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► **To cite this version:**

D. Viggiano, A. Bruchfeld, S. Carriazo, A. De Donato, N. Endlich, et al.. Brain dysfunction in tubular and tubulointerstitial kidney diseases. *Nephrology Dialysis Transplantation*, 2021, 37 (Supplement_2), pp.ii46–ii55. 10.1093/ndt/gfab276 . inserm-03582045

HAL Id: inserm-03582045

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Submitted on 21 Feb 2022

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Brain dysfunction in tubular and tubulointerstitial kidney diseases

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ABSTRACT

Kidney function has two important elements: glomerular filtration and tubular function (secretion and reabsorption). A persistent decrease in glomerular filtration rate (GFR), with or without proteinuria, is diagnostic of chronic kidney disease (CKD). While glomerular injury or disease is a major cause of CKD and usually associated with proteinuria, predominant tubular injury, with or without tubulointerstitial disease, is typically non-proteinuric. CKD has been linked with cognitive impairment, but it is unclear how much this depends on a decreased GFR, altered tubular function or the presence of

proteinuria. Since CKD is often accompanied by tubular and interstitial dysfunction, we explore here for the first time the potential role of the tubular and tubulointerstitial compartments in cognitive dysfunction. To help address this issue we selected a group of primary tubular diseases with preserved GFR in which to review the evidence for any association with brain dysfunction. Cognition, mood, neurosensory and motor disturbances are not well characterized in tubular diseases, possibly because they are subclinical and less prominent than other clinical manifestations. The available literature suggests that brain dysfunction in tubular and tubulointerstitial diseases

is usually mild and is more often seen in disorders of water handling. Brain dysfunction may occur when severe electrolyte and water disorders in young children persist over a long period of time before the diagnosis is made. We have chosen Bartter and Gitelman syndromes and nephrogenic diabetes insipidus as examples to highlight this topic. We discuss current published findings, some unanswered questions and propose topics for future research.

Keywords: brain, chronic kidney disease, cognitive function, electrolyte, tubulointerstitial

INTRODUCTION

An acute or chronic decrease in glomerular filtration rate (GFR) is often associated with (mild) impairment of cognitive function and alterations in mood [1]. The mechanism by which acute kidney injuries (AKIs) or chronic kidney diseases (CKDs) affect brain activity is still unknown [1–3]. The changes in blood composition caused by a decrease in GFR are many, as is the number of blood components that can affect neuronal cell function [4–8]. However, replacement of kidney function by dialysis does not fully correct these changes. As discussed in the accompanying articles in this special issue [5, 6, 8], dialysis reduces uremia and patients with severe uremia may improve in their cognitive function after the start of dialysis. At the same time, hemodialysis introduces new problems, e.g. a repetitive decrease in brain perfusion due to hemodialysis-induced hypovolemia or hypotension, as well as osmotic changes, which do not occur in peritoneal dialysis.

However, this article analyses the problem from a different perspective. Here we examine the impact of tubular and tubulointerstitial (non-glomerular) kidney disease with minimal or no proteinuria on brain function. As detailed below, cognitive disturbances can accompany specific non-glomerular kidney diseases. We begin by reviewing the current literature and some unpublished data on cognitive defects in kidney tubular diseases and explore the possibility of a shared genetic defect contributing to brain dysfunction. To this end, we have screened PubMed articles dealing with each of the tubular diseases listed in Downie *et al.* [9] and in Table 1 using keywords ‘cognitive,’ ‘brain’ and ‘behavior.’ Even though the focus of this review is intellectual disability, we also report other forms of brain and peripheral nerve dysfunction in Table 1.

Due to space constraints, only a few genetic disorders can be discussed in more depth. We selected Bartter and Gitelman syndromes (BS and GS) and nephrogenic diabetes insipidus (NDI) as prototypical disorders of the thick ascending limb, distal convoluted tubule and collecting duct, respectively. Among the proximal tubule disorders, proximal renal tubular acidosis is partially covered in a companion article on the effect of acid–base balance on cognitive functions [7]. Conversely, there is not enough information on brain function available for the widely known Fanconi syndrome to justify a detailed description. The interested reader can find cited references on other proximal tubulopathies and the brain in Table 1.

We have also assessed the expression and distribution of tubule-related genes in the brain, allowing some separation of the shared genetic effects from the indirect effects of

tubular dysfunction. Finally, we discuss our findings, list some unanswered questions and propose topics for future research.

