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Review Article

Uremic autonomic neuropathy

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ABSTRACT

Autonomic symptoms are frequently encountered in chronic renal disease patients, either as a part of distal symmetric polyneuropathy and small fiber sensory polyneuropathy or as primary autonomic polyneuropathy independent of somatic neuropathy. Pathogenesis of latter remains elusive. Sudomotor, gastrointestinal and cardiological involvement is common. Renal replacement therapies are not as efficacious in curing autonomic neuropathy as in somatic polyneuropathy of uremia. A greater awareness of this entity across various disciplines and subsequent multidisciplinary approach involving nephrologists, gastroenterologist and cardiologist, as needed, is probably the best bet at present, to ease the suffering patient.

1. Introduction

Uremic neuropathy is well recognized complication of end stage renal disease (ESRD) and is subdivided into motor, sensory and autonomic neuropathy.[1] Peripheral neuropathy whether overt or subclinical is very commonly encountered and is well studied, but detail studies on autonomic neuropathy in uremia are sparse. Nevertheless a basic understanding about uremic autonomic neuropathy is very important. As the ESRD population on renal replacement therapy (RRT) continue to increase, nephrologists would be seeing more and more of these patients. Confronted by ESRD patients with disturbances of autonomic function, nephrologists may find themselves victims of the autonomic ramifications of fear and anxiety. This review aims at veering such "fight or flight" response towards the former!

2. Autonomic nervous system

Briefly reviewed, the basic organization of autonomic nervous system (ANS) consists of three divisions: sympathetic (thoracolumbar), parasympathetic (craniosacral), and enteric. These sub-systems may operate independently of each other or may interact amongst themselves. Autonomic functions are involuntary. Previous simplistic view was that sympathetic system is excitatory and parasympathetic system is inhibitory but the system is much more complex.

The sympathetic division supplies all parts of the body. Its neurons begin at the thoracic (T1) and lumbar (L2/3) portions of the spinal cord (thoracolumbar outflow). Its functions are catabolic and directed toward the utilization of energy. It accelerates heart, dilates coronary vessels, increases arterial blood pressure, empties blood reservoirs, dilates bronchi,

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liberates glucose, and inhibits GI activity. It is an emergency protective mechanism that is called into action under emotional stress and causes the individual to react strongly to stimuli of rage and fear. As such sympathetic nervous system is often considered the "fight or flight" quick response mobilizing system.

The parasympathetic division supplies special structures, such as the pupils, salivary glands, heart, lungs, GI tract, bladder, and portions of the genital system. It has craniosacral "outflow" (begin at the cranial nerves (III, VII, IX, and X) and sacral S2–S4spinal cord.) It controls anabolic, excretory, and reproductive functions, conserves and restores bodily resources and energy and is often considered the "rest and digest" or "feed and breed" system.

The enteric nervous system is later recognized mesh like nervous system located in the walls of the gastrointestinal tract. It is truly autonomous and the digestive tube can function very well in isolation.[2] As discussed below, all the components of ANS may be involved in uremic autonomic neuropathy.

3. Clinical features

In neurological practice, polyneuropathies are generally classified as predominantly large fiber polyneuropathies (usually presenting as distal symmetric peripheral neuropathy-DSPN), predominantly small fiber sensory neuropathies, (SFSN), and predominantly pure autonomic neuropathies, besides mixed patterns. In both DSPN and SFSN, subtle autonomic involvement is also present.

In clinical practice, patients with ESRD too present with a myriad of such large fiber, small fiber and pure autonomic symptoms. This is more true in light of the fact that many of ESRD patients are also diabetics. It is useful, therefore, to approach such patients on the general lines of autonomic neuropathy as a part of predominant DSPN, SFSN and as disproportionate to somatic (large and small fiber) neuropathies.

Viewed on these lines, autonomic neuropathy in ESRD may present as abnormalities of sweating and circulatory instability in the feet. This is usually in association with the most common pattern of DSPN with length dependence which means that there is greater involvement of lower limbs compared to upper limbs. There is male preponderance and predominant large fiber symptoms such as paresthesias, reduction of deep tendon reflexes, impaired vibration sense, muscle wasting, weakness and abnormal nerve conduction studies[1,3,4].

There could be burning feet, allodynia (pain due to a stimulus which normally does not produce pain) and erythromelalgia (periodic burning pain and redness of extremities precipitated by pressure, heat, stress or exertion) as part of distal SFSN5 and there could be features of pure autonomic neuropathy, ranging from orthostatic giddiness, impaired sweating, bowel, bladder and sexualdysfunction (diarrhea, constipation, urinary incontinence, impotence etc), and cardiovascular complications such as hypertension, decreased left ventricular contractility, persistent hypotension or dialysis induced hypotension.[1,5–9]

When other uremic symptoms are predominant, needless to say, early autonomic symptoms may be overlooked. Impotence, often indicate early autonomic failure in men and may precede other symptoms by years. A decrease in the frequency of spontaneous early morning erections may occur much before loss of nocturnal penile tumescence and development of total impotence.

Bladder dysfunction may appear early in men and women, Disease of PNS autonomic nerve fibers results in large bladder volumes, urinary frequency, and overflow incontinence (lower motor neuron flaccid bladder). Measurement of postvoid residual urine volume is a useful test for distinguishing between upper and lower motor neuron bladder dysfunction in the early stages of dysautonomia. Bladder dysfunction is not only an irritating symptom for patient but it may also lead to recurrent urinary tract infection and rapid progression of chronic kidney disease.

Gastrointestinal autonomic dysfunction typically presents as severe constipation. There is occasional diarrhea due to rapid or uncoordinated small-bowel motor activity, or due to bacterial overgrowth associated with small-bowel stasis. Impaired saliva secretion may cause difficulty with food intake. As symptoms of uremia are similar, they may be missed initially. Persistence of these gastrointestinal symptoms after adequate dialysis will warrant further evaluation.

Postural hypotension is very commonly encountered and perhaps it is the most disabling feature of autonomic dysfunction. Associated diabetes mellitus, amyloidosis or aging increase its prevalence. This may cause a variety of symptoms, including lightheadedness, diaphoresis, dimming or loss of vision, diminished hearing weakness and syncope. Other associated symptoms are supine hypertension, postprandial hypotension, and nocturnal BP surge. This may be multifactorial in origin due to antihypertensive treatment, cardiac causes, fluid disturbances or as a result of an autonomic disorder. Its detail evaluation is important because abnormal baroreceptor response during fluid shift of intermittent dialysis makes dialysis delivery inadequate and risky.[10,11]

4. Incidence

Sensorimotor peripheral neuropathy is well recognized component of the uremic syndrome. Studies of conduction velocity and other nerve functions have proved that most patients of renal failure with uremia have at least subclinical peripheral neuropathy. In one study, prevalence of neuropathy in ESRD patients was 81%. 19% had stage 1 (asymptomatic neuropathy),48% had stage 2 (symptoms nondisabling) and 14% had stage 3 neuropathy (disabling symptoms).[12] In another study involving ESRD patients receiving adequate dialysis, 93% had neuropathic symptoms, with 72% diagnosed with stage 2 and 21% with stage 3 neuropathy.[13] In an exclusive study of autonomic dysfunction in 36 ESRD patients, 42% had gastrointestinal autonomic symptoms and 45% had impotence. Postural hypotension was uncommon but, 36% had postural dizziness, especially elderly.[14] In studies in which objective assessment of autonomic function in ESRD patients on dialysis have been done by R–R interval variation for parasympathetic function and sustained handgrip and