CHAPTER

78 Nervous System Manifestations of Renal Disease

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Patients with chronic kidney disease (CKD) manifest a variety of neurologic disorders involving central, peripheral, and autonomic nervous systems. The severity of these nervous system manifestations increases in parallel to the advance of CKD. Without dialysis, patients with end-stage renal disease (ESRD) will develop uremic encephalopathy, uremic neuropathy, and uremic autonomic neuropathy. Some of these symptoms are partially or completely reversed by renal replacement therapy (i.e., dialysis or kidney transplantation). On the other hand, neurologic complications may occur due to improper hemodialysis, such as dialysis disequilibrium syndrome (DDS) and dialysis dementia, or due to complications of arteriovenous fistula (AVF) placement, such as ischemic monomelic neuropathy and vascular steal syndrome. In this chapter, CKD-associated neurologic disorders are reviewed in three sections: the central nervous system (CNS), the peripheral nervous system (PNS), and the autonomic nervous system (ANS).

CENTRAL NERVOUS SYSTEM

Several distinct CNS syndromes have been recognized in patients with ESRD: uremic encephalopathy,[1] DDS,[2] and dialysis dementia.[3] In addition, dementia and cognition impairment, common in elderly populations, are significantly worsened by renal impairment, but poorly recognized in ESRD patients.[4] These disorders are multifactorial and associated with prolonged hospitalization and an increased risk of mortality. Lastly, restless leg syndrome (RLS), a poorly understood syndrome, probably related to dopaminergic dysfunction in the subcortical system, affects 10% to 20% of ESRD patients[5] and is discussed under the CNS section.

Uremic Encephalopathy

Manifestations

Uremic encephalopathy is an acute or subacute organic brain syndrome that occurs in patients with advanced renal failure and is frequently associated with GFR less than 10 mL/min/1.73 m^2. The term uremic encephalopathy is used to describe the early appearance and dialysis responsiveness of the nonspecific neurologic symptoms of uremia. Patients with uremic encephalopathy display variable disorders of consciousness, psychomotor behavior, thinking, memory, speech, perception, and emotion.[6,7] The symptoms may include sluggishness and easy fatigue; daytime drowsiness and insomnia with a tendency toward sleep inversion; inability to focus or sustain attention or to perform mental (cognitive) tasks and manipulation; inability to manage ideas and abstractions; slurring of speech; anorexia, nausea, and vomiting probably of central origin; imprecise memory; volatile emotionality and withdrawal; myoclonus and asterixis; paranoid thought content; disorientation and confusion with bizarre behavior; hallucinosis; transient pareses and aphasic episodes; coma; and convulsions.[6,8]

With an early recognition of CKD and the timely initiation of renal replacement therapy, severe uremic encephalopathy has been rare and is mainly related to acute kidney injury or unattended CKD due to a lack of health care. The severe neurologic symptoms of uremic encephalopathy such as seizure, confusion, myoclonus, and asterixis, are usually improved after a few runs of dialysis, and rarely recur if dialysis clearance is adequate. However, uremic encephalopathy may occur in patients on maintenance dialysis if they are not compliant with dialysis treatment, or if their dialysis prescriptions are not adequate. It should be mentioned that even with adequate dialysis, patients on maintenance dialysis may still have mild CNS symptoms, such as cognitive dysfunction as part of a "residual syndrome" because dialysis only replaces a fraction of total renal function.[9]

Pathogenesis

The mechanisms of uremic encephalopathy are multifactorial and largely unknown.[1] It has been proposed that uremic encephalopathy is due to an accumulation of uremic toxins. Although many uremic toxins have been identified, exact toxins responsible for uremic encephalopathy are still unclear.[10] Table 78.1 lists selected examples of uremic toxins grouped according to their structure. The source and characteristics of these toxins are provided.[8]

78.1 Uremic Toxins[8]

Solute Group	Example	Source	Characteristics
Peptides and small proteins	β2-microglobulin	Shed from MHC	Poorly dialyzed because of large size
Guanidines	Guanidine, creatinine, guanidinosuccinic acid, methylguanidine	Arginine	Increased production in uremia
Phenols	p-Cresol sulfate	Phenylalanine, tyrosine	Protein bound, produced by gut bacteria
Indoles	Indican	Tryptophan	Protein bound, produced by gut bacteria
Aliphatic amines	Dimethylamine, trimethylamine	Choline	Large volume of distribution, produced by gut bacteria
Furans	CMPF	Unknown	Tightly protein bound
Polyols	Myoinositol	Dietary intake, cell synthesis from glucose	Normally degraded by the kidney rather than excreted
Nucleosides	Pseudouridine	tRNA	Most prominent of several altered RNA species
Dicarboxylic acids	Oxalate	Ascorbic acid	Formation of crystal deposits
Carbonyls	Glyoxal	Glycolytic intermediates	Reaction with proteins to form advanced glycation end products

MHC, major histocompatibility complex; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid.
Modified from Meyer TW, Hostetter TH. Uremia. N Engl J Med. 2007;357:1316–1325.

Among them, uremic guanidino compounds, including creatinine, guanidine, guanidinosuccinic acid (GSA), and methylguanidine, are highly elevated in both the serum and cerebrospinal fluid (CSF) of uremic patients. GSA is a potential candidate as a uremic neurotoxin because it induces convulsion in animals at a dosage that produces a brain GSA level comparable to that of uremic patients.[11] In vitro, GSA blocks both γ-aminobutyric acid (GABA) A receptors and glycine receptors. However, GSA-induced convulsions only respond to N-methyl-D-aspartate (NMDA) receptor antagonists. Further studies revealed that GSA causes neurotoxicity via activation of the NMDA receptor and by increasing Ca^{2+} influx.[11] Whether these in vitro and in vivo findings have pathophysiologic significance in uremic encephalopathy is still controversial.

Parathyroid hormone (PTH) is another neurotoxin in a uremic state.[1] PTH causes neurotoxicity by increasing intracellular Ca^{2+} concentration in brain cells. The total brain Ca^{2+} content is elevated in uremic patients and animals.[1] The electroencephalogram (EEG) findings in uremic dogs are similar to those in patients with uremic encephalopathy. Both increased brain calcium content and EEG abnormalities in the uremic dog can be prevented by a parathyroidectomy.[12] Furthermore, the intracellular Ca^{2+} level in brain synaptosomes is increased in uremic animals, which can be prevented by parathyroidectomy or reduced by verapamil, a calcium channel blocker.[13] The increased intracellular Ca in uremic synaptosomes can be explained by an increased Ca^{2+} uptake and a decreased Ca^{2+} extrusion, both of which are mediated by PTH.[13–15] Because calcium is an essential mediator of neurotransmitter release and a regulator of intracellular metabolic and enzymatic processes, alterations in brain calcium are likely to affect cerebral function.

Abnormal neurotransmitter content or release in the brain has been reported in uremic animals. Decreased brain norepinephrine content, uptake and release,[16] and increased

acetylcholine content and release[17] are found in uremic rats. In addition, the basal outflow of GABA and glutamate, but not the K^+-stimulated outflow in the hypothalamus, which is measured by microdialysis, is increased in uremic rats. However, the K^+-stimulated release of GABA is less sensitive to Ca depletion.[18] Whether these changes in neurotransmitters in uremic rats are related to uremic encephalopathy in humans is not clear at present.

Diagnosis

Clinically, the diagnosis of uremic encephalopathy is suspected in patients with advanced CKD who present with a constellation of neurologic clinical signs and symptoms, as described earlier. The diagnosis can be confirmed with the resolution of signs and symptoms after a series of dialysis. Electroencephalographic findings in uremic encephalopathy are nonspecific. Typical findings are generalized slowing with an excess of delta and theta waves and sometimes bilateral spike–wave complexes.[19] EEG is rarely needed for diagnosing uremic encephalopathy.

Similarly, brain images are rarely performed for patients with uremic encephalopathy. In one study, a diffusion-weighted magnetic resonance imaging (MRI) was performed prior to the initiation of hemodialysis in eight ESRD patients. The average blood urea nitrogen (BUN) level was 161 mg per deciliter. None of these patients had prior neurologic disorders. MRI revealed diffuse interstitial brain edema with a increased apparent diffusion coefficient.[20] However, reversible diffuse cytotoxic brain edema was reported in a patient with left facial palsy, aphasia and confusion, and a BUN level of 220 mg per deciliter.[21] It appears that uremic encephalopathy is associated with brain edema, which may advance from interstitial form to cytotoxic form if left untreated.

In patients on maintenance dialysis, the diagnosis of uremic encephalopathy can be difficult. The neurologic symptoms and signs are similar between uremic encephalopathy and other brain pathologies such as strokes, hepatic encephalopathy, hypertensive encephalopathy, Wernicke encephalopathy, and others (Table 78.2). Other differential diagnoses include electrolyte and endocrine abnormalities, drug and food effects, dementia, and depression (Table 78.2). In ESRD patients, an altered mental status may occur due to electrolyte and endocrine abnormalities such as hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, and hypoglycemia. The drugs listed in Table 78.2 are commonly associated with neurotoxicity in patients with ESRD. They cause confusion or seizure probably due to changes in drug metabolism or clearance of the drugs, or their potentially toxic metabolites. Starfruit (Fig. 78.1), a popular fruit in Southeast Asia and Central and South America, can cause neurologic symptoms in patients with advanced CKD within hours. Symptoms include hiccups, vomiting, confusion, seizure, and even death.[22] In one series from Taiwan, the mortality was as high as 40%.[23]

78.2 Differential Diagnosis for Altered Mental Status in Patients with Advanced Chronic Kidney Disease[19,22,23,48]

Uremic encephalopathy
Hepatic encephalopathy
Hypertensive encephalopathy
Wernicke encephalopathy
Dialysis disequilibrium syndrome
Strokes and transient ischemic attack
Subdural hematoma
Electrolyte and metabolic abnormalities: Hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypoglycemia
Drugs: Opioid analgesics, antibiotics (cephalosporin), antiviral agents (acyclovir), gabapentin, cimetidine, metoclopramide, isoniazid, encainide, cinacalcet, and others
Food: Starfruit (Averrhoa carambola)
Dementia: Vascular dementia and Alzheimer dementia
Depression

If BUN and serum creatinine (Cr) levels are elevated, uremic encephalopathy due to inadequate dialysis can be diagnosed without difficulties. Frequently, BUN and serum Cr levels may not be elevated due to malnutrition and sarcopenia, which are frequently associated with inadequate dialysis. A careful evaluation of dialysis records and physical and laboratory findings are needed to eliminate possibilities of other encephalopathies because the management could be quite different for each disease. For example, Wernicke encephalopathy (ophthalmoplegia, ataxia, and disturbance of consciousness) is due to the depletion of thiamine from dialysis removal of this water-soluble vitamin, and can be treated with supplementation of thiamine along with other water soluble vitamins.[24] If uremic encephalopathy is highly suspected, a therapeutic trial with renal replacement frequently ameliorates CNS symptoms and confirms the diagnosis.

