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Can the Aggravation of Pruritus be a Sign of Worsening Peripheral Neuropathy in Uremic Disease? A Clinical and Neurophysiological Study

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Abstract

Introduction: Neuropathy is a frequent complication of uremic disease, causing motor and sensorial symptoms, mostly localized in the lower limbs. Another symptom related to uremic disease is pruritus, which may be diffuse all over the body, but usually occurring in the lower limbs. In the terminal phase therapeutic measures are taken, targeting the sensitive components of neuropathy, with the use of drugs against pain, and targeting itching, using different substances, the most widely used of which is gabapentin.

Methods: The severity of neuropathy is variable, ranging from slight to severe and may or may not be associated with the length of chronic dialysis treatment. The use of measurement scales of pain, VAS type adapted to the itching, may link both conditions of neuropathy and itching.

Results: We noted that a severe intensity of pruritus can be related to severity of neuropathy in uremic subjects and may become predictive of progressing neuropathy.

Conclusions: In this study we examined a group of uremic subjects, clinically and with neurophysiological investigations, discovering a remarkable association between the intensity of pruritus and the severity of neuropathy. Pruritus can be considered a marker of progressing neuropathy and it might to be helpful in undertaking more effective therapeutic strategies.

Keywords: Pruritus; Uremic disease; Neuropathy; Renal disease.

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Introduction

Peripheral neuropathy represents a frequent complication of uremic disease, with a prevalence of 60 - 80 % of cases[1], while pruritus is a symptom considered present in 30 - 60 % of uremic patients[2]. In this study, we have observed 12 uremic patients who had been admitted to our Unit to determine whether or not their pruritus was a clinical sign of a uremic neuropathy. The patients underwent neurophysiological tests (electroneurography) that confirmed the suspected diagnosis of uremic neuropathy. We noted that the patients affected by more severe neuropathy, complained of a greater intensity of pruritus, associated with marked skin le-

sions due to severe scratching. Therefore, we hypothesized that pruritus can be a marker of progression of uremic neuropathy.

Materials and Methods

Our study is based on a 12 case series of uremic patients examined for peripheral neuropathy. This group was composed by 11 males and 1 female, aged between 46 - 82 years, (average 63 years). All patients were under three days weekly hemodialytic treatment and referred clinical symptoms, evoking the presence of peripheral motor and sensory neuropathy: weakness of the legs, pain and paresthesias of lower limbs, associated with pruritus. The dosage of serum urea before and after hemodialysis, the KT/V, the percentage of URR and the adequacy ratios of hemodialysis, showed the efficacy of the hemodialysis treatment, as shown in Table 1.

Table 1: Sex, age, years in hemodialysis, severity of neuropathy and pruritus intensity of the patients under study.

No. of patient	Sex	Age	Hemodialysis period	Neuropathy ENG results	Pruritus intensity
1	F	46	3 years	Moderate	+
2	M	50	4 years	Moderate	+
3	M	58	4 years	Moderate	+
4	M	60	4 years	Moderate	+
5	M	64	8 years	Severe	++
6	M	72	9 years	Severe	++
7	M	80	9 years	Severe	++
8	M	82	4 years	Severe	++
9	M	68	3 years	Moderate	+
10	M	72	3 years	Severe	++
11	M	60	2 years	Moderate	+
12	M	51	3 years	Moderate	+

