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Mechanisms of cognitive dysfunction in CKD

Viggiano, Davide ; Wagner, Carsten A ; Martino, Gianvito ; Nedergaard, Maiken ; Zoccali, Carmine ; Unwin, Robert ; Capasso, Giovambattista

Abstract: Cognitive impairment is an increasingly recognized major cause of chronic disability and is commonly found in patients with chronic kidney disease (CKD). Knowledge of the relationship between kidney dysfunction and impaired cognition may improve our understanding of other forms of cognitive dysfunction. Patients with CKD are at an increased risk (compared with the general population) of both dementia and its prodrome, mild cognitive impairment (MCI), which are characterized by deficits in executive functions, memory and attention. Brain imaging in patients with CKD has revealed damage to white matter in the prefrontal cortex and, in animal models, in the subcortical monoaminergic and cholinergic systems, accompanied by widespread macrovascular and microvascular damage. Unfortunately, current interventions that target cardiovascular risk factors (such as anti-hypertensive drugs, anti-platelet agents and statins) seem to have little or no effect on CKD-associated MCI, suggesting that the accumulation of uraemic neurotoxins may be more important than disturbed haemodynamic factors or lipid metabolism in MCI pathogenesis. Experimental models show that the brain monoaminergic system is susceptible to uraemic neurotoxins and that this system is responsible for the altered sleep pattern commonly observed in patients with CKD. Neural progenitor cells and the glymphatic system, which are important in Alzheimer disease pathogenesis, may also be involved in CKD-associated MCI. More detailed study of CKD-associated MCI is needed to fully understand its clinical relevance, underlying pathophysiology, possible means of early diagnosis and prevention, and whether there may be novel approaches and potential therapies with wider application to this and other forms of cognitive decline.

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Mechanisms of cognitive dysfunction in CKD

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Abstract

Cognitive impairment is an increasingly recognized major cause of chronic disability, and is commonly found in patients with chronic kidney disease (CKD). A better understanding of the relationship between kidney function and cognition may help us to understand better other forms of cognitive dysfunction. Patients with CKD have an increased risk (compared with the general population) of both dementia and its earlier stage of mild cognitive

impairment (MCI), with deficits in executive functions, memory and attention. Brain imaging in CKD patients has detected damage to white matter in the prefrontal cortex and, in animal models, in the subcortical monoaminergic and cholinergic systems, accompanied by widespread macro- and micro-vascular damage. Unfortunately, current interventions that target cardiovascular (CV) risk factors (anti-hypertensives, anti-platelet agents and statins) seem to have little or no effect on MCI-CKD, suggesting that the accumulation of uremic (neuro)toxins may be more important in this disorder than disturbed hemodynamic factors or lipid metabolism. Experimental models show that the brain monoaminergic system is susceptible to uremic neurotoxins and that this system is responsible for the altered sleep pattern commonly observed in CKD patients. Neuronal stem cells and the brain glymphatic system, shown to be important in Alzheimer's disease (AD), may also be involved. MCI-CKD needs to be studied in more detail to understand fully its clinical relevance, underlying pathophysiology, and possible means of early diagnosis and prevention; and whether there may be novel approaches and potential therapies with wider application to this and other forms of cognitive decline.

Key points

Cognitive impairment is more common in patients with chronic kidney disease (CKD) and reduced renal function than in the general population.

Brain dysfunction in CKD patients likely results from uremic (neuro)toxins interacting with neuronal stem cells, the brain vascular and glymphatic system, and catecholaminergic neurons.

Targeting these mechanisms could potentially reduce the burden of dementia in CKD and might help in finding better treatments for other forms of cognitive impairment.

Introduction

The widely used term 'cognitive dysfunction' has been defined in many different ways, but collectively refers to a combined deficit of brain processes that affect learning, memory, and sensory processing. It varies from mild cognitive impairment (MCI. See Box 1) to severe dementia, the latter characterized by a loss of independence in carrying out activities of daily living [1]. MCI may be considered as a prodromal state before established dementia with an annual conversion rate of 1. 9% per year [2]. Although MCI is inherently unstable (patients may

progress or revert to normal cognition), some investigators consider it to be a distinct clinical entity [3]. Despite the increasing prevalence and incidence of MCI and dementia, there remains a lack of disease-modifying drugs and a comprehensive biological understanding of MCI, as well as an understanding of the mechanisms that determine the transition from MCI to dementia.

A significant number of patients with chronic kidney disease (CKD) suffer from cognitive dysfunction, and CKD is among the strongest risk factors for MCI and dementia. When considering the odds ratio, a 6-year longitudinal study in the general population listed CKD as the third major risk factor for MCI and dementia after stroke and chronic use of anxiolytics, and ahead of genetic factors [4]. Cognitive impairment can already be evident at early stages of CKD [5] (Figure 1). However, the relationship between the severity of CKD (based on estimated Glomerular Filtration Rate, eGFR) and the severity of dementia/MCI is unclear. When taking into account age, cognitive changes at different CKD stages may be related to the presence and degree of albuminuria [6–10]. Indeed, a separate study suggests that the duration of kidney disease, rather than the degree of renal impairment, correlates with brain dysfunction. Available long-term follow-up studies in CKD patients also suggest greater cognitive decline in those with higher levels of albuminuria, but an unclear effect of eGFR [6,11].

Current techniques of renal replacement therapy have different effects on cognitive dysfunction: hemodialysis (HD) and peritoneal dialysis (PD) can treat effectively the acute uremic encephalopathy seen in some non-dialyzed patients with end-stage renal failure (ESRF), but have little effect on MCI, although there may be a slightly better outcome with PD [12,13] compared with HD. Conversely, kidney transplantation is likely to play a protective role, although without complete reversal to normal cognition in healthy subjects [14] (Figure 1). Several mechanisms have been proposed to explain the brain dysfunction seen in CKD, particularly focusing on the vascular damage and altered extracellular *milieu* that accompanies CKD.

The CKD-cognitive impairment conundrum has become a major focus of the scientific community, as evident from the increasing number of published meta-analyses and review articles (see e.g. [15–17]). However, much of the current literature does not discuss the topic in the context of recent developments in neuroscience and neurology, such as neural stem cells, brain glymphatics or subcortical modulatory systems (e.g., dopamine and norepinephrine systems); furthermore, the pace of new findings is so rapid that an updated perspective can be

justified. This is an ongoing and active field of research, and new functional tools to study both the brain and kidney hold the promise of advancing our understanding of MCI-CKD.

This review summarizes our current knowledge of the pathogenesis of brain lesions associated with CKD and their likely effects on cognition. The changes observed are discussed in the context of uremic neurotoxicity and vascular damage [18,19] . We focus on brain dysfunction occurring in CKD, rather than in acute kidney injury (AKI), which has been considered in detail elsewhere [20]. Finally, our review does not discuss depression, which is also detailed elsewhere [21].

1. Epidemiology of CKD and cognitive dysfunction

With a prevalence ranging from 27% up to 62% [18,22–24] (depending on the age and the study) MCI is more common among CKD stage 1-4 patients than in a matched non-CKD population (prevalence 11%-26%) [22,23,25]. While MCI does not affect activities of daily living, 5-10% of those affected will eventually progress to clinical dementia [26]. The prevalence of dementia is 8-37% among HD patients [10,25,27–29], 4-33% among those on PD [25,29] and around 7-22% in kidney transplant patients [14,30]. In contrast, the prevalence of dementia in the general population is 5% (95% CI 4. 5%–5. 7%) [31]. Most of the studies comparing the prevalence of MCI/dementia in CKD with the general population take into account age, gender and education (which may affect the estimates). In Figure 1 we summarize an estimate of the MCI trend in CKD, PD and HD patients according to kidney function and the age.

Regarding the age of onset of cognitive decline (in relation to first diagnosis) the data are scanty. In the general population the incidence rate is negligible (less than 1%) below age 65 years and then increases exponentially as a function of age (7.4% at 70 years) [32,33]. Conversely, in kidney transplant patients the 10-year risk of dementia is 5% in those aged 55 years, but also increases linearly with age [32]. Similarly, the 10-year risk of dementia after HD initiation is 20% in patients aged 65 years and again increases linearly with age [30]. In addition, data by Kurella Tamura et al [34] suggest a higher prevalence (about 10%) of cognitive impairment even in relatively young subjects (21-44 years) with end-stage renal failure (ESRF).

According to a 2019 study, the incidence rate for dementia per 1000 patients-years is 1.4 in the non-CKD population and 10.7 in the ESRF population [35]. In patients with eGFR levels >60 ml/min, albuminuria, an early marker of endothelial damage and microvascular

disease, is associated with the presence of MCI [8]. This has been confirmed repeatedly, with an unclear relationship to age: some papers report a greater effect of albuminuria in older patients [7], others only in younger patients.

Nephrologists need to be aware that a substantial proportion of their patients may have mild to severe forms of cognitive impairment, and the neurologist also needs to be cognizant of the presence and form of cognitive deficits occurring in patients with CKD. Indeed, MCI-CKD might be qualitatively different from the MCI seen in the general population in respect of its neuropsychological test patterns (e.g., better performance on Trail Making Test B) and EEG studies [36], MRI findings[3]. Ideally, current guidelines for MCI diagnosis and management should require an assessment of kidney function as part of the routine neurological work-up [37].

2. Cognitive domains and correlated brain features in CKD

"Cognitive decline" is an umbrella term that encompasses all forms of dementia (such as AD), delirium or confusional states, and mild cognitive slowing. It should be noted that the terms "cognitive impairment" and "dementia" are often used as synonymous, the first being introduced as a non-stigmatizing term [38]. Cognitive function is tested by various means, including by recalling memorized lists of numbers or drawing an object on request, or naming a figure. Cognitive impairment is subdivided into specific cognitive domains, such as attention, memory, visuospatial, language skills and executive functions (see Box 2).

