Mild cognitive impairment and kidney disease: clinical aspects

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Mechanisms of phosphate transport

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Abstract: Over the past 25 years, successive cloning of SLC34A1, SLC34A2 and SLC34A3, which encode the sodium-dependent inorganic phosphate (P_i) cotransport proteins 2a-2c, has facilitated the identification of molecular mechanisms that underlie the regulation of renal and intestinal P_i transport. P_i and various hormones, including parathyroid hormone and phosphatonins, such as fibroblast growth factor 23, regulate the activity of these P_i transporters through transcriptional, translational and post-translational mechanisms involving interactions with PDZ domain-containing proteins, lipid microdomains and acute trafficking of the transporters via endocytosis and exocytosis. In humans and rodents, mutations in any of the three transporters lead to dysregulation of epithelial P_i transport with effects on serum P_i levels and can cause cardiovascular and musculoskeletal damage, illustrating the importance of these transporters in the maintenance of local and systemic P_i homeostasis. Functional and structural studies have provided insights into the mechanism by which these proteins transport P_i, whereas in vivo and ex vivo cell culture studies have identified several small molecules that can modify their transport function. These small molecules represent potential new drugs to help maintain P_i homeostasis in patients with chronic kidney disease - a condition that is associated with hyperphosphataemia and severe cardiovascular and skeletal consequences.

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Mild cognitive impairment and kidney disease: clinical aspects

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INTRODUCTION

Chronic kidney disease (CKD) is now seen as a systemic disease involving also the central nervous system [1], but the link between the kidney and different organ systems and disease went unnoticed for a long time. The king of Poland, Stephen Bathory (1533–86), suffered from CKD due to polycystic kidney disease and depression [2]. Similarly, Wolfgang Amadeus Mozart was also thought to have had CKD [3] and depression [4]. A list of 'Famous People Who Have Died from Kidney Disease' [5] includes many who suffered from both CKD and depression or other signs of mental illness.

Is this a coincidence or actually evidence of a link between kidney disease and brain dysfunction? This is not merely an academic question because all forms of mental illness can seriously impair an individual's quality of life, and are frequently associated with progression of diseases and premature mortality, so it is worth the effort of trying to answer it.

Europe and much of the industrialized countries are experiencing growing numbers of patients with CKD within their ageing populations [6]. CKD is complex and potentially fatal: (i) all organs are affected, sooner or later; (ii) the balance of plasma volume, electrolytes, acid–base and minerals, metabolites, hormones and proteins is disturbed; and (iii) patients often need a multidisciplinary team approach managing complex comorbidities, drug regimens and special diets. Although the prognosis of patients with CKD remains poor, their increasing life expectancy has shifted medical attention from life-threatening emergencies to long-term complications and sequelae, and how to improve quality of life [7]. Indeed, kidney failure has detrimental effects on health-related quality of life (HRQoL), reaching levels similar to those seen in patients with metastatic cancer [8]. This might be due to psychological factors, both kidney disease and cancer being chronic diseases with a bad prognosis. However, although the effect of CKD on quality of life is more evident in advanced stages (stage G4+) and in older patients [9, 10], a large study has shown a significant decrease in HRQoL as early as CKD stage G2 [11].

Notably, neurological and cognitive impairments [12], and depression [13] are among the most debilitating consequences of CKD contributing to the significantly reduced HRQoL [14].

MILD COGNITIVE IMPAIRMENT IN CKD

Historical perspective

The recognition of the association of uraemia with brain dysfunction goes back to the 1930s when Toulouse, Marchand and Courtois postulated 'a specific disease entity with azotemia as one of the most characteristic symptoms: azotemic acute psychotic encephalitis' [15]. The disease was subsequently renamed 'uraemic encephalitis' or 'uraemic encephalopathy' [16], including 'the full spectrum of organic brain syndromes, progressing from mild impairment of intellect to coma' [17].

At the same time, post-mortem studies in humans, particularly by Olsen [18], and in animal models were devoted to identifying the underlying brain abnormalities. The major anatomical changes observed in uraemia were white matter abnormalities, brain atrophy and neuronal degeneration [17]; functional alterations were also observed, consisting of changes in the

permeability of the blood–brain barrier with resultant brain oedema [19], and altered content of neurotransmitters [20].

