How the kidney may affect brain cognitive function

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Nephrology has historically had tight connections with other medical fields, such as cardiology, oncology, and gastroenterology. It shared the frontal line with pharmacologists to understand the effects of certain drugs, such as vasopressin-receptor antagonists and sodium-glucose cotransporter-2 inhibitors on renal function and other processes. Now, nephrology faces a new frontier – the interaction between the kidney and the brain, which is the focus of the recently established European CONNECT (Cognitive decline in Nephro-Neurology European Cooperative Target Action) project.
The CONNECT project, funded by the COST action program, formed a multidisciplinary network of scientists to interpret the nature and origin of mild cognitive impairment (MCI) in chronic kidney disease (CKD) patients, not only from a clinical point of view but also from a scientific perspective. For this purpose, it assembled nephrology clinicians, neurology clinicians, pre-clinical kidney science, pre-clinical neuroscience, and bioinformatics experts into five working groups, engaging in pre-clinical research, clinical research and trials, clinical practice, data management, and bioinformatics, and inclusiveness and dissemination. The target of the project is to consider all factors that may influence brain function and to shed light on those that impact the progression of MCI in CKD patients. Also, since CKD patients represent a very definite endophenotype, the CONNECT group aims to understand factors that may induce MCI in this particular group and further, which, from a neurological point of view may be beneficial for the study of pathophysiology and possible treatment options for dementia.

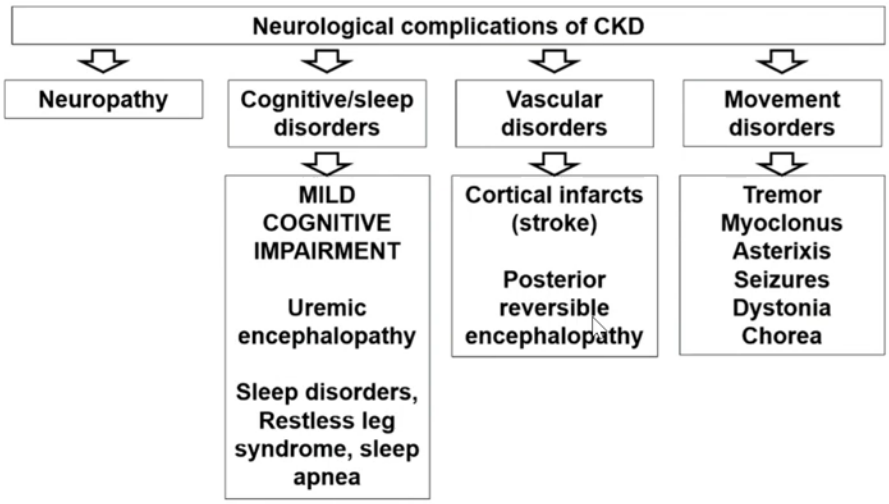

Figure 1. Neurological complications of CKD

Plasma volume, electrolytes, acid-base balance, hormones, and protein metabolism are only a few of the key physiological parameters that are altered by CKD. Although dialysis and transplantation have greatly extended the lives of these patients, their quality of life is still subpar, due to the many comorbidities affecting various organs, including the brain. With the development of novel diagnostic

tools in the field of brain studies, such as functional magnetic resonance (fMRI), tractography, and optogenetics, and the implementation of metabolomics, proteomics, peptidomics, and 2-photon microscopy in kidney research, a great deal of data can be collected and processed.

In addition to neuropathy, which is common in long-term CKD patients, the neurological complications of CKD also include cognitive/sleep disorders such as mild MCI, vascular disorders, and even motion disorders. Mild cognitive impairment is found in 30 to 60 % of the overall number of dialysis patients and it involves persistent cognitive decline and behavioral disturbances, without interference with independence and daily functioning characteristic of dementia, which affects 14% of dialysis patients. One of the hypotheses on how CKD influences cognitive impairment is vascular damage coupled with malnutrition or inflammation, and compelling data is demonstrating a decline in cerebral mean flow velocity and white matter hyperintensities progress related to hemodialysis. On the other hand, the most plausible hypothesis is that the damage may be caused by uremic (neuro) toxins produced in the course of CKD. It is also speculated that kidney failure prevents the production of neuroprotective factors, resulting in the suffering of the brain in CKD. The complicated puzzle of risk factors associated with neurological disorders in patients with CKD involves factors that are non-specific to CKD - such as age, hypertension, lifestyle risk factors, dyslipidemia, and hyperglycemia, and factors directly linked to CKD - such as calcification, uremic toxicities, and dialysis itself.

