Nephrol Dial Transplant (2022) 37: ii1–ii3
https://doi.org/10.1093/ndt/gfab301
Advance Access publication date 11 November 2021

EDITORIAL

Present and future of CONNECT: a new and compelling project of modern medicine

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Epidemiological data collected in different countries indicate a strong increase in the number of patients with chronic kidney diseases (CKD). This phenomenon is evident at all ages but is particularly significant among elderly people. CKD is a complex and potentially fatal illness affecting all organs and altering many fundamental physiological parameters, such as plasma volume, electrolytes and acid–base balance, hormones and protein metabolism. Due to associated comorbidities, the treatment of choice requires a multidisciplinary approach involving the appropriate use of drugs and nutrient-specific interventions [1].

Although dialysis and transplantation have widely contributed to extend the life of CKD patients, the quality of life is still suboptimal. This is due to the numerous comorbidities related to the several compromised organs, including the nervous system.

In 30–60% of advanced CKD cases, patients have been diagnosed with cognitive injuries. In these patients, both the central and peripheral nervous systems are frequently affected by several symptoms, such as cognitive decline, peripheral neuropathies and epileptic seizures. The most frequently observed deficiency is Mild Cognitive Impairment (MCI), which is characterized by neurological injuries and cognitive dysfunctions. MCI is already present in the early phase of kidney failure and is significantly more common in CKD patients than in the age-matched general population [2].

To date, interdisciplinary collaboration aimed at interpreting the nature and origin of MCI-CKD has been very limited. Indeed, many of the fundamental questions about this pathology have remained unanswered, or even worse, they have been neglected and never addressed. The dramatic consequence is the lack of any pathogenetic therapy until now.

We thus express deep concern over the current state and strongly intend to propose effective actions. Concerning the brain field nowadays, there are many novel tools that have considerably enhanced our knowledge, including new imaging technologies applicable both for animal models (two-photon microscopy, optogenetics and functional neuroanatomy) and for humans (functional magnetic resonance imaging, brain tractography and brain resting state). In addition, innovative cognitive tests are available and Omics approaches are also widely used in neuroscience.

Precisely to achieve this goal, the European CONNECT (Cognitive decline in Nephro-Neurology European Cooperative Target Action) project was established and financed through the COST Action program. As is well described in the Memorandum of Understanding (MoU), CONNECT comprised of five working groups and has the clear aim to fill this gap. It engages clinical nephrologists and neurologists, scientists with pre-clinical expertise in the field of nephrology and neuroscience, and scientists with outstanding knowledge in clinical trials, epidemiology and data sciences (Figure 1). To date, CONNECT gathers 72 researchers with a wide range of scientific and clinical interests from 27 European countries plus the USA. The number is even expected to grow, as it holds enormous potential to involve other scientific fields such as geriatrics, infectious diseases and many basic sciences.

One of the main objectives of CONNECT, specifically in this first year of activity, is to target clinicians and scientists through publications, reports, conferences and satellite events. To this end, we believe that a good starting point would be to launch a special issue of *NDT* dedicated to our current understanding of the different topics in the complex kidney–brain relationship. We therefore brainstormed among all members of CONNECT to suggest themes to be discussed and to actively participate in drafting the manuscripts. Below is a brief presentation of the six articles published.

Imenez Silva *et al.* [3] dealt with the very important issue of a possible effect of metabolic acidosis, a characteristic clinical sign of CKD, on cerebral cognitive capacity and

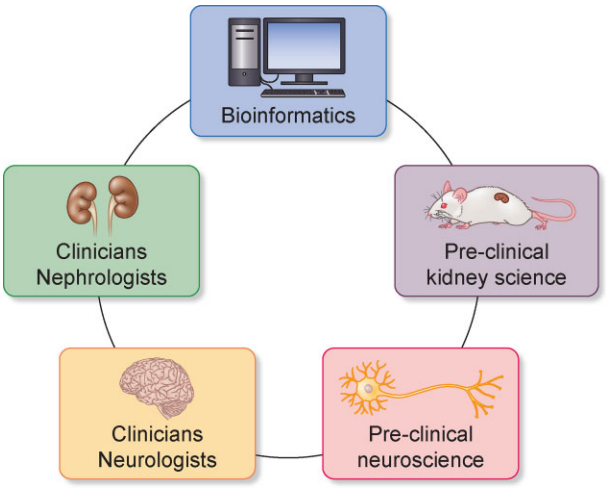

FIGURE 1: The high collaborative nature of the CONNECT Action disciplines.

motor function. The review, written with the collaboration of excellent experts in the field, highlights the evidence of the correlation between acidosis and cognitive abilities, and describes some of the mechanisms that entail an action of acidosis on brain functions.

Pépin *et al.* [4] have written a clinical review on the large topic of neurocognitive disorders in patients with CKD. They described the tests currently used to diagnose the disorders and verify the level of severity. The authors deserve credit for having tried to summarize a large amount of data that have been collected in recent years, although it is understandable that many aspects of this intricate relationship are still far from being completely clarified.

Liabeuf *et al.* [5] reviewed the factors that could influence cognitive abilities during CKD, focusing on uraemic toxins. Their timely and exhaustive review has the merit not only of having identified some specific neuro-damaging toxins, but also of having hypothesized their mechanisms of action, allowing a therapeutic perspective for patients.

Bikbov *et al.* [6] had the undoubted merit of addressing one of the newest and most debated topics in the kidney–brain relationship, namely the possibility that an increase in albuminuria could be a direct factor responsible for altering brain cognition. After recalling all the epidemiological studies concerning this relationship, the authors, including leading experts in the field, point out the aspects that are still unclear and suggest possible actions to overcome this knowledge gap.

Viggiano *et al.* [7] tackled a completely new topic: the potential effect of tubulopathies on brain function with particular regard to cognitive capacity. Although in literature there are only a few data, it is clear that the tubulopathies causing electrolyte disturbances, and in particular those able of altering the water metabolism, affect various brain functions. Certainly in the near future, this new chapter of medicine will provide us with much more knowledge, also because nowadays we have the required technologies to explore in detail the function of these two organs.

Zoccali *et al.* [8] discussed the role of neuropeptide Y (NPY) in the regulation of brain function. NPY is currently considered as a key regulator in the gut–brain cross-talk. Its plasma concentration increases with the progress of kidney failure and could play a crucial role in the impairment of cognitive abilities of patients with CKD and in dialysis patients. This hypothesis, if confirmed, could pave the way for new pharmacological treatments.

FUNDING

This article is published as part of a supplement financially supported by the COST Action CA19127—Cognitive decline in Nephro-Neurology European Cooperative Target (CONNECT).

CONFLICT OF INTEREST STATEMENT

None declared.

APPENDIX

CONNECT collaborators are

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Received: 7.9.2021; Editorial decision: 22.9.2021