2. 1. Attention

Patients with CKD show inattention (see Box 2) and impaired inhibitory control [39], which is the inability to suppress ongoing and inappropriate actions. Indeed, a young population with mild-moderate CKD has poor performance in a test of attention and inhibitory control, which depends on the duration of disease, rather than the severity of CKD [39]. Furthermore, CKD patients have a slower EEG reaction when paying attention to a visual stimulus (termed "P300 wave event related potential")[40], which was shown to be partially dependent on the presence of anemia [41]. Transplantation does not modify the attention and inhibitory control performances compared with non-transplanted CKD patients [42]. Many brain regions are required for attention and inhibitory control, such as the prefrontal cortex (PFc) and the Locus Coeruleus in the dorsal pons, which produces norepinephrine. Compared with normal controls, patients on HD show a reduced thickness and increased number of connections of the PFc [43]. Furthermore, PET studies also show decreased metabolic activity in this region in

ESRF patients compared with normal subjects[44]. In the non-CKD population, the frontal gray matter volume is less affected in MCI[45], but can be reduced in other forms of dementia (fronto-temporal dementia, Alzheimer's Disease (AD) and Levy bodies dementia [46,47]). An EEG study directly comparing MCI-CKD to MCI in the general population describes a more pronounced dysfunction in the frontal cortex[36].

Data from animal models of CKD suggest an altered activation (number of neurons active at rest, indexed by c-Fos expression) of the PFc and of the norepinephrine neurons of the Locus Coeruleus[48] (see also Figure 2), possibly due to neuroinflammation[49]. Another mechanism for the effect of CKD on norepinephrine neuronal function arises indirectly from the observation of altered tyrosine metabolism, the precursor for norepinephrine [50] . Interestingly, antioxidant therapies and angiotensin-converting enzyme inhibitors may reverse these changes and should be explored in future as a possible protection against MCI/dementia in CKD. Attention deficits in CKD patients may be attributable to altered catecholamine-PFc circuitry.

2. 2. Memory

Memory storage and processing are likely to be served by different brain regions according to the type of memory (see Box 1). Both the implicit and explicit forms of memory appear to be altered by CKD [51]. Indeed, patients on HD compared with healthy controls had poorer scores when trying to recall a list of words (explicit memory) or images (implicit memory). The memory performance did not change when comparing before and after dialysis treatment.

The storage/retrieval of explicit memories requires the integrity of the cerebral cortex and the hippocampus and the activity of cholinergic neurons in the Meynert nucleus. In animal models, CKD induces neuronal death in the hippocampus [52] and reduces the activity of cholinergic neurons in the Meynert nucleus [49] (Figure 2).

At the neuronal scale memories are stored as long-term modifications of their synapses. An experimental study in mice demonstrated a reduction in synaptic contacts in animals with reduced kidney function [49]. Since memory traces are stored in the ordered connectivity of synaptic contacts among neurons[53,54], synaptic loss may underlie the reduced memory in CKD. Overall, data suggest that the interaction between cholinergic neurons and the cortex may be responsible for memory dysfunction in CKD.

2. 3. Language, visuospatial performance and executive dysfunction

Language skills are also affected in CKD, and this is the only cognitive domain linearly dependent on eGFR decline ¹⁰. Language ability can be tested by presenting a

picture and asking the subject to name it (as with the Boston Naming test). Several studies document poor naming performance in patients with CKD[10,55–57]. MRI studies in CKD patients support the anatomical integrity of cortical language areas and the origin of language disturbances in CKD is still unknown.

Visuospatial abilities reflect the identification and localization of visual objects. It can be tested, e.g., by asking someone to copy a complex figure (as in the Rey-Osterrieth Complex Figure Test). Visuospatial performance is variably affected in CKD patients, depending on the study [56,58], possibly because its impairment can be observed only in advanced CKD stages and ESRF[5]. This is also supported by the absence of morphological alterations on MRI in the occipital cortex of CKD patients, this being the region involved in visuospatial attention [59].

Finally, most of the literature supports the presence of "executive dysfunction" in CKD, with an impairment in the Trail making tests (TMT-A and TMT-B), which addresses visual attention and executive functions. These tests have been found to be consistently altered in CKD patients in several studies. In a comparative study, the impairment in this cognitive domain occurs with greater frequency in CKD compared with language, memory and visuoconstructive abilities[56]; it worsens over time in HD patients[60]. It is also dependent on the degree of kidney impairment, with a linear relation between both TMT-A and TMT-B scores and eGFR[61]. Kidney transplant improves TMT-A scores when compared with patients on HD[62]. As discussed above, the frontal lobe, which is the brain structure that is mainly responsible for executive functions, is thinner in patients with CKD, possibly contributing to this behavioral disorder. Notably, pediatric and adolescent patients with CKD already show cognitive impairment in several domains [63], together with brain damage on MRI[64], strengthening the concept that these changes are not solely due to the effect of ageing in patients with CKD.

In summary, the cognitive impairment in CKD extends to several brain functional domains and might be the result of damage to multiple cortical regions (particularly the frontal lobe), and to subcortical modulatory neurons (particularly adrenergic neurons in the mesencephalon and cholinergic neurons in Meynert's nucleus). In contrast, non-CKD dementia is accompanied by structural MRI abnormalities of different brain regions: (i) in AD, at early stage, the entorhinal cortex and cingulate, closely followed by the hippocampus, amygdala, and parahippocampus; the atrophy then involves the temporal cortex and then other cortical sites [47,65]; (ii) in the Fronto-Temporal Dementia the frontal and temporal lobe are mostly affected at MRI [46]; (iii) in the Lewy Bodies Dementia the cingulate and superior temporal-

occipital cortex [47]; (iv) in vascular dementia there is global cortical atrophy with involvement of white matter (so-called "white matter hyperintensities"); compared to AD the frontal cortex is more often involved, with lesions to association tracts by MRI[66].

3. Intermediate phenotypes: Neuroanatomical alterations, sleep disorders and tremor

In this section, we will use the term "intermediate phenotype" to describe a brain feature that lies between the complex behavioral trait (e.g., dementia) and a putative underlying molecular cause. Sometimes the terms "intermediate phenotype", "biomarker" and "endophenotype" are used loosely and interchangeably[67]. This brain feature, measurable and quantitative, is linked to simple neuronal networks and may be used as a proxy for the more complex behavior: such a feature is likely to have a linear relationship to the molecular changes accompanying CKD. Potential intermediate endophenotypes are the MRI brain correlates of dementia/MCI (discussed above) and quantitative phenotypes such as altered sleep pattern and motor control.

3. 1. Sleep

Sleep disorders can be quantified using polysomnography and actigraphy systems. Sleep disorders in CKD are very common with the majority of patients complaining of some form of sleep disorder [68]. They include a reduction in total sleep time, insomnia/sleep fragmentation, daytime somnolence, altered circadian rhythm, sleep apnea or restless legs syndrome [69,70]. Sleep apnea affects 34-56% of adult CKD patients[71,72] and 56% of ESRF patients on HD[73,74]. It is usually absent in pediatric patients with CKD [75]. In 22-27% of adult CKD patients sleep apnea depends on a dysfunction of the neuronal drive (central sleep apnea, CSA) [76,77]. The nocturnal hypoxemia that accompanies sleep apnea in CKD patients is associated with autonomic dysfunction and left ventricular hypertrophy [78,79], and predicts a high risk for cardiovascular events in ESRF[78]. A meta-analysis concluded that sleep quality can be improved by renal replacement therapies (transplant, dialysis), even if it does not return to normal levels, and it does not depend on the intensity of therapy[69].

Sleep disorders are tightly linked to MCI and dementia[80]. They are indicative of an existing brain damage. It is unclear if they induce further brain dysfunction, as pharmachological restoration of sleep does not improve cognitive functions [81]. In humans inadequate sleep has been associated with lower gray matter volume[82]. In animal models of CKD, serotoninergic neurons in the dorsal raphe and histaminergic neurons in the hypothalamus (Figure 2), which are responsible for the maintenance of sleep patterns, show increased activity (indexed by cFos expression) [48]. Serotoninergic neurons influence the sleep-wake pattern and attention,

memory and locomotor activity[83] and contribute to the depression and uremic anorexia seen in advanced CKD[84].

Overall, the sleep patterns and sleep apnea in CKD could be an easily quantifiable and ideal parameter linking the behavioral scale phenotype to the molecular scale (Figure 3).

3. 2 Motor control and tremor

Motor control and hand tremor can be easily quantified using force plates and accelerometers. CKD is accompanied by changes in balance and gait control [85]. Specifically, patients with ESRF and MCI have a slower gait speed[23,61] and reduced single-leg standing time (indexing balance function)[23] that is not due to a reduced muscle strength. The control of hand posture (resulting in small oscillations or physiological tremor) is also likely to be modified in advanced CKD: it has been known for a longtime that acute uremic intoxication or "uremic encephalopathy" is accompanied by hand tremor [86]. The assumption that hand tremor is a result of uremic toxins derives from the observation that HD greatly improves tremor in cases of uremic encephalopathy[87]. The altered motor control in CKD patients is also evident as a slower reaction time to visual or auditory stimuli[88,89] and voice tremor[90].

The motor control modifications (postural instability, hand tremor, gait speed) in CKD are likely to be collateral features of cognitive impairment. Indeed, non-CKD cognitive impairment is accompanied (or preceded) by a slower gait speed[91] and postural instability [92]. Furthermore, some forms of AD are accompanied by hand and postural tremor and limb bradykinesia [93].

As discussed above, norepinephrine and serotonin neurons modulate sleep and subcortical motor circuits (e.g., the basal ganglia and the spinal cord), possibly mediating the gait and hand instability in CKD. A pictorial review of the hierarchical organization from molecular abnormalities to a complex behavioral scale is represented in Figure 3.