Of note, there are a few case reports of posterior reversible encephalopathy syndrome (PRES) in patients with ESRD and neurologic symptoms.[25–27] These patients had bilateral

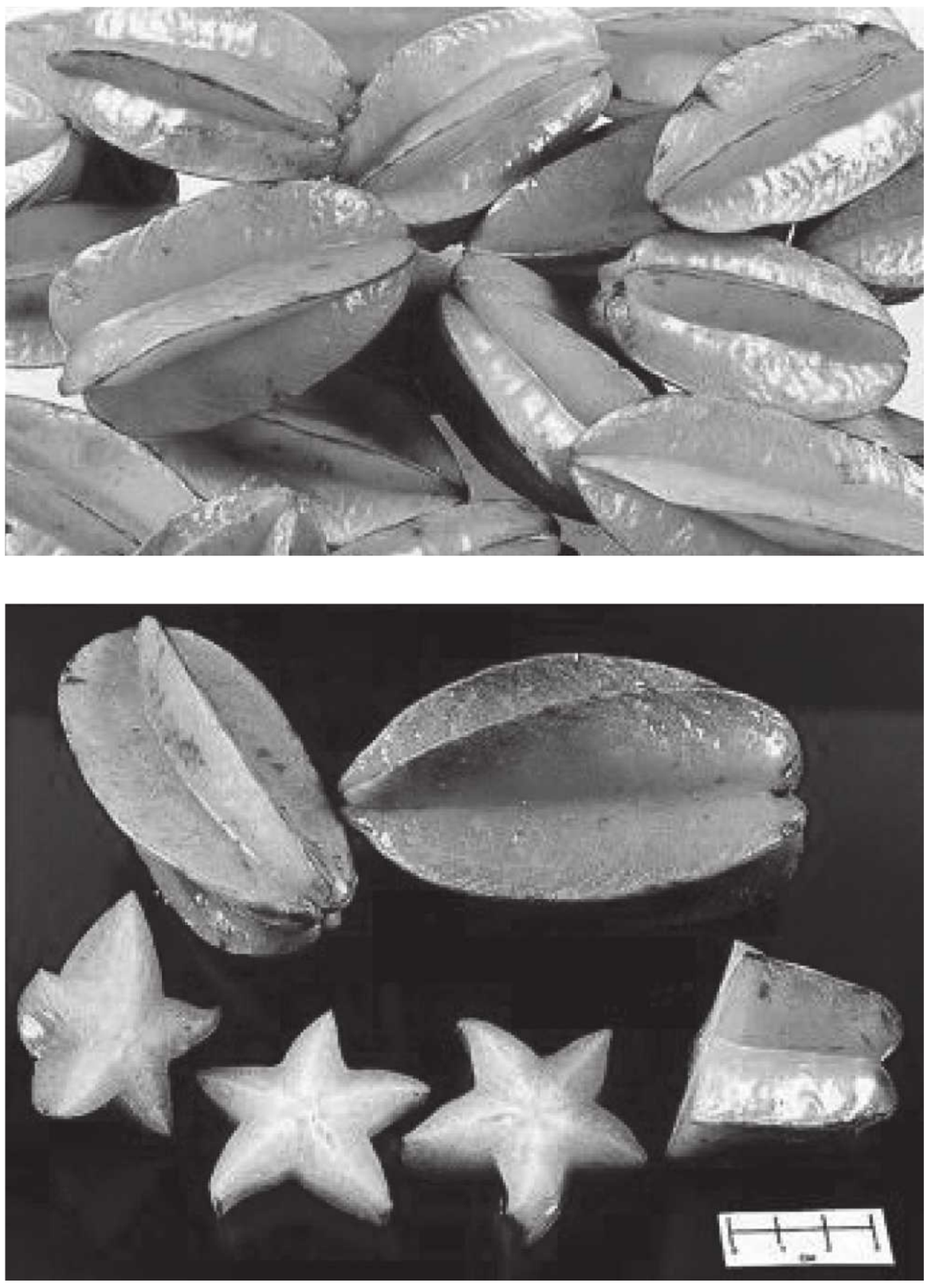

FIGURE 78.1 Starfruit (*Averrhoa carambola*), a lethal fruit for the ESRD patient. (From Neto MM, da Costa JA, Garcia-Cairasco N, et al. Intoxication by star fruit (Averrhoa carambola) in 32 uraemic patients: treatment and outcome. *Nephrol Dial Transplant*. 2003;18:120–125.)

symmetric hypodense lesions in the territories of the posterior circulation, which were reversible after hypertension was controlled. Almost all of them presented with uncontrolled hypertension (frequently > 200 mm Hg systolically). The brain edema is due to the leakage of fluid from hypertension-damaged blood vessels, so called "vasogenic edema." The edema occurs preferentially in the posterior of the brain, whereas brain edema associated with uremic encephalopathy is diffuse. Because the pathogenesis and treatment of these two diseases are different, it is critical to distinguish them as separate disease entities.

Prevention and Treatment

Uremic encephalopathy can be largely eliminated with the early referral of CKD patients to nephrologists and the timely initiation of dialysis. For patients on maintenance dialysis, the routine evaluation of dialysis adequacy and increased dialysis clearance for those who fall behind are effective in preventing uremic encephalopathy. As for treatment, intensive dialysis therapy—frequently, daily dialysis—should improve neurologic symptoms and signs within a week or two. A lack of response should prompt physicians to look for other etiologies. Although secondary hyperparathyroidism has been implicated in the pathogenesis of uremic encephalopathy, reducing the PTH level is rarely needed to improve neurologic symptoms. It is possible that repeated hemodialysis may reduce brain Ca^{21} content, thus reducing neurologic symptoms.[1]

Dialysis Disequilibrium Syndrome

Manifestations

DDS occurs rarely in current nephrology practice because of the early initiation of renal replacement therapy and routine orders of slow blood flow rate and short dialysis duration during the initial dialysis sessions. The cardinal symptoms of DDS are the symptoms caused by elevated intracranial pressure such as headache, nausea, and vomiting. These symptoms may progress into confusion, seizure, and even death if unrecognized and left untreated. The onset of DDS is usually during or immediately after aggressive hemodialysis, frequently in the setting of the first hemodialysis session.

Pathogenesis

The hallmark of DDS is brain edema that is induced by dialysis. Evidence accumulated that the "reverse urea effect" is the cause of DDS.[2] Hemodialysis rapidly removes urea from the blood, but does not remove urea from the brain as efficiently. As a consequence, the urea concentration is higher in the brain than in the blood. This brain–blood urea gradient drives water to enter into brain tissue and causes brain edema and raises intracranial pressure. Elevated brain urea concentration and increased brain water content have been demonstrated in animals undergoing aggressive hemodialysis.[28] When urea was added to the dialysate to keep the blood urea concentration equal to that in the brain, brain edema did not occur after hemodialysis. Using MRI, Galons et al.[29] reported that the apparent diffusion coefficient of brain water increased in nephrectomized rats after hemodialysis. These results strongly suggest that the brain edema induced by hemodialysis in uremic rats is due to interstitial edema rather than cytotoxic edema, further supporting the reverse urea effect as the pathogenetic mechanism of brain edema in DDS. The increased diffusion coefficient of brain water after fast hemodialysis has been confirmed in patients with ESRD.[20]

More recently, a potential molecular basis for the reverse urea effect has been identified. In uremic rats, the brain expression of urea transporter 1 (UTB1) is reduced by 50%, whereas water channels aquaporin 4 (AQP4) and AQP9 were upregulated. Because of low UTB abundance, urea exit from the brain is likely delayed during the rapid removal of extracellular urea through fast dialysis. This creates an osmotic driving force that promotes water entry into the brain and subsequent brain swelling.[30]

There are other hypotheses for the pathogenesis of DDS, such as the creation of idiogenic osmoles, or paradoxical intracellular acidosis by hemodialysis.[31,32] However,

Silva et al.[28] measured most known organic osmoles in the brain after hemodialysis and did not find any significant changes in their concentrations. As for the acidosis hypothesis, it is not clear how intracellular acidosis causes interstitial edema. Although frequently quoted as the pathogenesis of DDS, one may wonder if cerebral acidosis is the consequence, rather than the cause, of brain edema in DDS.

Diagnosis

The diagnosis of DDS is mainly based on the onset of symptoms, the history of prolonged and untreated renal failure, markedly elevated BUN levels, and the association with hemodialysis. Unfortunately, up to now there are no clinical criteria for the diagnosis of DDS. As a result, DDS has become a wastebasket for any neurologic symptoms that occur after hemodialysis. Although DDS is rarely encountered in current nephrology practice, there have been several cases reported in recent literature, including two lethal cases.[33–37] These cases are summarized in Table 78.3. Most of them are young, with a predialysis BUN level in the range of 109 to 241 mg per deciliter and a decrease in the BUN level of 60 to 92 mg per deciliter. The blood flow rate and dialysis time in some cases are excessive. The onset of symptoms is closely related to hemodialysis. Most of them had documented brain edema with imaging studies. Two out of 5 patients died, and the others recovered without sequelae. From these case reports, it appears that a predialysis BUN level greater than 100 mg per deciliter with a decrease in BUN level greater than 60 mg per deciliter are reasonable criteria for the diagnosis of clinically significant DDS (i.e., altered mental status, seizure, and neurologic defects). The onset of symptoms occurs immediately after hemodialysis and brain edema, which are demonstrated by imaging studies that may further confirm the diagnosis. It should be mentioned that uremic patients with a head injury, subdural hematoma, stroke, malignant hypertension, and other conditions associated with brain edema are at a higher risk of DDS due to existing conditions that predispose them to cerebral edema.[36]

Prevention and Treatment

It has been well established that limiting dialysis efficiency at the initiation of hemodialysis is the best way to prevent DDS (i.e., performing hemodialysis with a low blood flow rate, short dialysis time, and a small dialysis filter). This gentle dialysis treatment does not remove blood urea rapidly, thus preventing the formation of the brain–blood urea gradient.[36] It is helpful to estimate the urea reduction rate from the dialysis prescription and target urea reduction to less than 60 mg per deciliter. Another common practice for preventing DDS is infusing mannitol during hemodialysis to raise serum osmolarity in order to reduce the brain–blood osmolarity gradient. The infusion of mannitol during hemodialysis is recommended for preventing DDS only in high-risk patients with marked azotemia (BUN level > 150 mg per deciliter) or in those with preexisting risk factors, as mentioned earlier. Mannitol infusion can cause acute volume expansion and congestive heart failure, and thus should not be used routinely for the initiation of hemodialysis.

78.3 Clinical Parameters of Cases with Dialysis Disequilibrium Syndrome

Reference	Age (years)	Sex	Pre-HD BUN	Post-HD BUN	ΔBUN	BFR (mL/min)	HD Time (hour)	Onset (hour after HD)	Brain Edema	Outcome
Harris et al., 1989 (33)	22	F	109	47	62	NA	1.5	0	Yes	Death
DiFresco et al., 2000 (35)	22	F	199	110	89	150	1.5	0	Yes[a]	Recovery
Bagshaw et al., 2004 (34)	22	M	130	38	92	250–350	4	0	Yes	Death
Patel et al., 2008 (36)	54	M	131	71	60	250–300	4	1	No	Recovery
Attur et al., 2008 (37)	15	M	241	160	81	150	4	0	Yes	Recovery

[a]Dialysis disequilibrium syndrome with brain edema recurred during the second hemodialysis session (pre- and post-HD BUN levels were not available for the second hemodialysis session).
Pre-HD, prehemodialysis; post-HD, posthemodialysis; ΔBUN, change in BUN after hemodialysis; BFR, blood flow rate; F, female, M, male; NA, not available.

Dialysis Dementia

Manifestation

This mysterious syndrome haunted dialysis patients in the 1970s, but it has now nearly vanished completely. Dialysis dementia, also named dialysis encephalopathy, is a progressive, frequently fatal neurologic disease almost appearing exclusively in patients being treated with chronic hemodialysis for more than 2 years. Early manifestations consist of a mixed dysarthria–apraxia of speech with slurring, stuttering, and hesitancy. Patients subsequently develop personality changes, including psychoses, paranoid thinking, or delirium, and global dementia, myoclonus, and seizures. In most cases, the disease progressed to death within 6 to 12 months.[3] Observation studies revealed that dialysis dementia is a part of a multisystem disease that may include encephalopathy, osteomalacic bone disease, proximal myopathy, and anemia.[3,38]

Pathogenesis

Aluminum intoxication was first implicated in this disorder by Alfrey et al.[39] Aluminum content of the brain's gray matter, of bone, and of other soft tissue is markedly elevated in patients with dialysis dementia. Strong epidemiologic evidence links dialysis dementia to aluminum intoxication from the dialysate water and/or from oral phosphate binders containing aluminum.[3] Furthermore, citrate was frequently used to correct metabolic acidosis in patients with advanced CKD. The gastrointestinal (GI) absorption of aluminum is markedly enhanced by the concomitant use of citrate.[40] After a routine deionization of dialysate with reverse osmosis for removing contaminated aluminum in dialysis facilities and the limited use of aluminum containing phosphate binders, dialysis dementia has been nearly eliminated.