Tubular functions and tubulointerstitial kidney disease

It should be noted that CKD is an umbrella term for many kidney diseases that often involve the tubular and tubulointerstitial compartments. Therefore it is desirable to understand if cognitive impairment in CKD is related to reduced glomerular filtration (e.g. accumulation of filtered uremic toxins and/or associated proteinuria) or if the tubular and tubulointerstitial compartments also play a role (e.g. decreasing the production of molecules of tubular origin or disturbed homeostasis resulting from tubular dysfunction). Unfortunately, no studies so far have reviewed the literature on cognitive impairment in disorders with a selective loss of tubular function. Therefore, we collected the available data on cognitive testing in tubular and tubulointerstitial kidney diseases that do not involve significant glomerular dysfunction. Tubular diseases are primary defects of tubular reabsorption or secretion and are usually characterized by electrolyte and water disturbances. Tubulointerstitial diseases are histologically characterized by damage (e.g. peritubular fibrosis with inflammatory infiltrates) of the interstitium and functionally with a urine concentration defect and low molecular weight proteinuria, but little or no glomerular proteinuria [10]. Notably, the term ‘interstitial disease’ was introduced as ‘interstitial nephritis’ in 1898 by the Harvard pathologist William Councilman (1854–1933) [11]. Tubulointerstitial diseases are often secondary and sometimes inherited. In 2005 cystinosis and Dent disease were included in the inherited forms [12]. More recently, autosomal dominant tubulointerstitial disease, due to *UMOD* [13], *HNF1 β* [14] or *REN* [15] mutations, has been introduced and additional diseases (such as Bardet–Biedl syndrome) were also classified in this category.

Tubular function includes adjusting urine composition, urine-concentrating or urine-diluting ability, catabolism of small peptides and the secretion of bioactive compounds, e.g. renin, angiotensin II, endothelin, calcitriol, Klotho and others.

In tubular and tubulointerstitial diseases, the tubular function is affected while the GFR is relatively preserved, at least initially. However, only one or a few tubular functions may be altered in primary tubular diseases (e.g. urine-concentrating ability in NDI or several proximal tubular functions in Fanconi syndrome). In addition, tubulointerstitial disease may develop as part of the progressive global loss of kidney mass and function during CKD of any cause. In this case, multiple tubular functions may be lost along with the loss of GFR. Therefore the potential impact of global tubular and tubulointerstitial function loss in CKD may be significant although difficult to differentiate from the concomitant loss of GFR.

A list of the non-glomerular (tubular and tubulointerstitial) kidney disorders, together with associated brain alterations, is given in Table 1. This list includes most known forms of tubular and tubulointerstitial disorders, except for some very rare genetic disorders (such as Kenny–Caffey syndrome, neonatal inflammatory skin and bowel disease).

Table 1. Tubular and tubulointerstitial disorders, together with genetic defect and associated brain function/peripheral nervous system alterations

