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Neurological complications in chronic kidney disease patients

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FULL REVIEW

ABSTRACT

Chronic kidney disease (CKD) is associated with a high prevalence of cerebrovascular disorders such as stroke, white matter diseases, intracerebral microbleeds and cognitive impairment. This situation has been observed not only in end-stage renal disease patients but also in patients with mild or moderate CKD. The occurrence of cerebrovascular disorders may be linked to the presence of traditional and non-traditional cardiovascular risk factors in CKD. Here, we review current knowledge on the epidemiological aspects of CKD-associated neurological and cognitive disorders and discuss putative causes and potential treatment. CKD is associated with traditional (hypertension, hypercholesterolaemia, diabetes etc.) and non-traditional cardiovascular risk factors such as elevated levels of oxidative stress, chronic inflammation, endothelial dysfunction, vascular calcification, anaemia and uraemic toxins. Clinical and animal studies indicate that these factors may modify the incidence and/or outcomes of stroke and are associated with white matter diseases and cognitive impairment. However, direct evidence in CKD patients is still lacking. A better understanding of the factors responsible for the elevated prevalence of cerebrovascular diseases in CKD patients may facilitate the development of novel treatments. Very few clinical trials have actually been performed in CKD patients, and the impact of certain treatments is subject to debate. Treatments that lower LDL cholesterol or blood pressure may reduce the incidence of cerebrovascular diseases in CKD patients, whereas treatment with erythropoiesis-stimulating agents may be associated with an increased risk of stroke but a decreased risk of cognitive disorders. The impact of therapeutic approaches that reduce levels of uraemic toxins has yet to be evaluated.

Keywords: cerebrovascular disease, chronic kidney disease, cognitive impairment, end-stage renal disease, epidemiology

INTRODUCTION

Individuals with chronic kidney disease (CKD) have a high prevalence of cerebrovascular disorders. Stroke is the third most common cardiovascular cause of death in CKD patients and patients with end-stage renal disease (ESRD) show a 4- to 10-fold greater risk of hospitalization for ischaemic and haemorrhagic stroke [1], an increased risk of cognitive impairment and dementia [2, 3] and poor long-term post-stroke prognosis [4] when compared with non-ESRD patients. It has also been observed that the prevalence of asymptomatic silent cerebral infarctions is four to five times greater in dialysis patients than in age- and gender-matched controls [5] and that patients on dialysis with cognitive impairment appear to have a high number of cortical defects reminiscent of multiple infarct–related damages [6].

Given this context, we reviewed current knowledge on CKD-associated cerebrovascular and cognitive disorders. We first assess recent reports on the high incidence of cerebrovascular diseases in patients with ESRD or mild to moderate CKD. We then briefly describe putative factors of CKD-associated neurological disorders before evaluating potential treatments. To this end, we searched the PubMed database with the keywords 'kidney disease' and 'stroke', 'white matter disease' or 'cognitive disorders' with a focus on work published in the last 10 years.

EPIDEMIOLOGICAL STUDIES

Cerebrovascular disease and ESRD

It has been known for some time that the incidence of stroke is elevated in dialysis patients. Most studies have been performed in Asian patients [7, 8], a population characterized by a high prevalence of haemorrhagic strokes and intracranial vessel atherosclerotic lesions. In Taiwan, the hazard ratio for ischaemic stroke was

three times higher in both haemodialysis and peritoneal dialysis patients as compared with non-dialysis patients, and that for haemorrhagic stroke was six times higher (Table 1). Although studies in European populations are scarcer, they also show a higher incidence of ischaemic and haemorrhagic stroke in haemodialysis patients, the latter being more likely in patients of south Asian ethnicity [13]. Furthermore, the high incidence of haemorrhagic stroke in haemodialysis patients was associated with high mortality [13]. This high lethality rate might be linked (at least in part) to poor hypertension management and to

Table 1. Incidence rates and adjusted hazard ratios of ischaemic or haemorrhagic stroke associated with end-stage and non-end-stage CKD: large cohort studies, 2007–2015

