Review of the structural and functional brain changes associated with chronic kidney disease:

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Summary

Chronic kidney disease (CKD) leads to profound metabolic and hemodynamic changes, which damage other organs, such as heart and brain. The brain abnormalities and cognitive deficit progress with the severity of the CKD and are mostly expressed among hemodialysis patients. They have great socio-economic impact. In this review, we present the current knowledge of involved mechanisms.

Key words: structural brain changes; cognitive impairment; hemodialysis

Introduction

„Insidious" is an adjective that in a simple way describes many complications of chronic kidney disease (CKD). CKD leads to profound metabolic and hemodynamic changes, that damage other organs, such as heart and brain. CKD is defined as a decreased kidney function shown by glomerular filtration rate of less than 60 mL/min per 1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration (Webster et al. 2017).

CKD is an emerging problem. In Europe, it affects between 3.3% and 17.3% (Bruck et al. 2016) and its prevalence tends to increase (Hill et al. 2016). This occurs especially due to increased prevalence of two main causes of renal failure: diabetes mellitus and arterial hypertension (Jha et al. 2013). The progression of the disease is slow, but gradual decline of the kidney function can lead to renal failure and necessity to initiate renal replacement therapy.

Cardiovascular and neurological CKD complications bring most morbidity and mortality. Stroke is the second leading cause of death worldwide (Masson et al. 2015). Among the CKD patients its incidence is 5–30 times higher (Nayak-Rao and Shenoy 2017) than in non-CKD population and is strongly associated with higher prevalence of atrial fibrillation, especially after the initiation of dialysis (Reinecke et al. 2009). Also, as the glomerular filtration declines, the kidneys are unable to eliminate all uremic metabolites. Retention of neurotoxins leads to neuronal damage and to uremic encephalopathy (Bugnicourt et al. 2013). The symptoms range from mild cognitive impairment

to severe symptoms such as seizures and coma (McQuillan and Jassal 2010).

Uremic toxins, anemia, oxidative stress, inflammation and hyperhomocysteinemia are the non-traditional cardiovascular risk factors specific to CKD. They contribute to vascular injury along with traditional cardiovascular risk factors such as arterial hypertension, smoking and diabetes (Brouns and De Deyn 2004; Malyszko 2010), causing endothelial dysfunction and thus acceleration of atherosclerosis (Arnold et al. 2016; Malyszko 2010) that affects also cerebral arteries. These risk factors play a significant role in the development of dementia (Arnold et al. 2016). Cognitive impairment of any level affects up to 80% of CKD patients (Krishnan and Kiernan 2009). As the cognition worsens, the quality of patient´s and his/her relatives' lives decline and mortality increases (Griva et al. 2010). Socioeconomic impact of central nervous system (CNS) impairment is profound.

In end stage renal disease (ESRD), renal replacement therapy is necessary for survival. Hemodialysis (HD) is the most frequent method. On the other hand, HD per se has many effects on the CNS. The dialysis disequilibrium syndrome is one of the most menacing and still poorly understood condition (Zepeda-Orozco and Quigley 2012). Prevalence of dementia among HD patients is more than three times higher than in non-dialysis population aged ≥ 65 years (Murray et al. 2006). Cognitive impairment is positively correlated with HD duration (and also positively correlated with age of the patient and negatively correlated with years of education as in the general population) (Gesualdo et al.

2017). Although many mechanisms have probably not been revealed, the presence of ESRD and the hemodialysis therapy itself have strong detrimental effects on the brain (Etgen et al. 2012). These effects often prevail over other mechanisms, such as hypertension or diabetes mellitus.

The etiology of CNS changes in CKD patients is complex and the understanding of them is the first step in their prevention and therapy. The aim of this manuscript is to review known mechanisms and methods necessary for understanding these changes, their causes, and their impact.

Cognitive impairment

General population

By definition, cognitive impairment is present when there is evidence of decline in one or more of the following domains: memory, executive functioning, attention, speed of information processing, perceptual motor ability, or language (Van Sandwijk et al. 2016). Some degree of cognitive slowing is, however, typical of normal aging. Dementia is diagnosed when acquired cognitive impairment has become severe enough to compromise social and/or occupational functioning. The most common types of dementia are Alzheimer's disease, vascular dementia, Lewy body dementia and frontotemporal dementia. These conditions and others, such as Parkinson's disease, Huntington's disease, Creutzfeldt-Jakob's disease, and Pick's disease lead to progressive irreversible dementia. Among conditions which can lead to reversible dementia are brain

tumors, head injuries, metabolic changes, nutritional deficiencies, chronic alcohol abuse and many others (Tripathi and Vibha 2009). Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, with essentially preserved functional abilities (Hugo and Ganguli 2014).