Diagnosis

Dialysis dementia is suspected in patients on maintenance dialysis who develop speech disorders, personality changes, and dementia. EEGs are diagnostic for dialysis dementia. The characteristic EEG changes are a mild slowing of the dominant rhythm with increased low voltage theta and bursts of anteriorly predominant high voltage delta. Occasionally, the paroxysmal activity may take the form of a 1.3 to 3.0 c per second spike and wave, mainly in the frontocentral region.[3] Blood aluminum levels may not be elevated, but should be increased after the infusion of the chelating agent, deferoxamine (DFO).[41] The concurrence of osteomalacia and microcytic anemia also prompts physicians to look for aluminum toxicity.

Prevention and Treatment

As mentioned earlier, dialysis dementia is nearly eliminated due to the use of reverse osmosis and the replacement of aluminum-containing phosphate binders with calcium-based binders or sevelamer. As mentioned earlier, citrate-containing alkylating agents enhance aluminum absorption and should not be used in conjunction with aluminum-based binders. As for treatment, DFO has been used for chelating aluminum. DFO is usually given at the end of hemodialysis. During the following dialysis session, the DFO-Al complex can be removed effectively by a polysulfone dialyzer.[42] Aggravation of dialysis dementia by DFO may occur due to the release of aluminum from tissue.[43]

Dementia and Cognitive Impairment

Manifestations

With the marked reduction in the occurrence of uremic encephalopathy, DDS, and dialysis dementia, cognitive impairment and dementia have become the major CNS disorders in patients with ESRD. Dementia is characterized by a loss of function in multiple cognitive domains such as a decline in memory from previously higher levels of functioning, together with at least one of the following: aphasia, apraxia, agnosia, or disturbances in executive functioning. Cognitive impairment indicates that a patient's ability to function in their work, personal, or social environment is affected.[4] Both dementia and cognitive impairment are highly prevalent in patients with ESRD. Murray et al.[44] reported that in 338 prevalent hemodialysis patients, 37% had severe cognitive impairment, qualified as dementia, 36% had moderate impairment, and 13% had mild impairment. In addition, the prevalence of cognitive impairment in ESRD patients increases with aging. It is 20% to 30% in patients 55 to 84 years of age, and increased to 50% to 60% in those 85 years or older.[4]

Cognitive impairment may already be present in patients with CKD stages 3 and 4. In the Heart Estrogen/Progestin Replacement (HERS) study, which involves 1,015 menopausal women with coronary artery disease, there is a fivefold risk of cognitive impairment if the estimated glomerular filtration rate (eGFR) is < 30 (stages 4 and 5) and patients with cognitive impairment tend to have a rapid progression of CKD.[45] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study[46] involving over 23,000 adults > 45 years of age, it was found that eGFR < 60 is associated with a 23% increase in the prevalence of cognitive impairment after adjustment for demographic characteristics, prevalent cardiovascular disease, and cardiovascular (CV) risk factors.[46] The prevalence of cognitive impairment increases in multiple areas with the decline of eGFR, as shown in Figure 78.2.[47] For example, the prevalence of global cognition increases by 5% for each reduction of eGFR by 15 mL/min/1.73 m^2. Other studies also confirm the association of CKD and cognitive impairment.[46,48] In addition, the decline in cognitive function is faster in patients with CKD compared with non-CKD patients.[49]

Pathogenesis

There is strong evidence that indicates CKD-associated cognitive impairment is predominantly vascular in nature.

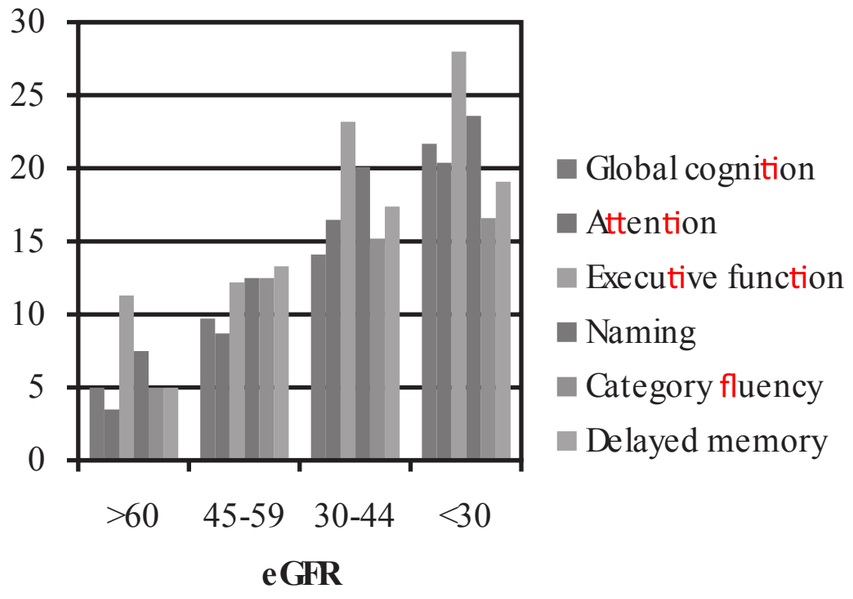

FIGURE 78.2 The unadjusted prevalence of cognitive impairment among 825 older adults (55 years or older) with mild-to-moderate renal insufficiency, according to estimated glomerular filtration rate (eGFR). Data taken from Yaffe K, Ackerson L, Kurella Tamura M, et al. Chronic Renal Insufficiency Cohort Investigators. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc*. 2010;58:338–345. (See Color Plate.)

In the Cardiovascular Health Cognition (CVHS) study, it was found that moderate renal impairment in elderly adults (65 years or older) is associated with a 58% increase in the incidence of vascular dementia, but with no increase in the incidence of pure Alzheimer dementia. The overall incidence of vascular dementia and pure Alzheimer dementia in this cohort is 1.5% and 1.7% per year, respectively.[50] In the Northern Manhattan Study (NOMAS), a prospective, community-based cohort of which a subset of stroke-free participants underwent MRIs, CKD stages 3 and 4 are associated with an increase in white matter hyperintensity volume, which is a marker for stroke, cognitive decline, and dementia.[51] The increase of white matter lesions in CKD patients is confirmed by Ikram et al.[52] More recently, Kobayashi et al.[53] demonstrated that CKD also increases silent brain infarcts, and both the prevalence and the number of silent brain infarct increase with declining GFR.[53] Furthermore, CKD is also associated with a rapid progression of carotid intima-media thickness in a community study.[54]

The incidence of vascular dementia in ESRD patients is even higher than in those with moderate renal impairment. Fukunishi et al.[55] reported that the 1-year incidence rate of vascular dementia and Alzheimer dementia is 3.7% and 0.5%, respectively, in aged Japanese hemodialysis patients. The incidence of vascular dementia was 7.4 times of that in the general elderly population. Furthermore, although in patients with moderate renal impairment the incidence of vascular and Alzheimer dementia is about the same, vascular dementia outgrows the Alzheimer dementia by sevenfold in ESRD patients.[50,55]

Therefore, it is likely that patients with CKD are at risk of vascular dementia and the progression of CKD is parallel to the progression of cerebrovascular disease—primarily, atherosclerotic disease. The pathogenesis of dementia and cognitive impairment in patients with ESRD is multifactorial, as illustrated in Figure 78.3. There are shared mechanisms for both CKD and neurovascular disorders, but nephrogenic and dialysis-associated mechanisms also play important roles in the development of dementia. The shared risk factors for CKD and cerebrovascular disease are aging, nonwhite race, low socioeconomic status/low education, diabetes, hypertension, hyperlipidemia.[4] In addition, with declining renal function, several nephrogenic risk factors are likely to facilitate cerebrovascular disease, such as sympathetic overactivity, inflammation, oxidative stress, anemia, uremic toxins, and vascular calcification.[4] Lastly, complications of hemodialysis such as intradialytic hypotension, hyperviscosity, thrombotic events, and hemorrhage due to heparin use will further worsen cerebrovascular disease.[4,48]

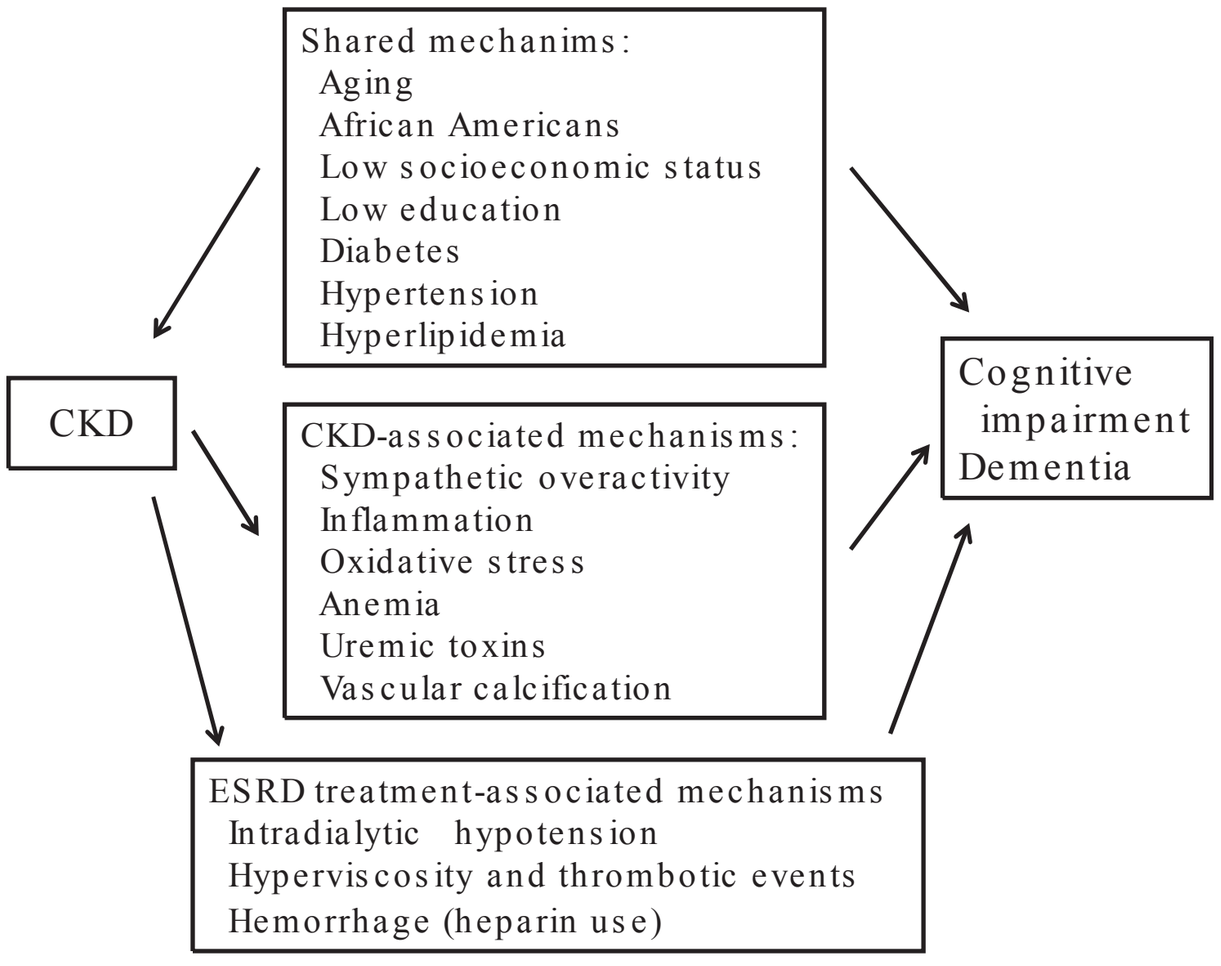

FIGURE 78.3 The proposed mechanisms of cognitive impairment and dementia in end-stage renal disease (ESRD). *CKD*, chronic kidney disease. (Modified from Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. *Kidney Int*. 2010;79:14–22.)

