions, as can be seen in Figure 1. Although much is known, gaps in knowledge remain in this area. Further research needs to be done, including the establishment of cognitive test sensitivity for the CKD and KT populations, a description of cognitive patterns and the establishment of optimal timing for cognitive assessment in dialysis patients and after KT, among others. Further research may be useful to provide guidelines for clinicians, as comprehensive clinical assessment and aetiological workup will help to provide suitable therapeutic management taking into consideration CKD specificities.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

APPENDIX

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