Prevalence of dementia increases exponentially with increasing age, and doubles with every five years of age after the age of 65. In higher income countries, its prevalence is 5–10% in patients aged 65 years and more and affects more frequently women than men. The prevalence of MCI is at this point difficult to determine as it depends on the precise definitions and subtypes of MCI being studied (Hugo and Ganguli 2014).

To diagnose these entities, clinicians use a standardized framework such as the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5). In accordance with the terminology of DSM-5, Major Neurocognitive Disorder corresponds to dementia and Mild Neurocognitive Disorder corresponds to MCI. The substantial (in the case of dementia) or modest (in the case of MCI) impairment should be both observed by clinician or a reliable informant and documented by objective cognitive assessment (Association 2013).

The worldwide number of persons affected by dementia and MCI is increasing (Fratiglioni and Qiu 2011). In contrast to dementia, MCI does not interfere notably with activities of daily life, but its diagnosis permits early

identification of high-risk patients. This opens a potentially larger therapeutic window and increases the significance of identification, diagnosis and treatment of modifiable risk factors (Fratiglioni and Qiu 2011). CKD is one of them.

Chronic kidney disease

CKD appears to be a significant and independent somatic risk factor for the development of cognitive decline. The prevalence of MCI is estimated to be 7-26% in general population. The prevalence of MCI in patients with advanced CKD (stages 4 and 5) is 16-38% (Viggiano et al. 2020). Hemodialysis patients have even higher prevalence of MCI: “26-60%” (Viggiano et al. 2020).

A meta-analysis comprising 54,779 participants revealed increased risk of MCI with the gradual decreasing estimated glomerular filtration rate (eGFR), i.e. with the severity of CKD (Etgen et al. 2012). In general, pre-dialysis and pre-transplant occurrence of cognitive deficit is relatively modest in well cared for, dementia- and stroke-free community samples (Elias et al. 2013), but among patients that reach ESRD, the rates of dementia are already approximately three times higher than in age-matched general population (Tamura and Yaffe 2011).

Renal replacement methods

Renal replacement methods include HD, peritoneal dialysis (PD) and kidney transplantation. HD is most frequent. Up to 70% of HD patients aged 55 and older suffer from moderate to severe chronic cognitive impairment (Murray

2008). Cognitive decline is faster in HD patients compared to non-dialysis patients with advanced CKD. Cognitive functions also deteriorates faster in HD patients compared to PD patients. (Iyasere et al. 2017). Why is the cognitive impairment the greatest in patients treated with HD?

One explanation is in the levels of the uremic toxins, small molecules, which concentrations rise with decreasing kidney function. Indoxyl-sulfate, p-cresyl sulfate, asymmetric and symmetric dimethylarginine (SDMA, ADMA) and trimethylamine N-oxide (TMAO) are examples (Stubbs et al. 2016; Oliva-Damaso et al. 2019; Dobrian 2012; Liu et al. 2018c). The blood concentration of asymmetric dimethylarginine (ADMA, a small water-soluble uremic toxin) was increased in CKD patients approximately 2 to 8-fold, more in HD than in PD patients (Vanholder et al. 2003). ADMA is an endogenous inhibitor of nitric oxide synthase, so its increased levels lead to endothelial dysfunction. Higher serum levels of another toxin, indol-3 acetic acid, were associated with cognitive impairment (Lin et al. 2019). The small uremic toxins could easily cross the blood-brain barrier and their increased serum levels would probably drive such crossing.

Modern HD provides better clearance of large solutes and protein-bound solutes than PD (Meyer and Hostetter 2014). However, the plasma levels of protein-bound uremic toxins were lower in PD patients compared to HD patients (Lameire et al. 2001; Vanholder et al. 2009). The plasma concentration of glycation free adducts is increased 18-fold in PD patients and 40-fold in HD

patients (Lisowska-Myjak 2014). This might be explained due to better residual kidney function among PD patients (Pham et al. 2008; Lee et al. 2010a). Other possible explanation is in the change of the intestinal microbiome in HD patients and increased production of toxins (Vanholder et al. 2009).

Additional possible mechanism, by which conventional HD can contribute to cognitive decline, is intradialytic hypotension that affects especially anuric patients and subjects with increased arterial stiffness and heart failure (Malik 2018). The changes of blood pressure can cause episodes of acute cerebral ischemia. However, blood pressure per se is a poor predictor of cerebral ischemia. This is because of variable lower limits of cerebral autoregulation and varying ability to increase oxygen extraction (MacEwen et al. 2017).

Hemodialysis sessions also bring the risk of states of acute cognitive decline – i.e. delirium, which, although reversible, often have a negative impact on long-term cognitive performance (Murray 2008). The cause of delirium is probably due to electrolyte disbalances, that occur during dialysis (Yasui-Furukori et al. 2017).