| Disease name | Genetic defect | Kidney defect | CNS or PNS alteration | Reference |
|---|---|--|--|-----------|
| Proximal convoluted tubule | | | | |
| Proximal renal tubular acidosis (RTA), type II | SLC4A4 | Bicarbonate wasting in urine, Fanconi syndrome, hypokalemia | Intellectual disability | [50] |
| Primary Fanconi reno-tubular syndrome | GATM, NDUFAF6, EHHADH, SLC34A1, HNF4A | Glycosuria, hypophosphatemia, hyperphosphaturia, aminoaciduria, hyperuricosuria | Not reported | |
| Acquired Fanconi syndrome | From cisplatin, aristolochic acid, lead, mercury, aminoglycosides | Glycosuria, hypophosphatemia, hyperphosphaturia, aminoaciduria, hyperuricosuria | Attention deficit (cisplatin), intellectual disability (lead and mercury) | [51–53] |
| Dent disease (type 1) | CLCN5 | Fanconi syndrome, proteinuria, hypercalciuria, nephrocalcinosis, hypophosphatemia, CKD | Not reported | |
| Lowe syndrome (oculo-cerebro-renal; Dent type 2) | OCRL | Bicarbonate wastage and proximal RTA, Fanconi syndrome | Intellectual disability, stereotypic behavior | [54] |
| Cystinuria | SLC3A2, SLC7A9 | Defective absorption of cystine and cationic amino acids (lysine, arginine, ornithine) | Not reported | |
| Cystinosis | CTNS | Fanconi syndrome, proteinuria, CKD | Neuromuscular dysfunction, intellectual disability | [55, 56] |
| Hereditary renal hypouricemia | SLC2A9, ABCG2, SLC22A12 | Hypouricemia, hyperuricosuria with nephrolithiasis and exercise-induced AKI | Not reported | |
| Familial juvenile hyperuricemic nephropathy | UMOD | CKD, gout | Not reported | |
| Lysinuric protein intolerance | SLC7A7 | Defective absorption of cationic amino acids (lysine, arginine, ornithine) | Hyperammonemia encephalopathy | [57] |
| Hartnup disease | SLC6A19 | Defective absorption of non-polar aminoacids (tryptophan) | Intellectual disability, seizures | [58] |
| Joubert syndrome, Meckel–Gruber syndrome | NPHP3/NEK8, ANKS6/INVS | Nephronophthisis | Brain malformations | [59] |
| Hereditary renal glycosuria | SLC5A2 | Asymptomatic | Not reported | |
| Hereditary hypophosphatemic hypercalciuria rickets | SLC34A3 | Nephrolithiasis, rickets | Not reported | |
| Thick ascending limb | | | | |
| Bartter syndrome | SLC12A1, CIC-Kb, BSDN, ROMK, MAGE2 | Hypokalemia, metabolic alkalosis, polyuria, and polydipsia, hypercalciuria (with nephrocalcinosis) | Intellectual disability (unconfirmed), deafness (if Barttin mutation) | [30] |
| Familial hypomagnesemia with hypercalciuria | CLDN16, CLDN19 | Nephrocalcinosis; polyuria and polydipsia | Ocular involvement | |
| Distal convoluted tubule | | | | |
| Gitelman syndrome | SLC12A3 (NCC) | Hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria | Brain calcifications, intracranial hypertension, encephalopathy, brain cauda equina syndrome, depression | [21, 22] |
| EAST syndrome | KCNJ10 (KCNJ10/Kir4.1) | Tubulopathy (Gitelman type) | Seizures, ataxia, deafness | [60] |
| Hypokalemic nephropathy | KCNJ16 | Renal salt wasting, disturbed acid–base homeostasis | Deafness | [60] |
| Gordon syndrome or pseudohyperaldosteronism type II | WNK4, WNK1 (NCC activating) | Hypertension, hyperkalemia, metabolic acidosis | Not reported | |
| Liddle syndrome | SCNN1A, SCNN1B, SCNN1G (ENaC activating) | Hypertension, hypokalemia, metabolic alkalosis | Not reported | |
| Pseudohyperaldosteronism type I | SCNN1A, SCNN1B, SCNN1G | Resistance to aldosterone, hypotension, hypercalcemia, acidosis | Not reported | |
| Hypomagnesemia, seizures and intellectual disability type 1 and 2 | CNNM2 | Hypomagnesemia | Seizures, intellectual disability | [7] |

Table 1. Continued

| Disease name | Genetic defect | Kidney defect | CNS or PNS alteration | Reference |
|---|-----------------------------------|---|---|--------------|
| Collecting duct (principal cells) | | | | |
| Nephrogenic diabetes insipidus | AVPR2, AQP2 | Polyuria, polydipsia (sometimes with consequent hyponatremia) | Intellectual disability, attention deficit | [32, 33, 61] |
| Nephrogenic SIAD | AVPR2 (activating) | Chronic hyponatremia | Gait disturbance, intellectual disability | [62] |
| Adult dominant polycystic kidney disease (ADPKD) | PKD1, PKD2, FCYT, GANAB | Progressive CKD | Intracerebral aneurysms, depression | [63] |
| Adult recessive polycystic kidney disease (ARPKD) | PKHD1 | CKD | Intellectual disability | [64] |
| Collecting duct (intercalating cells) | | | | |
| Renal tubular acidosis type III | CA II (carbonic anhydrase II) | Bicarbonate wasting, alkaline urine | Intellectual disability, brain calcifications, deafness | [65–67] |
| Distal tubular acidosis type I | ATP6V1B1, ATP6V0A4, SLC4A1, Foxi1 | Metabolic acidosis, hypercalciuria, nephrolithiasis | Deafness | [68, 69] |
| All nephron segments | | | | |
| Autosomal dominant tubulointerstitial kidney disease (ADTKD)/medullary cystic kidney disease (MCKD) | HNF1 β , MUC1, UMOD, REN | CKD, gout | Intellectual disability, attention deficit, bipolar disorder | [70, 71] |
| Bardet–Biedl syndrome (BBS) | BBS1–21 | Progressive CKD and hyposthenuria | Intellectual disability | [72] |
| Familial hypocalciuric hypercalcemia | CaSR | Kidney stones | Altered brain excitability, encephalopathy, attention deficit, coma | [73] |
| Mitochondrial tubulointerstitial nephritis | tRNA(Phe) (mitochondrial genome) | Tubulointerstitial nephritis with giant cells | Stroke, seizures | [74] |

Nephron segment affected was retrieved using the Human Protein Atlas database.
CNS: central nervous system; PNS: peripheral nervous system; tRNA: transfer RNA.