Initially, ‘uraemic encephalopathy’ was thought to be reversible by haemodialysis based on the assumption that it was caused by retained small molecule toxins. Already in 1967 Fishman and Raskin, however, predicted that ‘it is very likely that no single toxic compound will be identified’ [17], meaning that brain alterations might be due to multiple individual and additive causes.

At the end of the 1960s, another neurological state, caused by aggressive dialysis in advanced uraemic states, was identified and called (dialysis) ‘disequilibrium syndrome’ [21]. In the 1970s, a peculiar form of dementia associated with chronic dialysis, called ‘dialysis dementia’, was also described and attributed to trace metals, most likely aluminium [22].

In the 1990s, significant improvements in dialysis methods and regimens were achieved, and the occurrence of advanced, untreated uraemic states was significantly reduced. The incidence of ‘disequilibrium syndrome’, ‘dialysis dementia’ and ‘uraemic encephalopathy’ was beginning to decline and attention shifted to the potentially beneficial brain effects of epoetin and growth hormone in CKD [23]; probably due to the wider availability of these new therapeutic options.

Furthermore, as dialysis outcomes were steadily optimized, in part due to working groups such as DOQI in the 1980–90s, the meaning of the term ‘uraemia’ was changing from the terminal stages of body intoxication to the ‘residual syndrome’ defined by Depner [24] as the effects were not corrected by dialysis and possibly the result of other retained metabolic waste products.

With the success of the KDOQI classification of CKD in 2002, the term uraemia was confined to the terminal condition of (often more acute) intoxication. Dialytic techniques then focused on the removal of medium-sized molecules, such as β-2 microglobulin, responsible for amyloid deposition in tissues, including the brain [25]. Unfortunately, no data are available yet on the prevention of mild cognitive impairment (MCI) using these new techniques.

At the same time, milder neurological disease states, and more specifically cognitive decline in earlier CKD stages, came into focus. Thus, current studies no longer consider ‘uraemic encephalopathy’ as such, but are more commonly concerned with the recognition and nature of cognitive decline in CKD.

Cognitive assessment

Cognitive decline is one of the behavioural manifestations of brain damage in CKD. Other manifestations of brain dysfunction are sleep disturbances and depression, which represent a wide topic that is not covered in the present review.

Patients with CKD show high prevalence of depression that can often appear as a reversible form of cognitive impairment, hence it is often called ‘pseudodementia’ or ‘functional dementia’ [26]. The identification of this form is difficult and the reader should refer to more specialized reviews (see e.g. [27]).

Depression might itself be an effect of cognitive impairment. Prototypical forms of dementia such as Alzheimer's disease and dementia with Lewy bodies, are, in fact, accompanied by a high prevalence of depression [28]. Furthermore, cognitive impairment usually persists after significant improvements in depressive symptoms (see e.g. [29]). Therefore, the coexistence of depression and MCI-CKD might be part of a more general phenomenon, rather the presence of two different nosological entities.

Similarly, the association of peripheral neuropathy and cognitive impairment in patients with CKD can be observed in other conditions such as diabetes [30], vitamin B12 deficiency [31] and amyloidosis [32]. These associations wait to be better understood in the population of patients with CKD.

The cognitive decline can manifest with a continuum from mild involvement, or MCI, up to clinically relevant dementia, when interference with daily life and independency is present. Being a prodromal stage, MCI should be identified and studied in CKD before irreversible damage is present. MCI is characterized by mild impairment in several key cognitive domains, that is, executive functions of memory (learning and attention), problem solving (processing) and self-control (emotion—depression).

These domains can be captured by screening tests, for example, the Montreal Cognitive Assessment (MoCA), and neuropsychological tests, often leading to the diagnosis of MCI (Figure 1). The MoCA has been specifically designed for the detection of MCI, with a sensitivity of 80–100% and specificity of 50–76% using a cut-point of 25/26 [33].

Routine screening for MCI in CKD patients is not yet recommended, notwithstanding the high prevalence of the condition. This could be partially explained by the lack of intervention strategies once the condition has been recognized. However, the nephrologist should suspect cognitive impairment when the patient (or the caregiver) reports forgetfulness/confusion about medications, appointments or inappropriate calls, or when the patient reports depression or altered sleep patterns, and when the patient is not able to answer questions without the family member/caregiver, and in all cases of history of stroke or unexplained falls.