Cognitive performance improves after kidney transplantation (Gupta et al. 2016; Findlay et al. 2019; Joshee et al. 2018). However, cognition of these post-transplanted patients remains worse when compared to a healthy group. Some of the cognitive functions such as attention, executive functions, verbal fluency and language do not improve at all (Joshee et al. 2018).

Cerebral oxygenation and blood flow

Determinants and measurement of cerebral oxygenation and cerebral blood flow

The brain has a remarkably high metabolic rate – it utilizes approximately 50 mL of oxygen per minute, which equals 20 % of the total oxygen consumption of the human body at rest. Most of the energy is used for maintaining the ion homeostasis with sodium-potassium ATPase, proteosynthesis and synthesis of neurotransmitters. The brain, therefore, depends on aerobic metabolism and on glucose and oxygen supply. This makes it very vulnerable to hypoxia, and the metabolic demand of the tissue is one of the factors that affect the cerebral blood flow (CBF). The main determinants of cerebral oxygenation (CrSO2) are arterial oxygen concentration, blood oxygen carrying capacity (hemoglobin concentration), cerebral blood flow and cerebral oxygen consumption. Traditional determinants of cerebral energy metabolism are cerebral metabolic rate of oxygen ($CMRO_2$), CBF and venous blood oxygenation (Catchlove et al. 2018). A novel method of measuring brain tissue oxygenation is near-infrared spectroscopy (NIRS). It employs a non-invasive transcutaneous approach. The resulting value, regional oxygen saturation (rSO_2), combines venous, arterial, and microcirculatory oxygen saturation. This method is widely used for monitoring in intensive care units or during anesthesia (Moerman and Wouters 2010).

General population

CBF is about 50 mL/100 g/min at birth, peaks around the age of 5 with average value of 70 mL/100 g/min (Tasker 2013). Then CBF slowly decreases to the normal average adult value of 50 mL/100 g/min, reaching it at around 19 years of age (Lassen 1985; Tasker 2013).The average CBF of the white matter is approximately 20 mL/100 g/min, perfusion of the grey matter is higher, about 80 mL/100 g/min (Vavilala et al. 2002). During healthy aging the CBF progressively decreases, mainly in cortical regions (Chen et al. 2011). Decreased brain metabolism (Leenders et al. 1990), elevation of the blood pressure (Tarumi and Zhang 2018) and/or pathologic changes of brain vessels could be the underlying causes (Wagner et al. 2012).

A recent study (Catchlove et al. 2018) reported higher oxygen extraction rate in older subjects with no age-dependent change in $CMRO_2$; this finding suggests that there is certain disproportion between oxygen demands and supply in the brain in elderly population

Chronic kidney disease

Recent studies have shown that patients with CKD have significantly lower cerebral oxygenation when measured by the non-invasive near-infrared spectroscopy (NIRS) (Malik et al. 2016; Prohovnik et al. 2007; Ito et al. 2015; Hoshino et al. 2014) than the healthy population; the results are summarized in **Table 1**. Patients treated with HD have even lower regional oxygen saturation

(rSO_2) than patients treated with PD (Papadopoulos et al. 2013). There is no significant difference in rSO2 before vs. after hemodialysis session (Hoshino et al. 2014; Valerianova et al. 2019). However, brain oxygenation is not stable during hemodialysis; our previous study showed that rSO2 values drop after the beginning of hemodialysis and reach their minimum in 35th minute (Malik et al. 2016). Furthermore, CBF can decline by 10-15% during hemodialysis cycle (Polinder-Bos et al. 2018). These hemodynamic changes occurring during fast fluid removal could be responsible for brain hypoxia (Malik et al. 2016) and participate on cognitive decline.

Lower rSO_2 is independently associated with higher pH, longer HD duration and lower serum albumin concentration, rSO_2 is also lower in patients with diabetes mellitus (Ito et al. 2015) and heart failure (Valerianova et al. 2019). Decrease of pH induces dilation of cerebral arteries (Kontos et al. 1977) resulting in cerebral blood flow increase. The association of rSO_2 with changes of pH could thus be explained by changes in oxygen delivery (Ito et al. 2015).

Prohovnik et al. (2007) reported lower rSO_2 and lower cerebral blood flow in ESRD patients before HD. CBF declined to 60% of its normal level during interdialytic interval and was once again restored by HD procedure. The recent study demonstrated that lower eGFR was associated with lower CBF (Sedaghat et al. 2016). This could be due to impaired cerebral autoregulation and/or accumulation of vasoactive substances, such as ADMA, what can lead to vasoconstriction of cerebral vessels (Sedaghat et al. 2016; Zoccali et al. 2002).

