Review

Uraemic neuropathy: A review

Basilio Vagner Ramírez[1,2]* and Paula Andrea Bustamante Gómez[3]

[1]Clinical Neurology Specialist, Neurology Division Director, Pablo Tobón Uribe Hospital, Medellín, Colombia.
[2]Clinical Neurology, School of Medicine, Pontifical Bolivarian University and CES University, Medellín, Colombia.
[3]Physician Pontifical Bolivarian University, General Physician, Pablo Tobón Uribe Hospital, Medellín, Colombia.

Uraemic neuropathy is an increasingly common condition, it is therefore important to understand its pathophysiology as well as its clinical manifestations. The objective of this study is to make a clear diagnostic approach and to provide treatment following the patient's condition.

Key words: Uraemia, dialysis, renal transplantation, kidney failure, chronic kidney disease (CKD).

INTRODUCTION

The prevalence of chronic kidney disease (CKD) has increased progressively, becoming a public health issue. In the United Kingdom are reported at 10% of the population, 15% in developing countries, and rising up to 40% among people over 65 (Ahmed et al., 2010). The term uraemia is used to describe the condition accompanying kidney failure that cannot be explained by derangements in extracellular volume, inorganic ion concentrations, or lack of known renal synthetic products. Uraemic disease is largely due to accumulation of organic waste products normally cleared by the kidneys, of which not all have yet been identified. No specific time point demarcates the onset of uraemia in patients with progressive loss of kidney function. Traits of uraemia may be present to a lesser degree in people with glomerular filtration rates barely 50% below normal (Meyer and Hostetter, 2007).

Neurological complications occur in approximately 60% of patients suffering from severe CKD (Brouns and De Deyn, 2004), affecting the nervous system at all levels, central as well as peripheral, yielding weakness, prolonged disability and alteration of mental state (Krishnan and Kiernan, 2009). Amongst the many manifestations of uraemia, the most common is uraemic neuropathy. This is defined as predominantly sensory distal symmetrical sensorimotor polyneuropathy, most often affecting the lower, rather than upper, limbs, occasionally present as mononeuropathy, resulting from compression, trauma or ischemia (Fraser and Arieff, 1988).

Uraemic neuropathy characteristically progresses over the course of months, but can occasionally take a faster course, triggering a marked disability (Krishnan et al., 2009). It is believed that Uraemic neuropathy is caused by the accumulation of medium-sized molecules that have not been adequately filtered. The best treatment is therefore Hemodialysis or, ideally, kidney transplant (Al-Hayk and Bertorini, 2007).

HISTORY

The existence of uraemic neuropathy was first suspected by Charcot (1880) and Osler (1892). Since the introduction of hemodialysis and kidney transplants in the early 1960s, uraemic neuropathy has been studied in detail. Asbury et al. (1962) described the clinical and pathological characteristics (Asbury et al., 1963; Asbury, 1971). The current concept of uraemic neuropathy was established in 1971 by Dyck and colleagues, in an extensive study of nerve conduction *in vivo* and *in vitro*, as well as in studies with light and electronic microscopy. Using quantitative histology, they demonstrated axonal retraction: neuronal dysfunction resulted in the decrease of axonal diameter, reorganization of myeline and ultimately, complete degeneration of the axon (Dyck et al., 1971). Several authors, such as Nielson and Bolton (1970), published an articles demonstrating how nerve conduction was slowed in the clinically affected segments, with a correlation between the degree of renal failure and the decrease in the speed of conduction. Also demonstrated was the improvement in the neuro-physiologic parameters after renal transplantation,

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*Corresponding author. E-mail: basilio_vagner@hotmail.com.

thereby suggesting that a uraemic toxin was responsible for the development of neuropathy in patients with CKD. This hypothesis has formed the basis of many studies on this subject (Krishnan and Kiernan, 2007).