4. Mechanisms of cognitive dysfunction in CKD

The link between CKD and cognitive dysfunction or its intermediate phenotype is not well understood. In pediatric populations, genetic factors may play a role, whereas in adult populations CKD-related vascular factors and uremic (neuro)toxins may have a greater impact. Every proposed mechanism should be examined in more detail, because of the potential for new therapeutic approaches, which are still limited.

4. 1 Genetic Factors

There has been little attention paid to the role of genetic factors in the relationship between CKD and cognitive function. However, a distinction must be made between pediatric and adult CKD. In the pediatric population kidney diseases may have a clear genetic determinant [94], for example, in up to 30% of steroid-resistant nephrotic syndrome patients [95]. In these cases, neurocognitive impairment may derive from a genomic disorder that causes both CKD and cognitive impairment[96]. Indeed, some rare genetic syndromes are well known to cause both cognitive impairment and kidney dysfunction, such as Bardet Biedl syndrome[97], Fabry disease [98], Schmike immunoosseus dysplasia[99], Joubert syndrome[100], tuberous sclerosis[101] and oculocerebrorenal syndrome of Lowe[102].

Conversely, in adult CKD a genetic diagnosis is found in only 10% of cases[103] and in pediatric steroid-sensitive CKD, almost no patient has a genetic diagnosis [95]. In these cases a genetic predisposition to cognitive impairment has been suggested from the observation that genetic variants of α-*Klotho,* a CKD-dependent factor, affect cognition[104]. Furthermore, circulating α-*Klotho* has been linked to cognitive decline[105]. The analysis of genetic loci associated with adult CKD obtained from one million subjects, published in 2019, reports 147 loci relevant for kidney function[106]. Among these, 13 polymorphisms had an Exonic effect (SLC47A1, EDEM3, SLC22A2, PPM1J, RPL3L, EPB41L5, TSPAN9, KLHDC7A, CPS1, C9, CACNA1S, SLC25A45, CERS2). Intriguingly, some of these genes are also expressed in the brain, particularly in the striatum (SLC47A1, KLHDC7A, SLC25A45; Allen Brain Atlas database), cortex (EDEM3, PPM1J, CERS2; Human Protein Atlas database), cerebellum and hippocampus (TSPAN9, EPB41L5; Human Protein Atlas database). Furthermore, some of these are related to diseases of the nervous system such as Infantile onset spinocerebellar ataxia (TSPAN9, CACNA1S, RPL3L; Rare Diseases AutoRIF ARCHS4 Predictions database) or AD (CACNA1S, WikiPathways database).

Finally, it is likely that any genetic predisposition to cognitive impairment in the general population is also operative in CKD. In fact, experimental data in rodent models suggest that the number of genes influencing memory and cognition is likely to be quite large [107]. Unfortunately, the quest for genetic risk factors in dementia and MCI using Genome-Wide Association Studies (GWAS) has only identified gene variants with a small effect size. The GA@ACE study comprised 4120 AD cases and 3289 controls, analyzing 7.7 million gene variants[108] and found only one already known marker with Genome Wide significance,

APOE-rs429358. Other genetic variants had very small effects (such as CD33-rs3865444, with OR=0. 92). An additional genetic predisposition to MCI in CKD patients derives from the genetic control of autoregulation of both renal and cerebral blood flow, which is discussed further below.

When summing each small effects of all genetic variants in an individual, the "calculated total risk score", results are promising [109]. For example, a genetic risk score based on eight gene variants found a two-fold more rapid progression from MCI to AD when six or more alleles were present[110].

In summary, genetic risk for MCI/dementia in CKD is more easily recognized and important in the pediatric population; in the adult population a genetic risk score from multiple variants needs to be considered.

4. 2 Non-genetic Factors

Many different mechanisms have been proposed to link CKD and cognitive impairment. It should be emphasized that the MCI/dementia link with CKD might actually represent one of the very few established causes of cognitive impairment.

Most proposed mediators of brain damage are retained because of kidney dysfunction and affect the brain through direct or indirect mechanisms. There are, however, notable exceptions: (i) iatrogenic factors, namely dialysis, medications[111] and nutrition/diet; (ii) comorbid conditions that cannot be easily separated from CKD such as hypertension and cardiovascular disease; (iii) social factors and functional impairment (such as impairment in using the telephone, preparing meals or shopping) that affect the psychological state of patients with CKD.

Complex changes affect the blood composition of patients with CKD, which complicates attempts to identify a unifying causative mechanism for CKD-MCI. Moreover, evaluation of the mechanisms by which CKD-related changes in blood constituents might affect cognitive function requires consideration of the time-scale over which cognitive decline occurs. Some blood constituents (e.g., oxygen free radicals, volume status, electrolyte and acid-base disturbances, and some uremic toxins and drugs) have effects within a short time-scale, whereas others (e.g., amyloid deposits, inflammation, vascular dysfunction, nutrition, anemia) require months or perhaps years to have an effect on the brain. Furthermore, the blood-brain barrier (BBB) and blood-cerebrospinal fluid (BCB) barriers do not allow all blood

constituents to freely enter the brain parenchyma [112]. The brain is likely to develop MCI/dementia over a relatively long time-scale (months to years) [39] and clearly MCI/dementia is a phenomenon that occurs at a higher scale of organization of neuronal networks or above.

In the section that follows, we briefly review the few attempts that have been made so far to interfere with MCI/dementia-CKD, before considering some possible underlying mechanisms in more detail.

4. 2. 1 Vascular dysfunction in CKD and cognitive decline

4. 2. 1. 1 Morphology of the brain vessels in CKD

CKD has a high prevalence of atherosclerosis and endothelial dysfunction is almost universal[113]. Vascular disease is associated with cognitive decline in non-CKD patients and is an important factor in CKD morbidity [114]. Brain capillaries and small vessels are not accessible in patients with CKD; hence, a useful proxy is the study of retinal capillaries, which can be quantified *in vivo*. In the retina, CKD stage 3 (or proteinuria >500mg/g creatinine) is accompanied by greater arteriolar wall-to-lumen ratio, greater wall thickness and greater inter-capillary distance[115]. Therefore, anatomical alterations in the brain macro- and micro-circulation are present in patients with CKD.

The endothelial dysfunction (indexed by sVCAM-1, thrombomodulin, sICAM-1 and sICAM-3) is a feature of CKD, HD and PD[116], and is accompanied by an increased permeability of the blood brain barrier [49,117].

4. 2. 1. 2 Hemodynamic changes that occur in CKD

In non-CKD patients the vascular hypothesis of cognitive dysfunction is based on the hypothesis that anatomical vascular changes are accompanied by reduced cerebral blood flow, and consequent impairment in neuronal activities. Dysfunction of vascular pericytes in the brain, mediated by, for example, endothelin, has been shown to participate in the altered blood flow observed in dementia[118].

As we shall see, patients with CKD show actually increased cerebral blood flow, which does not support the more general paradigm of vascular dysfunction.

CKD is invariably accompanied by an increase in arterial blood pressure. Hypertension is a known risk factor for dementia in non-CKD patients[119].

Unexpectedly, in adult patients with CKD the global cerebral blood flow (measured by MRI arterial spin labeling) is increased compared with healthy controls. The increase was more evident in non-dialysis ESRF patients than in HD and PD patients. The changes did not correlate with neuropsychological tests when anemia was taken into account[120]. These results were also confirmed in pediatric patients with CKD, who also showed an increase in global cerebral blood flow (measured by MRI arterial spin labeling) compared with healthy controls, though possibly due to a reduced hematocrit[121]. These findings lead to the counterintuitive interpretation that a decrease in cerebral blood flow may improve cognition in CKD[122]. It is plausible that the increased blood flow represents, in this case, a compensatory effect of anemia.

These data and the lack of efficacy of anti-hypertensive drugs in MCI/dementia-CKD strongly suggest that the vascular hypothesis of dementia in the general population may not be correct or a complete explanation in CKD. However, it should be noted that patients with ESRF on HD have more complex, acute and variable hemodynamic changes triggered by the presence of an arterovenous (AV) fistula and the need for intermittent ultrafiltration.

The AV fistula has a remarkable cardio-circulatory effect. Its effect on cognition compared with central venous catheter is unknown, although overall it is likely to be associated with a better quality of life for dialysis patients[123]. However, intermittent ultrafiltration, which acutely reduces the blood volume, is also expected to reduce cardiac output and mean arterial pressure[124], which in turn reduces splanchnic and brain perfusion. Indeed, at the end of an HD session, cerebral blood flow is reduced, as demonstrated by [15O]H_2O PET-CT scan[125].

Similarly, at the end of PD a reduced cerebral blood flow (measured by MRI arterial spin labeling) has been observed compared with pre-dialysis[120,122]. However, in the interval between HD sessions (48h after the last dialysis session) a rebound effect has also been described, with an increase in the mean blood flow velocity (measured by Doppler ultrasound), partially related to changes in hemoglobin levels[126].

Therefore, the blood flow changes in HD and PD are of short duration, but whether these chronic intermittent changes worsen cognition is unclear. However, the similar prevalence of MCI/dementia in advanced CKD, in HD and in PD suggests that the effect of dialysis treatment on brain hemodynamics is reversible and not additive in any way.

4. 2. 1. 3. A genetic factor that causes impaired autoregulation

Patients with CKD show on MRI focal white matter hyperintensities that are interpreted as small ischemic regions[127]. This poses the problem of whether cognitive dysfunction in CKD is a form of "vascular dementia", which has been studied widely in the general population. Unfortunately, a formal comparison between vascular dementia and CKD-dementia has never been carried out. An additional point of confusion is that vascular dementia is often linked to hypertension, which is a common finding in CKD.

Hypertension has usually been associated with small lacunar infarcts and diffuse areas of chronic ischemia (leukoaraiosis), chronic hypoperfusion and impaired cerebral autoregulation. It also has a genetic predisposition, associated with genes governing endothelial function, such as polymorphisms of angiotensin-converting enzyme, angiotensinogen, endothelin, eNOS, and methylenetetrahydrofolate reductase (MTHFR)[128]. In rats, a genetic variant of the Add3 gene and a genetic deficiency of 20-HETE have been associated with impaired autoregulation of both renal and cerebral blood flow [129,130]. Specifically, genetically hypertensive rats (Dahl salt-sensitive) show deficient formation of 20-HETE with an impaired myogenic response of cerebral arteries and blood-brain-barrier leakage [130].