MCI is a transitional stage, preceding clinical dementia, with cognitive impairment exceeding normal ageing and age-associated decline [34]. The main difference between dementia and MCI is that in the former the severity of cognitive impairment usually interferes with activities of daily living; however, it is almost certainly a spectrum with evidence that modifiable cardiovascular risk factors, physical exercise and cognitive training can slow progression [35].

Nature of cognitive impairment

In recent years, several clinical studies have concentrated on the burden of MCI in CKD patients (see e.g. [36–38]). Among patients with CKD, the prevalence of MCI has been estimated to be as high as 30% [39] to 63% [40], which is approximately twice as high as in the age-matched general population. The stage of CKD is apparently related to the risk of MCI: the lower the estimated glomerular filtration rate (eGFR) the higher the risk of MCI (see also Table 1). Notably, discernible cognitive changes may appear already in early CKD stages [51].

Table 1

Prevalence of MCI and dementia in different populations

Population	Prevalence of MCI (%)	Prevalence of dementia (%)	References
Healthy subjects	7–26	13	[41–43]
Early CKD (Stage 3)	14	Unknown	[39, 44]
Late CKD (Stage 4 and 5)	16–38	Unknown	[45, 46]
Haemodialysis	26–60	15–36	[47, 48, 51]
Peritoneal dialysis	35	3.9–31	[42, 49, 51]
Transplantation	(Only studies comparing pre–post transplant scores)	22	[50]

Interestingly, patients with end-stage renal disease (ESRD) have a similar MCI burden with or without haemodialysis, or peritoneal dialysis (Table 1). This is surprising because recent data show that haemodialysis modifies cerebral blood flow as a function of ultrafiltration volume [52]. However, after 12 months, this brain haemodynamic effect correlates with a better performance with the MoCA test for MCI [53]. This observation is also supported by the improvement of the cognitive functions after the start of dialysis, possibly with better results using peritoneal dialysis compared with haemodialysis [54]. Therefore, the decline of cerebral blood flow observed during haemodialysis may not contribute to MCI.

This might be interpreted as the presence of toxins not eliminated by the dialysis process, or the deficit of (as yet unknown) neuroprotective substances produced by the kidney that have not been directly replaced yet.

Much effort has been devoted to identifying specific risk factors for MCI in patients with CKD. To address this problem, investigators had to control several risk factors known for MCI in the general population, such as age, a family history for MCI, the education level, exposure to environmental chemicals, physical inactivity, diabetes, heart disease, stroke or other past brain injuries, male gender, hypertension, smoking, weight and hypercholesterolaemia [55]. Genetic susceptibility towards MCI, such as apoE genotype, is likely to play the same role in the general population and in CKD patients [56]. Nephrologists can easily recognize that many of these factors accompany CKD itself.

However, when these confounders are taken into consideration, other CKD-specific risk factors can be identified such as albuminuria [57], normalized brain tissue volume, haemoglobin levels, glycaemia, serum parathyroid hormone and uric acid levels [58]. Another CKD-specific risk factor for MCI is the frequent presence of electrolyte disorders. Among these, hyponatraemia is relatively frequent in ESRD and has been associated with lower scores for tests of MCI [59]. However, it should be underlined that hyponatraemia is also a risk factor for MCI in non-CKD patients [60]. Other possible CKD-related factors for

MCI are the duration of CKD, poor nutrition/protein energy wasting, neuro-psychological aspects, functional impairment, anaemia, acidosis, disturbed sleep and polypharmacy [61], although they are difficult to assess and have not been explored in any detail. The relative contribution of these and other factors and the still poorly understood underlying mechanisms remain major obstacles to prevention and treatment.

In the population of CKD patients under dialysis, additional risk factors for MCI are related to the process and adequacy of renal replacement therapies. Specifically, risk factors for MCI are the total number of dialysis-related hypotension events [62] and, counterintuitively, a high equilibrated $K_t/V > 1.2$ [39].

With respect to the dialysis modality, the risk for MCI is lower when the patients are placed on peritoneal dialysis or a central venous catheter is avoided [63]. However, the effects of different dialysis modalities on MCI could be spurious because of a selection bias of the patients, since randomization is usually not feasible.

Kidney transplantation appears to reduce MCI (see Table 1), and this change is likely to be stable at 1 and 2 years after transplantation, suggesting the potential for some reversibility [64]. The reasons for this effect are still unclear. An attractive and untested hypothesis is that the kidney produces neurotrophic factors that are necessary for normal cognition in the long term. However, several other hypotheses are equally possible at this stage.