EPIDEMIOLOGY

Uraemia is considered to be the second leading cause of frequent metabolic neuropathy. It has been demonstrated that 60 to 100% of patients undergoing dialysis experience neuropathic symptoms. These rates vary on account of the selected diagnostic approach: the choice of nerve segments, the measurement index, and the number of nerves studied (Bolton, 1976; Yatzidis et al., 1984; Laaksonen et al., 2002; Krishnan et al., 2005; Tilki et al., 2007; Krishnan and Kiernan, 2007; Krishnan et al., 2009; Krishnan and Kiernan, 2009). Studying with chronic renal failure Danish patients, Nielsen (1971) found 77% with clinical symptoms and 51% with signs of clinical neuropathy. It is, however, difficult to make an accurate determination, as they are presented along with other systemic diseases such as diabetes (Nielsen, 1971). In the EPINEURIM study, carried out in Colombia in 2003, peripheral neuropathy affected 30% more women than men, predominantly in those over 40, and mononeuropathy was predominant in 65.8% of cases. However, owing to lack peripheral neuropathy standard definitions, variety of causes, disease mechanisms and severity, population pattern descriptions in the area where the condition occurred were limited. Consequently, epidemiological data on the behavior of this neurological disorder is rather poor in Colombia (Pradilla et al., 2003).

PATHOPHYSIOLOGY

The development of neuropathy is determined, in a clinical context, by the degree of renal failure, after glomerular filtration rate falls below 12 ml/min (Krishnan et al., 2009). The way in which uraemic neuropathy operates is not quite clear: It has been associated with a spinal cord secondary demyelination process involving posterior columns and other sections of the CNS (Fraser, 1988). Fraser and Arieff (1988) postulated that neurotoxins deplete axon energy supplies by hindering nerve fiber enzymes required in their production. This deprivation of energy is especially critical at the nodes of Ranvier, on account of higher levels of impulse conduction and axonal transport. Enzyme resupply from neural soma may not satisfy the axon growing demand, thus causing a critical drop in distal areas, leading to a local energy block with multiple pathological changes and degeneration of nerves and distal fibers (Fraser and Arief, 1988; Pereira et al., 2005). Various membrane dysfunctions have also been described: in the perineurium, which acts as a diffusion barrier between

the interstitial liquid and the nerve; and within the endoneurium, which acts as a barrier between blood and nerve.

Consequently, uraemic toxins may enter the endoneural space and cause direct nerve damage, with hydroelectrolytic changes producing shrinkage or expansion of endoneural space (Pan, 2009). Krishnan and colleagues investigated axonal membrane properties in patients with chronic renal failure, measuring nerve excitability before, during, and after hemodialysis. They suggested that motor and sensory axons in patients with uraemic neuropathy are depolarized before dialysis, meaning that hyperkalemia is the foremost factor in the development of neuropathy. There is evidence of hyperkalemia induced chronic depolarization of uraemic nerves, which improves after dialysis (Krishnan et al., 2006). Researchers have reported a correlation between creatinine clearance and the severity of reduced nerve conduction speed present in uraemia. It has also been proposed that neuropathy is caused by the accumulation of medium-sized molecules (300 to 12.000 Daltons), which are dialyzed more slowly than both urea and creatinine (Vanholder et al., 1994; Vanholder and De Smet, 1999). For this reason, filtration membranes permeable to medium-sized molecules improve or stabilize the nerve conduction velocities, more so than cellophane membranes. Furthermore, ultrafiltration, which removes a large portion of medium-sized molecules, improves the NCV (Nerve Conduction Velocity) and the clinical parameters (Babb et al., 1981). Nielsen (1973) proposes that nerve dysfunction is related to uraemic serum toxic factors contents inhibiting axon membrane function and $Na^+/K^+ATPase$ pump activation.

It is thought that conduction speed reduction results from $Na^+/K+ATPase$ pump related axolemma associated to uraemic toxins, producing intracellular sodium accumulation and altering membrane resting potential. This eventually leads to axonal degeneration and secondary segmental demyelination (Krishnan et al., 2006). The identification of other potential uraemic toxins are related to elevated concentrations in plasma, correlated to speed reduction of motor conduction. Within these, small, water-soluble compounds guanidines, dimethylarginine, creatinine, purines, oxalate, phosphorrus, and urea can be found, as well as both medium- and large-sized molecules: glycosylated end products, parathyroid hormone (PTH) (Stompor et al., 2011), oxidation products, peptides (beta-endorphin, beta-lipoprotein, methionine-enkephalin, adrenomedullin), beta 2 microglobulin, complement factor D and protein-bound compounds such as indole compounds, hippuric acid, homocysteine, indoxyl sulfate, and polyamines (Vanholder and De Smet, 1999). The PTH is recognized as one of the main uraemic toxins. It is one of the few substances which exhibit a causal relation: a correlation can be seen between the plasma level of this hormone and the speed of motor conduction in patients with

chronic renal failure.

