REVIEW ARTICLE

Uremic neuropathy: an overview of the current literature

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SUMMARY

INTRODUCTION: *Peripheral neuropathy is a disorder that affects the cell body, axon or myelin of motor or peripheral sensory neurons and occurs in 60-100% of patients who are submitted to dialysis due to chronic kidney disease. Uremic neuropathy (UN) is attributed to the accumulation of organic waste, evident in patients with reduced glomerular filtration rate.*

OBJECTIVES: *This review aims to make clinical characteristics of uremic neuropathy evident enabling early diagnosis and treatment.*

METHODS: *This is a literature review of articles published on PubMed over the last 10 years using "Uremic Neuropathy" as "Title/Abstract".*

RESULTS: *A total of nine articles that met the inclusion criteria were included. UN is a distal symmetric sensorimotor polyneuropathy that occurs due to the accumulation of uremic toxins associated with an oxidative stress-related free radical activity. Hyperkalemia is thought to play an important role in its pathophysiology. Diagnosis depends on nerve conduction studies, and treatment includes dialysis or renal transplant.*

CONCLUSION: *Clinical presentations of UN are broad and non-specific; nonetheless, it is important to detect early changes in order to avoid its progression. The earlier UN is diagnosed and treated, the more successful are the clinical outcomes.*

KEYWORDS: *Neural conduction. Dialysis. Kidney Transplantation. Peripheral Nervous System Diseases. Uremia/complications.*

INTRODUCTION

Peripheral neuropathy (PN) is a disorder that affects the cell body, axon or myelin of motor or peripheral sensory neurons and can respectively be classified as neuropathological, axonal or demyelinating. This condition is either hereditary or acquired and may be further subdivided into sensory, motor or autonomic [1]. PN has a large spectrum of causes (such as nutritional deficiencies and toxic neuropathies [2] as well as clinical presentations [3]; however, constant and recurring pain occurs in almost all types of this disorder [4].

The overall prevalence of peripheral neuropathy is 2.4%. However, this number increases exponentially in certain age groups, and it may even be an under-

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estimate since traumatic causes are not included in this percentage [3].

Peripheral neuropathy occurs in 60-100% of patients who are submitted to dialysis due to chronic kidney disease (CKD) [5]. Uremic neuropathy (UN) occurs when renal dysfunction impairs filtration, leading to the accumulation of organic waste. This is evident in patients with reduced glomerular filtration rate (GFR) usually attributed to end-stage renal disease (ESRD) [6].

This review aims to make the clinical characteristics of uremic neuropathy evident enabling early diagnosis and treatment in order to prevent the effects of the advanced stages of this condition. The secondary purpose is to discuss the prognosis of uremic neuropathy based on data hinted in literature.

METHODS

This is a literature review of articles published on PubMed over the last 10 years using "Uremic Neuropathy" as "Title/Abstract". A total of 15 articles were found and 11 of them were available. Then, 9 articles were included as they met the inclusion criteria (Figure 1) – they were clinical studies and discussed uremic neuropathy.

RESULTS

Prevalence

In 1961, Martin and Tyler published the first report on uremic neuropathy in patients with hereditary intestinal nephritis with distal sensory-motor polyneuropathy [7,8]. Asbury et al, in 1963 used the term uremic polyneuropathy to describe distal sensorimotor changes due to uremic toxins. Uremic neuropathy is more frequent in males than in females [8] and is a common condition: studies have shown that it's prevalence varies from 50-100% in patients with chronic kidney disease [7,9-11]. This large range of values is due to the application of different criteria for the diagnosis of UN. The prevalence of UN in the pediatric population is unknown [10].

Pathology and pathophysiology of Uremic Neuropathy

UN is a distal symmetric sensorimotor polyneuropathy that typically affects lower limbs [7,12] and is due to length-dependent axonal degradation and secondary focal loss of myelin sheaths [7,8]. This is considered a demyelinating condition which leads to axonal degeneration and loss [8-10].

The accumulation of uremic toxins (the "middle toxins": guanidine compounds, parathyroid hormone, and myoinositol) [10,11] associated to oxidative stress-related free radical activity causes motor, sensory and autonomic nerve damage which leads to UN [8,13,14]. Although this exact mechanism remains unknown [10], there are hypotheses supporting the role of electrolytes in this process [8,9,12]. Hyperkalemia and hyperphosphatemia cause chronic uremic depolarization of nerves, contributing to the development of UN [8,12]. This occurs because potassium disrupts the normal ionic gradient and therefore activates calcium-mediated processes leading to axonal death [9].