Recent data suggest that a specific mechanism of brain impairment in CKD may be linked to chronic inflammation [13], altered levels of serum uric acid, parathyroid hormone levels, low glycaemia [58] and of neuropeptide Y (NPY), a sympathetic neurotransmitter thought to be involved in cognition and memory [65] and dysregulated in CKD [50]. The relevance of NPY is partially supported by the presence of autonomic dysfunction in CKD [66]. MCI itself is a risk factor for mortality, as already mentioned, and contributes significantly to the poorer quality of life of CKD patients [61].

Is MCI-CKD a new and recognized clinical entity?

MCI represents highly heterogeneous phenotypes with different underlying aetiologies (Figure 2). The MCI diagnosis relies (at least in part) on questionnaires testing multidimensional abilities of the patient (arithmetic, basic motor skills, time and place perception, repeating word list, language use and comprehension). This multidimensional testing procedure may lead to the grouping of different disease entities under a single heading of ‘MCI’.

Indeed, the concept of MCI was developed in the field of dementia, particularly for the population at risk of Alzheimer’s disease. Only much later, this concept has been applied to the study of cognitive changes in CKD.

Therefore, it is very instructive to use the large body of neurophysiological and imaging data available from patients with MCI in the general population and to compare these with the MCI pattern found in the population of CKD patients. To distinguish these two populations, we will use the term MCI-GP when referring to the general population and MCI-CKD when referring to the CKD population.

A large body of data comes from electroencephalographic (EEG) recordings. The first EEG studies in CKD were performed in the early 1960s [67, 68]. In a recent study comparing EEGs from MCI-GP with MCI-CKD, subtle differences emerged between the two populations: MCI-GP was characterized by alterations in the alpha rhythm (8–13 Hz), whereas MCI-CKD was characterized by alterations in the delta frequencies (<4 Hz) [69]. The interpretation of these differences is speculative: the alpha rhythm in the occipital cortex is normally present during quiet wakefulness and is thought to represent sensory information processing, modulated by the cholinergic input to the cortex. Conversely, the delta rhythm is normally present during sleep and is thought to derive from abnormal interaction between the thalamus and the cortex. Therefore, MCI-GP might be characterized by an altered cholinergic input, whereas in MCI-CKD an altered cortico-thalamic connectivity might prevail, although this is entirely speculative.

Imaging data based on magnetic resonance imaging (MRI) yielded results concerning the brain alterations in MCI-CKD. Unfortunately, no study directly compared patients with MCI-GP and MCI-CKD using MRI. Morphological data on the brain in CKD were initially available only on post-mortem samples; the first imaging study in living patients with CKD, using MRI, was published in the 1990s and focused on uraemic encephalopathy, the involvement of basal ganglia and its reversibility with dialysis [70].

Recent data show a reduction in grey matter (particularly in amygdala, hippocampus) with sparing of white matter in MCI-GP [71, 72]. Conversely, MCI-CKD presented with mostly white matter loss (demyelination), particularly in deep white matter, and reduced grey matter volume (possibly correlated to the axonal damage following demyelination) [73]. Again, the interpretation of these morphological differences is speculative, and toxic effects of uraemic substances cannot be excluded.

An advanced MRI technique called ‘Diffusion Tensor Imaging’ (DTI) provided more detail of damages in the white matter. DTI allows the visualization of major brain axonal bundles (such as the corpus callosum) and is therefore also called ‘brain tractography’. No direct comparison between MCI-GP and MCI-CKD exists, and so we must rely on separate reports. In MCI-GP, modifications in white matter tracts were found in right and left frontal lobe, fornix, corpus callosum, right temporal lobe, hippocampus head, corpus callosum right and forceps major [74], with lower connectivity at the level of the basal nucleus [75]. Conversely, in MCI-CKD, DTI showed abnormal myelination in the anterior limb of the internal capsule [76, 77] and whole-brain microstructural changes [78].

Finally, functional imaging data relying on brain oxygenation levels (fMRI) or positron emission tomography (PET) scans have been used to characterize brain activity in MCI-GP and MCI-CKD, but again without direct comparison. The first PET study of the brain in uraemia was conducted in 2004, again focusing on the basal ganglia [79]. fMRI data showed similarities in cerebral blood flow in patients with MCI-CKD and those with affective disorders [80], whereas this finding has not been observed in patients with MCI-GP.