Nonetheless, not all studies are in accordance with these observations. Some observed increased and not decreased CBF in CKD patients, both in non-dialysis (Jiang et al. 2016; Tamura et al. 2016) and in those undergoing the dialysis treatment (Vorstrup et al. 1992; Mathew et al. 1985; Jiang et al. 2016; Cheng et al. 2019). Increased CBF is most likely the result of decreased oxygen carrying capacity of the blood due to anemia (Liu et al. 2018b). This explanation is supported by CBF correction after anemia treatment (Hirakata et al. 1992). Other possible explanation includes impaired cerebrovascular autoregulation (Tamura et al. 2016). Alternatively, the brain "overperfusion" could be just a presentation of hyperkinetic circulation typical for CKD patients because of water retention, anemia and arteriovenous access (Malik 2018).

Both cerebral hypoperfusion and hyperperfusion could contribute to brain damage. The former can cause ischemia and the latter can be involved in the disruption of the blood brain barrier (BBB) and subsequent white matter (WM) degeneration (Mansour et al. 2019).

Blood brain barrier

Physiology of the blood brain barrier

The human brain weighs approximately 2 % of the body mass, but receives 12-15 % of the cardiac output at rest (Williams and Leggett 1989). This disproportion demonstrates that the brain is a highly perfused organ, immensely dependent on the supply of nutrients and oxygen. The function of the blood

brain barrier (BBB) **(Fig.1)** is to maintain the CNS microenvironment stable and to prevent the entry of neurotoxic metabolites, blood cells and pathogens (Daneman and Prat 2015).

The BBB is formed by the endothelial cells, pericytes, astrocyte end-feet, interneurons and immune cells. Endothelial cells are the core component. They possess specific attributes that ensure BBB integrity and homeostasis. Unlike other parts of the human body, the capillaries here are non-fenestrated and the adjacent cells are sealed together by protein complexes forming the tight junctions **(Fig.1)**. Endothelial cells have low pinocytic activity, which significantly reduces the vesicle-mediated transcellular passage of the molecules through the BBB (Engelhardt and Liebner 2014). However, endothelial cells possess high amount of specific transporters that regulate the transcellular influx of nutrients and ensure the efflux of waste products (Stamatovic et al. 2008). Higher concentration of mitochondria within endothelial cells provides energy for transporters and the maintaining of CNS homeostasis (Daneman and Prat 2015).

The extraluminal surface of the endothelial cells is surrounded by a vascular basement membrane. It is an extracellular network of proteins secreted by the endothelial cells, pericytes and astrocytes (Hallmann et al. 2005; Daneman and Prat 2015). Pericytes **(Fig.1)**, embedded in the basement membrane, are cells that incompletely cover the abluminal surface of the blood vessels. They communicate with adjacent cells by both direct physical contact

and paracrine signaling, and thus they participate in BBB regulation (Liu et al. 2012).

Astrocytes **(Fig.1)** represent the supporting cells of the CNS. These specialized glial cells have foot-like extensions of their cell membranes, called end-feet. The end-feet ensheath both the endothelial cells and the neuronal processes. Therefore, astrocytes serve as a „bridge", physically and functionally connecting the neurons and vessels (Liu et al. 2018a).

These structures, along with neurons, interneurons and immune cells (microglia and perivascular macrophages), form a dynamic multicellular structure called the neurovascular unit (Sharif et al. 2018) **(Fig.1)**. The complex interaction within results in a highly effective system, essential for the normal function of the brain (Netto et al. 2018). Disruption of the neurovascular unit on any level could have direct consequences on neuronal functions (Keaney and Campbell 2015). Disruption of the BBB is associated with numerous diseases, such as ischemic stroke, epilepsy and neurodegenerative disorders (Palmer 2010; Obermeier et al. 2013).

Chronic kidney disease and blood brain barrier

The data about the association of BBB disruption and CKD is limited.
Mice model of CKD was developed to study BBB integrity and behavioral abnormalities (Mazumder et al. 2016). Albumin-bound Evans blue was administered to the mice circulation and later observed in the brain parenchyma

due to BBB disruption. Moreover, the mice with CKD presented psychomotor and behavioral abnormalities. Other animal model study showed erosion of the tight-junction proteins among uremic CKD rats (Jing et al. 2018). Urea in concentration like in dialysis patients damaged the actin cytoskeleton and decreased expression of claudin-5 (protein of tight junctions) (Lau et al. 2020).