As discussed above, in CKD cerebral blood flow is augmented, rather than decreased, which is opposite to what has been shown in vascular dementia. Thus, it is possible that a dysfunction of endothelial cells or glial cells modifies the exchange of substances between blood and neurons. Cerebral blood flow may be adequate or even increased, but the blood brain barrier or brain glymphatic system might be dysfunctional.

4. 2. 1. 4 Brain glymphatic system

The glymphatic or perivascular system is a CNS clearance system formed by astroglial cells - a cell species covering the whole cerebral vasculature - that efficiently eliminates soluble proteins and various metabolites from the CNS[112], and is responsible for ~60% of β-amyloid clearance [131] (Figure 4). Vascular diseases, hypertension, diabetes, and neurodegenerative diseases may all reduce glymphatic clearance [132]. Moreover, neuroinflammation and depression have also been shown to suppress glymphatic clearance, perhaps explaining why these conditions increase the risk of developing dementia [132]. Interestingly, glymphatic clearing of waste products occurs primarily during sleep and in particular in stages 3-4

NREM sleep [133]. Although it is not known how CKD affects the glymphatic system, the existing literature suggests that glymphatic fluid transport may be suppressed in CKD and that glymphatic dysfunction can lead to an accumulation of potential neurotoxic waste products. As discussed above, sleep disturbance is common in CKD patients[68] and accompanies the cognitive decline in MCI[134] and dementia [135]. Furthermore, sleep apnea and AD are both linked to reduced level of Amyloid-β in cerebrospinal fluid, indicating that glymphatic clearance is suppressed in these conditions[136,137].

4. 2. 2 Uremic (neuro)toxins and kidney neurotrophins

The EUTOX database (http://www. uremic-toxins. org/DataBase. html) provides an updated list of all known uremic toxins and their characteristics. According to EUTOX, 9% of the known uremic toxins (7 over a total of 75 solutes) are associated with neurological and CNS effects. HD efficiently eliminates water-soluble toxins and improves acute uremic encephalopathy, but it is relatively ineffective when it comes to protein-bound or middle-sized toxins, and does not ameliorate chronic cognitive dysfunction in patients with ESRF (Table 1). The fact that this extracorporeal treatment does not improve cognitive dysfunction in ESRF implicates protein-bound and larger molecular weight toxins in MCI/dementia in these patients.

Many of the uremic bioproducts reported in Table 1 are known to exert a protective effect on neurons, but most of them do not cross the BBB under basal conditions (as reported in Table 1), and so cannot make contact with neurons *in vivo* and are unlikely to provide neuroprotection. Leakage of most of these products in uremia is currently untested, although it is known that the BBB is less functional in advanced CKD. Conversely, some uremic toxins easily cross the BBB under basal conditions and have detrimental effects on the endothelium and vasculature**.** NPY is of particular interest among uremic toxins. This 36-amino acid peptide has been implicated in neurodegenerative diseases such as AD[138]. It is produced centrally (within the brain by specific neurons) and peripherally in nerve endings. Plasma NPY mostly derives from peripheral nerve endings, with an unclear correlation with the NPY coming from the cerebrospinal fluid[139]. However, it has been reported to readily enter the brain from blood by diffusion across the BBB [140]. Independent of BMI, serum NPY levels are elevated in CKD patients[141] and in patients with sleep apnea; continuous airway positive pressure reduces NPY levels in these patients [142]. NPY levels predict a high risk for cardiovascular events both in CKD and in ESRF patients [143].

Because cognitive impairment is much more frequent in patients with cardiovascular disease, particularly in those with heart failure [144], NPY may be implicated in the pathogenesis of these alterations in CKD. In fact, high NPY levels in supratentorial cerebrospinal fluid, at least in the short term, are associated with cognitive impairment in patients with subarachnoid hemorrhage [145]. Finally, NPY is also responsible for endothelial dysfunction [146], which makes this substance a good candidate for brain impairment in CKD.

CKD patients often present with disturbed calcium and phosphate metabolism, high PTH and FGF23 levels, and low α-klotho (see earlier) and calcitriol levels. PTH is listed among the uremic toxins, but the evidence that this hormone is directly implicated in cognitive impairment is uncertain [147]. PTH is a polypeptide of 84 amino acids, which is unlikely to cross the BBB under normal conditions. Furthermore, the level of expression of the PTH receptor in the brain is fairly low according to the Allen Brain Atlas. However, disturbed mineral metabolism may have an impact on cognitive impairment in CKD patients through pathways independent of PTH. The liver/bone/kidney isoform of alkaline phosphatase, an enzyme key to bone metabolism, is also expressed in neurons of the cerebral cortex (data from The Human Protein Atlas database: https://www. proteinatlas. org/). PTH is elevated in patients with AD and correlates inversely with cognitive function in these patients [148]. Experimental evidence suggests that high alkaline phosphatase, by dephosphorylating the tau-protein, a protein considered central to the pathogenesis of AD, may promote the binding of the same protein to muscarinic receptors (M1 and M3) in the hippocampal area, thereby triggering a marked increase in intracellular calcium levels and triggering cell death [149].

The phosphaturic hormone FGF23 increases early during the course of CKD and has been associated with cardiovascular disease and cardiovascular mortality [150]. Moreover, in the Framingham study, higher FGF23 levels are associated with a higher risk for dementia [151]. α-klotho, the obligatory co-ligand of FGF23 is highly expressed in brain after the kidney and parathyroid glands [152]. Circulating α-klotho, as well as kidney and parathyroid α-klotho, are downregulated in CKD, but whether brain α-klotho is also affected is unknown. A recent MRI-based study found that reduced circulating α-klotho associated positively with the risk for dementia and cerebral deep white matter lesions, even after correction for reduced kidney function and other risk factors [153]. Several genetic variants altering α-klotho protein levels are associated with β-amyloid burden and risk for dementia [104,105,154]. Experimental evidence links α-klotho with the function of serotonergic neurons, hippocampal function, depression and dementia-like symptoms in animals [115]. While low α-klotho or high FGF23 appear to

exert negative effects on brain function, α-klotho or FGF23 deficiency also impair neuronal processes, particularly in the hippocampus and possibly also cerebellum, affecting memory, behavior, and motor functions [155,156]. A common denominator of α-klotho or FGF23 deficiency is high calcitriol and reducing calcitriol levels to normal reverses or prevents brain alterations in experimental animal models [157]. In contrast, patients with CKD often suffer from low calcitriol levels. This apparent contradiction that both high and low calcitriol levels are linked to impaired brain functions may indicate an optimal range of calcitriol levels necessary for neuroprotection, microglial immune function, and vascular integrity [158,159]. At present there is no evidence supporting calcitriol supplementation to delay loss of psychomotor functions in elderly populations with CKD [160] (Figure 5).

4. 4 Role of brain stem cells and neuroinflammation in CKD-dependent cognitive impairment

CKD is a pro-inflammatory dysmetabolic state with associated brain dysfunction. Surprisingly little attention has been payed to the role of neural stem cells (or neural precursor cells, NPCs) in CKD patients, given that NPCs play a key role in several homeostatic brain functions and are extremely sensitive to their micro-environment. While NPCs located within the sub-granular (SGZ) zones contribute via neurogenesis to maintaining memory circuitry, behavior and spatial learning (e.g., endogenous NPCs produce a constant albeit slow increase in hippocampal volume, which is needed for cognitive functions and mood)[161,162], NPCs residing in the subventricular (SVZ) exert little or no neurogenic functions, but contribute to counteracting metabolic dysfunction and/or inflammatory processes), the so-called 'bystander (or paracrine) effect' [163]. This is due to the ability of undifferentiated NPCs to secrete a milieu of homeostatic and/or neuroprotective molecules (e.g., stem cell regulators, trophic factors and immunomodulators) that are thought to be important, because, depending on the tissue microenvironment, they may stimulate endogenous precursors to promote re-myelination or rescue (directly and indirectly) of damaged axons and neurons [162–164]. As a consequence, an additional pathogenic mechanism that might contribute to irreversible glial and/or neuronal loss, and the neuronal functional impairment underlying cognitive dysfunction in CKD patients, could be the effect of uremic toxins, inflammatory cytokines (e.g., IL-1β, IL-18, IL-6, TNFα), as well as anti-inflammatory cytokines (e.g., IL-10) and free-radicals (Figure 4).

Among the inflammatory cytokines, IL-6 is increased 5-fold in HD patients, and permanently perturbs NPC proliferation and neurogenesis[165]. IL-10, which is increased in HD, maintains NPCs in an undifferentiated proliferation state, rather than promoting differentiation[166]. Both TNFα and IL-1β also increase in HD and can stimulate NPC proliferative capacity[167]. At present it is not clear if the differential effects of IL-10 and IL-1β on NPCs have also different cognitive effects. Free radicals, which are increased in HD and CKD patients may strongly and negatively impact NPC function [168]. Finally, cell-mediated innate immunity, thought to be involved in toxic uremia as a potential pathogenic mechanism causing cognitive impairment in CKD patients, might also be impaired when NPC homeostasis is disturbed[169]. In kidney transplant patients cyclosporin and mycophenolate have direct inhibitory effects on NPCs[170], unlike everolimus[171].

NPCs also play a role in neurodegenerative diseases such as AD: the deletion of genes necessary for NPCs and neurogenesis (such as Tet1, 5hmC) lead to learning and memory deficits in animal models[172,173].