Additional information on brain architecture/function comes from animal models. Different animal models of MCI (without CKD) have been proposed, including aged or hypertensive rodents, and transgenic mice overexpressing Aβ at an early phase before extensive brain deposits [81]. These animals show various degrees of cortical atrophy and damage to the cholinergic system [82]. Conversely, animal models of CKD (subtotal nephrectomy or high

adenine diet) with cognitive impairment [56, 83] show altered sleep patterns [84] with normal neural architecture [85].

The electrophysiological, imaging and animal model data suggest differences between MCI-GP and MCI-CKD (see Table 2). These differences are likely to stem from the underlying pathogenesis of cognitive impairment in individuals with and without CKD. Since MCI-GP is likely to be a clinical entity distinct from MCI-CKD, the latter should be considered as a distinct reno-cerebral syndrome. However, formal testing of this difference has not yet been carried out and further questions are still open: is gender influencing/modifying the development of MCI-CKD, the same way it is known to influence MCI-GP? Is the CKD stage important? Is the aetiology of CKD relevant (there is evidence that albuminuria and eGFR are associated with MCI)?

Table 2

Morphological, functional and pathogenetic features of MCI-CKD

Feature	MCI general population	MCI-CKD	References
Pathogenesis	Unknown	Uraemic (neuro)toxins	
Tractography	Lower connectivity of the basal nucleus	Internal capsule demyelination	[74, 75, 77]
MRI	Reduced amygdala and hippocampus grey matter	Deep white matter demyelination	[58, 70, 73, 76, 78, 80]
EEG	Altered cortical synchronization at alpha frequencies	Altered cortical synchronization at delta frequencies	[67–69]
Animal models	Cortical atrophy, damage to the cholinergic system	Normal neural architecture	[81–83]

Taking an historical standpoint, this reno-cerebral syndrome differs from ‘uraemic encephalopathy’, because it appears well before the uraemia and does not improve with dialysis. It might be (partially) reversible although data on this are still scarce. Finally, it is a milder neurological phenotype, presumed to be a very early stage of what may become full-blown clinical dementia. In that respect, it is a potential health and resource-demanding ‘time bomb’ in the CKD population and urgently needs to be addressed.

OPEN QUESTIONS AND OPPORTUNITIES FOR MCI-CKD: IMAGING AND 'OMICS'

Although the first description of uraemic encephalopathy was published some 80 years ago, our understanding of brain dysfunction in CKD, prevention and treatment is still in its infancy. The pathogenesis MCI-CKD remains in the realm of hypothesis and its specificity when compared with MCI-GP is based on limited data. Nevertheless, the problem has gained increasing attention among nephrologists as shown by a rapidly increasing number of publications describing neurological and psychological changes in CKD patients: the number of published papers containing the keywords 'CKD' and 'brain' was only 130 up to the year 2012, whereas in the years 2013–18 they are 328 (data from PubMed).

The main advance in our understanding of this syndrome in the last 80 years has been more of a change in terminology, from uraemic encephalopathy to (what we call here and today) MCI-CKD. While this suggests a growing recognition of the problem of MCI, it also risks failing to take full account of earlier data and published findings.

We will try to summarize what we believe are the main open questions worth addressing with the aid of newer technologies:

- Does the distinction between MCI-GP and MCI-CKD really exist or does MCI-CKD only represent an 'extreme' or 'accelerated' phenotype of MCI-GP?
- What is the contribution of accelerated aging and conventional cardiovascular risk factors to MCI-CKD?
- Do we have firm criteria for the diagnosis of MCI-CKD?
- What is the 'natural history' of MCI-CKD?
- Can MCI-CKD be treated, prevented or even reversed?
- Can we properly assess the personal and socio-economic burden of MCI-CKD?

Why should we be more optimistic today about an advance in this field? There are at least two reasons: one is the theoretical approach, and the second is technological.

On the theoretical side, the formal comparison of MCI-CKD and MCI-GP is urgently needed and is likely to deepen our understanding of all forms of MCI. At present, the ability to diagnose and treat MCI is almost non-existent. Psycho-therapeutic approaches or physical exercise can be helpful, but are of limited efficacy. Newer dialysis techniques (e.g. haemodiafiltration) in patients with MCI-CKD represent an opportunity to evaluate these potential therapeutic approaches. Furthermore, most studies have been focused on the association of eGFR and/or albuminuria and MCI, but it is plausible that other measures of kidney function could be useful in understanding the kidney–brain link [86]. Moreover, the axis involving sympathetic-para-sympathetic imbalance and inflammation in CKD warrants further investigation.