UN is usually asymptomatic until renal function is under 15%, and glomerular filtration is lower than 10–12 ml/min, which usually happens 10-15 years after the onset of the underlying disease, such as diabetic neuropathy [7,8,10,11]. This type of neuropathy is one of the most frequent neurological manifestations of end-stage renal disease (ESRD) [11].

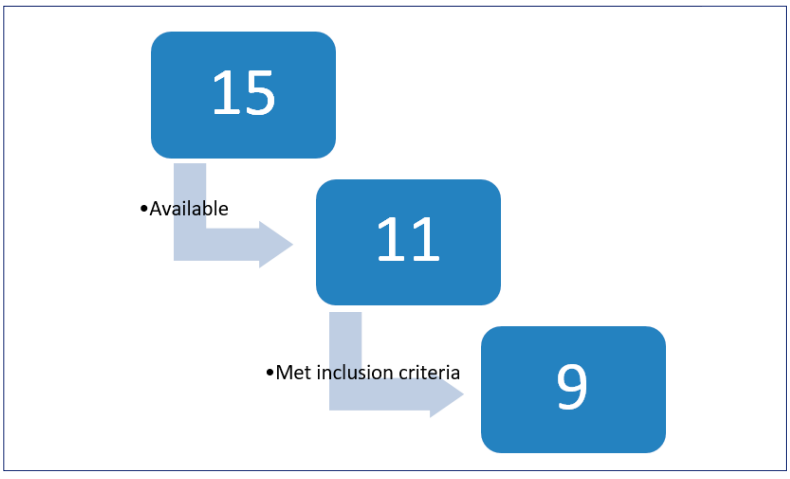


FIGURE 1. SELECTION PROCESS OF ARTICLES INCLUDED IN THIS REVIEW.

Both slowly and rapidly progressing sensorimotor axonal neuropathies are relatively common [10]. However, there have also been reports of fulminant motor neuropathies, which occurred under specific clinical conditions such as sepsis and severe CRF [8].

Hyperkalemia and hyperphosphatemia increase the risk of developing UN [9]. Other risk factors for UN are diabetes, advanced age and low creatinine and clearance [10].

A schematic representation of uremic neuropathy causes can be seen in Figure 2.

Symptoms of Uremic Neuropathy: Sensory and motor changes due to Uremic Neuropathy

Symptoms of UN vary, but it typically presents as a slowly progressing sensorimotor axonal neuropathy [9] which advances proximally, starting from the lower limbs and may spread to upper extremities [7]. Early symptoms are paresthesia, paradoxical heat sensation, restless leg syndrome, increased pain sensation, and cramps [7,9]. Long-term symptoms include weakness, impaired deep tendon reflexes, imbalance, numbness, and atrophy of the lower limbs [7-11].

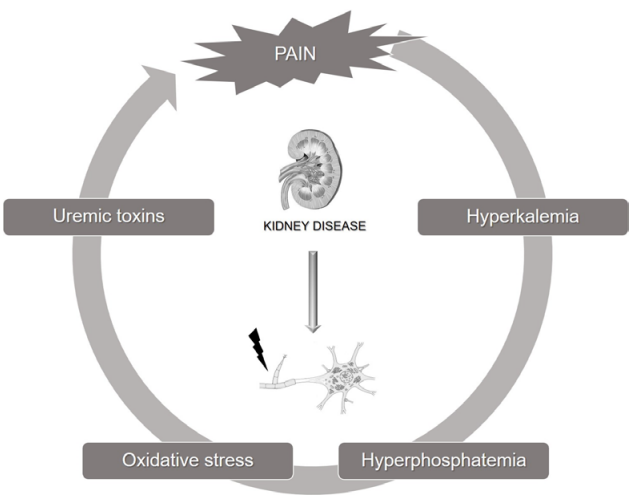
Nerve conduction and quantitation of sensory loss

Quantitation of sensory loss and nerve conduction is one of the main tools used to evaluate UN, as well as electromyography [11]. In patients suffering from this condition, nerve conduction velocity usually falls to 50-60% of normal values [8]; however, light touch and vibratory perception thresholds are more sensitive to evaluate either progression or recovery of UN than conduction velocity [8].