However, uremia is not the only factor that can damage BBB. Various CKD-associated comorbidities causing systemic inflammation (such as arterial hypertension, type 2 diabetes, dyslipidemia) and chronic cerebral hypoperfusion can be involved in the process (Varatharaj and Galea 2017; Setiadi et al. 2018; Malkiewicz et al. 2019; Ueno et al. 2002). Increased permeability of the BBB allows infiltration of noxious agents, cytokines and immune cells into CNS (Jabbari and Vaziri 2018; Malkiewicz et al. 2019) what can contribute to neuroinflammation. Dysfunction of the neurovascular unit could impair CBF autoregulation, lead to reduction in CBF and cause ischemic injury (Iadecola 2017). Jin M. et al. (2020) reported neurovascular coupling impairments in HD patients. Furthermore, dysfunction of the neurovascular unit can decrease production of trophic factors by neurovascular unit cells and alter clearance of neurotoxic molecules and some proteins, such as β amyloid and tau protein (Iadecola 2017).

Accumulated uremic toxins in the brain inhibit brain-blood efflux transporter (Organic anion transporter 3). This transporter provides efflux of indoxyl sulfate (possibly some other uremic toxins such as: hippuric acid and 3-

Carboxy-4-methyl-5-propyl-2-furanpropionate, indoleacetate) and neurotransmitter metabolites (Ohtsuki et al. 2002; Deguchi et al. 2006). The cerebrospinal fluid-blood efflux transporter (Organic cation transporter 3) is also inhibited by increased concentrations of uremic toxins in brain. This transporter provides efflux of creatinine (Hosoya and Tachikawa 2011).

Some guanidino compounds can activate glutamatergic pathways and are involved in GABAergic inhibition (De Deyn et al. 2001). This pathological process, excitotoxicity, can lead to nerve cell death. Indoxyl sulfate induces oxidative stress and inflammatory mediators in glial cells. Indoxyl sulfate also alters function of glial cells (astrocytes and mixed glial cells) and increases production of various cytokines and pro-inflammatory enzymes with toxic effect on CNS (Adesso et al. 2017). Methylguanidine contributes to neurodegeneration most likely via alteration in mitochondrial calcium homeostasis and pro-apoptotic effect of H_2O_2 in astrocytes (Marzocco et al. 2010). Quinolinic acid (uremic toxin and brain endogenous excitotoxin) is a neurotoxin, proinflammatory mediator and alters the BBB integrity (Ting et al. 2009; Guillemin 2012). Moreover, quinolinic acid is a gliotoxin and can induce astrocyte apoptosis via excessive stimulation of N-methyl-D-aspartate receptors (NMDARs) (Lee et al. 2010b). The increase of neurotransmitter metabolites in the brain impairs metabolism of neurotransmitters and causes accumulation of neurotoxic intermediate metabolites (Ohtsuki et al. 2002).

The deficits in cholinergic function is associated with cognitive decline. In

a recent study, the activity of the acetylcholinesterase was globally reduced in the brain of the CKD mice (Mazumder et al. 2019) Furthermore, the study reported reduction of neuronal arborization in hippocampus and loss of dendritic spines in the cortex and hippocampus. CKD mice had increased superoxide dismutase activity and decreased catalase activity (markers of oxidative stress) in the cortex and hippocampus. The study also showed mitochondrial dysfunction and increase in reactive glial cells (indicator of inflammation). Increase of inflammation and oxidative stress can be an explanation for reduced acetylcholinesterase activity, loss of dendritic arborization and spines, and cognitive decline observed in these mice (Mazumder et al. 2019).

Structural brain changes and imaging methods

CKD can affect brain structure on many levels and the morphologic alterations can be both acute and chronic. The most valuable method to assess the cerebral changes is magnetic resonance imaging (MRI). However, imaging modality of choice in the acute setting is computed tomography (CT). The advantages of CT include shorter scanning time, better availability and lower cost.

Freedman et al. 2017, performed MRI structural analysis of the brain in the early stages of CKD caused by type 2 diabetes mellitus. The mildly higher urine albumin-creatine ratio and lower eGFR correlated with decreased gray matter (GM) volume. White matter (WM) lesions volume were increased, which was

associated with the cerebral microvascular disease. The CKD patients had poorer digit symbol coding performance. These findings suggest that the structural brain changes begin in the early stages of the CKD and affect cognition. Several other studies associated reduced kidney function with smaller GM volume (Tsuruya and Yoshida 2018) and higher WM disease burden (Sink et al. 2015; Tamura et al. 2016; Khatri et al. 2007). Decreased GM volume (in bilateral medial orbito-prefrontal cortex, left middle temporal gyrus, left dorsal lateral prefrontal cortex and right dorsal lateral prefrontal cortex) of the ESRD patients was related to the functional brain deficits. Regions with GM volume reduction had altered functional connectivity with other brain regions (Qiu et al. 2014).