On the technological side, new high-throughput tools have become available that may provide new information on the early identification and pathogenesis of MCI-CKD. These techniques promise to unravel (novel) (neuro)toxins and to systematically verify their neurotoxic potential.

So far, fMRI and brain tractography have not been used systematically in this field, particularly to compare MCI-CKD and MCI-GP. The ability of these techniques to combine morphological and functional imaging of the human brain *in vivo* with neuro-psychological

testing is a unique opportunity. Furthermore, new transgenic animal models are now available that allow studying brain activity at the single neuron level *in vivo*: transgenic animals with neurons expressing proteins that are constitutively fluorescent or that change their fluorescence with activity to localize and define particular neuronal populations, and also neurons that can be selectively activated using laser pulses (optogenetics). New technologies such as two-photon microscopy and super-resolution microscopy should allow us to overcome some of the major limitations of previous imaging techniques. The 'Clarity' method can facilitate an unprecedented ability to investigate the 3D location of neurons in great detail. Robotic systems for drug identification and well-characterized neuronal cell lines would allow us to formally and thoroughly test large lists of potential uraemic (neuro)toxins, as well as new drugs, and their combined effects. The possibility of deriving stem cells from patients and brain organoids could represent a new *in vitro* model for studying the pathogenesis and reversibility of MCI.

The widespread availability of 'omic' technologies (proteomics, peptidomics, genomics, transcriptomics, metabolomics, etc.) provides a large amount of data that may predict or explain the occurrence of MCI and its neurological counterparts. Finally, new statistical techniques to handle 'big data', such as Systems Genetics [87] and Imaging Genetics [88], network analysis and the application of artificial intelligence algorithms promise a new level of understanding.

These new technological and methodological advances promise the opportunity to gain a new and better understanding of MCI-CKD, as well as MCI-GP. MCI-CKD will become an increasing problem faced by the nephrology community and it is therefore essential that we liaise closely with our clinical colleagues in neurology, neuro-psychology and radiology, as well as basic scientists in neuroscience, to address this anticipated major personal health and socio-economic burden.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest related to this work.

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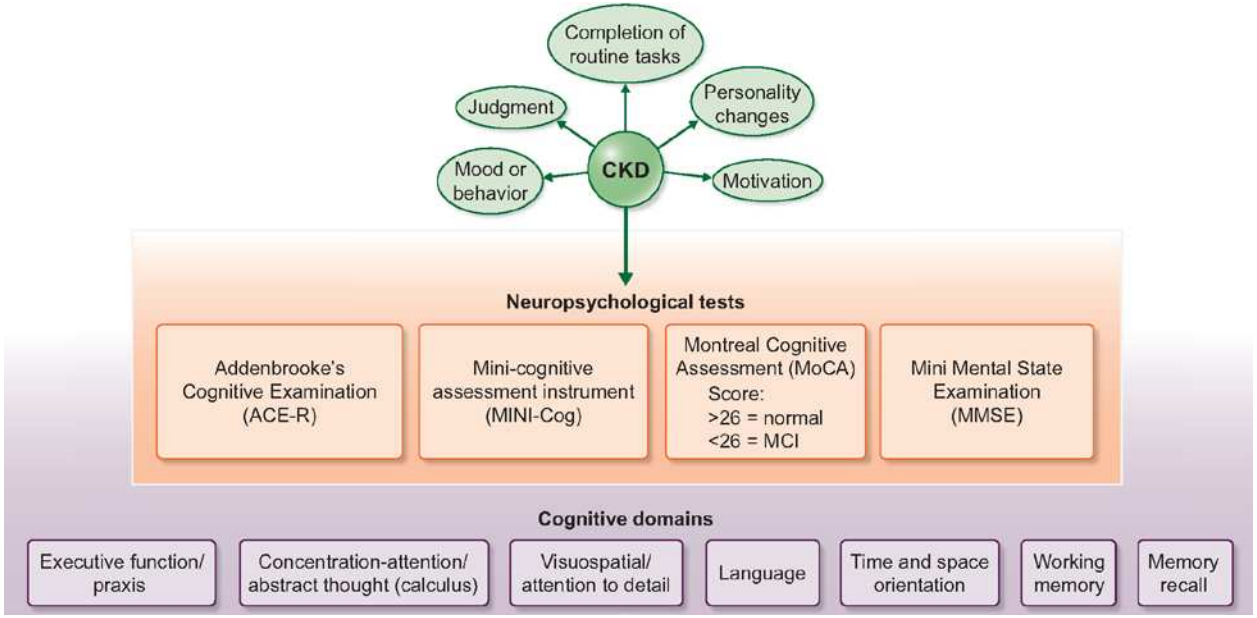

