RISK FACTORS FOR STROKE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Stroke is a public health problem especially in developed countries, being an important cause of death and disability. The prevalence of chronic kidney disease (CKD) in the general population varies from country to country. The percentage of afflicted patients is on the rise, mainly due to the high incidence of diabetes mellitus (DM) complicated with diabetic nephropathy (DN) and of the kidney vascular diseases (hypertensive nephroangiosclerosis and ischemic nephropathy). In patients with CKD, strokes are relatively frequent, especially hemorrhagic ones, due to a host of risk factors, both modifiable and unmodifiable.

Cardiovascular complications (which may be prevented by risk factors control) are the main culprit for the relatively high mortality rate of CKD patients, frequently leading to their death before the initiation of renal replacement treatment (dialysis, kidney transplant).

Keywords: stroke, risk factors, CKD, hemodialysis.

Rezumat

Accidentul vascular cerebral este o problemă de sănătate publică, în special în țările dezvoltate, fiind o cauză importantă de deces și dizabilitate. Prevalența bolii renale cronice în populația generală variază de la o țară la alta. Procentul pacienților afectați este în creștere, în principal ca urmare a incidenței ridicate a diabetului zaharat complicat cu nefropatie diabetică și a bolilor vasculare renale (nefroangioscleroză hipertensivă și nefropatie ischemică).

INTERNAL MEDICINE

General Reviews

La pacienții cu boală renală cronică, accidentele vasculare cerebrale sunt relativ frecvente, în special cele hemoragice, din cauza unei multitudini de factori de risc, atât modificabili cât și nemodificabili.

Complicațiile cardiovasculare (care pot fi prevenite prin controlul factorilor de risc) sunt principalul vinovat pentru rata relativ mare de mortalitate a pacienților cu boală renală cronică, ducând frecvent la decesul lor înainte de inițierea tratamentului de substituție renală (dializă, transplant de rinichi).

Cuvinte cheie: *accident vascular cerebral, factori de risc, boală renală cronică, hemodializă.*

Introduction

Stroke is an important cause of death and disability. Stroke is the second most common cause of death in the general population (after ischemic heart disease), and the third most common cause of disability. Disability is evaluated as disability-adjusted life years (DALY) which sums up the loss of human life by early death and the years lived with disease-induced incapacity⁽¹⁾.

Strokes are a heterogeneous complex of clinical-pathologic conditions produced by hemorrhagic or ischemic mechanisms. Hemorrhagic strokes may be intracerebral or subarachnoid, while the ischemic ones may be thrombotic, embolic or hemodynamic.

CKD is defined by National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) as kidney damage and/or decrease in kidney function

(GFR < 60 ml/min/1.73 m²) persisting for three or more months, irrespective of the cause⁽²⁾.

The prevalence of CKD in general population is reported to be between 10.2 and 16.8% in various countries^(3,4). Consequently, CKD has become all over the world a major public health problem⁽⁵⁾. Among the risk and etiological factors of CKD, an important place is held by high blood pressure (HBP) and DM, besides race, gender, age, family history, birth weight, smoking, obstructive nephropathy, exposure to heavy metals, excessive alcohol consumption, analgesics, viral infections^(6,7).

The life expectancy surge in recent times, as well as the growing number of obese patients have certainly contributed to the higher prevalence of DM. As CKD is one of the chronic complications of DM, it goes without saying that the rising number of DM patients

will boost the number of CKD patients^(8,9). HBP is another extremely important factor involved in the pathogenesis of CKD⁽¹⁰⁾.

The percentage of patients treated by renal replacement therapy has doubled every ten years for the last two decades, mainly due to the increasing incidence of DM complicated with DN and of renal vascular diseases (hypertensive nephroangiosclerosis and ischemic nephropathy)⁽¹¹⁾.

Epidemiology

Recent data suggest that 72-86% of strokes are ischemic, 9-20% are hemorrhagic, for the remainder the cause remaining undefined (cryptogenic stroke). Many of those deemed cryptogenic, on further exploration proved to be cardioembolic, in most cases the background pathology being atrial fibrillation (AF)^(1,12,13).