Some patients suffer thermal sensitivity impairment before they have sensory and motor damage. The number of functional axons in a nerve is evaluated according to changes in the amplitude of muscle response and sensory nerve action potentials [8]. The myelination of nerve fibers and their density is tested by velocity conduction. The most common morphological change in UN is the loss of large myelinated fibers, and positive neuropathic symptoms tend to correlate with quantitative results in conduction and sensory tests [8].

After nerve transplantation, there is an increase in nerve conduction due to remyelination [8]. Studies have shown that motor nerve conduction (MCV) is a significant predictor of mortality [13] in hemodialysis patients and achieves statistically significant values: (HR= 0.92; CI (0.86–0.99); $p < 0.05$) [15]. MCV correlates significantly with dialysis dose; however, further investigation is needed in order to confirm this hypothesis [13].

FIGURE 2. REPRESENTATIVE SCHEME OF UREMIC NEUROPATHY POSSIBLE CAUSES



Uremic Neuropathy in Children and Teenagers

The prevalence of UN in children is unknown [10], and this population usually does not present clinical evidence of UN; however, nerve conduction is altered, likewise in adults [8]. Authors showed that mean peroneal motor nerve conduction velocity (MNCV) was significantly decreased in children with mild renal failure (serum creatinine concentration, 1.5 to 2.9 mg/dL, normal range: 0.8–1.2 mg/dL), while ulnar MNCV was significantly decreased only when the serum creatinine value was at least 9 mg/dL. Within a year of renal transplantation, ulnar MNCV tends to return to normal values, and it takes 3 years for peroneal MNCV to go back to baseline values.

These parameters could potentially be used to evaluate the development of UN. However, they are only meaningful when renal function is very low or after a long period of time. Therefore, the periodic measurement of nerve conduction velocity is not useful to follow UN in children undergoing chronic hemodialysis [8].

Uremic Optic Neuropathy

Uremic optic neuropathy (UON) is a possible manifestation of UN that causes sudden vision deterioration and involves focal edema of the optic nerve

head [14]. Other related ophthalmic disorders include swelling of optic nerve heads, blurred margins of the optic disks seen using an ophthalmoscope. This disease should be taken into consideration as a possible diagnosis when patients with advanced chronic kidney failure present vision deterioration.

Seo et al. [14] described a patient suffering from UON who presented all the manifestations mentioned above, and the visual-evoked potential tests revealed reduced amplitude and increased latency in one of the eyes. This patient was treated with hemodialysis and corticosteroids, and his visual acuity and visual field improved, and the optic disk swelling was resolved.

The pathogenesis of UON is not well known. However, it has been shown to be related to the accumulation ofthat dialyzable toxin metabolites. Hemodialysis in combination to corticoids is the standard treatment for UON [14].

Diagnosis

The gold standard method to diagnose UN is a nerve conduction study [7,9]. Complementary methods include neurological assessment and biopsy of distal axons [12]. Since some UN symptoms are subjective and cannot be quantified using clinical tests, it might also be interesting to include psychological evaluation in order to investigate UN [15]. UN, however, may remain asymptomatic for a long time and only cause symptoms when severe damage has already been done. Therefore, an investigation should take place even in asymptomatic patients who present risk factors for UN [7].

Treatment of Uremic Neuropathy

Treatments that may reverse the effect of UN and improve nerve function are dialysis and renal transplantation [7,9,10]. Studies have shown a more significant reduction in the progression of UN due to an increase in dialysis dose, be it peritoneal or conventional dialysis [9]. It is controversial whether patients submitted to peritoneal dialysis have inferior results in the treatment of UN compared to those submitted to conventional hemodialysis [11]. Hemodiafiltration is another therapeutic option that also benefits motor nerve excitability.

Renal transplantation is the only definite treatment that interrupts the progression of UN and reverts symptoms. It is important to note that results are inversely proportional to the disease duration prior to the transplant: a shorter disease time leads to better post-transplant clinical outcomes [10]. Nonetheless, in patients who may not undergo this procedure, either due to clinical restrictions or personal denial, effective dialysis is definitely a good therapeutic option [11] as it also normalizes most nerve excitability parameters [8].

Comparison of uremic neuropathy with other types of neuropathies:

There are many different types of neuropathies other than Uremic, including Diabetic, Alcoholic, Chronic Inflammatory, and Infectious. Below is a comparative table with the symptoms and treatments of these main types of neuropathies.