It is important to note that its increase during end-stage kidney disease is caused more by a great glandular secretion than by a decrease in renal excretion; the excess of PTH gives rise to an increase in intracellular calcium, altering the functions of effectively every organ and system, including heart, liver, bone mineralization, pancreatic response, erythropoiesis, and immune response. It is noted, however, that in patients with hyperparathyroidism without uraemia there has been no pronounced effect on peripheral nerve function. At the start of dialysis, motor conduction speed stabilizes and improves, although PTH plasma levels remain high. PTH is also associated with a number of uraemic symptoms, such as pruritus (Fraser et al., 1988; Vanholder and De Smet, 1999). Many mechanisms have been put forward as causes of uraemic neuropathy; however evidence suggests that these could be associated with structural damage and the accumulation of multiple toxic agents (Fraser et al., 1988).

CLINICAL MANIFESTATIONS

Symptoms of uraemic neuropathy typically appear either slowly or subacute, and can be described as axonal symmetric neuropathy, slowly progressive and dependent on large nerve fibers. It initially affects the distal regions of the extremities as it progresses proximally. Early symptoms resemble sensory dysfunction, bringing about paraesthesia, pain, progressive loss of sensitivity, and a reduction in deep tendon reflexes (DTR). As it progresses, greater motor impairment is seen, characterized by loss of strength and distal muscular atrophy (Al-Hayk and Bertorini, 2007). During the development of clinical symptoms consistent with the involvement of large-sized fibers, both sensory and motor, a disturbance is produced in the vibration and proprioception that causes sensory ataxia, loss of DTR, decrease in NCV and loss of strength. Small-sized fibers can also be compromised, with changes in temperature perception, pain (described as burning sensation), allodynia, distestesias, visceral pain, paraesthesias and autonomic dysfunction. An isolated presentation such as this is infrequent and rarely seen absent large-sized fibers compromise. Other types of neuropathies are to be ruled out when the disorder appears in this manner (Krishnan et al., 2009; Apfel, 1999).

The earliest finding of uraemic neuropathy is loss of Achilles reflex and increased vibrating sensation threshold. The earliest clinical finding is compromise of myelinating sensory fibers, yielding paraesthesia and hypoesthesia (Al-Hayk and Bertorini, 2007). Loss of vibrating and position sensation is also present. A paradoxical hot feet sensation has been reported by 42% chronic renal failure patients. Compromise of the cranial nerve is unusual, as is transient nystagmus, miosis,

impaired extraocular movement and facial asymmetry. Focal weakness, loss of sensitivity and positive Tinel's sign are indicative of compressive mononeuropathies (Pan, 2009). Autonomic dysfunction is seen in 45 to 59% of uraemia patients. Patients may complain of dizziness, postural hypotension usually associated with changes in heart rate, dyshidrosis, gastroparesis, erectile dysfunction and abnormal ejaculation (Apfel, 1999).

DIAGNOSIS

The first step towards uraemic neuropathy diagnosis is the exclusion of other causes of neuropathy especially glucose metabolism alterations that frequently go hand in hand with the CKD. A serology test must be performed in patients with rapid progressive weakness in order to rule out vasculitic neuropathy or demyelinating neuropathies particularly Guillain-Barre syndrome and acute or chronic inflammatory demyelinating glomerulonephritis and membranous or focal sclerotic glomerulonephritis (Panjwani et al., 1996; Kohli et al., 1992; Schaublin et al., 2005; Krishnan et al., 2009). Nerve conduction studies are still the gold standard to diagnose uraemic neuropathy, which presents axon type generalized neuropathy, sensorial amplitude reduction and to a lesser degree, of motor amplitudes with relative conservation of conduction velocity (Krishnan et al., 2005; Bolton et al., 1971; Nielsen, 1973). Prolonged distal latencies due to distal nerve wrappings alteration and reduction of amplitude of action potential are mainly caused by reduction in density of long sensitive and motor fibers and H-reflex elongation; replicable abnormalities in chronic renal failure patients (Angus-Leppan and Burke, 1992).