Gitelman syndrome

GS is an autosomal recessive disease due to mutations in the *SLC12A3* gene encoding the thiazide sensitive Na⁺-Cl⁻ cotransporter expressed in distal convoluted tubules, a transporter that is implicated in salt-sensitive hypertension [16, 17].

These mutations cause a salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis, hypocalciuria, hypomagnesemia and activated renin–angiotensin–aldosterone system (RAAS) [18]. GS is usually diagnosed at >6 years of age [19]. Typical symptoms include tetany (particularly during fever, vomiting, diarrhea), paresthesia, fatigue, chondrocalcinosis and QT prolongation. Blood pressure is lower than in the general population because of salt wasting [20].

A few cases have been described presenting with neurological symptoms such as ataxia. However, these represent a different GS-like syndrome caused by mutations in the *KCNJ10* gene encoding a potassium channel (KCNJ10/Kir4.1). The acronym of EAST/SeSAME syndrome describes the clinical features of this syndrome (epilepsy, ataxia, sensorineural deafness and tubulopathy) [18]. Kir4.1 is widely expressed in the brain (data from Allen Brain Atlas database) and its loss of function in the brain explains the neurological phenotype.

No studies have analyzed intellectual disability in more typical GS; however, GS has been associated with depression and anxiety [21]. A single case study also reports encephalopathy following major trauma [22], although genetic data are not available for this patient. A cauda equina syndrome-like

presentation has been reported [23]. A second case report describes a patient with an R642C mutation of the *SLC12A3* gene and a familial form (unknown inheritance pattern) of intellectual disability that is probably unrelated to the tubulopathy [24].

Due to the possible effects of electrolyte derangements on brain functions, it would be useful to test cognitive function formally in larger epidemiological studies for more evidence in GS patients. Concurrently, hypokalemic metabolic alkalosis, hypocalciuria, hypomagnesemia and activated RAAS with secondary hyperaldosteronism do not have strong neurological effects in these patients. However, magnesium deficiency might have cognitive effects [25]. It is worth noting that GS patients are often polysymptomatic (e.g. fatigue, cramps, weakness, polydipsia, salt craving), which may have psychological effects [20] and can resemble chronic fatigue syndrome.

Bartter syndrome

BS is a rare genetic disorder of the loop of Henle (prevalence around 1 in 1 million) [26] identified by American endocrinologist Frederic Bartter in 1962. Five BS types have been classified according to the genes responsible (see Table 1). The first four BS types are recessive disorders characterized by hypokalemia, metabolic alkalosis, hypercalciuria with hyperreninemic hyperaldosteronism and hyperplasia of the juxtaglomerular apparatus. The fifth BS type is an autosomal dominant form of hypocalcemic hypercalciuria.