In patients on chronic dialysis, hemorrhagic strokes are more frequent than the ischemic ones, due to HBP and high intradialytic blood pressure (BP) oscillations on the one hand and to the frequent and difficult to manage coagulation disorders on the other hand. The bleeding may occur in the subarachnoid space secondary to a Berry saccular aneurism rupture or in the brain parenchyma (primary intracerebral hemorrhage from a vascular malformation).

HBP is associated with an increased risk of stroke, irrespective of subtype. Anatomical anomalies (saccular aneurysms or arteriovenous malformations) and hemostasis disorders contribute significantly to hemorrhagic stroke, while ischemic strokes are more closely linked to the major risk factor which is atherosclerosis.

Hemorrhagic strokes are more frequent in patients with polycystic kidney disease. The family tree of patients with autosomal

dominant polycystic kidney disease provides a typical example of family clustering of hemorrhagic strokes⁽¹⁹⁾.

Risk factors for strokes in patients with CKD

The concept of risk factor includes a series of characteristics present in healthy individuals, which are statistically associated with the possibility of later developing certain diseases. The notion of „global risk” means assessing the risk factors cumulated in a given individual (the level of „high risk”)⁽¹⁴⁾. In order to achieve adequate prevention, identifying risk factors must be followed by classifying them as unmodifiable or modifiable⁽¹⁴⁾.

Unmodifiable risk factors for stroke are age, gender, ethnic origin and family history of stroke. Age is the most important risk factor for stroke, the incidence of stroke more than doubling for each ten years over the age of 55, for both men and women⁽¹⁴⁾.

Modifiable risk factors, shared with coronary heart disease, are HBP, smoking, DM, dyslipidemia, valvular heart disease, atrial fibrillation, oral contraceptives, and sedentarism. In CKD patients specific risk factors should also be taken into account, namely: chronic inflammation, oxidative stress, hyperhomocysteinemia, hyperparathyroidism, platelet dysfunction, high level of prothrombotic factors, advanced glycation end products, treatment with erythropoiesis-stimulating agents, vitamin D deficiency, and nitric oxide inhibitors buildup in the blood^(15,16).

In patients with CKD, cardiovascular morbidity and mortality are significantly higher than in general population. In these patients, the risk of cardiovascular disease, the main cause of stroke, is 20 times higher

INTERNAL MEDICINE

General Reviews

than in general population. In dialysis patients, uremic environment and the specific metabolic and hemodynamic changes promote atherosclerosis, resulting in an increased number and severity of atheroma plaques⁽¹¹⁾.

Risk factors control contributes to the prevention of cardiovascular complications in patients with CKD, which are the main cause of death in these patients, frequently leading to their demise before the initiation of renal replacement therapy (dialysis, kidney transplant)⁽¹⁷⁾.

CKD is an independent and potent risk factor for atherosclerosis, stroke, and cardiovascular events, predicting also an unfavorable outcome after such events. Cardiovascular mortality secondary to generalized atherosclerosis is high in patients with CKD, mainly due to arterial stiffness and to the aggregation of risk factors characteristic for these patients. Strokes are about 10 times more frequent in patients with advanced stage CKD than in general population⁽¹⁸⁾.

Atheroma plaques in the aortic arch and in the extracerebral arteries may provoke stroke by vascular lumen narrowing leading to diminished blood flow to the brain or by embolic mechanism. Moreover, coronary atherosclerosis contributes to cardioembolic stroke by means of myocardial infarction or atrial fibrillation⁽¹⁾.

High blood pressure

High blood pressure (HBP) is involved in about 70% of the cases of stroke, being the most important risk factor for both ischemic and hemorrhagic stroke. The risk increases as BP increases, in both genders and at all ages; the risk doubles for each 7.5 mmHg increase in diastolic BP⁽¹³⁾.

HBP is present in 60-100% of the patients with CKD, the percentage varying with the etiology and the stage of CKD. HBP is the most frequent cardiovascular disorder in CKD patients⁽¹⁹⁾. HBP is a major risk factor for vascular injury, involving especially the target organs (heart, brain, kidney). Vascular complications occur relatively early, are very frequent, and involve large and small arteries (HBP both initiates and aggravates atherogenesis), as well as arterioles. Typical arterial lesions that may occur in the cerebral circulation of hypertensive patients are hyaline and hyperplastic arteriosclerosis in small arteries, which results in higher cerebral vascular resistance and fibrinoid necrosis of the arterial wall, which leads to miliary saccular aneurysms formation (Charcot-Bouchard) especially in putamen, thalamus, pons, cerebellum, subcortical areas. Fibrinoid necrosis leads to arterial occlusion and lacunar infarction, while the rupture of small saccular aneurysms provoked by BP surges leads to intracerebral hemorrhages⁽¹¹⁾.