It is becoming clear that uremic (neuro)toxins in CKD not only exert a detrimental effect on neural cells, but also on NPCs, although this is still not yet widely appreciated. Given the pleiotropic actions (homeostatic and reparative) of NPCs, and the accumulating evidence showing that during CKD circulating uremic toxins (whose CNS trafficking is facilitated by BBB damage) may impair CNS structure and function, this seems to be a new research avenue and opportunity in MCI-CKD worth pursuing.

5. Interventional studies

Interventional studies are essential for the identification of mechanistic links between kidney disease and brain alterations. At present most of the attempts to improve, prevent or delay MCI/dementia in CKD have been unsuccessful. We will review some of these attempts to make the reader aware of what has been already done. However, new drugs are now available to relieve some of the symptoms of dementia, relatively new dialysis regimens are being used today, and new anti-inflammatory therapies have been introduced for atherosclerosis and stroke: we list these approaches, which may yet prove beneficial.

HD is life-saving in patients with ESRF and reverses acute encephalopathy. The acute uremic encephalopathy or uremic delirium presents with impaired memory and attention, altered consciousness and disorganized thinking in untreated patients with ESRF. Today it is a rare

clinical presentation, because patients with ESRF usually undergo planned dialysis before this neurological syndrome can develop. When it does occur, neurological recovery may take days after dialysis initiation and in at least one case report a patient remained comatose for 5 days after correction of uremia[174]. This supports the notion that circulating and brain-permeable small molecules, which are removed by dialysis, are likely to be responsible for acute uremic encephalopathy. In contrast, MCI and dementia develop over longer time-scales and reversibility is potentially possible only for MCI, rather established dementia.

However, the question is whether the clearance of blood toxins by HD can decrease the risk of developing MCI-CKD. Unfortunately, the partial correction of blood composition with HD seems unlikely to prevent or slow down MCI-dementia progression, which is suggested by a similar prevalence of MCI/dementia among patients on HD compared with those with advanced CKD who are not yet on dialysis[175]. This inability of HD to attenuate MCI might be due to a suboptimal and discontinuous treatment regimen (with a rapid increase in toxin levels between dialysis sessions); however, more intensive dialysis regimens with improved dialysis adequacy (Kt/V) also do not improve MCI-related outcomes[176]. Therefore, it is possible that some uremic (neuro)toxins, for example, medium-large size toxins and protein-bound toxins (listed in Table 1) are not adequately removed by HD. Unfortunately, no data are available on the effect of hemodiafiltration (HDF), which can potentially remove larger size toxins, on cognitive function. A meta-analysis suggests that PD treatment may be more advantageous than HD[45,175]. However, there is inconsistency among studies, possibly because the effect is very small. In a large study enrolling 52'332 HD patients and 3'292 PD patients, the higher risk for cognitive impairment in HD disappeared after controlling for demographic characteristics and competing risks of death[177].

Therefore, the slower dynamics of ultrafiltration/dialysis of the peritoneal system or better removal of protein-bound toxins do not seem to lead to greater clinical improvement. Similarly, kidney transplantation attenuates MCI, but does not lead to the recovery of cognitive function to the levels of a control healthy population (see Figure 1)[178,179]. This suggests that MCI-CKD is not easily reversible or that the immunosuppressive drugs used to avoid rejection also impinge on cognitive function.

Neuropsychological approaches are unlikely to improve MCI, because they do not remove the organic substrates causing the problem, nor are interventions (alone) that aim at better control of blood pressure or prevent cerebrovascular accidents (stroke and myocardial

infarction) [180]. This suggests that the vascular alterations observed in CKD are not the main cause MCI or that they do not respond to standard preventive strategies.

Few interventional studies are available examining the diet/nutritional changes in CKD-MCI progression. Vitamin B and folate supplementation to reduce homocysteine did not result in a reduction in MCI-CKD[181]. L-carnitine improves cognitive function in a rat model of CKD, but no data are available in humans[182]. Vitamin D 25(OH)2 levels can be low in CKD and hypo-vitaminosis D is associated with cognitive decline; however, no data are available on its supplementation to prevent MCI in CKD (see earlier).

Antioxidants such as Vitamin E have been proposed to reduce brain oxidative stress and slow cognitive impairment in the general population, although with minimal effects in AD[183]. Tempol, an antioxidant, has been tested in animal models of CKD with some neuroprotective effect[184].

Unsaturated fatty acids such as omega-3, Mediterranean diet, and malnutrition are other dietary factors and nutritional aspects considered relevant in the general population, but with minimal effects on cognitive protection[185,186]. No information on MCI-CKD is currently available with these approaches.

Iron deficiency is also common in CKD and anemia is a risk factor for poor scores at neuropsychological tests. Unfortunately, no information is available on iron supplementation in CKD to prevent MCI. However, erythropoietin appears beneficial for cognitive dysfunction in CKD[187,188], which supports the role of CKD-dependent anemia in poor cognitive function. The recent introduction of hypoxia inducible factor (HIF) stabilizers as an oral alternative to injectable erythropoietin for anemia in CKD patients[169]awaits further assessment for its effect on MCI-CKD.

The hypothesis of altered PTH/phosphate homeostasis in MCI-CKD has not been tested. At present there is only a single case report of the reversal of cognitive impairment after cinacalcet treament[189].

The neuroinflammatory hypothesis might have an additional support after the attempt to reduce atherosclerosis/endothelial dysfunction by targeting a postulated inflammatory mechanism. Canakinumab, an anti-interleukin-1β antibody[190], and cholchicine[191] both reduced the effects of atherosclerosis and showed some effect on brain function. Specifically, Canakinumab reduced infarct size, cerebral oedema and improved neurological performance in an animal model of stroke [192]. Conversely, colchicine is neurotoxic when injected into the

brain[193] , but if delivered in the bloodstream has anti-neuroinflammatory action potentially useful for AD[194] . Consistently, a trial on 4754 patients assigned to receive colchicine or placebo showed neuroprotective effect of colchicine, with lower risk of stroke[191]. This may support the hypothesis linking MCI-CKD to wider endothelial dysfunction.

6. Conclusions

Nephrologists need to be more aware of cognitive impairment in CKD. However, a major problem is the lack of any mechanistic understanding and the paucity of data, and therefore for any interventional strategies. More systematic and standardized neurophysiological testing of CKD patients recruited to the increasing number of large prospective CKD cohorts will help in defining more reliably the true extent of the problem of MCI-CKD and the biomarkers linked to it. Hemodiafiltration or other high permeability membranes await testing of their effect on cognition. Memantine, and acetylcholinesterase inhibitors (e.g., donepezil) that are used in dementia have an unclear role in CKD patients. Strategies to improve endothelial and glymphatic function, and neuronal stem cell production in CKD are still in their infancy. However, if any of these approaches can prove useful in MCI-CKD, this could also be a significant step forward in treating dementia itself.

BOX 1: MCI

Mild cognitive impairment (MCI): a term used to identify subjects at risk to develop dementia, but whose cognitive deficit is so mild that it does not impinge upon daily activities. The diagnosis is based on symptoms reported/observed by patients, caregivers, informants and clinicians. The symptoms include memory impairment, language difficulties, attention deficit, disorientation and altered visuospatial skills. MCI is only a risk state: 90-95% of subjects with MCI actually do not progress to dementia. However, while dementia is irreversible, 14-44% of MCI subjects can recover to normal cognitive function. After the introduction of the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5), dementia has been renamed as major Neurocognitive disorder (major NCD) and MCI as mild NCD. Correspondingly, the criteria for MCI have changed. The Petersen's criteria for MCI are: (a) subjective decline in memory (b) memory impairment on neuropsychological test (c) intact daily functioning (d) no dementia. The DSM-5 criteria for MCI are: (a) concern (of the

patient or of the clinician) of a mild decline in cognitive function (b) cognitive decline by standard cognitive assessment (c) independence in everyday activities (d) cognitive deficits not explainable by delirium, psychosis, severe depression.

BOX 2: glossary

Attention: the cognitive domain involved in the selection of a specific information within a sensory channel (filtering), ignoring all the other data. It requires the activity of the prefrontal cortex, with modulation by the dopaminergic system

Inhibitory control: the ability to suppress ongoing and inappropriate responses to potentially relevant stimuli. A classical test is the Stroop task, requiring to name the font color of a printed word, neglecting the meaning of the word itself.

Memory: the cognitive domain involved in the registration and recall of information. Different and independent types of memory exist, such as explicit memory (for words, history etc), implicit memory (for actions, skills), short term and working memory (with limited number of items that can be recorded and short permanence) and long-term memory. Although no single brain region can be linked to memory, at the neuronal scale the phenomenon most likely correlated to memory is called “long term potentiation” and “long term depression”, which are sustained modifications of the efficiency of the neuronal contacts or synapses.

Language skills: the cognitive domain dealing with repeating, understanding and producing words, sentences, language. They require the function of two main areas in the dominant (left) cortex, that is the motor- and sensitive- language areas (Broca’s and Wernicke’s areas)

Visuospatial ability: the cognitive domain dealing with the analysis of visual information, recognition of images and reproducing drawings. It requires the integrity of the occipital cortex.

Executive functions: a psychological construct indicating mental processes necessary for goal-directed behavior. The term derives from subjects with damage of the frontal lobe, who can show normal language, learning, memory and reasoning on specific tasks; notwithstanding, their everyday tasks are disorganized and poorly planned: their “cognitive resources” such as learning, memory, reasoning, language are poorly coordinated,

that is they exhibit an "executive dysfunction". No direct access to executive functions is possible, therefore they comprise many different psychological terms such as attention and of inhibition, working memory, cognitive flexibility, planning, fluid intelligence, reasoning and problem solving etc. It requires the integrity of the frontal lobe and its modulation by dopamine and cholinergic neurons from the mesencephalon and basal forebrain respectively.

Catecholamine neurons: a small group of neurons (less than one million) mainly localized in the encephalic trunk and comprising adrenergic/noradrenergic and dopaminergic neurons. These neurons innervate large parts of the brain through a massive harborization of their axons. They can subserve both simple computational task (such as indicating the presence or absence of a reward) and tonic activity on target regions, such as the striatum and the cortex, thereby controlling wakefulness and attention.