Reference, country, publication year	Study population	Follow-up (years)	Participants	Number of events and incidence rate	Adjusted hazard ratios (95% CI)
Cohorts of ESRD patients on haemodialysis (HD) or peritoneal dialysis (PD) compared with non-dialysis (ND) patients					
Kuo *et al.* [7], Taiwan, 2012	National Health Insurance Database, 1999–2003	5	644 HD patients	119 strokes (HD), 41.76/1000 py	2.16 (1.57–2.97) for IS
			3220 ND patients	369 strokes (ND), 24.29/1000 py	3.78 (1.90–7.55) for HS
Wang *et al.* [8], Taiwan, 2014	National Health Insurance Database, 1998–2009	HD: 4.2 PD: 3.0 ND: 10.5	28 940 incident HD patients	2134 strokes in HD patients IS: 10.26/1000 py HS: 7.47/1000 py	HD as compared with ND patients: 2.88 (2.60–3.19) for IS 6.83 (5.89–7.92) for HS
			5974 incident PD patients	290 strokes in PD patients IS: 10.01/1000 py HS: 5.94/1000 py	PD as compared with ND patients: 3.21 (2.69–3.83) for IS 6.15 (4.83–7.84) for HS
			29 870 ND patients	1742 strokes in ND patients IS: 4.24/1000 py HS: 1.30/1000 py	
Population-based cohorts					
Bos *et al.* [9], The Netherlands, 2007	Population-based cohort, Rotterdam study	10.2	4937 subjects	586 stroke events: 338 IS, 44 HS, 204 unspecified	HR for HS associated with eGFR: 1.79 (0.59–5.38) for Q2 vs. Q4 (ref) 3.12 (1.08–9.03) for Q2 vs. Q4 4.10 (1.25–13.42) for Q1 vs. Q4 No association between IS and eGFR
Holzmann *et al.* [10], Sweden, 2012	Population-based cohort	12	539 287 subjects	17 678 stroke events: 12 856 IS, 2696 HS and 2126 unspecified	HR for IS associated with eGFR in mL/min/1.73 m^2: 1.09 (1.04–1.14) for eGFR 60–89 vs. ≥90 1.24 (1.10–1.39) for eGFR 30–59 vs. ≥90 2.27 (1.63–3.17) for eGFR <30 vs. ≥90 HR for HS associated with eGFR: 1.04 (0.93–1.15) for eGFR 60–89 vs. ≥90 1.26 (0.96–1.64) for eGFR 30–59 vs. ≥90 2.31 (1.10–4.87) for eGFR 30–59 vs. ≥90
Mahmoodi *et al.* [11], USA, 2014	Pooled population-based cohorts, USA (ARIC, CHS, MESA), The Netherlands (PREVEND)	9.5	29 595 subjects	1261 all stroke events: 4.49/1000 py 1105 IS 156 HS	HR of stroke at eGFR of 45 (vs. 95) mL/min/1.73 m^2: 1.30 (1.01–1.68) for IS 0.92 (1.27–2.07) for HS At urinary albumin:creatinine ratio of 300 (vs. 5) mg/g: 1.62 (1.27–2.07) for IS 2.57 (1.37–4.83) for HS
Li *et al.* [12], China, 2015	Population-based cohort, Kailuan Study	4	92 013 subjects	1575 stroke events: 1128 IS, 447 HS	HR for stroke associated with dipstick proteinuria: 1.61 (1.35–1.92) for all stroke 1.53 (1.24–1.89) for IS 1.90 (1.35–2.67) for HS No association between eGFR and stroke

HD, haemodialysis; HR, hazard ratio; HS, haemorrhagic stroke; IS, ischaemic stroke; ND, non-dialysis; PD, peritoneal dialysis; py, person-years; Q, quartile; RR, relative risk.

anticoagulant use during haemodialysis [13, 14]. Maintenance dialysis was also independently associated with early death in patients with intracerebral haemorrhage [15]. Finally, in a recent large population-based study, patients with ESRD had a higher risk of stroke, with differences depending on sex, age and stroke subtype [16]. The excess risk of stroke was greater for women than men and decreased with age. Even if it was present for both ischaemic and haemorrhagic strokes, excess risk was greater for intracerebral haemorrhage [16].