TABLE 1. ASSOCIATION OF DIFFERENT TYPES OF NEUROPATHY AND ITS TREATMENTS

NEUROPATHY	MAIN SYMPTOMS	TREATMENT
Uremic Neuropathy	-Pain, numbness, and tingling in feet and legs; -Cramps, muscle twitches, or increased pain sensation in the feet and legs; -Muscle weakness [16]	-Dialysis -Kidney Transplant [16]
Diabetic Neuropathy	-Slowly and progressive primarily sensory deficit following a "stocking-glove distribution" [17]	-Treatment can range from lifestyle modification and strict glucose control to the use of immunosuppressant medications [17,18]
Alcoholic Neuropathy	-Painful paresthesia; -Muscle weakness; -Sensory and motor symptoms extend proximately into the arms and legs; -Gait impairment may be present [19,20]	- Thiamine treatment has been shown not to be effective; - Therapy ought to include cessation of alcohol ingestion, aiming at the toxic target(s) of alcohol [22]
Chronic Inflammatory Neuropathy	-Weakness is typically symmetric and characteristically involves proximal and distal muscles; -Sensory symptoms include numbness, tingling, gait imbalance, and, at times, painful paresthesias [21]	-Steroids, plasma exchange, and intravenous immunoglobulin may be used as 1st line treatment options [21]
Infectious neuropathy (HIV, HCV, CJ, LD[23])	-HIV, HCV, LD: pain, weakness, paresthesia and absent ankle reflexes -CJ: acute, ascending, motor neuropathy associated with Guillan-Barré syndrome (GBS) [23,24]	-HIV: analgesics, anticonvulsants [24] -HCV: steroids, antiviral therapy, rituximab, interferon alfa [25,26] -LD: doxycycline, amoxicillin, cefuroxime,ceftriaxone [27-29] -CJ: azithromycin, erythromycin, fluoroquinolones; treatment for GBS such as plasmapheresis, plasma exchange and intravenous immunoglobulin [30,31]

CONCLUSION

UN is a prevalent condition, affecting 60 to 100% of patients who suffer from chronic kidney disease, depending on the classification criteria used. The exact mechanism of the demyelinating process leading to axonal degeneration and loss is still uncertain. However, electrolytes, such as potassium, have shown to play an important role in the pathophysiology of UN. Clinical presentations of UN are broad and may be non-specific; nonetheless, it is essential to detect early changes in order to diagnose UN and avoid its progression. The earlier the signs and symptoms of UN are detected, the earlier UN is diagnosed using nerve conduction studies and treated with dialysis or renal transplant, leading to greater clinical success.

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RESUMO

INTRODUÇÃO: *A neuropatia periférica (NU) é um distúrbio que afeta o corpo celular, o axônio ou a mielina do motor ou neurônios sensoriais periféricos e ocorre em 60%-100% dos pacientes que são submetidos à diálise por doença renal crônica. A neuropatia urêmica é atribuída à acumulação de resíduos orgânicos, evidente em pacientes com taxa de filtração glomerular reduzida.*

OBJETIVO: *O objetivo desta revisão é fazer com que as características clínicas da neuropatia urêmica sejam evidenciadas, permitindo o diagnóstico e tratamento precoce.*

MÉTODO: *Esta é uma revisão da literatura de artigos publicados no PubMed nos últimos dez anos usando "Neuropatia Urêmica" como "Título/Resumo".*

RESULTADOS: *No total, foram incluídos nove artigos que atendem aos critérios de inclusão. A NU é uma polineuropatia sensório-motora simétrica distal que ocorre devido ao acúmulo de toxinas urêmicas associadas à atividade de radicais livres relacionados ao estresse oxidativo. A hipercalemia tem um papel importante na sua fisiopatologia. O diagnóstico depende de estudos de condução nervosa e o tratamento inclui diálise ou transplante renal.*

CONCLUSÃO: *As apresentações clínicas das NU são amplas e não específicas; no entanto, é importante detectar mudanças iniciais para evitar sua progressão. Quanto mais precoce for a detecção e tratamento da NU, melhor será o resultado clínico.*

PALAVRAS-CHAVE: *Condução nervosa. Diálise. Transplante de rim. Doenças do sistema nervoso periférico. Uremia/complicações.*

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