Diagnosis

Cognitive impairment and dementia in CKD patients are frequently ignored. As a result, they tend to progress rapidly to an irreversible state. The prevalence of dementia in ESRD patients has been reported to be as high as 37%[44]; however, in a cohort of 16,694 patients in the Dialysis Outcomes and Practice Patterns Study, dementia was documented in the medical records as a comorbid condition in 4% of the entire study population.[56] It is recommended that screening for cognitive impairment should start from the onset of ESRD. There are many screening tests available. The Mini-Mental State Exam (MMSE) is perhaps the most studied cognitive test for dementia. There are other tests such as Mini-Cog and the Kidney Disease Quality of Life test, which can be used annually to assess the progression of cognitive impairment.[4,48] The most critical part of the evaluation of dementia is the search for reversible causes of altered mental status, including electrolyte abnormalities, drug effects, infections, depression, uremia, hepatic or cardiac failure, and others (Table 78.2). The laboratory evaluation should include HIV serologies, vitamin B12 levels, and thyroid function tests.[4]

Brain imaging studies are valuable for diagnosing cognitive impairment and dementia in CKD patients, particularly for identifying vascular dementia. Two major MRI findings are related to cerebral small vessel disease: lacunar infarct and white matter lesions. Both of them are increased in patients with CKD.[51–53] However, these findings are common in CKD patients; thus, the presence of these findings does not exclude other causes of cognitive impairment.

Prevention and Treatment

Because cognitive impairment and dementia associated with CKD are vascular in nature, reducing all cardiovascular risks before progressing to ESRD is critical for preventing these CNS disorders. Treatments targeted at controlling blood pressure, blood sugar, lipid profiles, proteinuria, and mineral metabolism may slow down the progression of both CKD and neurodegenerative diseases. Whether increasing dialysis clearance has a benefit on cognitive function has been controversial. Higher dialyzer urea clearance × time/urea volume of distribution (Kt/V) values have been associated with poorer cognitive function in patients on maintenance hemodialysis.[44,57] However, in a small study with 12 patients, switching from conventional hemodialysis to nocturnal daily hemodialysis for 6 months resulted in a 22% reduction in cognitive symptoms, a 7% improvement in psychomotor efficiency and processing speed, and a 32% improvement in attention and working memory.[58] Further studies are needed to substantiate these benefits from nocturnal hemodialysis.

Once dementia is diagnosed, the prognosis is poor in general because current drugs for treating dementia can only provide modest clinical benefit and none of them have been tested in patients with ESRD.[4] The management of dementia associated with ESRD requires a multidisciplinary approach involving the primary care physician, caregiver, nephrologist, and staff at the dialysis facility and nursing facility to define the goals of care and to facilitate end-of-life care planning.

Restless Leg Syndrome

Manifestations

RLS is a common neurologic condition in patients with ESRD. The prevalence is 10% to 20% based on clinical diagnosis,[5,59,60] but increases to 58% if diagnosed with a polysomnogram.[61] RLS is characterized by an imperative need to move the leg because of uncomfortable and unpleasant sensations in the legs. It occurs primarily at rest, which is usually worse in the evening and alleviated by movement.

Pathogenesis

RLS is predominantly a disorder of the central rather than the peripheral nervous system. Dopaminergic dysfunction in the subcortical system appears to play a central role in idiopathic RLS. Reduced iron stores in the brain have been demonstrated, suggesting that the homeostatic control of iron is altered.[62] Because iron is necessary for the activity of tyrosine hydroxylase, the rate-limiting step in dopamine synthesis, it is possible that a link exists between CNS iron deficiency and dopaminergic dysfunction. Compared with idiopathic RLS, RLS associated with ERSD progresses faster and responds poorly to a dopaminergic agent.[63] Interestingly, iron deficiency seems to be linked to RLS in CKD patients with[5] or without dialysis.[64] Further studies are needed to define the role of disturbed iron homeostasis in the development of RLS in CKD patients. In addition, RLS tends to be exacerbated by caffeine, alcohol, and medications including dopamine antagonists, lithium, selective serotonin reuptake inhibitors, and tricyclic antidepressants.[65]

Diagnosis

The diagnosis is mainly based on symptomatology and the effects of resting and movement on restless legs. The neurologic examination is typically normal in RLS. Polysomnography is useful for diagnosing RLS, and 90% of patients with RLS manifest an increased rate of periodic limb movements.[61]

Prevention and Treatment

Based on the association between iron deficiency and RLS in CKD patients, it is possible that the early detection and treatment of iron deficiency may prevent RLS; however, this hypothesis has not been proven. As for treatment, many drugs have been tried with variable success including dopaminergic agonists, gabapentin, and benzodiazepines.[65] Fortunately, successful kidney transplantation leads to the resolution of RLS symptoms within 1 to 21 days, which may remain in remission for several years. However, RLS tends to recur when transplants fail.[66]

THE PERIPHERAL NERVOUS SYSTEM

There are several unique PNS abnormalities that are caused by ESRD or due to an AVF created for hemodialysis. Uremic neuropathy is a common neurologic complication caused by unknown uremic toxins.[19] Carpel tunnel syndrome (CTS) in patients with prolonged hemodialysis treatment is the early symptom of dialysis-related amyloidosis caused by β2-microglobulin.[67] AVF may also cause CTS and other syndromes such as vascular steal syndrome and ischemic monomelic neuropathy.[68]

Uremic Neuropathy

Manifestations

Uremic neuropathy typically presents as a slowly progressive symmetrical peripheral neuropathy, initially affecting the distal regions of the limbs, and later progressing proximally. The earliest symptoms reflect sensory loss, resulting in symptoms of paresthesia, pain, and numbness in lower extremities. With disease progression, motor involvement develops, which is characterized by weakness and muscle atrophy, again most prominent distally.[69] Finally, the proximal regions of lower extremities as well as the upper extremities are affected. Uremic neuropathy usually occurs after GFR is less than 10 mL/min/1.73 m^2. Unlike uremic encephalopathy, which improves with renal replacement therapy and remains stable, uremic neuropathy may improve initially, but progresses slowly in spite of adequate dialysis treatment.[70] As a result, the prevalence of uremic neuropathy in ESRD patients is 60% to 90%, which is increased with the vintage of dialysis.[19,69] Laaksonen et al.[71] evaluated 21 patients on maintenance hemodialysis for a mean of 2 years with a battery of neurophysiologic parameters. None of those patients had other causes of peripheral neuropathy such as diabetes, alcoholism, or amyloidosis. They found that only 4 patients had no detectable sign of neuropathy, 4 had asymptomatic neuropathy, 10 had nondisabling symptomatic neuropathy with two or more positive neurologic tests, and 3 had disabling neuropathy. They also found that positive sensory symptoms correlated well with both motor and sensory neurologic tests.[71] Overall, uremic neuropathy affects the majority of ESRD patients and may cause significant morbidity in 10% to 20% of these patients. The increased severity appears to correlate with the vintage of dialysis treatment.[70]

Pathogenesis

Uremic neuropathy presents as a length-dependent polyneuropathy involving large, myelinated sensory and motor fibers. Although small fibers may be involved in some cases, isolated small fiber involvement has not been reported in association with uremic neuropathy.[72] Axon degeneration occurs in uremic neuropathy and is different from demyelination, or a loss of the myelin sheath, as seen in chronic inflammatory demyelinating neuropathy (Fig 78.4).[72] Clinically significant

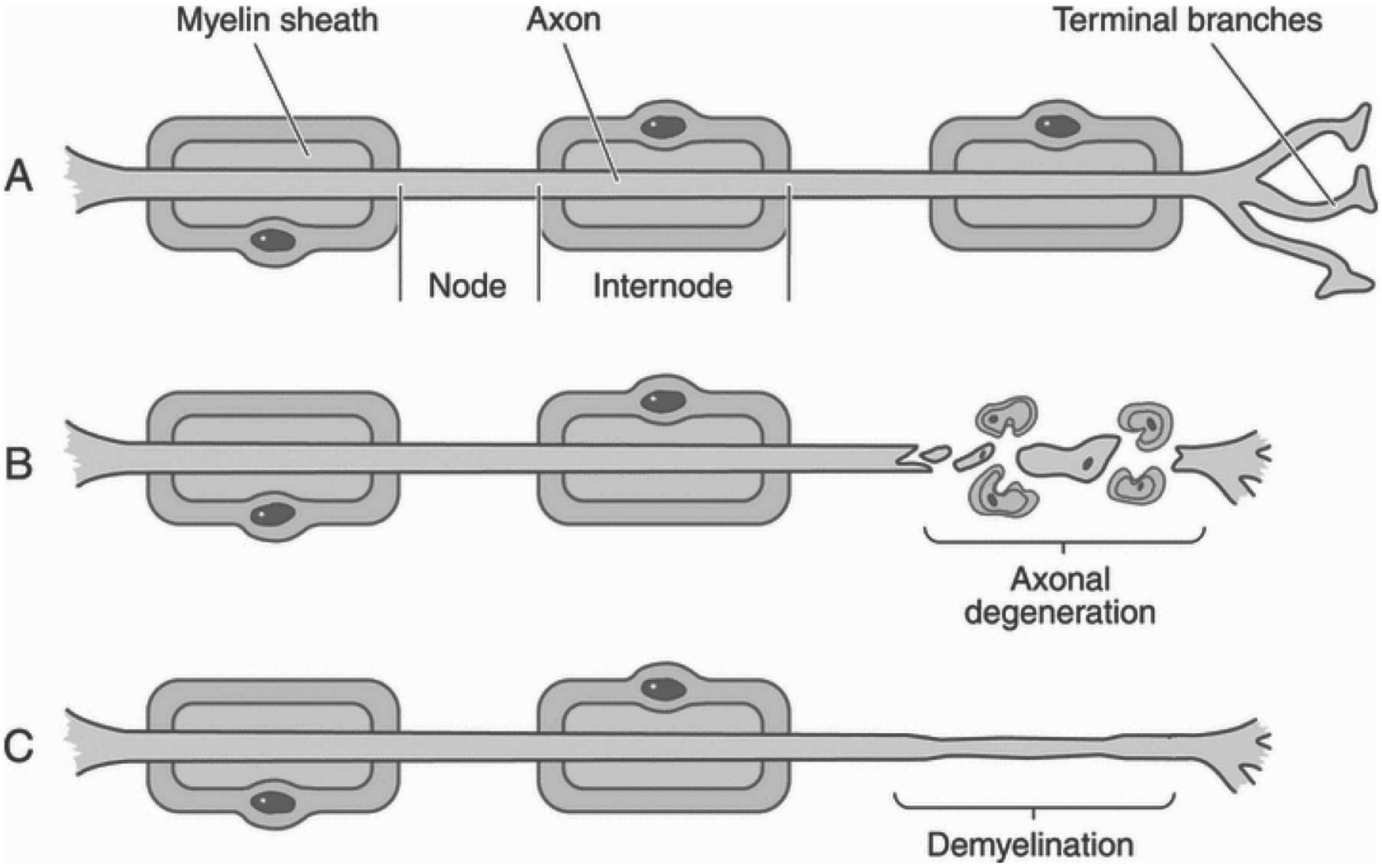

FIGURE 78.4 Differences between axonal degeneration and demyelinating disease of the peripheral nerve fibers. **A:** The normal axon, surrounded by myelin, laid down by Schwann cells and arranged in a multilamellar spiral fashion, which provides an insulating sheath, which is essential for rapid saltatory conduction of action potentials. **B:** Axonal degeneration ("dying-back" phenomenon), as occurs in length-dependent uremic neuropathy. **C:** Demyelination, with loss of the myelin sheath, occurs in chronic inflammatory demyelinating polyneuropathy. (From Krishnan AV, Pussell BA, Kiernan MC. Neuromuscular disease in the dialysis patient: an update for the nephrologist. *Semin Dial*. 2009;22:267–278.)

uremic neuropathy does not occur until patients reach ESRD. Although symptoms of uremic neuropathy, particularly paresthesia, improve after the initiation of dialysis, long-term dialysis does not reduce the prevalence of uremic neuropathy. These observations suggest that uremic toxins, particularly middle molecules, may be involved in axon degeneration; however, such molecules have not been identified.