FIGURE 1 Clinical testing of MCI in CKD patients. The diagnosis of MCI requires normal execution of routine tasks, and without interference with daily activity. Neuropsychological testing can be useful for screening although a full diagnosis requires further documentation. The neuropsychological tests usually evaluate multiple cognitive domains that are summarized in a single score. The MoCA has been validated as having better sensitivity then Mini Mental State Examination for MCI screening.

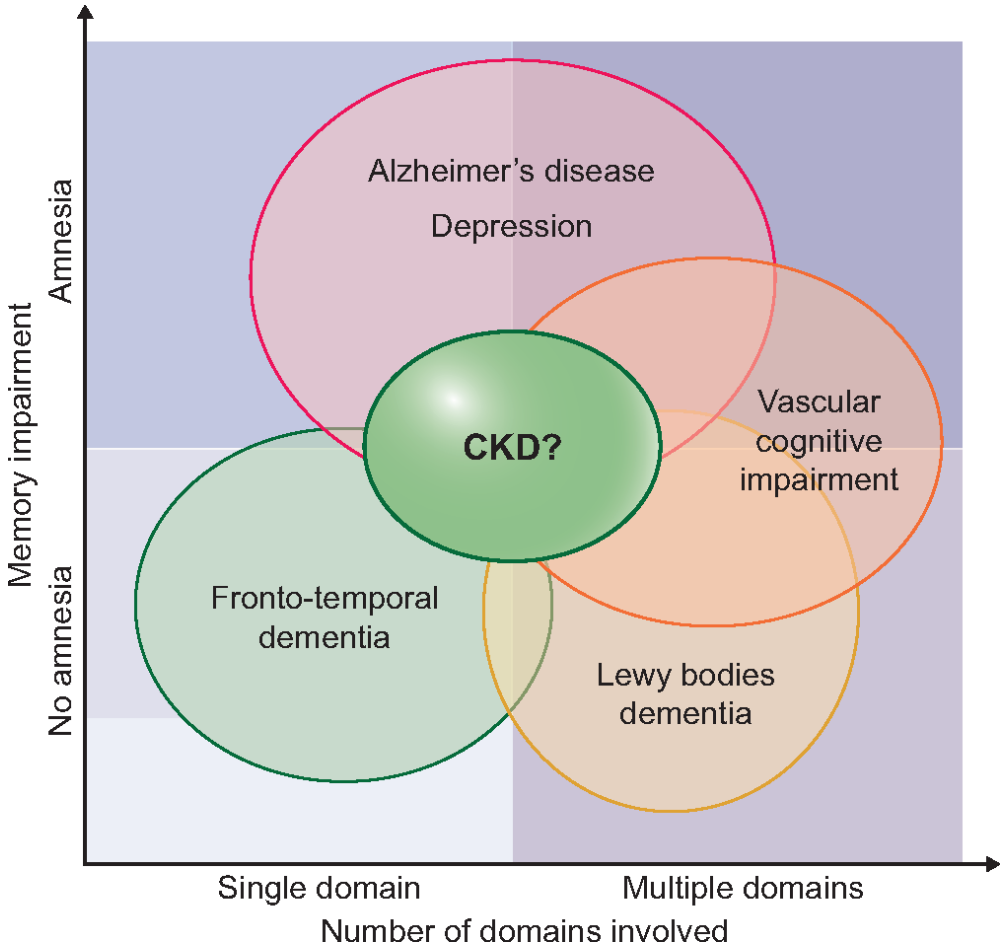

FIGURE 2 MCI subtypes. According to the number of cognitive domains involved, and the presence of memory impairment, MCI is further sub-classified, which can partially separate MCI into different aetiologies.