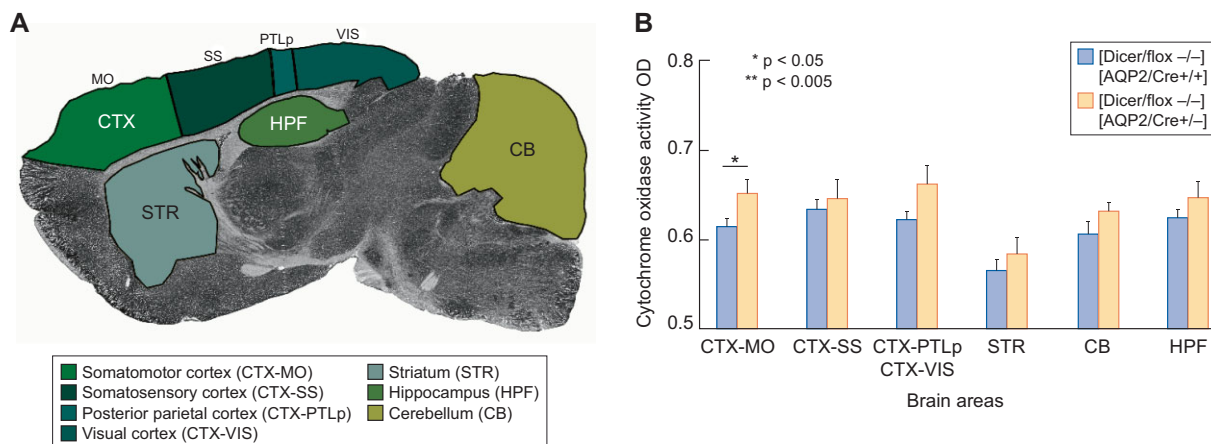


FIGURE 1: Neuronal metabolic activity with cytochrome oxidase histochemistry in different brain areas in sagittal sections. (A) Graphic representation of the different brain areas analyzed. (B) Representative graphed data of the comparison of cytochrome oxidase activity [optical density (OD)] between the different brain areas in *Dicer/flox^{-/-}; AQP2/Cre^{+/-}* mice, an experimental model of NDI type II and *Dicer/flox^{-/-}; AQP2/Cre^{+/+}* mice, as a littermates control. The data shown are mean \pm standard deviation from at least three independent experiments. * $P < 0.05$ compared with controls (unpublished data; detailed protocols in Supplementary material).

At diagnosis, BS patients are young (50% are diagnosed within the neonatal period) [27], have normal blood pressure and often present with growth retardation. This syndrome is associated with an increased antenatal and neonatal mortality [26, 28].

Older studies report that many children with BS have intellectual disability [29]. In an early report, 9 of 12 (75%) patients had intellectual disabilities [30]. Unfortunately, more extensive cohorts of these patients have not been studied for their cognitive functions. The reported mental defects might be due to the retarded growth pattern, although the effect of prolonged hypovolemia and hypokalemia cannot be excluded. Indeed, the relationship between intellectual disability and tubular function in this syndrome is complex because neonatal dehydration due to a delayed diagnosis may have played a role [21].

Nephrogenic diabetes insipidus

NDI is a tubular disorder resulting from acquired or genetic causes. The hereditary form is due to mutations of the *AVPR2* gene (X-linked recessive) encoding for the vasopressin 2 receptor [31] or to mutations of the aquaporin-2 (*AQP2*) gene (autosomal recessive and dominant). NDI is characterized by the excretion of large volumes of hypotonic urine and polydipsia. Severe hypernatremia may develop if access to drinking water is limited [32].

NDI was thought to be accompanied by intellectual disability. However, a study conducted on 17 NDI patients ages 3–16 years showed a low prevalence of intellectual impairment (only 1 patient in 17). Furthermore, a high prevalence of attention deficit hyperactivity disorder (ADHD) was suggested [33]. Accordingly, a 2019 article showed that only 1 in 33 NDI patients had cognitive problems, while 5 (18%) showed ADHD [34]. For comparison, the prevalence of ADHD in children from the UK is 3.6%.

It is unclear whether ADHD derives from polyuria or polydipsia, repeated bouts of hypernatremia or the treatments for this disorder. The study [33] did not find any correlation between cognitive performances and natremia but could not account for past bouts of hypernatremia or nighttime hypernatremia.

It is instructive to compare these observations with those deriving from central diabetes insipidus (CDI), which is caused by the lack of vasopressin (VP) release. A confounding factor is that VP is released by neurons (brain VP) and may have local effects on learning, memory and social behavior [35]. In a familial form of CDI (familial neurohypophysial diabetes insipidus), memory retrieval processes and sustained attention were significantly impaired [34]. However, no studies are available on cognitive or attentional problems in acquired forms of CDI.

These observations can be compared with results from animal models of CDI and NDI. In an animal model of CDI caused by an inability to produce VP, the Brattleboro rats, showed altered prenatal brain development of the cerebellum and medulla oblongata [34]. In these rats, learning and memory processes involving emotional processes were impaired, whereas spatial learning and memory were not seriously impaired [34]. Finally, these animals also show modified metabolic activity (cytochrome oxidase activity) in hypothalamic nuclei compared with control rats [34]. Notably, these animals have a deficit in both the peripheral and brain VP systems. No data are available on the brain and behavior of *AQP2* and *AVPR2* knockout mice. However, we recently generated the *Dicer/flox^{-/-}; AQP2/Cre^{+/-}* mice that present a dysregulation of miRNA maturation in *AQP2*-positive cells [36]. This experimental model mimics NDI because of VP resistance secondary to defective *AQP2* expression and function. *Dicer/flox^{-/-}; AQP2/Cre^{+/-}* mice presented with alterations in brain metabolic activity (Figure 1; detailed data in the Supplementary material). The neuronal metabolic