Neurological examination showed in all patients a reduction or abolition of patellar and Achilles tendon reflexes of the lower limbs, while it was normal to the upper limbs. Particularly, 5 of these patients reported a progressive worsening of intensity of pruritus, associated to serious skin alterations like dyscromias and redness, until severe excoriations, mainly at the lower limbs. All patients underwent neurophysiological procedures, as Electroneurography (ENG), consisting of Nerve Conduction Sensory Velocities Study (NCSVs) and Nerve Conduction Motor Velocities Study (NCMVs), in the upper and lower limbs, included CMAPs (Compound Motor Action Potentials) and SAPs (Sensory Action Potentials), with study of latency and amplitude, of Median nerve, Peroneal nerve, Sural nerve bilaterally. We considered the following normal values: Median nerve: CMAP with distal latency < 4 milliseconds (ms), 2,8 ± 0,8, amplitude > 4,5 millivolts (mV), 14 ± 9, NCMV > 50 meters per second (m/s), 59 ± 5; SAP: distal latency < 2,6 ms, 2,3 ± 0,2, amplitude > 22 micronvolts, 50 ± 15, NCSV > 46 m/s, 56 ± 5. Peroneal nerve: CMAP distal latency <4,9, 3,8 ± 0,5, amplitude >3,5 mV, 10 ± 5, NCMV > 42 M/S, 49 ± 4. Sural nerve: distal latency < 3,2 ms, 2,5± 0,4, amplitude > 7 micronvolts, 18 ± 8, NCSV > 43 m/s, 53 ± 5. Regarding pruritus, we prepared a VAS (Visual Analogic Scale) pain rating scale, itch- adapted, consisting in asking the patient to localize over a line or colored bar, over a length of 10 cm, the point corresponding to pruritus intensity. Inferior and superior limits of this scale were zero (absence of pruritus) and 10 cm (maximum pruritus).

Results

The ENG results of our examined patients were as follows. A reduction in NCMV (Nerve Conduction Motor Velocity) of the peroneus nerve bilaterally in all patients, mostly marked in 5 patients, who had reported a greater intensity of pruritus. NCSV reduction (Nerve Conduction Sensitive Velocity) was also observed in all patients, as well as SAPs (Sensitive Action Potentials) was reduced in 7 patients, who revealed an increase in distal latency. Conversely, SAPs were absent in the same patients who reported a greater intensity of pruritus. The results regarding the investigation of the median nerve were normal. Details of the results of neurophysiological tests are shown in Table 2. These results have confirmed the clinical diagnosis of bilateral sensory- motor neuropathy of the lower limbs, while the examination of the upper limbs showed normal values, upon exploration of the median nerve.

Table 2: Results of the electroneurography studies on the Median, Peroneal and Sural nerves.CMAP: compound motor action potential; NCMV: nerve conduction motor velocity; SAP: sensory action potential; CMAP: compound motor action potential. RIG: right; LEF: left.

Number patient	Median nerve	Peroneal nerve	Sural nerve
1	Normal	CMAP 5,0, NCMV 39 RIG CMAP 5,1 NCMV 40 LEF	SAP 3,4 NCSV 40 SAP 3,5 NCSV 39
2	Normal	CMAP 5.3 NCMV 41 RIG CMAP 5,2 NCMV 40 LEF	SAP 3,5 NCSV 40 RIG SAP 3,6 NCSV 39 LEF
3	Normal	CMAP 5,3 NCMV 42 RIG CMAP 5,2 NCMV 41 LEF	SAP 3,4 NCSV 40 RIG SAP 3,4 NCSV 40 LEF
4	Normal	CMAP 5,1 NCMV 42 RIG CMAP 5,1 NCMV 42 LEF	SAP 3,5 NCSV 41 RIG SAP 3,4 NCSV 42 LEF
5	Normal	CMAP 5,3 NCMV 40 RIG CMAP 5,4 NCMV 39 LEF	SAP absent RIG SAP absent LEF
6	Normal	CMAP 5,7 NCMV 39 RIG CMAP 5,8 NCMV 37 LEF	SAP absent RIG SAP absent LEF
7	Normal	CMAP 6,0 NCMV 35 RIG CMAP 5,9 NCMV 36 LEF	SAP absent RIG SAP absent LEF