Polysomnography. An overnight sleep study based on neurophysiologic parameters (EEG, electrooculography, electro-myography), respiratory patterns, pulse oxymetry, heart rate. In clinical practice it is used, for example, for the diagnosis of Sleep Apnea and the characterization of sleep disturbances.

Actigraphy. Usually a portable device (e.g. in the form of a bracelet) equipped with motion sensors (accelerometers, gyroscopes, GPS), aimed at recording and characterizing the motor activity and posture of a subject during the day or over several days. Step-meters are a cheap and simple type of actigraphic recordings. Since sleep is accompanied by specific postures (usually supine position) and immobility, actigraphic recordings can be used as a first approach to study 24h sleep patterns in large populations, being inexpensive and comfortable to wear (as opposed to polysomnography).

Sleep apnea. This is a common respiratory problem characterized by recurrent episodes of apnea/hypopnea (no or reduced airflow) during sleep. The apneic episodes can originate from a dysfunction of the brain respiratory centers (central sleep apnea) or from alteration of the upper airways (e.g., pharynx and larynx) or the tone of their muscles (peripheral sleep apnea).

Dysautonomia. Altered function of the autonomic nervous system (sympathetic and parasympathetic) with consequent maladaptive control of orthostatic blood pressure, digestion, and bladder emptying.

Force plates. A device to study where the body weight is released onto the floor over time, and its magnitude. The position of the sum of all forces acting between the body and the

floor can be measured by force plates and is called Center of Pressure. The position of the Center of Pressure changes over time during movements (such as walking) or even during simple stance.

Accelerometers. Devices measuring the acceleration of an object over time. These sensors are usually very small and can be applied onto the hand to measure hand tremor. Even the widely available smartphones or game controllers may serve for this purpose.

Blood-brain barrier (BBB) and blood-cerebrospinal fluid (BCB) barrier. The phenomenon by which many substances (such as India ink) and drugs injected into the blood remain within the cerebral capillary bed without entering into the parenchyma (BBB) or the cerebrospinal fluid (BCB). The anatomical substrate for this phenomenon is thought to involve the peculiar structure of the brain capillary endothelium and the presence of a pericapillary glial sheet.

NREM sleep. Using EEG it is possible to appreciate the oscillatory dynamics of sleep, which is composed of 4-5 cycles of a long period without eye movements (non-rapid-eye movements: NREM) followed by short rapid eye movement stage (REM). The NREM state is further composed of progressive EEG alterations which can be classified in 4 stages.

Table 1. List of uremic neurotoxins uncleared or insufficiently cleared by dialysis and current therapeutic regimens. The impact on the brain is analyzed on cellular/tissue scale, intermediate phenotype scale and behavioral scale. BBB+: the toxin crosses the blood brain barrier; BBB-: the toxin does not cross the BBB (predicted from https://www.cbligand.org/BBB/). NA: data not available

Name	**Impact on the CNS**			**Solubility-protein bound; BBB crossing**
	Microscopic scale (Cells/tissue)	**Intermediate phenotypes**	**Behavioral scale**	
Asymmetric Dimethyl Arginine (ADMA)	Endothelial dysfunction[210]	Vascular brain injury [217], slower gait speed[218]	Cognitive impairment	Water-soluble BBB-
beta-2-microglobulin	NA	NA	NA	Middle BBB-
3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF)	Inhibition of brain-to-blood transport of metabolites[211]	Sleep [219]		Protein-bound **BBB+**
Cystatin C	NA	Glymphatic solute clearance [220]	NA	Middle BBB-
FGF23	Endothelial	NA	Memory	Middle

	dysfunction [212]		deficits[151]	BBB-
Hippuric acid	Endothelial dysfunction[213]	BBB dysfunction	Uremic encephalopathy	Water-soluble **BBB+**
IL-1 beta	Neurodegeneration of dopamine neurons[195]	NA	Executive function, memory	Protein-bound BBB-
IL-6, TNF-alpha	Neuroinflammation[196]	Reduced glymphatic drainage[214]	NA	Middle BBB-
Indole-3-acetic acid	Effect on neuronal stem cells[197]	NA	NA	Protein-bound **BBB+**
Indoxylsulphate/p-cresylsulphate	Neuroinflammation and altered glial function [198]	NA	Cognitive impairment [221]	Protein-bound **BBB+**
Leptin	Neuroprotective; apoptosis in neural stem cells ; adiposity-dependent neurotoxicity[199,200]	NA	NA	Protein-bound BBB-
Methylglyoxal	Effects on neural stem cells, Amyloid deposition[201,202]	Lower gray matter	Memory, executive functions[202]	Protein-bound **BBB+**
Neuropeptide Y	Endothelial	Sleep	NA	Middle

(NPY)	dysfunction[146]	regulation		**BBB+**
Parathyroid hormone (PTH)	NA	Gait instability[215]	NA	Middle BBB-
Spermidine/putrescine	NA	NA	NA	Protein-bound BBB-
Putative kidney neurotrophins				
Erythropoietin	Increases brain aquaporin 4 (glymphatic pathway)[203]	Neuronal oxygenation	Improves behavioral deficit	Middle BBB-
Hydrogen sulfide (H2S)	Promotes neuronal stem cell differentiation; Neuroprotective effects[204,205]	NA	Improves behavioral deficit	Water-soluble **BBB+**
Uric acid	Protective on dopamine system; Promotes neuronal stem cell differentiation[206,207]	Increases brain perivascular spaces (glymphatic pathway) [216]	NA	Water-soluble **BBB+**
Vitamin D-calcitriol	Decreases neuroinflammation; promotes neuro-genesis[208,209]	NA	Maintains global cognitive performance[222]	Protein-bound **BBB+**

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Conflicts of interest

All authors report no conflict of interest

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Figure Legend

Figure 1. Schematic representation of the evolution of mild cognitive impairment (MCI) as a function of CKD stage at fixed age (A) and as a function of age (B). The effect of replacement therapies (HD, PD) in the end stage phase (ESRF) are also reported. A: The percent of mild cognitive impairment, screened with tests such as the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), increases as a function of CKD stage/eGFR (and possibly as a function of the time spent in that stage). B: the risk for MCI increases as a function of time (age) in the general population. In patients with ESRF treated with hemodialysis (HD) the risk remains greatly above the general population. Peritoneal dialysis (PD) gives some advantage. Patients with mild CKD and kidney transplantation restores the slope of the risk curve towards that of the general population; however, the initial gap developed before transplantation is not "repaired" and therefore average cognitive performances in transplanted patients remain below the non-CKD population. Lines are estimates based on selected studies reported in Supplementary data. The confidence intervals are derived from the variations among selected studies.

Figure 2. Schematic representation of brain modifications accompanying chronic kidney disease (CKD), possibly mediated by uremic neurotoxins or lack of kidney neurotrophins. Catecholamine neurons in the encephalic trunk/hypothalamus may be particularly sensitive to the uremic milieu, thereby mediating the alterations in sleep patterns, mood, attention. These may in turn impinge on memory, thus giving the emergence of Mild cognitive impairment (MCI) and then dementia. LC: locus coeruleus. NE: norepinephrine neurons; 5HT: serotonin neurons; DA: dopamine neurons; SN/VTA: Substantia Nigra/Ventral Tegmental Area; H: histamine neurons; TM: tuberomammillary (hypothalamus), Ach: acetylcholine neurons; PFc: prefrontal cortex.

Figure 3. The hierarchical organization connecting CKD to behavior. Cognitive impairment is a complex behavioral pattern that can be screened using questionnaires and summarized in a single score but is actually a multidimensional phenomenon comprising multiple cognitive domains. Therefore, its relation with the direct effects of CKD (e.g. the biochemical changes in plasma) is complex and difficult to understand. Intermediate phenotypes are quantitative phenotypes connected to the complex behavioral alterations, but with simpler biological substrates, which are more easily connected to the molecular derangements of CKD.

Figure 4. Uremic neurotoxins enter the brain via the blood brain barrier (BBB) and blood-CSF barrier (BCB) and leave the brain via the glymphatic system that is a polarized brain fluid transport system that connects with meningeal and peripheral lymphatic vessels for export of metabolic waste. CSF in the subarachnoid space is driven into the periarterial space by arterial pulsatility and mixes with interstitial fluid thus dragging waste product not only for export along the perivenous spaces but also within different areas of the brain including NPC niches, located within the sub granular (SGZ) zone and the sub ventricular zone (SVZ). Within these NPC niches uremic neurotoxins might interfere with proper functioning of endogenous NPCs, such as neurogenesis and homeostatic functions, thus further contributing perturb brain tasks during CKD.

Figure 5. Mechanism of action of some of the uremic (neuro)toxins and their interaction with genetic predisposing factors.