ESRD may impact other aspects of cerebrovascular diseases with fewer clinical symptoms; these conditions include leukoaraiosis, silent cerebral infarcts and cerebral microbleeds. Indeed, a high prevalence of leukoaraiosis (observed on CT scans) or white matter hyperintensities (detected on MRI) has been observed in both patients on haemodialysis [17, 18] and patients on peritoneal dialysis [14]. An abnormally high incidence of cerebral microbleeds was also reported in haemodialysis patients [19–21]. Lastly, one study showed that ESRD patients on haemodialysis have a higher prevalence of silent cerebral infarction than control subjects [5].

One important question is whether the excess risk of cerebrovascular disease in ESRD patients results from renal disease *per se* or from dialysis treatment. Interestingly, the incidence of stroke reportedly increases during the month around the date of haemodialysis initiation and stabilizes approximately 1 year later [22]. This suggests that haemodialysis-related factors, including gas embolisms, anticoagulation treatment, cerebral oedema and rapid changes in blood pressure may impact the brain [23]. In patients on continuous ambulatory peritoneal dialysis, greater risk of stroke was linked to poorly controlled overhydration-related hypertension [24].

Cerebrovascular diseases and mild-to-moderate CKD

It has been reported that in high-risk patients (defined as those with either cardiovascular disease or cardiovascular risk factors), non-end-stage CKD was clearly associated with stroke [25, 26]. Several studies of Asian patients indicate that stroke is frequently associated with renal dysfunction [27]. In Table 1, we summarize the findings of selected recent large cohort studies worldwide providing hazard ratio estimates for stroke by subtype associated with CKD as defined by eGFR or albuminuria level. With few exceptions, they show increasing risk for both ischaemic and haemorrhagic strokes with decreasing eGFR and the presence of micro- or macroalbuminuria. Several meta-analyses also indicate that a low eGFR (<60 mL/min/1.73 m^2) [28] and/or albuminuria (>30 mg/g) [29–31] are associated with greater risk of stroke. The largest and most comprehensive meta-analysis of stroke in relation to eGFR and albuminuria was published by Masson *et al.* [32] this year in *NDT*, based on 83 cohort studies or randomized trials including 2 253 741 participants with 30 392 incident strokes. It showed that each 10 mL/min/1.73 m^2 decrease in eGFR was associated with a 7% increased risk of stroke {relative risk [RR] 1.07[95% confidence interval (CI) 1.04–1.09]} and each 25 mg/mmol increase in albuminuria was associated with a 10% increased risk [RR 1.10 (95% CI 1.01–1.20)]. The risk of stroke started to increase at an eGFR <90 mL/min/1.73 m^2 and albuminuria was an additive risk. Moreover, the effects were found to be similar for ischaemic and haemorrhagic strokes [32]. This study also provided the 10-year absolute risk of all-cause stroke (fatal and non-fatal) according to eGFR and albuminuria levels by age, gender and diabetes and smoking status (Figure 1, reprinted with permission). This absolute risk varied from <5% in non-smoking, non-diabetic men and women without albuminuria at any age and eGFR level to >25% in those with diabetes, smoking and both albuminuria and reduced eGFR.

As observed in dialysis patients, the presence of CKD is associated with a higher risk of death during hospitalization in stroke patients, regardless of the stroke subtype [33]. This elevated mortality was associated with severe CKD and was more pronounced in younger patients and women [33]. An age-dependent impact of eGFR on long-term survival has also been reported for ischaemic stroke [34]. In the latter study, a multivariate analysis of the study population as a whole showed that an eGFR <60 mL/min/1.73 m^2 was independently associated with death after stroke. When stratified by age group, a low eGFR was the sole independent predictor of death in individuals <65 years old [34].

The prevalence of other types of cerebrovascular damage (such as white matter disease) is also elevated in patients with mild-to-moderate CKD [35–38]. Some data indicate that this high prevalence may be independent of hypertension [37].