More recently, a new hypothesis suggests that hyperkalemia, even a mild form with serum K at 5.0 mEq per liter, is associated with significant abnormalities in nerve excitability.[72,73] These abnormalities are corrected after hemodialysis, which normalizes serum K levels. Most ESRD patients have persistent hyperkalemia, which would lead to chronic membrane depolarization and subsequent reverse activation of the Na^+/Ca^{2+} exchanger, leading to an influx of Ca^{2+} and, eventually, axonal degeneration.[69,72] Further studies are needed to validate this provocative hypothesis because until now, predialysis hyperkalemia has not been identified as an independent risk factor for uremic neuropathy. Furthermore, hyperkalemia rarely occurs in patients on peritoneal dialysis, yet the progression of uremic neuropathy is not significantly different between patients receiving peritoneal dialysis versus hemodialysis.[74]

Diagnosis

Nerve conduction studies remain the mainstay in the diagnosis of uremic neuropathy. In order to make a correct diagnosis of uremic neuropathy, nerve conduction studies should not be performed on the limb with AVF because AVF itself may affect peripheral nerve function.[71] In uremic neuropathy, nerve conduction studies demonstrate features of axonal degeneration with a reduction in sensory amplitudes and, to a lesser extent, motor amplitudes. However, the delayed latency of the F-wave on lower limb nerves is the most sensitive test. Sensory and motor nerve conduction velocities are relatively reserved.[71,75] In uremic neuropathy, denervation of a portion of muscle fibers is readily compensated for by collateral reinnervation from surviving motor units. Therefore, the motor amplitude remains normal in mild-to-moderate neuropathy. Because there is no compensatory mechanism for the sensory nerve, reduced sensory amplitude is more sensitive for detecting uremic neuropathy.[71] In addition, vibration detection thresholds on the foot are also a sensitive test for detecting uremic neuropathy.[71,74] Because diabetic nephropathy is also a length-dependent neuropathy, nerve conduction studies cannot distinguish between uremic neuropathy and diabetic neuropathy.[72]

The progression of uremic neuropathy is typically a slow process. When patients present with a rapidly progressive course with significant weakness, demyelinating neuropathy should be ruled out. Nerve conduction studies in these disorders demonstrate a significant reduction in nerve conduction velocities and relatively reserved sensory and motor amplitudes in the early stage. Serology tests, including inflammatory markers, antinuclear antibodies, rheumatoid factors, antineutrophil cytoplasmic antibodies, hepatitis antibodies (B and C), and cryoglobulins, should be performed. Combined nerve and muscle biopsies are likely needed for confirming the diagnosis if immunosuppressive therapy is indicated.[72]

Prevention and Treatment

Uremic neuropathy is one of indications for the initiation of dialysis treatment. Symptoms are usually improved after the initial dialysis treatment, but may recur if dialysis clearance is inadequate. Thus, adequate dialysis clearance is important for preventing uremic neuropathy.[76] However, even with adequate dialysis treatment, uremic neuropathy may progress slowly. Bazzi et al.[70] reported that about 50% of patients on hemodialysis for less than 10 years have mild uremic neuropathy, but for patients on hemodialysis more than 10 years, the prevalence of mild, moderate, and severe neuropathy is 81%, 11%, and 3%, respectively.[70] The only treatment for uremic neuropathy in patients on maintenance dialysis treatment is a kidney transplant, and the recovery may not be complete for those with advanced disease.[77,78]

For patients with neuropathic pain, antidepressants such as amitriptyline and anticonvulsants such as gabapentin, may be useful for symptomatic management.[72] Vitamin supplementation with pyridoxine[79] and methylcobalamin[80] has been shown to improve uremic neuropathy, probably through the stimulation of nerve metabolism and the enhancement of regeneration. However, these preliminary results need to be confirmed.

Carpal Tunnel Syndrome

Manifestations

The initial symptoms of CTS are paresthesia, numbness, and pain confined to the median nerve territory or diffusely in the hand, with a characteristic nocturnal exacerbation. In some patients, these symptoms are localized to more proximal regions of the affected arm. Symptoms are usually bilateral, but more severe in the dominant hand. As CTS progresses, it affects motor function, leading to weakness and muscle atrophy. The prevalence of CTS in ESRD patients ranges from 10% to 30%, but increases sharply to 50% in patients who have been on hemodialysis for more than 20 years.[67,81] In some patients, particularly those without prolonged dialysis vintage, CTS appears to be related to AVF.[82]

Pathogenesis

The carpal tunnel is narrow and bounded by the transverse carpal ligament superiorly and the carpal bones inferiorly. Given this narrow passageway, the median nerve is susceptible to injury. In the general population, the causes of CTS include chronic trauma, arthritis, amyloidosis, and myxedema. In patients with ESRD, there are two unique pathogenetic mechanisms accounting for most of the reported cases of dialysis-related CTS: deposition of β2-microglobulin

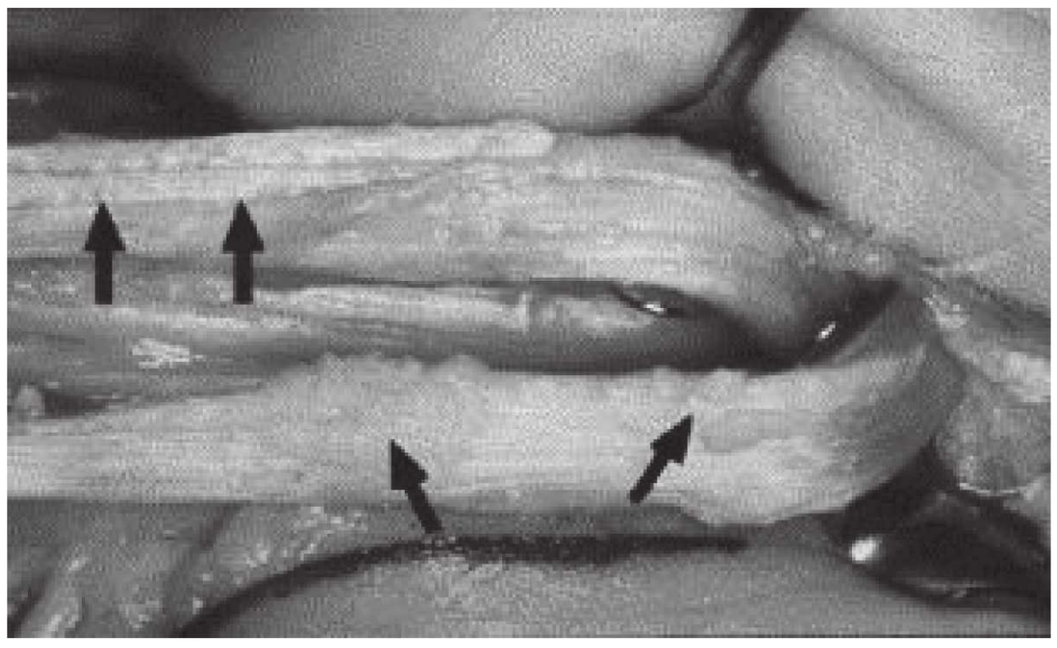

FIGURE 78.5 The dialysis-related amyloid (*arrows*) deposited in the peritenons and the synovial membranes of the carpal tunnel. From Yamamoto S, Gejyo F. Historical background and clinical treatment of dialysis-related amyloidosis. *Biochim Biophys Acta*. 2005;1753:4–10.

(Fig. 78.5)[67] and AVF.[82] The deposition of β2-microglobulin causes dialysis-related amyloidosis, which is characterized by CTS, arthropathy, and bone cysts. The pathologic specimens are positive for Congo red staining and for immunochemistry staining for β2-microglobulin. The accumulation of β2-microglobulin is related to the duration of ESRD and dialysis membrane.[67,83] Because of the switch to a high flux dialysis membrane, dialysis-related amyloidosis has been reported mainly in patients with prolonged dialysis, usually more than 10 to 20 years.[67] In Japan, where the survival of ESRD patients with prolonged dialysis is common, nearly all reported cases of CTS are due to β2-microglobulin.[81] This is not the case in other countries. In one series from France, β2-microglobulin accounts for 60% of dialysis-related CTS.[84] In a study from the United States, about one half of specimens from the transverse carpal ligament were positive for amyloid staining.[82] The presence of AVF does cause significant abnormalities in nerve conduction velocities and latencies in both median and ulnar nerves.[85] It is possible that nerve ischemia due to steal syndrome and venous congestion due to increased downstream pressure may contribute to the development of CTS.[85]

Diagnosis

Two bedside tests are useful for a diagnosis of CTS in patients who have typical symptoms of paresthesia, numbness, and pain in the median nerve territory: the Phalen test and the Tinel sign. The Phalen test involves placing the wrist into an end-of-range palmar flexion for 1 minute to increase intratunnel pressure. The test is positive if symptoms in the median nerve territory are reproduced.[86] The Tinel sign refers to a tingling sensation over the territory of the median nerve when it is tapped. The positive rate of the Phalen test and the Tinel sign in patients with CTS is 70% and 50%, respectively.[86] In advanced CTS, sensory loss in the median nerve territory and weakness and atrophy in distal median-innervated muscles, particularly the abductor pollicis brevis, are detected. Nerve conduction studies demonstrate a slowing of the distal median nerve conduction in sensory and motor fibers at the level of the wrist. Sensory and motor amplitudes are normal in the early stages, but may be reduced in the later stages, which is indicative of axonal loss.[72] The interpretation of nerve conduction studies may be complicated by coexisting uremic or diabetic neuropathy. The diagnosis of CTS is supported by significantly worse nerve parameters in the median nerve when compared with other nerves.

Because the management of β2-microglobulin-induced and AVF-induced CTS is different, it is important to distinguish between these two causes. Patients with CTS should be evaluated for bone cysts and arthropathy.[84] If patients undergo surgical treatment, biopsy samples should be submitted for a microscopic examination of β2-microglobulin. Of note, the predialysis serum β2-microglobulin levels are not helpful for diagnosing dialysis-related amyloidosis because the commonly used high flux membrane has effectively removed β2-microglobulin.[81] As for AVF-related CTS, signs of ischemia distal to AVF and limb swelling should prompt a thorough vascular examination to rule out vascular steal syndrome and venous hypertension. In addition, AVF-related CTS may involve nerves other than the median nerve.

Prevention and Treatment

The incidence of CTS has been reduced after the widespread use of high flux membrane for hemodialysis therapy.[83] Hemodiafiltration[87] and β2-microglobulin adsorption column[88] have been shown to remove β2-microglobulin even more efficiently. They can be used in patients at a high risk of dialysis-related amyloidosis; however, neither of them have been approved by the U.S. Food and Drug Administration (FDA) in the United States. For preventing AVF-related CTS, monitoring ischemic changes, arm swelling, and AVF function, and the early management of vascular steal syndrome and venous hypertension may be important for the prevention of AVF-related CTS.