Figure 1

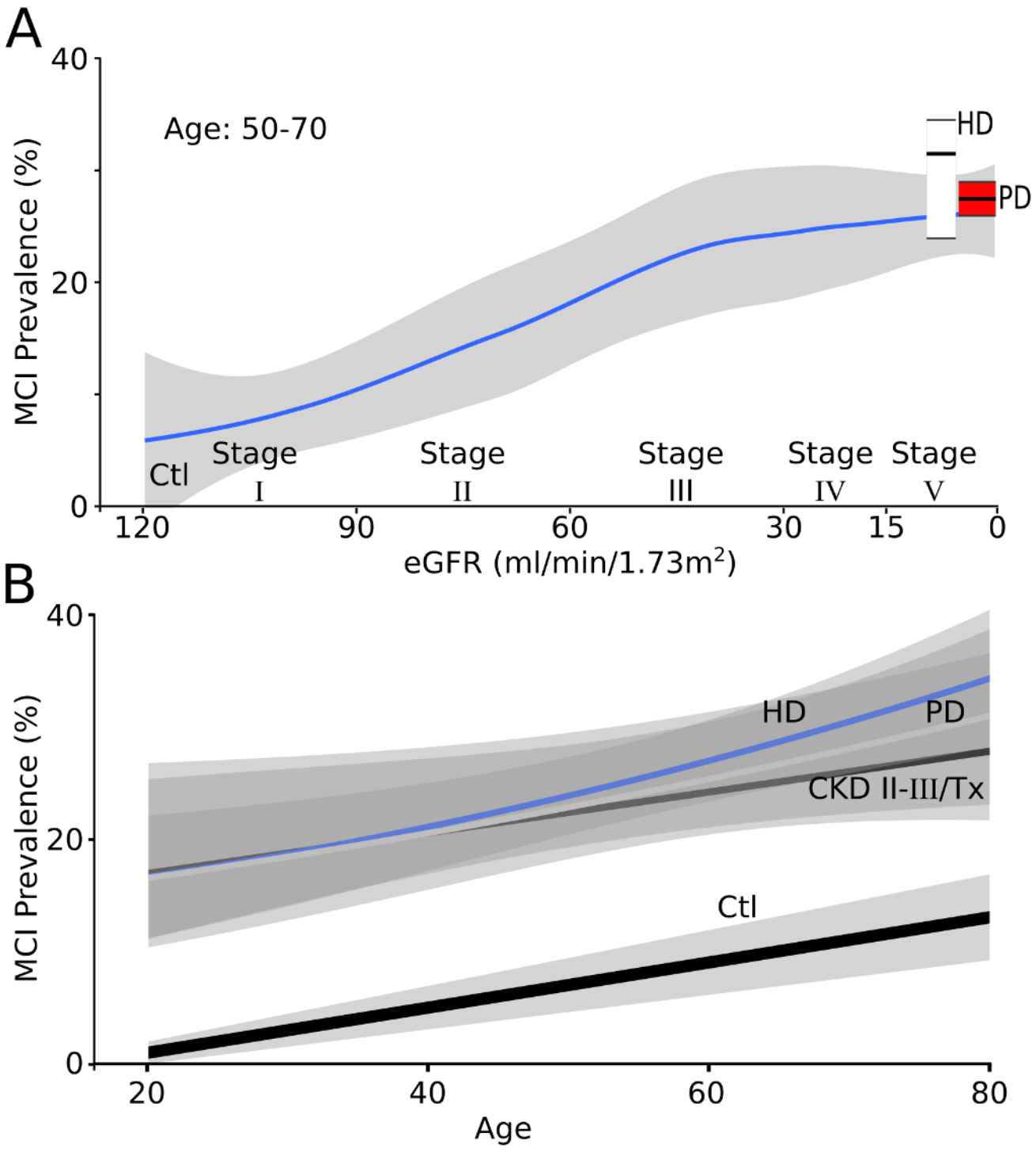

A
40
20
0
MCI Prevalence (%)
Age: 50-70
HD
PD
Ctl
Stage I
Stage II
Stage III
Stage IV
Stage V
120
90
60
30
15
0
eGFR (ml/min/1.73m²)
B
40
20
0
MCI Prevalence (%)
HD
PD
CKD II-III/Tx
Ctl
20
40
60
80
Age

Figure 2

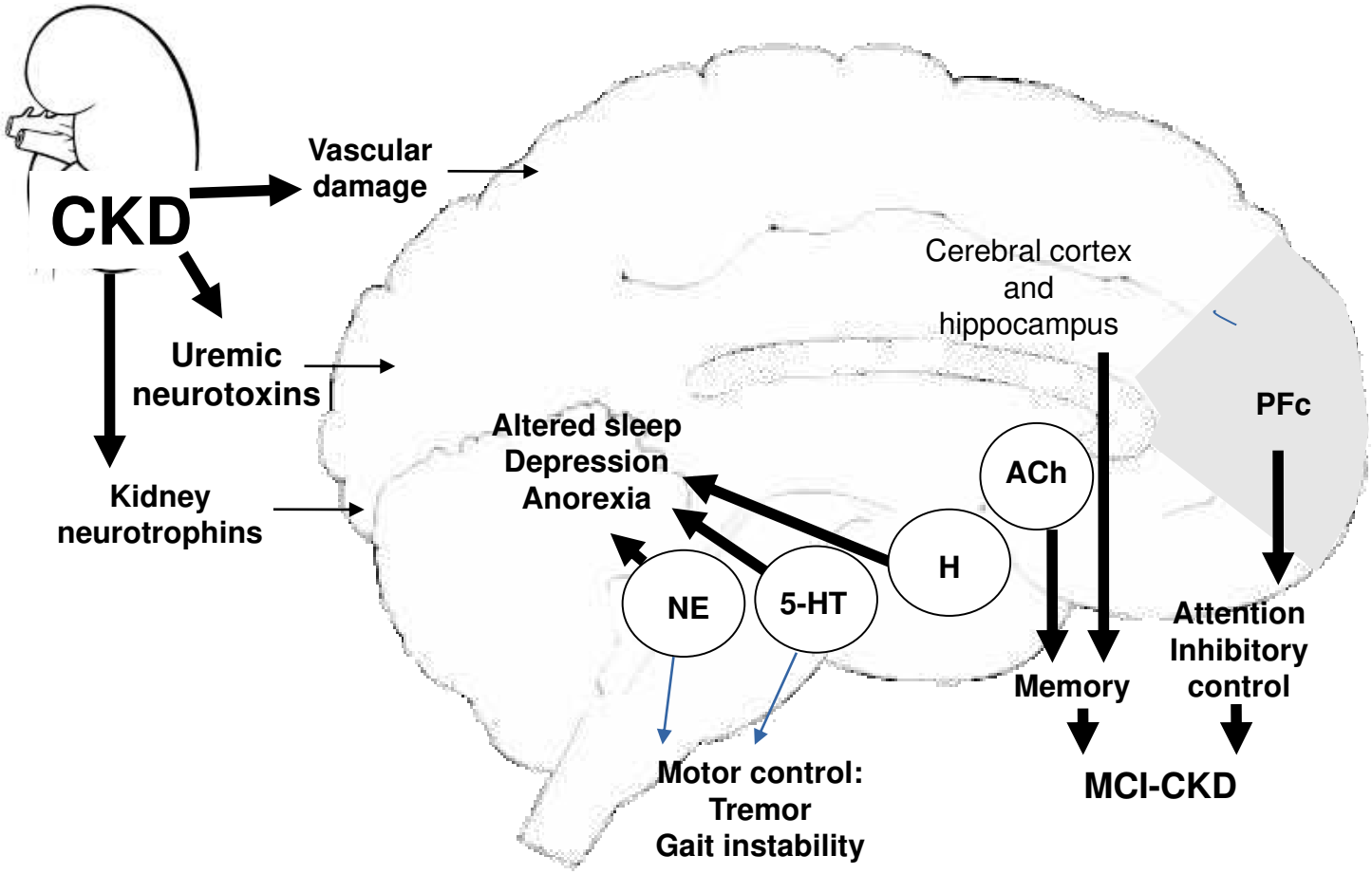

CKD
Vascular damage
Uremic neurotoxins
Kidney neurotrophins
Cerebral cortex and hippocampus
PFc
Altered sleep
Depression
Anorexia
ACh
H
NE
5-HT
Memory
Attention
Inhibitory control
Motor control:
Tremor
Gait instability
MCI-CKD