Similar findings have been reported for cerebral microbleeds in patients with primary intracerebral haemorrhage (particularly in African Americans) [39]. In another study, CKD was independently associated with cerebral microbleeds, but this was only in non-diabetic patients [40]. Lastly, microalbuminuria (but not eGFR) was associated with cerebral (deep or infratentorial) microbleeds in hypertensive patients [41]. However, it is not known whether a similar association is present in non-hypertensive CKD patients because only hypertensive patients were included in the latter study.

A similar trend has been described for CKD and silent cerebral infarcts [36, 38].

Cognitive impairment and CKD

Individuals at all stages of CKD have a higher risk of developing dementia and cognitive impairment than individuals without CKD, and the frequency of cognitive impairment is even higher in haemodialysis patients [42]. We recently published a review on cognitive disorders and dementia in CKD [43]. We listed the main studies (as of 2012) of associations between CKD on the one hand and dementia and cognitive impairment on the other, with a distinction between mild-to-moderate CKD and severe CKD (i.e. haemodialysis patients). As observed for cerebrovascular diseases and CKD, most studies have indicated an elevated prevalence of cognitive impairment and dementia in CKD patients. Furthermore, the increase was not restricted to haemodialysis patients and was also observed in patients with mild-to-moderate CKD [43]. Lastly, at least one study has reported that peritoneal dialysis patients also have moderate-to-severe cognitive impairments [44].

Other recent work has highlighted an increase in the incidence of cognitive impairment in CKD. Interestingly,