As for treatment, conservative treatment such as nocturnal splinting is appropriate for dialysis-related CTS with mild symptoms and mild conduction slowing with normal sensory and motor amplitudes. A corticosteroid injection may induce median nerve injury and should be avoided. In patients with severe CTS symptoms with marked reductions in median nerve compound amplitudes, surgical decompression is indicated.[67] Most patients have symptom relief after surgery, but the outcome is not as good as for nondialysis patients and CTS may recur if the primary cause is not eliminated.[82]

Arteriovenous Fistula-Related Neuropathy

Manifestation

AVF has been associated with a variety of peripheral neuropathies due to acute or chronic ischemia. Ischemic monomelic neuropathy refers to neurologic symptoms in the ipsilateral limb, which occurs immediately following the

78.4 Differential Diagnosis Between Steal Syndrome and Ischemic Monomelic Neuropathy[68]

	Vascular Steal Syndrome	Ischemic Monomelic Neuropathy
Onset	Usually insidious	Acute
Predilection for diabetes	Strong	Almost all
Access location	Wrist, forearm, upper arm	Forearm, upper arm
Degree of ischemia	Severe, diffuse	Mild–moderate
Radial pulse presence	No	Yes/No
Digital pressures	Very low	Mildly reduced or normal
Tissue affected	Skin > muscle > nerve	Nerve
Reversibility	Variable	Very poor with late intervention

Modified from Miles AM. Vascular steal syndrome and ischaemic monomelic neuropathy: two variants of upper limb ischaemia after haemodialysis vascular access surgery. Nephrol Dial Transplant. 1999;14:297–300.

creation of AVF. It is due to acute nerve ischemia induced by the shunting of arterial blood away from the distal parts of the limb. Patients manifest distal sensory loss and weakness in the muscles of the forearm and hand without soft tissue changes.[68] Vascular steal syndrome occurs insidiously usually days or weeks after the fistula creation. Neurologic symptoms include numbness and pain, which are worse during a dialysis session.[68] The comparison between ischemic monomelic neuropathy and vascular steal syndrome is summarized in Table 78.4. CTS and ulnar neuropathy with pain and numbness in the domain of the median and ulnar nerves, respectively, also have been reported to be associated with AVF.[85]

Pathogenesis

Ischemic monomelic neuropathy has been largely reported in patients with diabetes, particularly those with preexisting peripheral vascular disease or neuropathy.[89] It is likely that preexisting chronic nerve ischemia is the underlying mechanism of the catastrophic event after an AVF creation.[90] As for vascular steal syndrome, chronic ischemia is caused by retrograde flow from the distal and palmar arch arteries through the fistula, which acts as a low-pressure system.[91]

Diagnosis

Ischemic monomelic neuropathy is diagnosed by the immediate onset of severe pain and weakness in the ipsilateral limb after an AVF creation and frequently involves multiple nerves. Electromyogram (EMG), and nerve conduction studies, are useful to demonstrate axon loss in multiple nerves distal to the AVF.[68,90]

Vascular steal syndrome is characterized by cyanosis, coldness, reduced sensation, and the presence of ischemic ulcers. Vascular Doppler studies or a digital pressure measurement may demonstrate the steal phenomenon and nerve conduction studies reveal slow conduction and low amplitudes in multiple nerves distal to the AVF.[68,91]

Prevention and Treatment

Ischemic monomelic neuropathy occurs mainly in patients with diabetes; however, it is difficult to predict with preoperative evaluation. Early diagnosis is essential to preserve neurologic functions of the hand. Early ligation or revision of the fistula may cause significant clinical and electrophysiologic improvement,[72] whereas the outcome of delayed surgery is frequently poor.[89]

For vascular steal syndrome, vigilant monitoring of AVF functions and signs of ischemia may prevent the development of vascular steal syndrome. Several surgical treatments have been used for steal syndrome: access ligation, banding, elongation, distal arterial ligation, and distal revascularization–interval ligation.[91]

THE AUTONOMIC NERVOUS SYSTEM

Abnormalities in the autonomic nerve system are common in patients with CKD. Both sympathetic and parasympathetic nerve systems are involved. The severity of autonomic dysfunction increases as renal function declines. As a result, multiple organ systems are affected in patients with ESRD. All these abnormalities are discussed under uremic autonomic neuropathy.

Uremic Autonomic Neuropathy

Manifestations

Uremic autonomic neuropathy refers to renal failure-induced autonomic dysfunction, which is observed in patients with uremia. Unlike uremic encephalopathy or uremic neuropathy, which occurs when GFR is less than 10 mL per minute, autonomic dysfunction occurs early in patients with CKD. In those patients, autonomic dysfunction, mainly sympathetic overactivity, contributes to the increased risk of hypertension, heart failure, coronary artery diseases and strokes, as well as the progression of CKD.[92] For CKD patients with mild-to-moderate renal insufficiency, perhaps "nephrogenic" autonomic neuropathy is a better term because they do not have any uremic symptoms.

In ESRD patients, symptoms suggestive of autonomic dysfunction such as male impotency, dyspepsia, constipation, diarrhea, bladder dysfunction, postural dizziness, and intradialytic hypotension are reported from 40% to 70% of nondiabetic patients maintained on hemodialysis.[69,93] However, only male impotency correlates well with autonomic dysfunction diagnosed with traditional tests for cardiovascular autonomic functions.[93] The prevalence of autonomic dysfunction is much increased when diabetic patients are included.[94] Additional cardiac manifestations related to autonomic dysfunction include resting tachycardia with a fixed heart rate, exercise intolerance, silent myocardial infarction, arrhythmia, and sudden cardiac arrest or death.[94–99] Many of these symptoms and signs of autonomic dysfunction are nonspecific; therefore, autonomic function tests are required to confirm the diagnosis of uremic autonomic neuropathy.

Pathogenesis

The key elements of uremic autonomic neuropathy are sympathetic overactivity and parasympathetic hypoactivity. Sympathetic overactivity is primarily due to increased renal afferent signaling, which occurs at the beginning of renal injury.[92,100] The kidneys are subserved with abundant sympathetic innervation of the renal vasculature, renal tubules, and the juxtaglomerular apparatus. Renal injury stimulates afferent signaling via sensory renal nerves.[101] The increased sympathetic activity can be detected by recording muscular sympathetic nerve activity (MSNA) in patients with ESRD.[102] The role of renal injury on sympathetic overactivity in ESRD is confirmed by reducing MSNA with a bilateral nephrectomy.[102] Furthermore, even in the presence of a functioning renal graft, MSNA is still hyperactive until the removal of both native kidneys, as shown in Figure 78.6.[103]

The increased afferent signaling is independent of GFR because it occurs in patients with early stage polycystic kidney disease[104] or in animals with localized renal injury,[100] both of which have normal GFR. The generation, integration, and consequences of renal afferent signaling from renal injury are shown in Figure 78.7. These afferent signals from the injured kidney are centrally integrated and result in sympathetic outflow to the kidney, heart, and vasculature in order to restore renal perfusion. The suppression of brain nitric oxide synthase activity in CKD removes the tonic inhibition on the sympathetic outflow from the brainstem. With constant renal signaling and suppression of brainstem inhibition, organs receiving chronically elevated sympathetic outflow start to deteriorate resulting in left ventricular hypertrophy, arrhythmias, vasoconstriction, sodium retention, and renin-angiotensin-aldosterone system activation. These changes aggravate hypertension, which in return worsens cardiac and renal functions, atherosclerosis, and glomerulosclerosis.[92]

There are other mechanisms that may contribute to increased sympathetic activity in CKD patients. Tonic arterial chemoreceptor activation may be involved in sympathetic activation associated with renal impairment. The deactivation of arterial chemoreceptors by the inhalation of

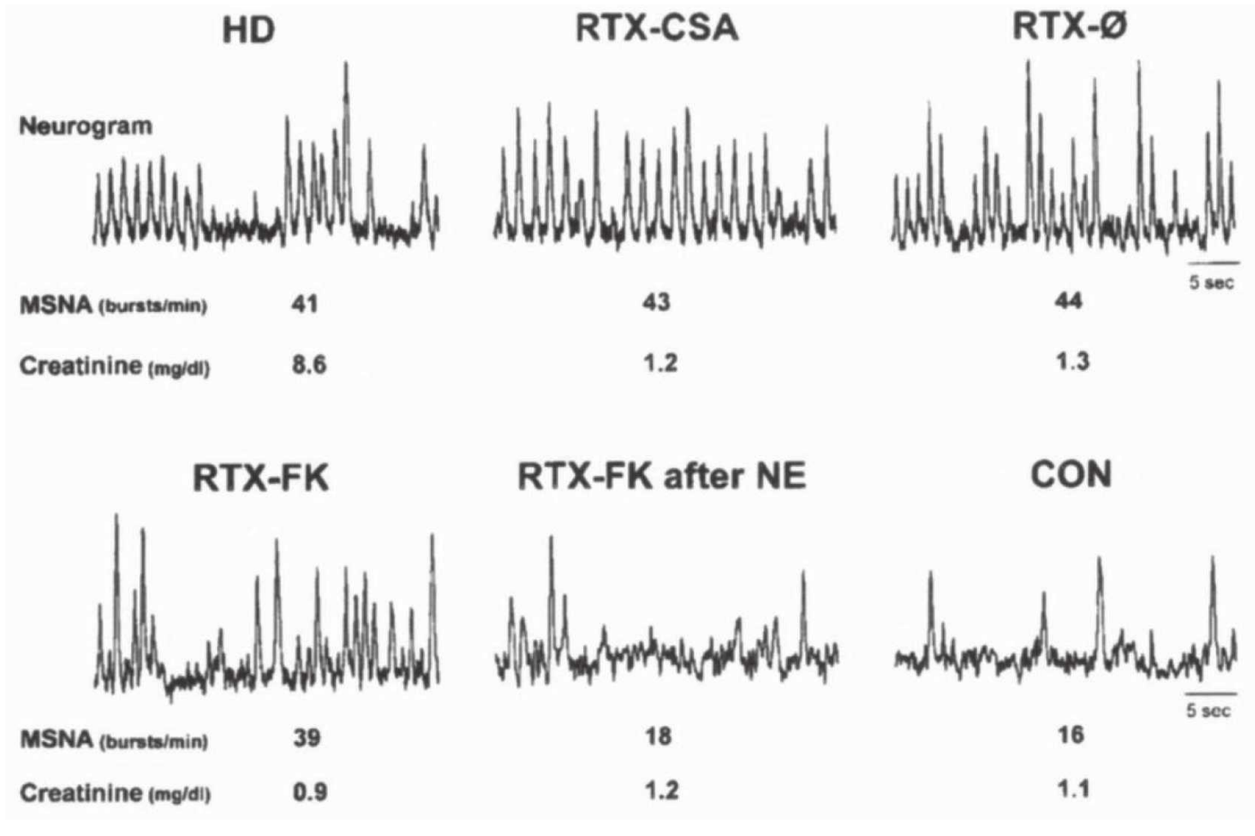

FIGURE 78.6 Representative tracings of sympathetic neurograms from a hemodialysis patient (*HD*), the same patient after a successful kidney transplantation receiving cyclosporine (*RTX-CSA*), a renal transplantation patient without calcineurin inhibitor treatment (*RTX-Ø*), a renal transplantation patient receiving tacrolimus before (*RTX-FK*) and after native kidney nephrectomy (*RTX-FK after NE*), and a healthy volunteer (*CON*). The renal transplant recipients had serum creatinine concentrations similar to that of the healthy volunteer; however, muscle sympathetic nerve activity (MSNA) declined not with transplantation but with native kidney nephrectomy. (From Hausberg M, Kosch M, Harmelink P, et al. Sympathetic nerve activity in end-stage renal disease. *Circulation*. 2002;106:1974–1979.)