HBP promotes the increase in dimension and rupture of the congenital saccular aneurysms in the circle of Willis, leading to subarachnoid hemorrhage⁽¹¹⁾.

In dialysis patients there are a series of specific factors involved in the pathogenesis of HBP, namely salt-water retention, renin-angiotensin-aldosterone system activation, sympathetic nervous system activation, high level of endothelium-derived vasoconstricting substances (endothelin 1), accumulation of NO-synthase inhibitors (asymmetric dimethylarginine – ADMA) due to decreased renal excretion and catabolism, erythropoietin treatment, structural changes in the arterial wall, arterio-venous fistula, etc.⁽¹⁹⁾.

Ambulatory 24 hours BP monitoring is better (than occasional BP measurement) in recognizing the subgroups of patients with the highest cardiovascular risk, by measuring the nocturnal BP and by highlighting the correlation between BP and the target organs involvement. In CKD patients nocturnal HBP is frequent, probably due to hypervolemia and to autonomous nervous system dysfunction, being an independent risk factor for cardiovascular morbidity and mortality in these patients⁽¹¹⁾.

In hemodialysis patients, a post-dialysis systolic BP less than 110 mmHg or more than 180 mmHg was associated with a significant increase in stroke-induced mortality, while a pre-dialysis systolic BP between 140 and 160 mmHg was associated with the lowest risk of cardiovascular mortality⁽¹³⁾.

Other risk factors for cerebral infarctions are cardiac diseases (especially atrial fibrillation), peripheral vascular diseases, a history of transient ischemic attack, DM, smoking, hypercholesterolemia, excessive alcohol consumption, coagulation disorders, neck arterial murmurs. Oral contraceptives almost treble the risk of stroke⁽¹³⁾.

Atrial fibrillation

Atrial fibrillation (AF) is the most frequent cardiac rhythm disorder and is the most important and frequent cause of cardioembolic stroke. AF prevalence increases with age, from a mere 0.5% in the forties to as high as 10-15% in individuals older than 80, as shown by Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study⁽²⁰⁾.

AF is associated with many cardiovascular and general conditions, including heart failure (HF), HBP, valvular heart disease, cardiomyopathies, CKD, etc. AF is present in about one third of the HF patients, these two conditions being intercorrelated: AF precedes HF onset, while HF favors AF development. In CHA2DS2-VASc risk scoring system, HF is assigned 1 point, corresponding to an annual risk of 2.8%, usually the patients having at least one further risk factor (DM, HBP, vascular disease)⁽¹⁾.

Risk factors for AF, acting on electrogenesis and on electrical or structural remodeling of the atrial myocardial cells are age, HBP, DM, valvular heart disease, excessive alcohol consumption, smoking, left ventricular dysfunction, CKD, coronary heart disease, inflammation markers, according to ACC/AHA guidelines for AF 2014⁽¹⁾.

Dialysis patients have a higher incidence of ischemic strokes associated with post-dialysis BP drop and with increased frequency of AF episodes during hemodialysis (HD) due to electrolyte changes, especially of potassium (either hyper- or hypokalemia)⁽¹⁹⁾.

Strokes are frequent in CKD patients, particularly in dialysis patients, being an important cause of death. On the other hand, CKD has been shown to be an important risk factor for cardiovascular morbidity and

INTERNAL MEDICINE

General Reviews

mortality, which highlights the importance of early diagnosis of CKD and of slowing the progression of CKD for reducing cardiovascular risk⁽¹⁷⁾.

Dyslipidemia

In CKD patients both qualitative and quantitative serum lipid anomalies are present from the early stages of disease. While in the general population the high level of cholesterol-rich lipoproteins (low-density lipoproteins (LDL)) is the main risk factor for atherosclerosis, in uremic patients LDL may be normal, decreased or slightly increased. In these patients lipid disorders associated with very high atherogenic risk have been described: high level of lipoprotein (a) due to diminished kidney metabolism and excretion, high level of apo B-rich lipoproteins and of triglycerides and low level of high-density lipoproteins (HDL).