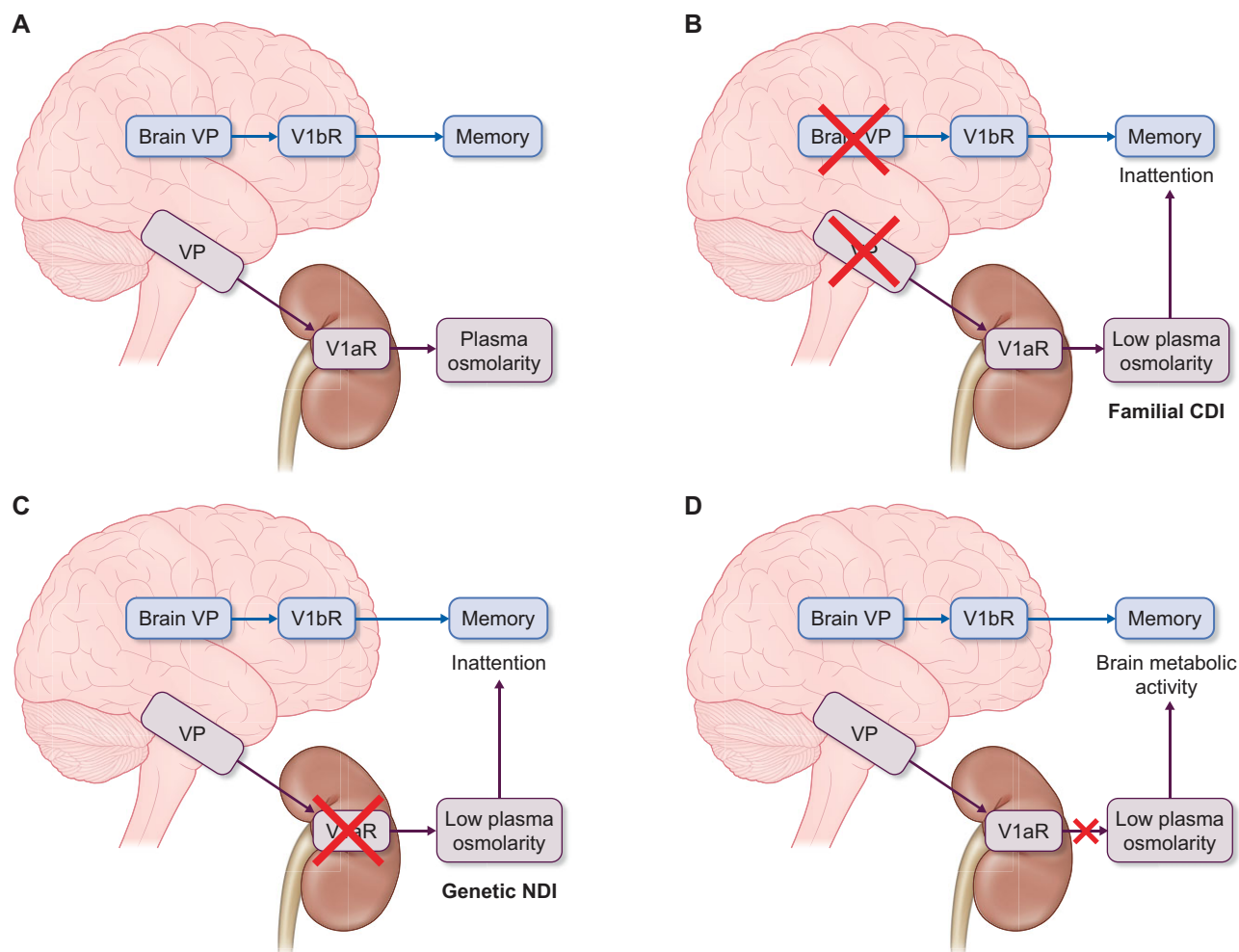


FIGURE 2: Proposed mechanisms for behavioral modifications in CDI and NDI. (A) Schematic representation of brain VP and peripheral VP systems. Peripheral VP is released by hypothalamic nuclei in the bloodstream and regulates urine (and plasma) concentration by acting on V1aR in the kidney distal tubules. The brain VP system is composed of the periventricular hypothalamic nucleus, which projects to the neurohypophysis and the preoptic nucleus and bed nucleus of stria terminalis, with fibers sent to various brain regions. Central VP acts through V1bR. Behavioral changes may be caused by this brain VP system or by changes in plasma osmolarity. (B) In familial CDI, both central and peripheral VP are suppressed. Therefore behavioral alterations may be due to an altered brain VP system, although an indirect effect of plasma osmolarity is still plausible. (C) In genetic NDI, only V1aR is lacking, whereas V1bR and brain VP remain intact. Indeed, memory is preserved, whereas a loss of attention has been described, which may derive from altered plasma osmolarity. (D) We have tested this hypothesis in animals with intact V1aR, VP and V1bR, in the presence of a distal tubule dysfunction (Figure 1). The resulting alterations in brain metabolic activity could be ascribed only to a change in plasma osmolarity.