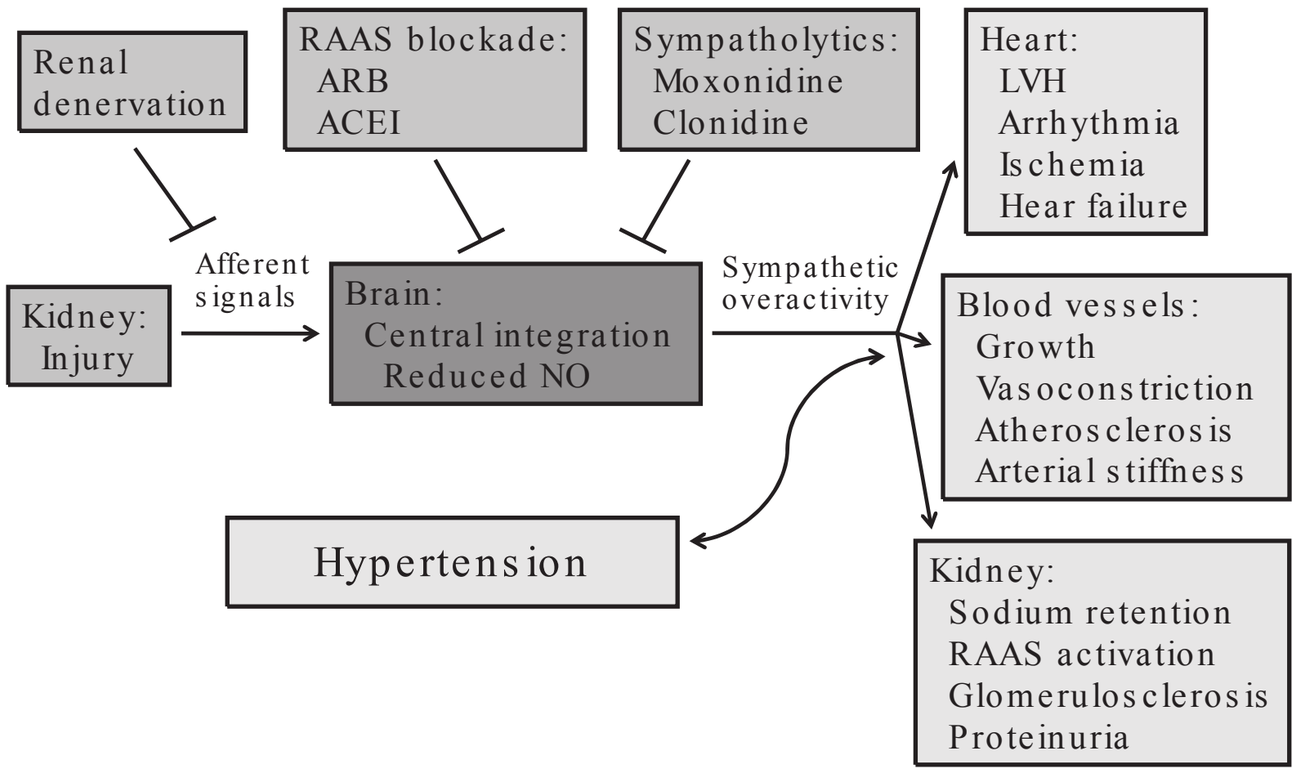

FIGURE 78.7 Causes and consequences of sympathetic activation in chronic kidney disease and the potential treatment. See text for explanation. Color codes: red: cause; blue: integration; yellow: consequences; and green: treatment. RAAS, renin-angiotensin-aldosterone system; ARB, angiosten receptor blocker; ACEI, angiotensinogen converting enzyme inhibitor; LVH, left ventricular hypertrophy; NO, nitric oxide. (Modified from Schlaich MP, Socratous F, Hennebry S, et al. Sympathetic activation in chronic renal failure. *J Am Soc Nephrol.* 2009 May;20(5):933–939.) (See Color Plate.)

100% oxygen substantially decreased MSNA in patients with chronic renal disease, but not in healthy control subjects.[105] Another novel mechanism for sympathetic overactivity is mediated by reduced renalase release. Renalase is a novel soluble monoamine oxidase that metabolizes catecholamines such as dopamine and norepinephrine.[106] Renalase is released from the kidney into the blood in an inactive form (prorenalase). Catecholamines not only activate prorenalase, but also induce its release from the kidney; as a consequence, active renalase metabolizes circulating catecholamines as an important regulatory mechanism for hemodynamic homeostasis.[107] In rats with 5/6 nephrectomy, blood levels of renalase are markedly reduced, which lead to increased plasma catecholamine levels and subsequent sympathetic overactivity.[107]

As for parasympathetic hypoactivity, it is likely to be mediated by impaired baroreceptor sensitivity (BRS). The baroreflexes are neurocardiovascular reflexes that maintain circulatory homeostasis. When systemic blood pressure (BP) rises, the arterial stretch triggers the firing of the baroreceptors in the carotid artery and aorta. The afferent impulses are transmitted to the CNS, signals are integrated, and the efferent arm of the reflex projects neural signals systemically via the sympathetic and parasympathetic branches of the ANS. By inhibiting the efferent sympathetic outflow, vascular tone, cardiac chronotropy, and inotropy are reduced, whereas the increase in parasympathetic outflow reduces cardiac chronotropy.[108]

CKD promotes carotid artery intimal thickening and increases arterial stiffness. The arterial stiffness becomes worse in patients with advanced CKD because of vascular calcification. Chesterton et al.[109] have demonstrated that decreased BRS in patients on hemodialysis correlates with arterial stiffness measured with central pulse wave analysis and vascular calcification measured with a computed tomography (CT) scan. Additionally, parasympathetic hypoactivity is associated with heart failure, which is common in ESRD patients.[110]

The cardiac parasympathetic function in experimental CKD animals has been studied.[111] Using a 5/6 nephrectomy model in rats, Kuncova et al.[111] reported diminished cardiac parasympathetic tone in CKD rats. These rats have resting tachycardia and a blunted response to atropine injection. However, there are no differences in negative chronotropic responses to the stimulation of the vagus nerves, nor in chronotropic and inotropic responses to carbachol. Furthermore, the relative expression of muscarinic (M2) receptors, the high affinity choline transporter, the vesicular acetylcholine transporter, and the choline acetyltransferase in cardiac tissues is also unchanged.[111] These studies indicate that in 5/6 nephrectomy rats, parasympathetic hypoactivity is mainly due to suppression of the afferent limb while the efferent parasympathetic limb remains intact. Similar mechanisms are likely to occur in patients with CKD or early stage ESRD. However, whether the efferent parasympathetic limb remains intact after a prolonged duration of dialysis treatment is unknown.

Although sympathetic overactivity may explain hypertension associated with CKD, particularly in those patients with adult-onset polycystic kidney disease,[104] it seems to be at odds with the fact that some ESRD patients develop baseline hypotension, orthostatic hypotension, or intradialytic hypotension, and that the prevalence of hypotension increases with dialysis vintage.[112,113] The majority of these hypotensive patients have relatively preserved cardiac function. Because ESRD patients without a nephrectomy have increased sympathetic afferent signaling from injured kidneys, how do they develop hypotension, which is associated with reduced peripheral resistance from decreased sympathetic activity? It is likely that in spite of a hyperactive afferent limb, these patients may develop end organ unresponsiveness. Reduced adrenoreceptor responsiveness has been reported in ESRD with hypotension before or during dialysis. Daul et al.[112] reported reduced platelet $\alpha 2$ adrenoreceptor, blunted blood pressure responses to phenylephrine injection, and elevated plasma norepinephrine levels in these patients. They found that these abnormalities correlated well with duration of dialysis. They proposed that elevated catecholamine may downregulate adrenoreceptors in platelets and, possibly, in blood vessels.[112] These results are confirmed by another study comparing ESRD patients

with or without hypotension. The mean duration of dialysis treatment was 10 and 3 years, for hypotensive and normotensive patients, respectively. Hypotensive patients had lower platelet α2 adrenoreceptor and lymphocyte β2 adrenoreceptor densities and elevated plasma epinephrine levels.[113] In animal studies, a reduced α1 adrenoreceptor in mesentery arteries and elevated plasma epinephrine levels are observed in rats with 5/6 nephrectomy. Interestingly, a parathyroidectomy did not affect adrenoreceptor or epinephrine levels in these animals.[114] In addition to adrenergic receptor downregulation, sympathetic denervation is another plausible possibility for reduced sympathetic activity in spite of increased sympathetic signaling. Recently, Chao et al.[115] reported that in patients with advanced CKD, mostly ESRD, there is a high percentage of skin denervation (67.5%), which correlates with the presence of autonomic dysfunction as measured by heart rate variability and sympathetic skin response. The skin denervation also correlates well with the duration of CKD and dialysis, suggesting that unknown uremic toxins may be responsible for the damage of small nerve fibers in the skin. Because these skin nerves are small myelinated or unmyelinated nerves that are similar to postganglionic autonomic nerves,[116] it is possible that a similar denervation may occur in sympathetic and parasympathetic nerve systems and results in reduced efferent sympathetic and parasympathetic flow in patients with prolonged ESRD. More studies are needed to test this hypothesis.

Autonomic dysfunction has been implicated in the pathogenesis of intradialytic hypotension. Converse et al.[117] elegantly demonstrated that patients with intradialytic hypotension did have increased sympathetic activities consisting of hypertension and tachycardia right before a hypotensive episode, but then developed a paradoxical withdrawal of sympathetic vasoconstrictor drive that is consistent with a vasodepressor syncope. An ECG (echocardiograph) right before hypotension showed a near collapse of the left ventricle at the end of systole, which may activate cardiac afferents and may trigger the reflex inhibition of sympathetic outflow (Bezold-Jarisch reflex).[117,118] Similarly, Chesterton et al.[119] reported that patients with reduced BRS, but who were resistant to intradialytic hypotension, were able to raise total peripheral resistance to maintain BP probably via increased sympathetic activity, whereas patients with reduced BRS who are prone to intradialytic hypotension were not able to do so, which is consistent with sympathetic withdrawal. The decrease in their cardiac output is closely related to the volume of fluid removal. Therefore, although autonomic dysfunction predisposes ESRD patients to intradialytic hypotension, the intrinsic cardiac disease and fluid removal are still the major factors for intradialytic hypotension.

Uremic autonomic neuropathy also contributes to increasing GI symptoms in patients with ESRD, including dyspepsia (nausea, vomiting, abdominal distension, early satiety, and anorexia), constipation, and diarrhea. The prevalence of GI symptoms in patients with ESRD is in the range of 70% to 80%.[120] However, the correlation between GI symptoms and autonomic dysfunction is poor.[93] Gastroparesis has been implicated in dyspeptic symptoms in patients with ESRD. Delayed gastric emptying is associated with autonomic dysfunction in ESRD patients,[121] but it does not consistently correlate with dyspeptic symptoms.[122,123] An electrogastrogram was also abnormal and consistent with gastric emptying delay.[124] Overall, it appears that uremic autonomic neuropathy may incur delayed gastric emptying that may or may not cause dyspeptic symptoms.