Tract based spatial statistics of the diffusion tensor imaging (an advanced MRI technique) has allowed visualization of the structural interconnectivity of the WM tracts by measurement of anisotropic diffusion of water. ESRD patients had lower fractional anisotropy and increased mean (Drew et al. 2017; Kong et al. 2014) and radial diffusivity (Zhang et al. 2015; Chou et al. 2013; Yin et al. 2018). These findings can be interpreted as the loss of the WM integrity, demyelination and diffuse interstitial brain edema.

Silent brain infarction (SBI) **(Fig. 2)** is characterized as a cerebral infarction detected by imaging method, but without clinical correlate. Shima et. al. (2011) reported SBI in 31.8% of predialysis CKD patients. Their typical localization is in the deep brain structures (Kobayashi et al. 2009; Kobayashi et al. 2004;

Shima et al. 2011). Likewise, the prevalence of the brain microhemorrhages **(Fig. 2)** is higher among CKD population (Vemuri et al. 2017). These are presumably caused by structural abnormalities of the small vessels and are typically found infratentorially and in the deep brain regions (Ovbiagele et al. 2013; Peng et al. 2016). Both cerebral microbleeds and silent brain infarction are associated with increased risk of stroke and their incidence rises with the progression of the CKD. (Akoudad et al. 2015; Kobayashi et al. 2009; Shima et al. 2011; Shima et al. 2016).

Xiao L. et al. investigated the relationship between chronic kidney disease and enlarged perivascular spaces **(Fig. 2)** using the FLAIR MRI sequence. As the eGFR decreased, the severity of the enlarged perivascular spaces increased together with the cerebral small vessel disease (Xiao et al. 2015).

In summary, it is possible to detect cerebral structural changes from the early stages of the CKD, both in the GM and the WM. Brain abnormalities and cognitive deficit progress with the severity of the CKD and are most expressed among hemodialyzed patients (Pi et al. 2016). The neurocognitive decline is most likely a result of the WM damage **(Fig.2)**, reflecting small vessel disease (Vogels et al. 2012; Wada et al. 2008; Knopman et al. 2008). Integrity of WM tract, structural and functional connectivity of brain networks and cognitive performance can improve after renal transplantation (Gupta et al. 2016; Findlay et al. 2019; Chen et al. 2020; Joshee et al. 2018).

Conclusion

Structural and functional brain changes can be observed since the early stages of CKD and the executive functions are affected first. The cognitive decline has progressive character, can eventually lead to dementia and is positively correlated with renal functions. The presence of ESRD and the hemodialysis therapy itself have detrimental effects on the brain, probably stronger than the general risk factors (Etgen et al. 2012).

Increased levels of pro-inflammatory cytokines, increased oxidative stress and other traditional and non-traditional vascular risk factors (which can be accented in CKD) accelerate CNS damage through vascular endothelial dysfunction. Findings on imaging methods confirm this hypothesis. The hallmark of CKD is degeneration and damage of WM, thus findings typical for vascular dementia. The BBB dysfunction can be the starting point of the WM lesions (Huang et al. 2018).

Increased levels of some uremic toxins have neurotoxic and/or gliotoxic effect and can contribute to brain damage. Other factors, known from the general population, such as education level, depression, psychiatric diseases, sleep disturbances, polypharmacy, malnutrition and superimposed neurodegenerative diseases could also alter cognitive functions of these patients.

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Table 1. Results of the cerebral oxygenation in chronic kidney disease patients, measured by NIRS.

Author	Year	Patients	ESRD group	Control group	p-value
Ito et al.	2015	54	50 ± 2 %	69 ± 2 %	< 0.001
Hoshino et al.	2014	18	56 ± 1 %	70 ± 3 %	< 0.001
Malik et al.	2016	27	52 ± 11 %	68 ± 7 %	< 0.0001
Prohovnik et al.	2007	7	41 ± 13 %	70 ± 2 %	< 0.01