The increased synthesis of apo-B-rich lipoproteins is probably explained by hyperinsulinism, which stimulates liver very low-density lipoproteins (VLDL) synthesis, and by carnitine deficiency. Factors contributing to dyslipidemia in uremic patients are decreased activity of lipoprotein-lipase resulting in decreased catabolism of chylomicrons and VLDL and reduced activity of liver triglyceride lipase leading to the accumulation of chylomicron remnants and intermediate-density

lipoproteins (IDL)⁽¹⁹⁾. The relationship between serum cholesterol level and general and cardiovascular mortality follows a “U”-shaped curve: the highest risk corresponds to a serum cholesterol level below 150 mg/dl, then the risk gradually decreases as the cholesterol increases and starts to rise again only for serum cholesterol levels above 300 mg/dl. In hemodialysis patients low cholesterol levels are associated with malnutrition and inflammation⁽¹⁹⁾.

Inflammation

Inflammation, malnutrition and vascular calcifications are among the non-traditional risk factors in CKD patients. A lot of epidemiological studies point out the role of C reactive protein (CRP) as a cardiovascular risk factor, its level being a strong predictor of mortality in patients on chronic dialysis. Although the direct involvement of CRP in the atherosclerotic process is not clearly proven, it seems to be supported by the presence of CRP in atheroma plaques and by the in vitro studies⁽²¹⁾.

CRP is a direct mediator of endothelial dysfunction and of inflammatory cells recruitment by inhibiting nitric oxide (NO), promoting LDL uptake by foam cells, activating and encouraging the proliferation of smooth muscle cells, stimulating tissue factor and plasminogen activator inhibitor-1 (PAI 1) secretion, thus contributing to fibrous

plaque formation⁽²¹⁾. Under normal circumstances, CRP is produced by hepatocytes and retained in the rough endoplasmic reticulum (RER). Acute-phase reaction brings about a stepup in the synthesis and delivery of CRP. The CRP production is stimulated by Interleukin 6 and by lipopolysaccharide⁽²¹⁾.

Interleukin 6 plays a role in atherogenesis and is associated with mortality in the adult population without kidney disease and in HD patients and also with the progression of carotid atherosclerosis in patients with early stage CKD⁽²¹⁾.

Malnutrition

In a study performed in 1999 on 109 patients with advanced stage CKD, Zimmerman and Stenvinkel have demonstrated malnutrition in 44% of the patients, inflammation in 32%, and carotid plaques (as an atherosclerosis token) in 72%. A high proportion of patients with atheroma plaques had also signs of malnutrition (24%), inflammation (13%) or both (30%). Most of the patients with inflammation and malnutrition had carotid plaques (97% and 89% respectively)^(21,22,23).

Several studies have demonstrated the role of the nutritional status in survival, both in HD patients and in peritoneal dialysis patients. A study by Cooper performed on 109 HD patients, pointed out the direct role of muscle mass, evaluated as the normalized protein nitrogen appearance (nPNA) in survival⁽²⁴⁾. A study performed by Kalantar-Zadeh on 331 HD patients has demonstrated that diminished appetite is associated with higher concentrations of proinflammatory cytokines, lower response to erythropoietin, a fourfold increase in mortality, and higher hospitalization rate⁽²⁵⁾.

Although the role of albumin and prealbumin in survival is proven, these indicators are not

direct parameters for nutritional status assessment, as they are influenced by inflammation and hydration status⁽²⁵⁾.

The strong association between malnutrition, inflammation, and atherosclerosis has led to the concept of MIA syndrome. The convergence of all these conditions presage a bad prognosis. Survival analysis in the study by Zimmerman and Stenvinkel has demonstrated a three-year mortality of 75% in patients afflicted with this pathological triad^(22,23).

In dialysis patients, malnutrition is associated with higher morbidity and mortality. Certain risk factors such as low body mass index (BMI) and low serum cholesterol, which are protective in the general population, incur increased risk in dialysis patients. A similar protective role has been demonstrated for higher levels of BP, serum creatinine, and serum homocysteine. This inverse association in dialysis patients has been called „reverse epidemiology” or the „paradox of risk factors”⁽²¹⁾.