Figure 3

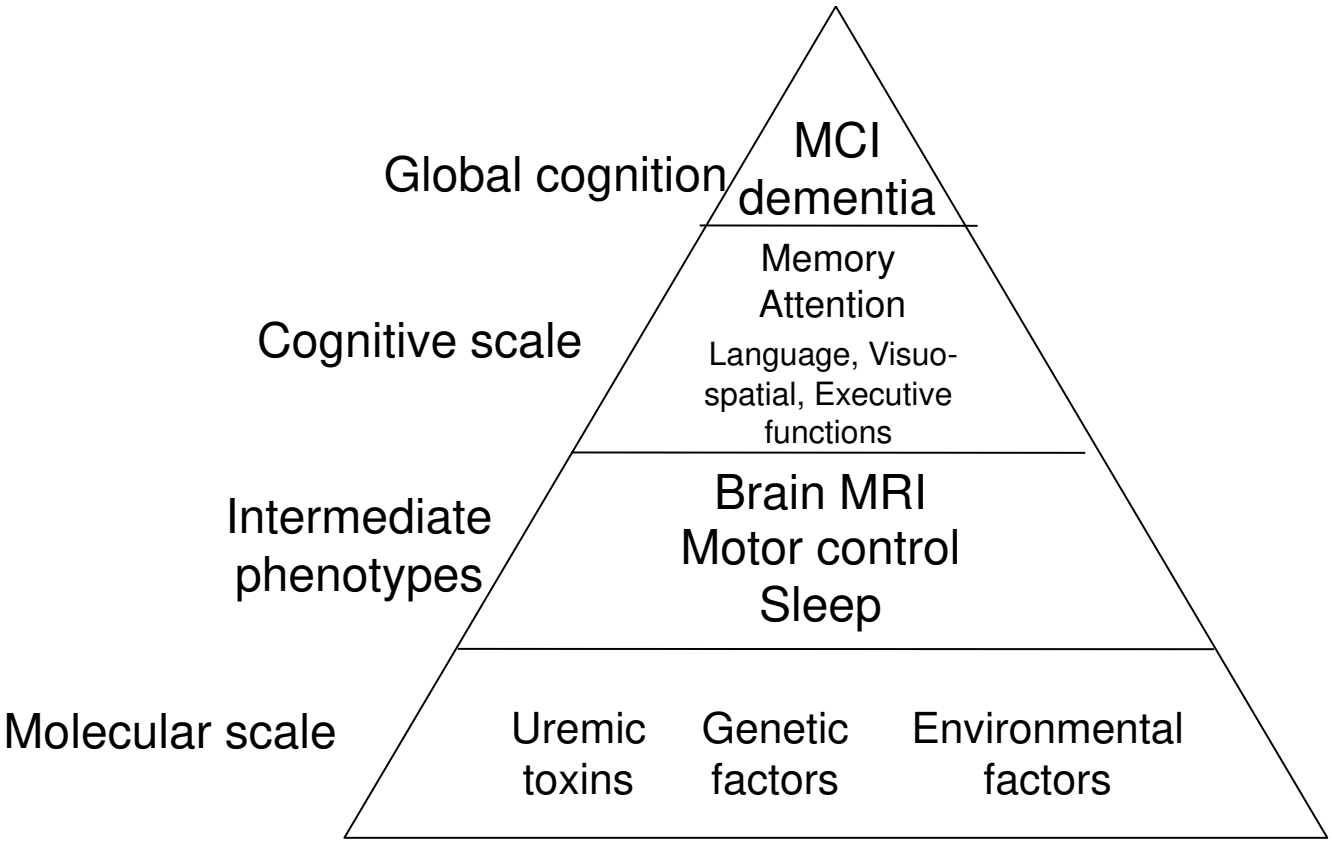
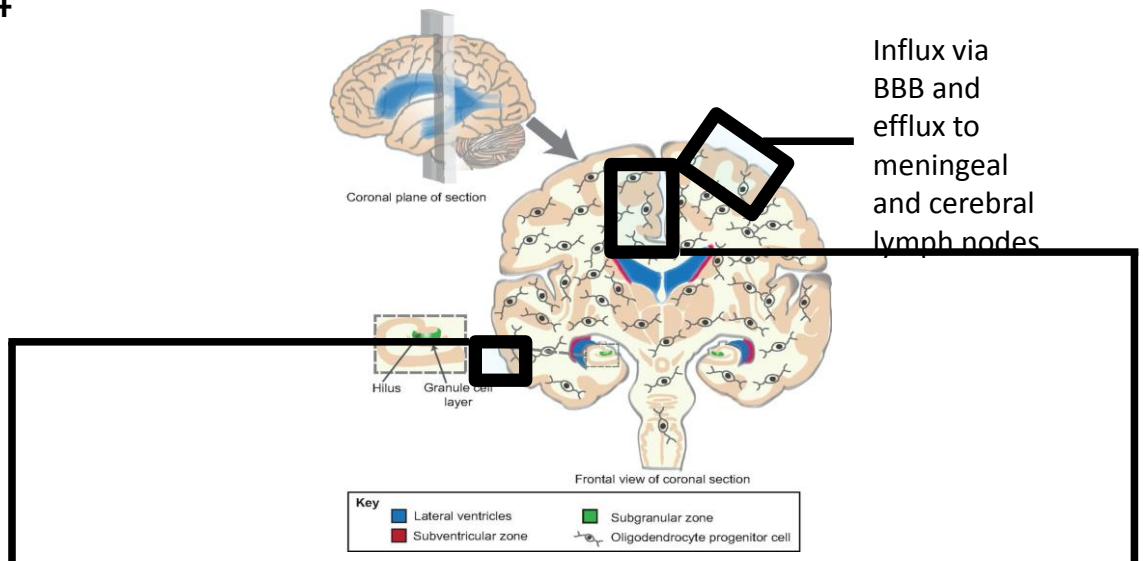

Global cognition
MCI
dementia
Cognitive scale
Memory
Attention
Language, Visuo-spatial, Executive functions
Intermediate phenotypes
Brain MRI
Motor control
Sleep
Molecular scale
Uremic toxins
Genetic factors
Environmental factors

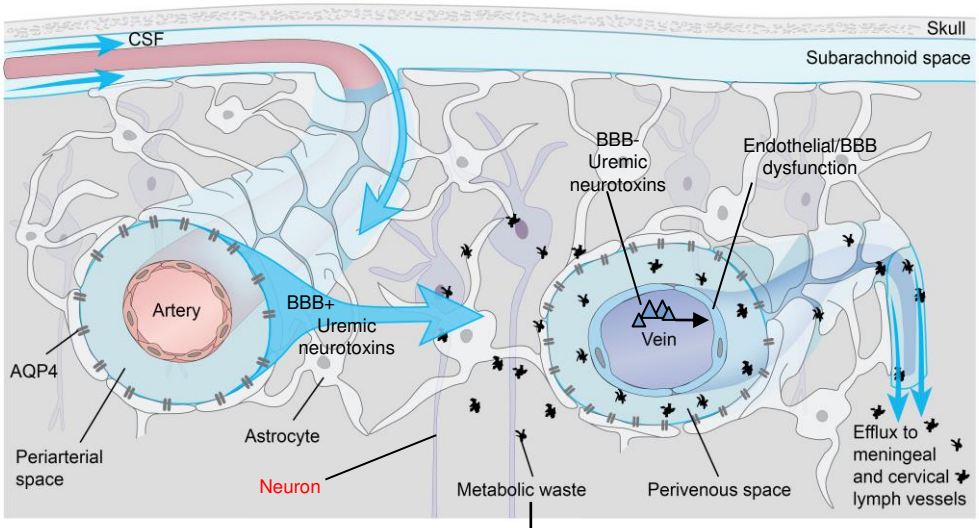
Figure 4



Influx via BBB and efflux to meningeal and cerebral lymph nodes

Metabolic waste

(e.g. uremic neurotoxins)



Inflammatory factors

(e.g. cytokines)

Diffusion to NPC niches

Diffusion to NPC niches

NPC niches

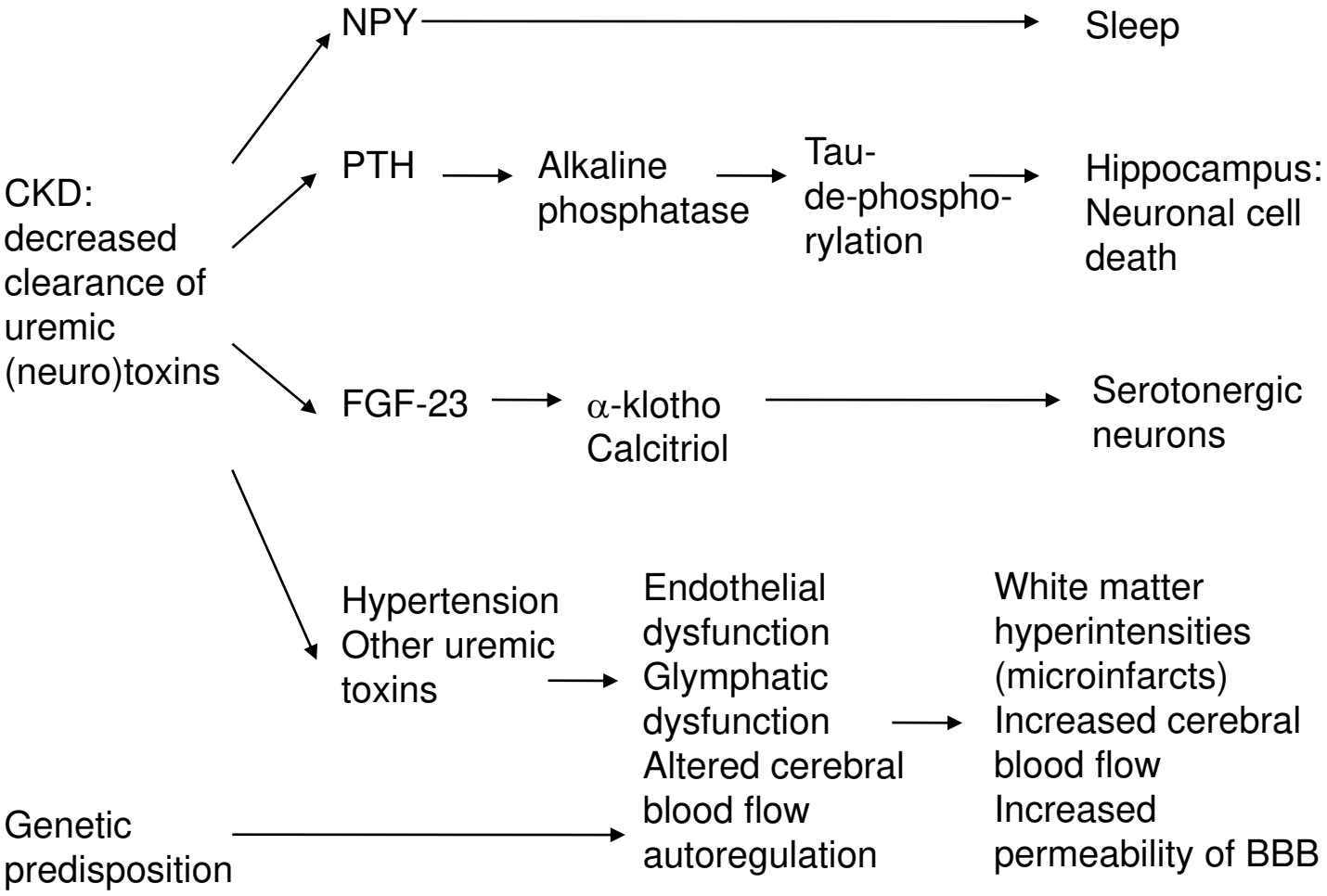
Sub-granular zone (SGZ)

- Impairment of hippocampal neurogenesis

Sub-ventricular zone (SVZ)

- Perturbation of homeostatic functions

Figure 5


NPY
Sleep
PTH
Alkaline phosphatase
Tau-de-phospho-rylation
Hippocampus: Neuronal cell death
CKD: decreased clearance of uremic (neuro)toxins
FGF-23
α-klotho
Calcitriol
Serotonergic neurons
Hypertension
Other uremic toxins
Endothelial dysfunction
Glymphatic dysfunction
Altered cerebral blood flow autoregulation
White matter hyperintensities (microinfarcts)
Increased cerebral blood flow
Increased permeability of BBB
Genetic predisposition