Out of the multiple nerve conduction parameters and consistent with the initial clinical compromise of lower limbs, sural nerve sensorial amplitude is the most sensible indicator of uraemic neuropathy as it decreases in 50% of all cases (Krishnan et al., 2005). Compared to axonal uraemic neuropathy, chronic renal patients with demyelinating neuropathy present slowing nerve conduction, usually preserving sensibility and motor amplitudes during the initial stages of the disease. Bolton et al. (1971) found through needle electromyography minimal or absent fibrillation or, an acute positive wave in the most advanced cases of uraemic neuropathy, with distal predominant muscular denervation (Bolton et al., 1971). Other parameters that have been considered as very sensible for uraemic neuropathy diagnosis are the abnormalities on the late responses or F waves (proximal motor conduction) (Kiernan et al., 2002) and H-reflexes (Krishnan et al., 2005; Krishnan et al., 2009), the vibration detection threshold on the feet and the decrease of the NCV (Laksonen et al., 2002). There is a correlation between neuropathy stage and nerve conduction parameters. Uraemic neuropathy is one of the symptoms of chronic renal failure; nevertheless it is always convenient

to rule out other possible causes (neurotoxic, metabolic or associated inflammatory alterations). The studies ordered should be related to the clinical frame, such as inflammatory markers, antinuclear antibodies, rheumatoid factor, hepatitis B and C antibodies, cryoglobulins, glycated haemoglobin, folic acid, vitamin B12, Thyroid-stimulating hormone (TSH), erythrocyte-sedimentation velocity, serum protein electrophoresis and screening for heavy metals in urine, if needed. The CSF proteins are usually high but cell count and glycorrhachia are normal (Krishnan and Kiernan, 2007).

TREATMENT

Even though there are multiple treatments, renal transplant continues to be the only effective treatment for uraemic neuropathy and should be considered in any patient with progressive neuropathy (Bolton, 1976) as standard dialysis plan, 3 times a week, generally stops the progression of the neuropathy but rarely generates an important clinical improvement. Rapid progressive neuropathy is frequently accepted as an indication for patients to be classified on the critical transplant list. After the transplant, clinical recovery generally occurs in a period of 3 to 6 months, nevertheless some patients continue to report an increased improvement for up to 2 years (Bolton, 1976). Nerve function changes have been examined in CKD patients before, during, and after dialysis treatment: pre-dialysis abnormalities are closely related to the K^+ level. These abnormalities occur at K^+ levels below those required to produce cardiac toxicity, presenting axonal changes with K^+ concentrations that fluctuate in the normal to high ranges. Before dialysis, multiple axonal excitability indicators are abnormal, with increase in the refractory period, increase in re-polarization threshold accommodation, and reduction of excitability; all these changes indicate axonal depolarization. Hemodialysis produces rapid and significant normalization of excitability parameters as well as improvement, although minor excitability abnormalities persisted (Krishnan et al., 2009; Kiernan et al., 2002).

In chronic renal patients, with demyelinating neuropathy, standard immunomodulation treatments, such as immunoglobulin IV, have been used with some success. Nevertheless, potential benefits should be assessed against small, but well documented, nephrotoxicity risk (Orbach et al., 2004), specially on patients with residual renal function for whom complications could accelerate the need for dialysis. Patients with painful neuropathy can benefit from treatment with tricyclic antidepressants such as amitriptyline; or with anticonvulsive drugs such as sodium valproate or gabapentin. Vitamin supplements with pyridoxine and methylcobalamin have also improved relief from neuropathic pain in CKD patients (Okada et al., 2000; Kuwabara et al., 1999). Yatzidis et al. (1984)

suggest the use of biotin. In a small study group an improvement was found in the higher mental functions, sensorial and motor symptoms after 3 months of treatment. Due to the potential role of K+ in the development of uraemic neuropathy, a diet with restriction of K+ intake has been considered as beneficial (Krishnan et al., 2006; Laaksonen et al., 2007); this could prevent the presence of neuropathy in early stage CKD patients.