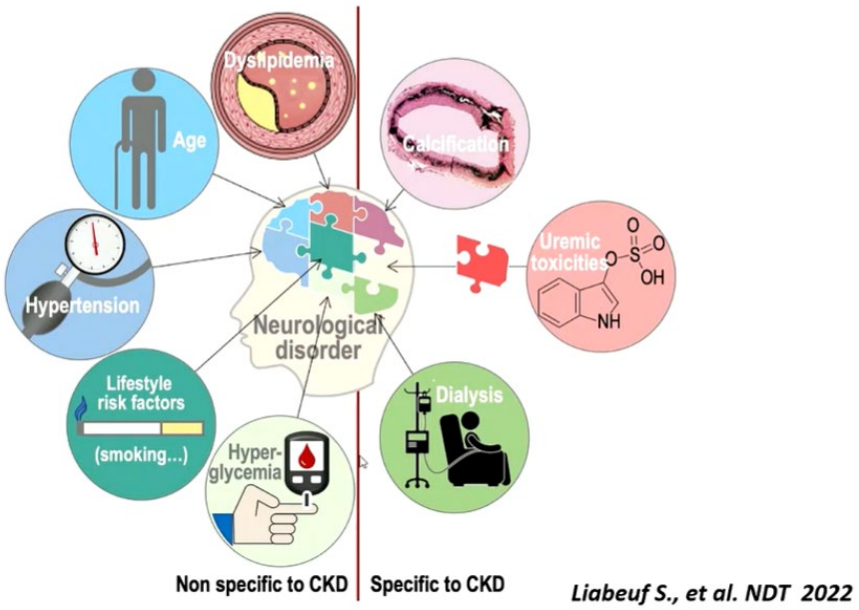

Figure 2. Risk factors associated with neurological disorders in CKD

One area of interest for the CONNECT project members is the concept of the extracellular spaces (ECS) network, responsible for the diffusion of soluble molecules in the brain, which plays an important role in brain homeostasis and metabolite clearance and serves as a channel for extrasynaptic signaling by volume transmission. In the yet unpublished study, Antonio de Donato and Davide Viggiano detected a reduced thickness of ECS in the cerebral cortex and increased dopaminergic activity (reflected by the changes in the dopamine- and cAMP-regulated phosphoprotein DARPP-32 activity in the striatum) of CKD mice. Another CONNECT research group, led by Pedro Imenez Silva, studied the correlation between CKD, cognitive dysfunction, and metabolic acidosis. They found that both accumulations of

uraemic toxins and metabolic acidosis associated with CKD may act on the brain to reduce its central functions. Furthermore, immune functions are also affected, leading to higher levels of pro-inflammatory factors that may also adversely affect brain activity. Decreased kidney function is also associated with reduced renal expression of α-klotho and diminished circulating levels of soluble α-klotho. Whether brain α-klotho expression, which has neuroprotective functions, is directly affected has not been examined.