Vascular calcifications

A characteristic of CKD patients is the excessive calcium deposition in the arterial media, which probably accounts at least partially for the higher percentage of cardiovascular complications in these population. Moreover, hyperphosphatemia (by stimulating bone-like transformation of vascular smooth muscle cells), secondary hyperparathyroidism (by spurring osteoclast activity), and vitamin D deficiency promote proliferation and osteoblastic differentiation of vascular smooth muscle cells and increase the activity of fibroblast growth factor⁽¹¹⁾.

Vascular calcifications result in stiffening of the arterial walls and, by means of HBP, in left ventricular hypertrophy, the combination of both leading to inadequate coronary

INTERNAL MEDICINE

General Reviews

perfusion. Many factors have been incriminated in the pathogenesis of calcifications, including fibroelastic thickening of the intima, calcification of the elastic lamellae, and osteoblastic transdifferentiation of vascular smooth muscle cells, promoting bone-like mineralization⁽¹⁸⁾. Intima calcifications are associated with advanced age and an augmented risk for atherosclerosis, while media calcifications are more common in younger patients with low risk for atherosclerosis, but with longer time in dialysis and with anomalies of the phosphocalcic metabolism⁽¹¹⁾.

The patients with CKD and secondary hyperparathyroidism have frequently mitral annulus calcifications which have been associated with stroke. After an eight years follow-up, the Framingham study estimates at 2.10 the relative risk for ischemic stroke in patients with mitral annulus calcification, which is therefore considered a marker of established atherosclerosis⁽¹⁾.

Obesity

Most of the studies performed on hemodialysis patients have reported a lower relative risk for death in obese patients than in normal weight ones. In uremic patients, nutrition exerts a stronger influence on survival than atherosclerosis. Malnutrition increases the death risk in patients with

cardiovascular complications, while a good nutrition status (big muscle mass and little fat) exerts a protective role⁽²¹⁾.

The patients with high BMI due to abundant adipose tissue have a high risk of cardiovascular events, while those with high BMI due to substantial musculature have little or no inflammation or atherosclerosis, being consequently at low risk for both cardiovascular and non-cardiovascular death⁽²¹⁾.

Diabetes mellitus

Diabetes mellitus (DM) affects 20-40% of the patients with DM, its prevalence being on an ascending trend. The risk of DN occurrence is greater in patients with relatives afflicted by type 1 or 2 DM with kidney complications. HBP, smoking, dyslipidemia may aggravate or speed up the progression of DN⁽⁵⁾. On the other hand DM, by inducing early arteriosclerosis, is associated with stroke independently of other cardiovascular risk factors (HBP, dyslipidemia, obesity), the relative risk for all types of stroke being 1.8 in diabetic males and 3.0 in diabetic females⁽²⁶⁾.

A particular type of stroke in dialysis patients is silent cerebral infarction (SCI), i.e. a symptomless cerebral infarction (defined as a focal area >5 mm in diameter, visible in both T1- and T2-weighted images as a low- and high-signal intensity area, respectively). Despite the lack of associated neurological

deficits, SCI is a risk factor for developing symptomatic ischemic or hemorrhagic strokes. *Nakatani and colab.* have demonstrated that hemodialysis patients are much more prone to SCI than normal individuals and SCI have a determinism distinct from that in the general population, as they do not seem to be favored by obvious risk factors such as HBP and dyslipidemia⁽²⁷⁾. However, in hemodialysis patients SCI has been shown to be favored by smoking, high uric acid, high hepatocyte growth factor, and low HDL-cholesterol and to be associated with hypertrophied left ventricles (as shown by echocardiography: thick walls, big mass of the left ventricle) and a non-dipping pattern on ambulatory 24 hours blood pressure monitoring⁽²⁸⁾.

Conflict of interest

The authors declare no conflict of interests.

Author contribution

Delia Timofte, Dorin Dragoș, Adina Măndiță, Andra-Elena Balcangiu-Stroescu, Maria-Daniela Tănăsescu, Daniela Gabriela Bălan, Laura Răducu, Adelaida Avino, Dorin Ionescu contributed equally to the present work and thus are main authors.

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