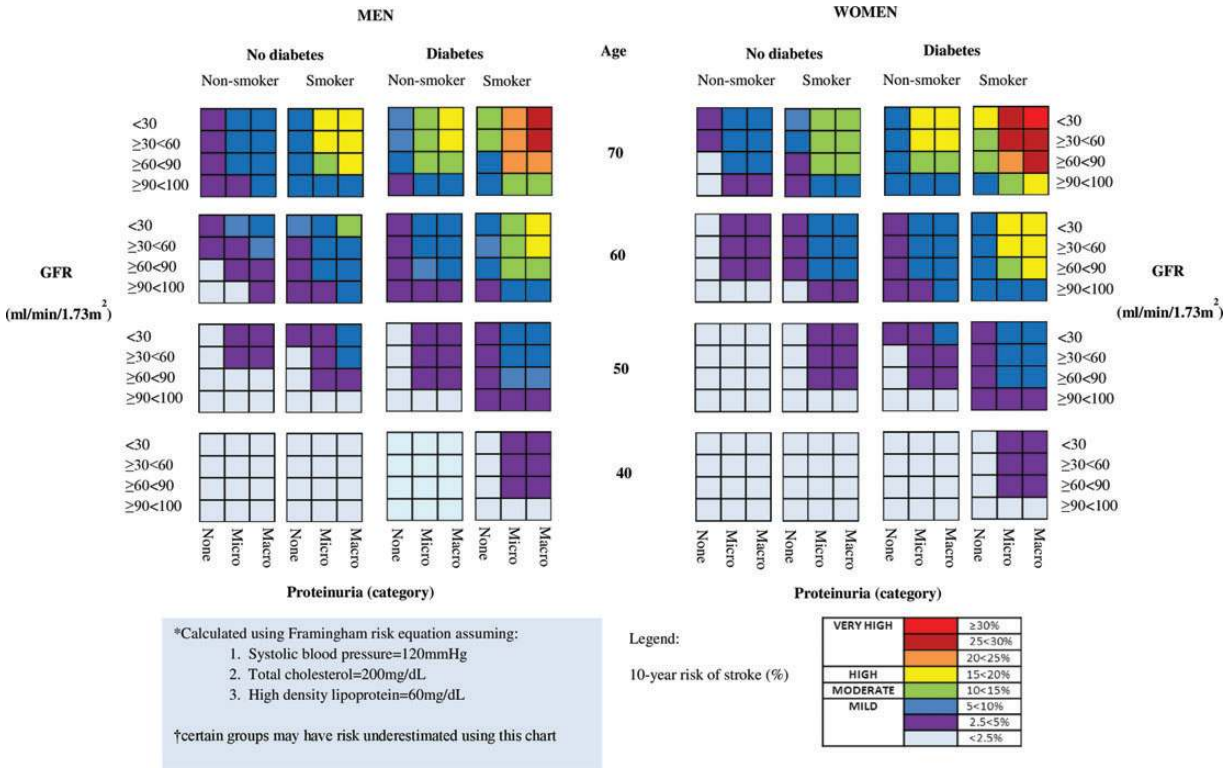

FIGURE 1: Ten-year absolute risk of all-cause stroke (fatal and non-fatal) according to albuminuria and eGFR levels, by age, gender and diabetes and smoking status (reprinted with permission from Masson *et al.* [32]).

the population-based Three-Cities Study failed to show an elevated risk of dementia or cognitive decline in participants with a low eGFR at baseline [45]. However, faster eGFR decline over 4 years and proteinuria (both markers of more severe CKD) were associated with global cognitive decline and incident dementia with a vascular component [45].

PUTATIVE CAUSES

There are several possible explanations for the elevated prevalence of cerebrovascular diseases in CKD. CKD patients have high levels of both traditional and non-traditional cardiovascular risk factors (for a review, see [46]). A recent cohort study confirmed that traditional risk factors (such as hypertension, diabetes and hypercholesterolaemia) are elevated in CKD patients [47]. However, another study found that CKD patients without hypertension, diabetes, hypercholesterolaemia or coronary heart disease had a higher risk of stroke than a control population without CKD but with hypertension, diabetes, hypercholesterolaemia or coronary heart disease [48]. This may suggest that CKD *per se* is a risk factor for stroke [48].

Indeed, CKD is also associated with non-traditional risk factors such as oxidative stress, inflammation, endothelial dysfunction, vascular wall calcification, uraemic toxins accumulation and CKD, all of which may contribute to the increased prevalence of cerebrovascular diseases (Figure 2). Indeed, clinical and animal studies indicate that these factors may modify the incidence and/or outcomes of stroke and are associated with white matter diseases and cognitive impairment. However, most of the time, direct evidence in CKD patients is still lacking. In this review we will briefly consider uraemic toxins and anaemia as potential contributors to cerebrovascular diseases during CKD.

Uraemic toxins

Uraemic toxins may impact on cerebrovascular diseases and/or cognition either directly or by modulating other putative factors mentioned above, such as inflammation, oxidative stress, endothelial dysfunction and vascular calcification and stiffness.

Direct impacts of uraemic toxins on cerebrovascular diseases and cognition. Uraemic toxins may have direct neurotoxic or vascular effects. In a recent review, Watanabe *et al.* [49] looked at reports of cerebrorenal interactions for 21 uraemic toxins. They found that uric acid, indoxyl sulphate, p-cresyl sulphate, interleukin-1β (IL-1β), IL-6, TNF-α and parathyroid hormone are likely to have an impact on cognition and the central nervous system under uraemic conditions. Guanidino compounds (creatinine, guanidine, guanidinosuccinic acid and methylguanidine) have also been identified as potential uraemic neurotoxins [50]. The neurotoxic effects of these compounds may be exerted via ligand- and voltage-gated calcium channels, suggesting the presence of calcium neurotoxicity [51]. It has been suggested that guanidine compounds act by blocking the GABA-A receptor and activating the glutamate *N*-methyl-D-aspartate receptor and voltage-gated calcium channels; this