Figures

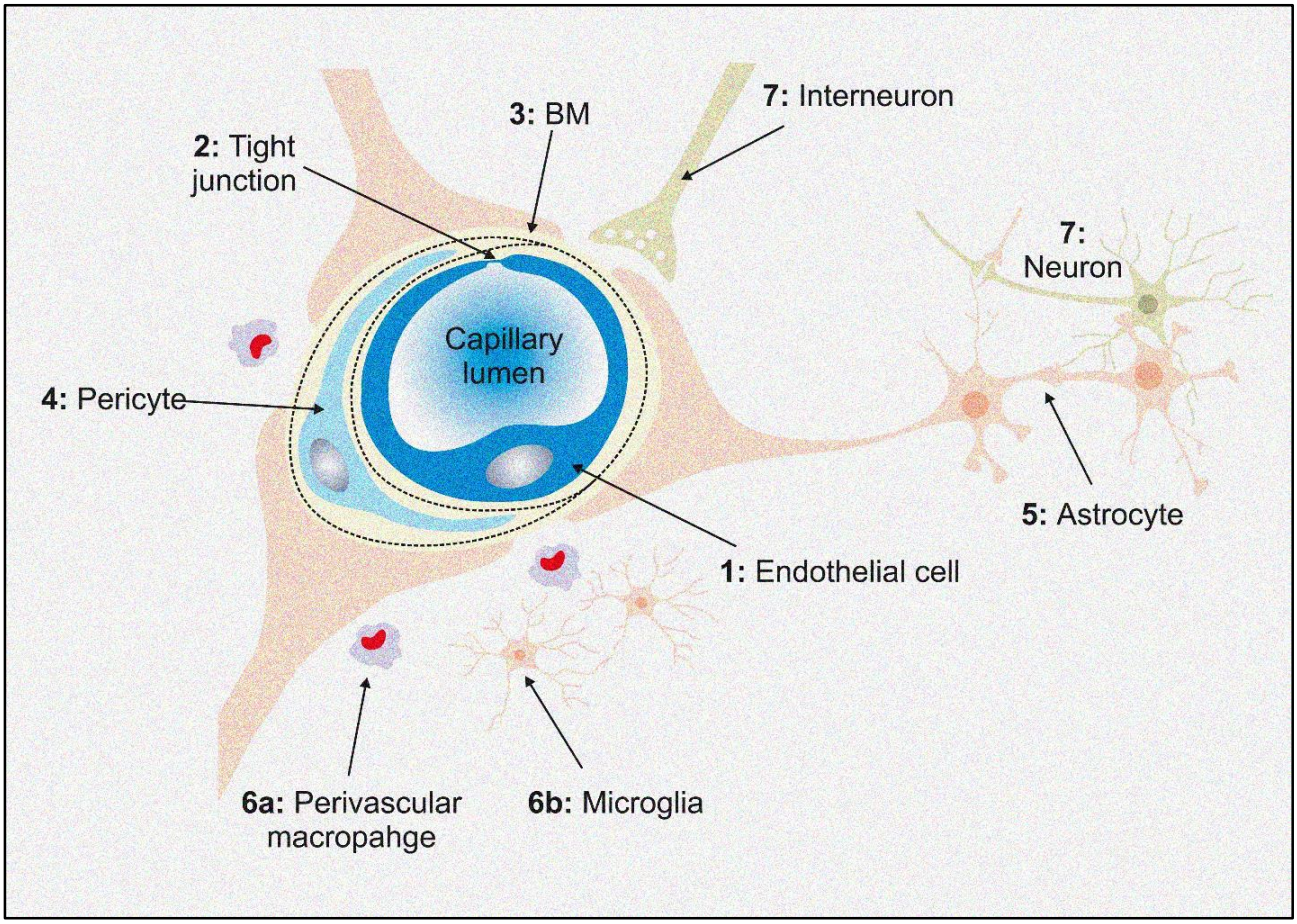

Figure 1. Neurovascular unit
1. Endothelial cells (EC) regulate the movement of the molecules, ions and cells through the BBB. **2. Tight junctions of the EC** limit the paracellular movement (passive diffusion) and cause polarization of the EC, what is necessary for the molecular transport in a polarized manner. **3. Vascular basement membrane** provides additional barrier, maintains the integration of the endothelial cells with pericytes and astrocytes. Also, vascular basement membrane ensures cell-cell and cell-matrix interactions.
4. Pericytes participate in the formation of the BBB during embryogenesis. Their contractive ability allows them to regulate blood flow at the capillary level. Other functions are: regulation of an angiogenesis, vascular stability, stem cell like activity and macrophage-like phagocytosis. **5. Astrocytes** coordinates cerebral blood flow. Also, the astrocytes have many functions related to the maintenance of the neural microenviroment, such as the management of the extracellular pH, water transport, osmotic balance and antioxidant system. **6. Immune cells** have two main populations in the CNS. **Perivascular macrophages** serve as phagocytes, providing first line immunity. **Microglial cells,** besides phagocytosis, participate in pro-inflammatory response as well as in the neurotrophic

pathways.
7. Neurons detect altered concentrations of the oxygen and nutrients. Neurons transmit signal to vessels through **interneurons** and astrocytes, influencing the vascular response depending on supply requirements.