activity was altered in the brain cortex, suggesting a link to tubular function independent of circulating VP levels and AVPR2 expression.

Taking this evidence and these preliminary data into consideration, it is possible to conclude that a separate group of neurons in the brain controls AVP secretion in the bloodstream, and therefore kidney function, whereas another group of neurons may control memory functions. Lacking both of these neuron groups (as in CDI) impairs both brain and kidney functions. However, the modification of kidney-concentrating ability can impair brain function, as demonstrated by the inattentive syndrome in genetic NDI (Figure 2).

In summary, changes in the regulation of kidney water handling may result in altered brain activity and attention without

consistent alterations in memory or cognitive performances (Figure 2).

Brain expression of tubular genes

The available literature suggests that major alterations in behavioral dynamics have seldom been noted in tubular dysfunctions, probably because attention to this has been limited and/or changes too subtle. For example, it would be interesting to explore which electrolyte abnormalities have the highest risk of affecting brain function long term and, if so, how. Furthermore, as described in an accompanying article [7], acid–base balance, which is also regulated by the kidney tubule, can modify brain functions. In DI, the altered water balance may affect brain function.

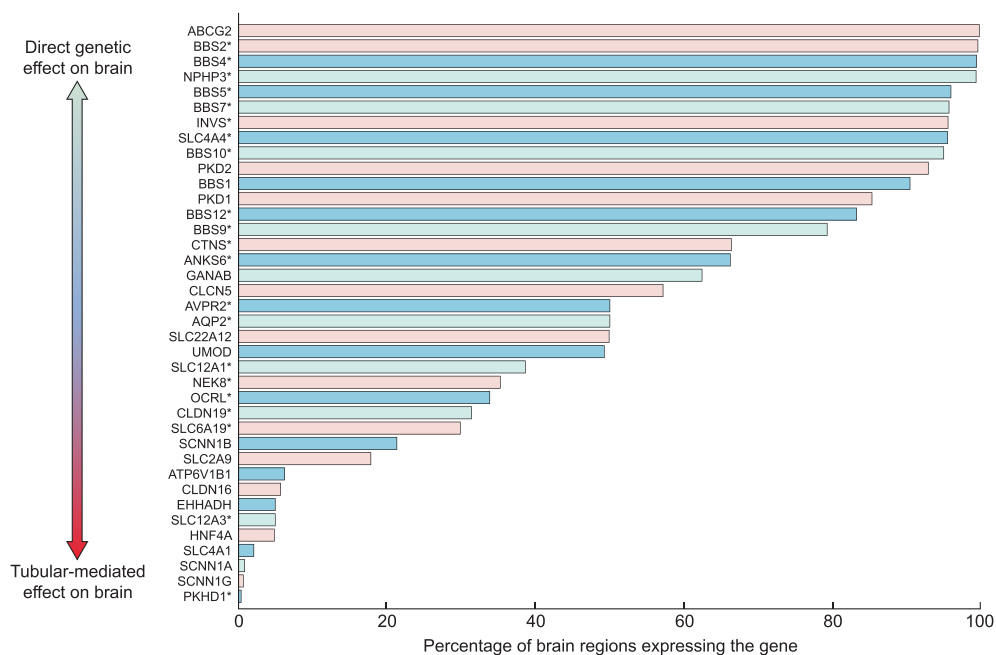


FIGURE 3: Brain expression pattern of genes involved in tubular and tubulointerstitial diseases (100% means that the gene is ubiquitously expressed in the brain). Data from the Allen Brain Atlas database.

We have also explored whether brain gene expression might explain cases in which a direct association between tubular disease and brain damage has been reported (as in Table 1). We used the Enrichr platform of gene enrichment to analyze the brain expression pattern of genes reported in Table 1 [37]. However, four available databases (Descartes Cell Types and Tissue 2021, Human Gene Atlas, ProteomicsDB 2020 and ARCHS4 Tissues) do not show any brain enrichment for these genes. A limitation of this finding is that the tagging of kidney-expressed genes might be poor. The Allen Brain Atlas reports brain expression for some of the genes on the list (Figure 3).