Erectile dysfunction is another common symptom of autonomic dysfunction in patients with ESRD. About 65% of male dialysis patients report a difficulty in achieving and maintaining an erection, and 40% report a difficulty in achieving orgasm.[125] Vita et al.[93] reported that erectile dysfunction is the only symptom that correlates well with abnormal autonomic tests. The correlation between erectile dysfunction and abnormal responses to the Valsalva maneuver has been demonstrated.[126] However, there are other factors that contribute to erectile dysfunction in patients with ESRD, such as hypothalamic-pituitary-gonadal axis imbalance, accelerated vascular disease, and medications such as antihypertensives, antidepressants, diuretics, and histamine receptor blockers.[125]

The erectile activity is completely dependent on autonomic innervation from the spinal cord.[127] Norepinephrine and neuropeptide Y (NPY) are released in the penis by the terminals of the sympathetic fibers. Norepinephrine is the major contractile agent of the smooth muscles of the penis and penile arteries, and NPY augments its effects. Norepinephrine plays a role in flaccidity and detumescence; thus, the sympathetic activity is antierectile. The terminals of the parasympathetic fibers release acetylcholine, vasoactive intestinal polypeptide (VIP), and nitric oxide. Acetylcholine activates endothelial cells that in turn release nitric oxide. Nitric oxide increases the production of cyclic guanosine 3′S′-monophosphate (cGMP) in smooth muscle fibers and is recognized as the most important activator of the local relaxation of the penis smooth muscle. VIP is also a smooth muscle relaxant. Therefore, parasympathetic activity is proerectile.[127] Most ESRD patients with erectile dysfunction have autonomic dysfunction and reduced HRV in high frequency (HF) and low frequency (LF), indicating that they have increased sympathetic activity and reduced parasympathetic activity, a combination affecting erectile activity negatively.[93]

Diagnosis

Patients with ESRD frequently report symptoms of autonomic dysfunction, such as impotence, GI symptoms, and postural dizziness. In addition to uremic autonomic neuropathy, autonomic dysfunction may be secondary to other etiologies. Diseases such as diabetes, amyloidosis, and Fabry disease may cause ESRD and autonomic dysfunction independently.[116] Autoimmune diseases such as systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue diseases, and Sjögren disease may also develop various forms of autonomic

78.5 Cardiovascular Autonomic Dysfunction Detected with Various Autonomic Function Tests in Patients with End-Stage Renal Disease

Tests	Measurement	ESRD pre-HD	ESRD on HD	Kidney TX
Valsalva maneuver	Ratio of longest R-R interval during release phase to the shortest R-R during strain phase	Reduced (parasympathetic hypoactivity)[102]	Improved[102,153]	Normalized[153]
Orthostasis	Changes in BP and HR during orthostasis	Abnormal fall in BP, but normal increase in HR due to NE resistance[102]	Improved[102,153]	Normalized[153]
Handgrip exercise	Changes in BP and HR during handgrip exercise	Reduced increment in BP (NE resistance) and HR (parasympathetic hypoactivity)[102]	BP but not heart rate improved[102]	Normalized[153]
Muscle sympathetic nerve activity	Microneurography of muscle sympathetic nerve	Increased (increased renal efferent signaling)[130]	Unchanged[103]	Unchanged[103]
Heart rate variability	Time domains	Reduced (parasympathetic hypoactivity and sympathetic overactivity)[131]	Improved[132]	Improved[135]
	Frequency domains	Reduced in LF (mainly sympathetic overactivity) Reduced in HF (parasympathetic hypoactivity)[131]	Not improved[132] Improved[134]	Improved[135]
Baroreceptor sensitivity	Regression slope between R-R intervals and beat-to-beat BP changes	Reduced[137]	Improved[137]	Improved/ normalized[137,138]

BP, blood pressure; HR, heart rate; HD, hemodialysis; TX, transplantation; NE, norepinephrine; LF, low frequency.

dysfunction, frequently before the development of ESRD.[116] These nonuremic causes of autonomic dysfunction should be recognized in patients with ESRD, which is likely to worsen uremic autonomic neuropathy.

Many tests have been used clinically or for research purposes to diagnose uremic autonomic neuropathy. Clinically, autonomic dysfunction has an important impact as an independent predictor for cardiovascular mortality and morbidity.[96,98] Most studies of autonomic activity in patients with ESRD used cardiovascular parameters to assess autonomic dysfunction. Table 78.5 lists the tests used for CKD-associated autonomic dysfunction in the cardiovascular system, results in patients with ESRD, and the effects of dialysis and successful kidney transplantation.

The key components of autonomic dysfunction associated with CKD are sympathetic overactivity and parasympathetic hypoactivity. Tests for sympathetic activities include measurements of blood pressure responses to orthostasis change and handgrip exercises. Tests for parasympathetic activities include measurements of heart rate responses to blood pressure change (baroreceptor sensitivity), respiration, the Valsalva maneuver, and orthostasis.[128] More recently, noninvasive techniques have

been developed to assess BRS and heart rate variability (HRV). Using power spectrum analysis, these convenient bedside tests provide high volumes of quality data for determining autonomic functions and predicting outcomes of patients with ESRD.

The classic studies on autonomic dysfunction by Campese et al.[102] provide excellent insight of uremic autonomic neuropathy. Using classic physiologic methods, including the Valsalva maneuver, handgrip exercise, and orthostasis, they characterized uremic autonomic neuropathy prior to initiation of hemodialysis. These patients failed to reduce the heart rate at the release phase of the Valsalva maneuver and had fewer blood pressure and heart rate responses to handgrip exercise. When changing from a supine to a standing position, their blood pressure dropped in spite of a normal tachycardic response. Uremic patients had higher baseline plasma norepinephrine (NE) levels and a larger increment in plasma NE levels after ambulating for 60 minutes. When NE was injected intravenously, the increment in blood pressure and the reduction in the heart rate were significantly less in uremic patients when compared to normal individuals. This classic study demonstrates that uremic patients have markedly reduced parasympathetic activity, increased sympathetic activity, but resistance to NE. Dialysis treatment reduces NE resistance and improves orthostatic hypotension and parasympathetic hypoactivity.[102]

Increased sympathetic activity can be demonstrated using microneurography by inserting electrodes into muscle sympathetic nerves. MSNA is markedly increased in ESRD patients with or without hemodialysis.[129,130] Hemodialysis fails to correct sympathetic overactivity. In fact, even successful kidney transplantation fails to suppress MSNA. However, native kidney nephrectomy completely normalized MSNA in both hemodialysis[117] and transplant patients.[103]

HRV has been increasingly used for evaluating autonomic dysfunction. It refers to beat-to-beat alterations in heart rate as measured by periodic variation in the R-R interval. HRV provides a noninvasive method for investigating autonomic input into the heart. Normal individuals have a high degree of HRV, which can be analyzed in either time or frequency domains. The time domain analysis measures normal R-R intervals over a period of time and is expressed in many different ways, such as standard deviation of all normal R-R intervals during a 24-hour period (SDNN), a standard deviation of a 5-minute average of normal R-R intervals (SDANN), an average of a 5-minute SDNN (ASDNN), the root-mean square of the difference of successive R-R intervals (rMSSD), and the number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 hours (pNN50). The SDNN and its variables may represent the sympathetic limb of the autonomic nervous system, whereas rMSSD, NN50, and pNN50, in the presence of a normal sinus rhythm and atrioventricular-nodal function, represent the parasympathetic limb.[99] The frequency domain analysis splits the heart rate signal into constituent frequency components using the fast Fourier transformation. The clinically important frequencies are low frequency (LF), 0.04 to 0.15 Hz, and high frequency (HF), 0.15 to 0.40 Hz. The former is affected by the baroreceptor reflex and is thought to reflect sympathetic and parasympathetic tone, whereas the latter is influenced by respiratory frequency and is thought to reflect parasympathetic tone. The LF/HF ratio is an index of sympathovagal balance.[99,128] Reduced HRV is common (about 50%) in patients with advanced CKD with or without dialysis.[131] The reduction of HRV in HF is consistent with parasympathetic hypoactivity, whereas reduced LF or time domain may be related to sympathetic overactivity or the combination of these two abnormalities. Short-term hemodialysis improved time domain HRV, but not frequency domain HRV in one study.[132] On the other hand, dialysis vintage is an independent predictor for reduced HRV.[133] Preliminary studies have shown that nocturnal hemodialysis has improved both HF power and LF/HF ratio in nine ESRD patients after switching from a conventional hemodialysis.[134] A reduction in both time- and frequency-domain HRV can be improved or normalized after successful kidney transplantation.[135]

BRS is another test for evaluating autonomic dysfunction. BRS measures regression slope between R-R intervals and beat-to-beat BP changes. Reduced BRS accounts for parasympathetic hypoactivity, which is common in patients with advanced CKD[136] and patients on dialysis.[137] Interestingly, successful kidney transplantation is capable of normalizing BRS.[137,138]

Prevention and Treatment

Autonomic dysfunction is an independent predictor for cardiovascular events in patients with CKD.[98,128,139] Recent epidemiology studies have shown that reduced HRV in patients with CKD predicts ESRD and CKD-related hospitalization.[140] However, treatment options for CKD-induced autonomic dysfunction are limited (Fig. 78.7). Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers reduce sympathetic activity by 20% to 25%.[141–143] The addition of moxonidine, a centrally acting imidazoline-I1 receptor agonist and sympatholytic agent, to angiotensin receptor blocker (ARB) normalized sympathetic overactivity in patients with advanced CKD.[144] Moxonidine also reduced MSNA in patients with ESRD.[145] Notably, moxonidine is excreted by the kidney and dose adjustment is required for patients with reduced renal function. In the CKD and ESRD studies mentioned earlier, 0.2 mg and 0.3 mg per day was used, respectively, and was well tolerated.[144,145] Moxonidine reduces both blood pressure and MSNA in patients with CKD, but reduces MSNA only without affecting blood pressure in ESRD patients. Volume overload in patients with ESRD may account for this difference. Lastly, the modulation of sympathetic activity by angiotensin converting enzyme (ACE) inhibitors, ARB, or moxonidine in CKD patients does not affect the BRS.[141,144] Moxonidine has not been approved by the FDA in the United States. It has been shown to increase cardiac mortality and hospitalization rates in a clinical trial for heart failure, which may be related to the designed target dose, 3 mg per day, a dose 10 times higher than that in the

studies for renal patients.[146] Clonidine, an imidazoline and an α2-receptor agonist, has been shown to reduce sympathetic activity in heart failure patients.[147] Whether clonidine has similar effects as moxonidine in CKD patients has not been studied. In patients who tolerate clonidine, it may be an alternative drug for lowering sympathetic activities.

Renal denervation ideally is the treatment of choice for CKD-associated sympathetic overactivity because it specifically targets the pathogenetic mechanism without adverse effects from the suppression of a sympathetic reflex induced by sympatholytic agents. A novel catheter-based method using radiofrequency ablation of the renal sympathetic nerve has been developed and is effective for treating resistant hypertension.[148] Whether this procedure is cost-effective at reducing cardiovascular complications and the progression of renal disease in CKD patients remains to be tested.

As for parasympathetic hypoactivity, the main goal is to prevent arterial stiffness, vascular calcification, and heart failure in order to preserve BRS and improve parasympathetic activity.[128] The treatment plan should include controlling volume status, blood pressure, blood sugar, hemoglobin, lipid profiles, and mineral metabolism parameters (calcium, phosphorus, and parathyroid hormone).

Obviously, renal transplantation is the best option for treating uremic autonomic neuropathy. Successful kidney transplantation normalizes multiple parameters of both sympathetic and parasympathetic systems, except MSNA (Table 78.5).[103,138,149]

As for the symptomatic treatment for uremic autonomic neuropathy, sildenafil has been shown to be effective and well tolerated for erectile dysfunction.[150] Gastroprokinetic medications such as metoclopramide or erythromycin given before each meal and at bedtime have been shown to improve the nutritional status in ESRD patients probably through the improvement of gastroparesis.[151] For intradialytic hypotension, midodrine, an oral α1-adrenoceptor agonist, given 15 to 30 minutes before the hemodialysis session appears to be effective and safe.[152]

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