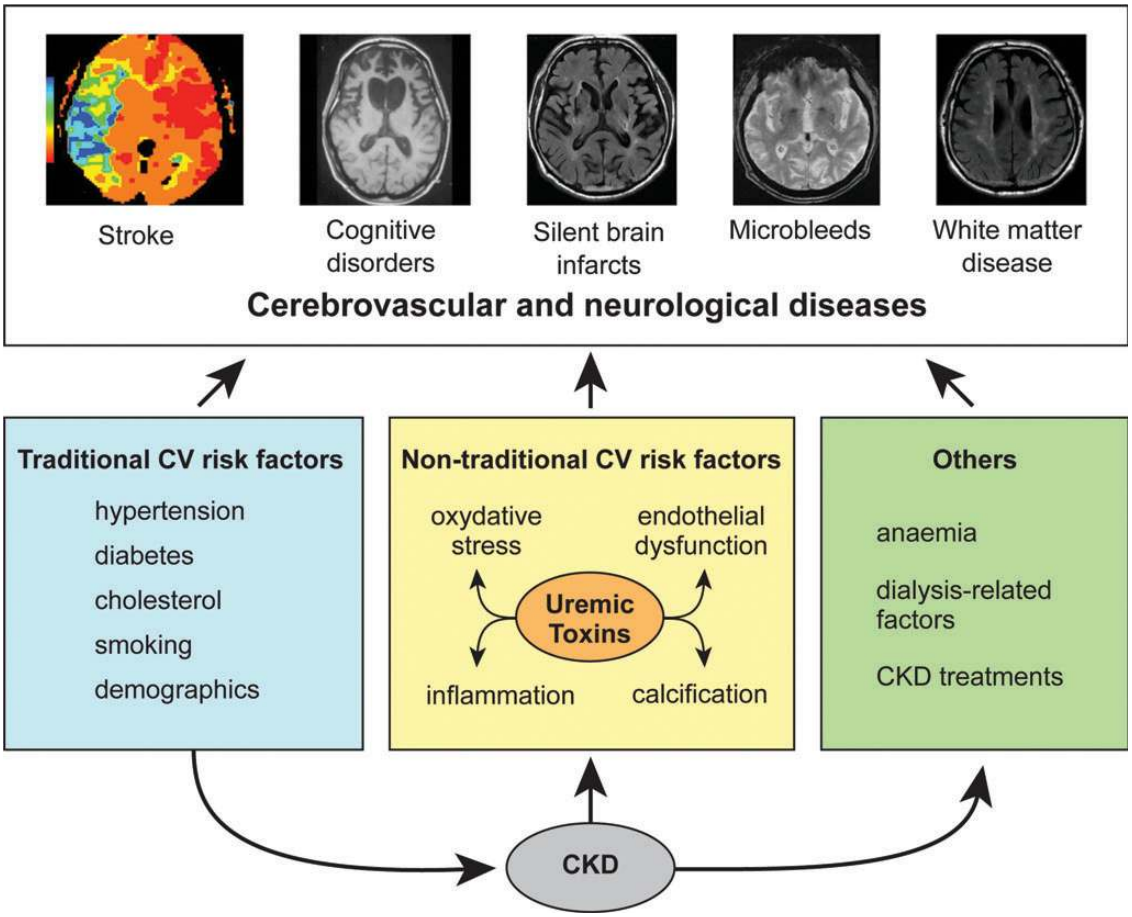

FIGURE 2: Putative causes of cerebrovascular and neurological diseases in CKD patients.

would increase post-synaptic calcium-triggered events such as the activation of nitric oxide (NO) synthase [52].

Uraemic toxins may also have a direct impact on cerebral blood flow. We have observed that the impairment of endothelium-dependent relaxation in our murine model of CKD was associated with an increase in the plasma concentration of asymmetric dimethyl arginine (a uraemic toxin that acts as an endogenous inhibitor of NO) [53]. It has also been shown in healthy adults that subpressor doses of asymmetric dimethyl arginine increase arterial stiffness (as estimated by the augmentation index of central aortic pressure) and decrease cerebral perfusion [54]. This observation suggests that asymmetric dimethyl arginine may be involved in the pathogenesis of cerebrovascular diseases in CKD patients [54]. Indeed, in another study, asymmetric dimethyl arginine was independently associated with small vessel disease and was correlated with leukoaraiosis severity [55].