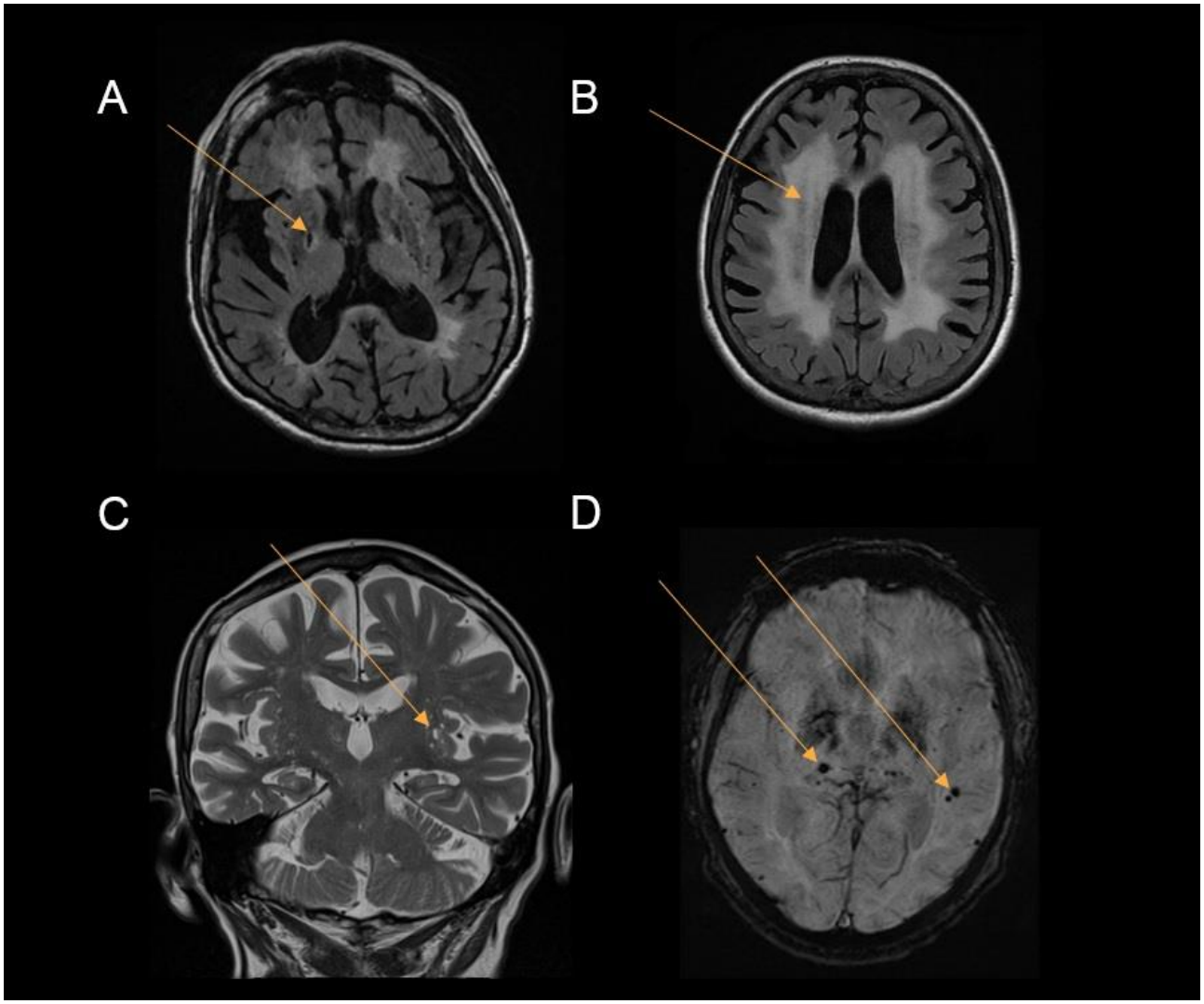

Figure 2. Structural brain changes
Source: Department of Radiology, Faculty hospital Kralovske Vinohrady
(Images are only an illustration of the comm.on pathologies among CKD patients)
A. FLAIR T2WI MRI, chronic lacunar infarction - low intensity lesion with hyperintense rim of gliosis in the right lobe (basal ganglia) **B.** FLAIR T2WI MRI, degeneration and gliosis of the white matter appear as extensive periventricular hyperintense lesions **C.** T2WI MRI, enlarged perivascular spaces **D.** SWI MRI, cerebral microbleeds - small areas of signal loss

List of abbreviations

Abbreviation	Meaning
ADMA	Asymmetric dimethylarginine
BBB	Blood brain barrier
CBF	Cerebral blood flow
CKD	Chronic kidney disease
CMRO2	Cerebral metabolic rate of oxygen
CNS	Central nervous system
CrSO2	Cerebral oxygenation
CT	Computed tomography
DSM-5	Diagnostic and statistical manual of mental disorders
eGFR	Estimated glomerular filtration rate
GM	Gray matter
ESRD	End stage renal disease
HD	Hemodialysis
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
PD	Peritoneal dialysis
rSO2	Regional oxygen saturation
SBI	Silent brain infarction
WM	White matter

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