In summary, data suggest that disturbed electrolyte and water balance may directly or indirectly affect brain activity. It is known that chronic dysnatremia impairs neurocognitive and neuromuscular function, including gait control [38] and cognitive functions [39], and that VP itself is important for normal brain development and function. Future studies are needed to better characterize the brain functions in patients with tubular diseases. The evidence to date is weak and based primarily on case reports or limited animal studies, and more extensive prospective studies are needed.

Secondary tubulointerstitial disease

Secondary tubulointerstitial disease leads to tubular cell injury and eventual loss of tubular cell mass. Injury or loss of tubular cells results in the loss of tubular function, including the loss of the ability to produce the anti-aging and anti-inflammatory protein Klotho. Kidney tubules are the main site of Klotho expression and the source of circulating Klotho. Local or systemic inflammation and albuminuria cause tubular cell injury characterized by an early decrease in kidney Klotho expression in CKD, which may precede the decrease in GFR

[40, 41]. This early decrease in Klotho may be reversible by targeting inflammation or albuminuria. Eventually the loss of tubular cell mass results in an irreversible decrease in Klotho production. Klotho-deficient mice develop accelerated aging that includes intellectual disability [42], and administration of Klotho induced cognitive enhancement and neural resilience in young, aging and transgenic α -synuclein mice, a model of Parkinson's disease [43]. In humans, Klotho gene variants are associated with brain volume and function [44, 45] and higher plasma Klotho concentrations were associated with a lower risk of global cognitive decline [46]. In line with these observations, in the Framingham Heart Study, higher circulating FGF23 (one of the consequences of kidney loss of Klotho) was associated with an increased risk of dementia [47]. Furthermore, calcitriol deficiency, another direct consequence of Klotho deficiency in tubular cells, has been linked to defective brain function and neuropsychiatric disease [48]. Age-related intellectual disability in the aged senescence-accelerated mouse prone-8 (SAMP8) mouse model is related to the downregulation of Klotho. These mice also develop age-related kidney inflammation, albuminuria and loss of Klotho, representing a potential mouse model for investigating the kidney-brain axis in the aging process [49].

CONCLUSIONS, UNANSWERED QUESTIONS AND FUTURE RESEARCH AGENDA

Table 2 summarizes a research agenda to address current unanswered questions. In some instances, the link between kidney tubules and the brain is the shared genetic defect causing complex phenotypes in both the kidney and the brain. As suggested in Figure 3, many membrane transporters or channels are shared by the kidney and nervous system. The

Table 2. Unanswered questions

- To what extent does generalized tubular dysfunction contribute to central nervous system (CNS) manifestations in advanced CKD?
- Does the contribution of generalized tubular dysfunction to CNS manifestations in advanced kidney disease explain the suboptimal response to kidney replacement therapy? Can it explain the better outcome on brain function after kidney transplantation?
- Does this putative contribution depend on a deficiency of tubular secreted factors (e.g. Klotho) and can it be addressed by replacing these factors?
- Does this putative contribution depend on defective tubular secretion of protein-bound 'uremic' toxins?
- Does this putative contribution depend on defective tubular catabolism of small proteins (e.g. β 2-microglobulin)?
- Does any putative impact of tubular dysfunction on brain function only become apparent in the presence of concomitantly decreased GFR?
- What are the optimal readouts in any future trial of the impact of tubular function replacement on brain functions? This should also consider secretory capacity for uremic toxins.
- Should one perform specific and sequential brain studies to better delineate the relationship between brain and tubular dysfunction? Is brain dysfunction underdiagnosed in these patients?

lack of data does not allow us to formulate a particular hypothesis as to how modifications in brain expression of these transporters/channels might change brain function. Further work is needed to disentangle the role of shared brain transporters and channels from the effect of a loss of tubular function and GFR. Focusing more on brain function in tubulopathies will be necessary to determine any relative contribution of glomerular versus tubular function to cognitive impairment in CKD.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](#) online.

ACKNOWLEDGEMENTS

R.U. is currently employed by AstraZeneca Pharmaceuticals R&D, CardioVascular Renal & Metabolism, Cambridge UK and Gothenburg, Sweden.

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. The results presented in this article have not been published previously in whole or part, except in abstract format.

APPENDIX

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Received: 26.5.2021; Editorial decision: 20.8.2021