Indirect impacts of uraemic toxins on cerebrovascular diseases and cognition. Uraemic toxins may also have indirect cerebrovascular and neurological effects by impacting on oxidative stress, inflammation, endothelial dysfunction and vascular calcification. Indeed, it has been reported that protein-bound uraemic toxins (such as indoxyl sulphate, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, p-cresyl sulphate, hippuric acid and indole acetic acid) may induce oxidative stress (for a review, see [56]). Uraemic toxins may also have an indirect impact on endothelial dysfunction. For example, studies in our murine model of CKD showed that high phosphate levels decrease endothelium-dependent relaxation and endothelium integrity and increase VCAM-1 and ICAM-1 levels [57]. Lastly, several groups have studied the impact of uraemic toxins (such as phosphate and indoxyl sulphate) on vascular calcification. Elevated phosphate may induce vascular smooth muscle cell calcification (after entering the cell via a sodium-dependent phosphate cotransporter) and increased cellular expression of the bone-specific transcription factor core binding factor a1 (Cbfa1), leading to the expression of a matrix prone to mineralization [58]. Indoxyl sulphate may induce calcification in human aortic smooth muscle cells [59] and in the aorta of hypertensive rats [60], with expression of osteoblast-specific proteins like Cbfa1 and osteopontin. It is not yet known to what extent these effects contribute to cerebrovascular and neurological diseases.

Anaemia

It is well known that CKD is associated with anaemia, which may also contribute to the increase in the prevalence and severity of stroke. In a case–control study in Taiwan, it was found that the odds ratio of having previously received a diagnosis of iron-deficiency anaemia was significantly higher in patients

hospitalized for stroke than in controls [61]. A similar observation was made in a study of the joint effects of CKD and anaemia on the risk of stroke [62]. As generally observed, in this study, CKD was associated with an elevated risk of stroke. However, when anaemia was taken into account, the association between CKD and stroke changed. CKD patients with anaemia had a significantly higher risk of stroke compared with no-CKD patients [62]. In contrast, patients with CKD and no anaemia had only a small non-significant increase in stroke risk [62].

TREATMENTS

Several studies have evaluated the impact of various treatments on cardiovascular disease (including stroke) in CKD patients. In contrast, few data are available on the impact of treatments on silent cerebral infarcts, white matter diseases or cognition in humans. In the last part of this review, we shall briefly discuss possible targets for treatments. In contrast, we shall not discuss the use of anticoagulants or anti-aggregants in the prevention of ischaemic stroke in CKD patients with atrial fibrillation. We shall present evidence (whenever available) indicating that a given treatment may or may not decrease cerebrovascular and neurological complications in CKD.

Lipid-lowering treatments

Several studies [63, 64] and at least one meta-analysis [65] have indicated that lowering of LDL cholesterol via the administration of statins is associated with a decrease in cardiovascular diseases (including stroke) in CKD patients. However, one must remain cautious in this respect because another meta-analysis found that treatment with statins reduced the incidence of major cardiovascular events and coronary events but had no significant effect on stroke [66]. In a Cochrane review, the authors concluded that statins did not necessarily have effects on stroke in CKD patients not requiring dialysis [67]. In contrast, another meta-analysis found that statin therapy in non-dialysis-dependent CKD patients (but not dialysis-dependent CKD patients) resulted in a significant reduction in the incidence of stroke. Thus, conflicting results have been reported for the impact of statins in CKD patients. According to a recent review, data from interventional trials and meta-analyses in CKD patients appear to plead in favour of reducing the atherosclerosis risk by adopting cholesterol-lowering treatment strategies except in treatment-naive dialysis patients and those on dialysis with inflammation and/or malnutrition [68].

Antihypertensive treatments and renin angiotensin system inhibitors

Results from the PROGRESS trial indicate that blood pressure lowering in CKD patients with prior cerebrovascular disease reduced the risk of stroke [69, 70]. This effect may not be related to the drugs used in the trial (perindopril and indapamide), since other studies have shown that the angiotensin receptor blocker olmesartan [71], the calcium blocker amlodipine and the angiotensin-converting enzyme inhibitor lisinopril [72] were not superior to other antihypertensive drugs in preventing cardiovascular events in CKD patients. The time of day at which antihypertensive treatments are taken may also be important, since one study has indicated that taking at least one medication at bedtime reduces the cardiovascular risk in CKD patients [73].