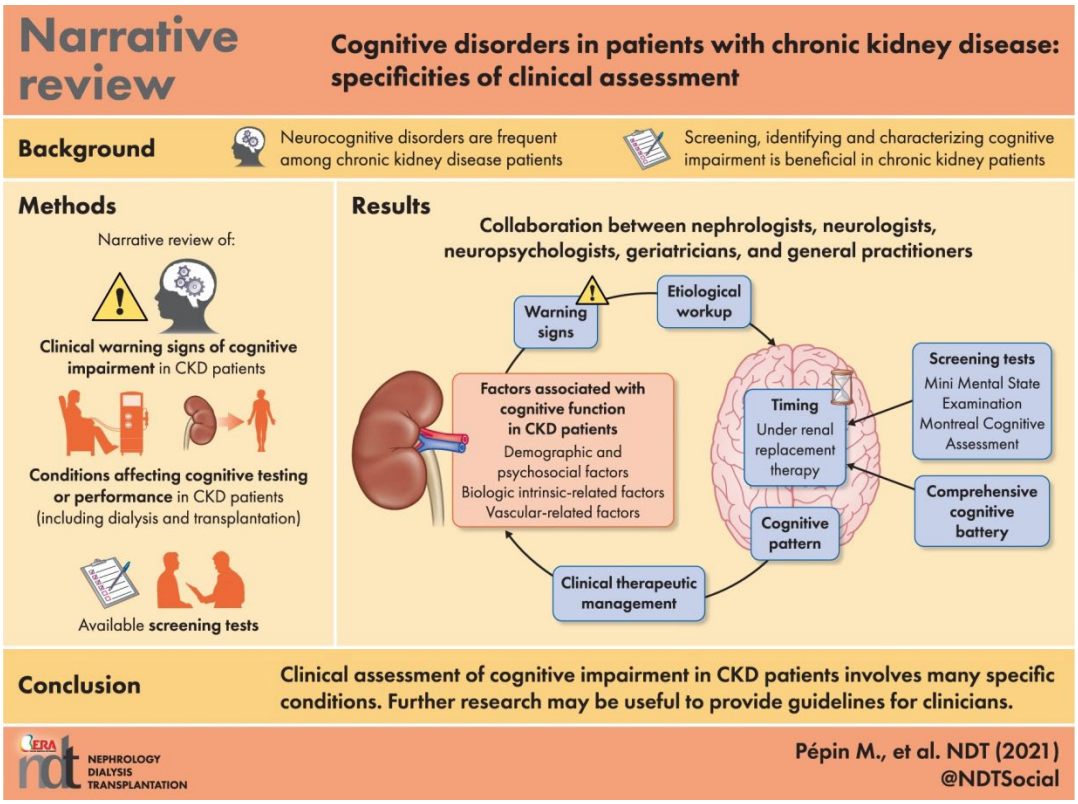

Figure 3. Clinical assessment of Cognitive disorders in CKD

In a recently published review, Pépin et al. summarized clinical warning signs that should prompt cognitive screening in CKD patients; conditions frequent in CKD at risk to interfere with cognitive testing or performance; and available tests for screening and observed cognitive patterns in CKD patients. Since clinical assessment of cognitive impairment in CKD patients involves many specific conditions, such as age, depression, sleep disturbances, anemia, uremic toxins, inflammatory mediators, and different cardiovascular risk factors, further research may be useful to provide guidelines for nephrologists, neurologists, neuropsychologists, geriatricians and general practitioners.

Key points

1. 30–60% of advanced CKD patients have been diagnosed with cognitive injuries, such as cognitive decline, peripheral neuropathies, epileptic seizures, and most commonly Mild Cognitive Impairment (MCI).
2. The international CONNECT (Cognitive decline in Nephro-Neurology European Cooperative Target Action) project assembles five working groups focused on exploring the correlation between CKD and MCI.

3. The CONNECT project targets clinicians and scientists through publications, reports, conferences, and satellite events to spread the latest knowledge on the complex kidney-brain relationship.
4. Several publications deriving from the CONNECT project tackled different topics in this area: the factors that could influence cognitive abilities during CKD, the potential effect of tubulopathies on brain function, the role of metabolic acidosis, neuroprotective substances, and extracellular spaces network in the brain.

Further reading

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(3) Capasso G, Wanner C; CONNECT Action (Cognitive decline in Nephro-Neurology European Cooperative Target). Present and future of CONNECT: a new and compelling project of modern medicine. Nephrol Dial Transplant. 2021;37(Suppl 2):ii1-ii3. doi: 10.1093/ndt/gfab301. PMID: 34788465; PMCID: PMC8713151.

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