Different dialysis membranes for treatment of uraemic neuropathy have been studied. For example the Djukanovic group found that hemodialysis membranes with high permeability to medium molecular weight molecules (300 to 12000 daltons), prevent plasma accumulation of these molecules with significant improvement. Bolton and his group reported poly-neuropathy improvement with high hemodialysis flow (Laaksonen et al., 2002). In the past, compared to hemodialysis, peritoneal dialysis was associated to lower incidence of uraemic neuropathy due to increased ability to remove medium-sized molecules; progressive neuropathy is an indication to start dialysis therapy and an important indicator of insufficient dialysis (Krishnan et al., 2009). In some cases, a program change to daily high flow dialysis may prevent clinical deterioration. Existing uraemic neuropathy therapies, including dialysis and vitamin supplements, are not satisfactory (Bolton, 1976). Erythropoietin has demonstrated nervous motor conduction velocity improvements on pre-dialysis patients.

In most patients, chronic hemodialysis can stabilize the neuropathy. Still, the progression of neuropathy does not improve simply by manipulating the hemodialysis schedule. Paraesthesia can quickly improve once the hemodialysis starts, but all other symptoms will persist (Laaksonen et al., 2002). For two years in average (4 to 68 months) after successful renal transplant, abnormal electrophysiological uraemic neuropathy patterns were studied on 17 patients, at first, motor and sensitive conduction velocities were reduced, distal latencies lengthened, and evoked action potentials reduced or absent. These abnormalities were especially high with clinically severe neuropathies, especially when axonal degeneration and demyelination were combined. Although some fibers continued to be degenerated in severe neuropathies, these patients presented clinical improvement; the results suggest segmental remyelina-tion as the main reason for improvement. In this study 4 patients presented late failure and recurrent neuropathy after renal transplant; still these patients underwent a second effective transplant with neuropathy improvement (Bolton, 1976). Nevertheless it has been reported that when axonal degeneration is highly extended and a great number of axons are lost, transplant results will not match the best expected (Galassi et al., 1998). There is clear evidence that cognitive function improves after renal transplant. In a study of CKD patients, 6 months after

transplant, improvement was demonstrated as regards their baseline (Griva et al., 2006).

CONCLUSIONS

CKD prevalence has been increasing progressively, becoming a global public health issue. CKD neurologic complications affect more than half of these patients, along with a fast and marked deterioration of their quality of life. Due to the increased number of CRD patients, we can often find this type of patients with multiple and unspecific complaints, which makes it a must to recognize the symptoms and diagnostic methods in order to make a precise identification of potential complications. Uraemia may appear in many ways, such as uraemic neuropathy, a polyprogressive, sensitive-motor, and symmetric distal neuropathy; it can also show autonomic CNS dysfunction. Uraemic neuropathy has been described as pathology since the late XIX century, but still its pathophysiology is not yet clear; multiple hypotheses are still being studied. The first symptoms of uraemic neuropathy are paraesthesias and hypo-esthesias, the physical exam will show a quick loss of Achilles reflex and increase in the vibratory sensation threshold.

The nerve conduction studies are still the gold standard for uraemic neuropathy diagnosis. Out of a number of possible parameters, sural nerve sensorial amplitude, late responses abnormalities, F waves, H-reflexes and NCV loss have been highlighted. Hemodialysis with high permeable membranes prevents excess accumulation of medium weight molecules, with significant improvement in these patients. Renal transplant continues to be the only effective treatment for uraemic neuropathy and should be considered in any patient with progressive neuropathy. Because of this it has been accepted as an emergency transplant list indication. Multiple medicines, vitamin supplements and strategies have been used trying to improve the quality of life of these patients but to date significant improvements have only been found with aggressive therapies such as dialysis and renal transplant.

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