Erythropoiesis-stimulating agents

Treatment of anaemia may have a harmful effect on stroke, since many different studies and one meta-analysis have indicated that erythropoiesis-stimulating agents increase the risk of stroke in CKD patients [74–77]. In contrast, the results on the impact of anaemia treatment on cognition are conflicting. Indeed, at least one study shows that administration of erythropoiesis-stimulating agents in both pre-dialysis and dialysis CKD patients with anaemia resulted in a significant improvement of electrophysiological markers of cognitive function [78]. However, in another study, the authors failed to observe an association between elevated haemoglobin levels and cognition in non-dialysed CKD patients [79]. In rats it has been reported that treatment with erythropoiesis-stimulating agents had a neuroprotective effect against intermittent hypoxia-induced spatial learning and memory impairments [80]. Mechanisms such as an antioxidant effect or effects on antioxidant defences, central chemical transmitters or neurotrophic factors may be involved in the neuroprotective action of erythropoiesis-stimulating agents [80].

Other treatments

As mentioned above, oxidative stress, inflammation, uraemic toxins and calcification may contribute to cerebrovascular and neurological disorders in CKD. Thus treatments decreasing these factors may improve cerebrovascular diseases and cognition. However, to the best of our knowledge, no or very few studies have been performed in this field. It has been reported that the antioxidant tempol had a neuroprotective effect on spatial working memory dysfunction induced by oxidative stress in uraemic mice [81]. However, a Cochrane analysis failed to detect an effect of antioxidants on cardiovascular death and cardiovascular events in CKD patients [82]. Several treatments (such as AST-120 and phosphate binders) can be used to decrease levels of uraemic toxins such as indoxyl sulphate or phosphate. However, it is not known whether these treatments have an impact on cerebrovascular diseases and cognition. Similarly, several therapeutic approaches (including the administration of phosphate binders or calcimimetics) may be used to attenuate vascular calcification in CKD patients; again, the treatments' putative effects on stroke prevention or cognition have not yet been evaluated. With regard to the treatments' hypothetical impact on cardiovascular and cerebrovascular alterations, the calcimimetic cinacalcet failed to reduce carotid-femoral pulse wave velocity in CKD patients with hyperparathyroidism on peritoneal dialysis [83] or the risk of death or major cardiovascular events (including stroke) in dialysis patients [84]. In the latter study, however, a subgroup analysis indicated that cinacalcet was

associated with a lower risk of cardiovascular events in older patients [85].

What is important?

It is well established that moderate and advanced CKD is associated with increased risk and severity of stroke and increased risk of dementia and cognitive impairment. CKD is also associated with a high prevalence of pre-clinical injury, including leukoaraiosis, silent cerebral infarcts and cerebral microbleeds.

The excess risk of stroke in CKD is only partly mediated by traditional cardiovascular risk factors (age, gender, smoking, hypertension, diabetes and lipids). Other putative causes include non-traditional cardiovascular risk factors and CKD-related factors such as uraemic toxins, anaemia, oxidative stress, inflammation, endothelial disorders and vascular calcification.

There is evidence that LDL lowering with statins and blood pressure lowering are associated with reduced risk of ischaemic stroke in the general population and in CKD patients. There is no such evidence for anti-oxidative or anti-cardiovascular calcification treatments. Erythropoietin-stimulating agents increase the risk of stroke but could improve cognitive function in dialysis CKD.

FULL REVIEW

CONCLUSION

Neurological complications are common in both early stage and end-stage CKD. Indeed, CKD is associated with elevated oxidative stress, inflammation, endothelial dysfunction, vascular calcification, accumulation of uraemic toxins and anaemia, all of which may increase the occurrence of cerebrovascular diseases or have direct neuronal toxicity in CKD patients. Few studies have evaluated the impact of treatments on cerebrovascular and neurological complications in CKD patients. Treatment with statins and blood pressure lowering may decrease the incidence of stroke in this population. In contrast, erythropoiesis-stimulating agents may have harmful effects on stroke but beneficial effects on cognition. Although other treatments for decreasing oxidative stress, uraemic toxins and vascular calcification are available, their respective impacts on cerebrovascular and neurological complications in CKD patients remain to be evaluated.

CONFLICT OF INTEREST STATEMENT

None declared.

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