8	Normal	CMAP 6,3 NCMV 34 RIG CMAP 6,2 NCMV 33 LEF	SAP absent RIG SAP absent LEF
9	Normal	CMAP 5,1 NCMV 41 RIG CMAP 5,0 NCMV 40 LEF	SAP 3,4 NCSV 40 RIG SAP 3,5 NCSV 39 LEF
10	Normal	CMAP 6,2 NCMV 33 RIG CMAP 6,1 NCMV 33 LEF	SAP absent RIG SAP absent LEF
11	Normal	CMAP 5,2 NCMV 41 RIG CMAP 5,1 NCMV 40 LEF	SAP 3,4 NCSV 42 RIG SAP 3,5 NCSV 41 LEF
12	Normal	CMAP 5,2 NCMV 41 RIG CMAP 5,1 NCMV 41 LEF	SAP 3,5 NCSV 41 RIG SAP 3,5 NCSV 41 LEF

Following the results obtained by neurophysiological tests, we divided the patients in two groups, one with moderate neuropathy (7 patients) and one with severe neuropathy (5 patients), as shown in Table 3. We noted, also a greater severity of neuropathy in older males, aged 64 - 82 years, who had been in chronic hemodialysis treatment for longer time[3].

Table 3: Serum Urea pre- and post-dialysis, KT/V and URR in the 12 patients under study.

No. of PATIENT	Serum Urea Pre-Dialysis	Serum Urea Post-Dialysis	KT/Veq	URR %
1	104	22	1.61	78.85
2	119	27	1.56	77.31
3	116	39	1.22	66.38
4	91	20	1.59	78.02
5	112	32	1.3	71.43
6	105	38	1	63.81
7	111	31	1.32	72.07
8	93	31	1.1	66.67
9	160	38	1.33	76.25
10	146	38	1.44	73.97
11	126	38	1.23	69.84
12	125	38	1	63.9

All patients underwent VAS (Visual Analogic Scale) assessment, itch adapted, to correlate the intensity of pruritus to the severity of neuropathic pain. The results showed that 7 patients reported a score between 5 - 6 cm, while the 5 patients who reported severe pruritus intensity, expressed a score between 9 - 10 cm. They were the same patients who showed severe alterations of neurophysiological parameters. This suggested a remarkable association between neuropathy severity in the lower limbs and worsening of pruritus.

Discussion

Uremic neuropathy has been thoroughly studied over the past many years and numerous articles have been published on this matter. Bazzi et al., in a clinical and electrophysiological study of an extensive series of 135 short and long term patients on hemodialysis, evaluated the presence and the grade of peripheral neuropathy, showing an 80% percent incidence of neuropathy and its prevalence in older patients[4]. Jurcic et al., noted that a 10 yearlong term dialysis and older age, were associated with a further worsening of neuropathy[5]. Jedras et al., however, found, by clinical and electrophysiological studies, a significantly more prevalent neuropathy among male patients[6].

Pharmacological treatment includes the use of anti-epileptic Gabapentin, which has proved effective in neuropathic pain. Gabapentin binds to the voltage-dependent calcium channels by decreasing the activity of several neurotransmitters such as glutamate, norepinephrine, substance P and amplifying the activity of the neurotransmitter GABA, by increasing its intersynaptic concentration. It is also active with a non-synaptic GABAergic activity. However, the use of Gabapentin, that is still used in neuropathic pain has not yet solved the problem of the affected patients, especially if used by itself, as evidenced by a recent study by Xu L et al[7].

Pruritus is a sensorial symptom similar to pain perception. Pruritus neuronal pathways are constituted by amielinic C sensitive nervous fibers that receive information from skin receptors and transmit to the spinal cord, reaching the thalamic region. These fibers that are not related to those nociceptive, are placed between the epidermis and dermis layers, where they interact with keratinocytes and mast cells which release chemical mediators, such as histamine, P substance, cytokines, proteases and others. A neurobiological signal seems to then arrive to the cortical brain structures, where it is processed as pruritus. Another hypothesis considers the possibility that in uremic disease, there may be the presence of an abnormal distribution of the cutaneous innervation, suggesting that uremic patients can develop specific dermal alterations, like different innervation pathways, which could be responsible for an elevated pruritus symptomatology, signs of hypersensitivity and reduced perception threshold, that could explain, for example, that the use of gabapentin, an effective treatment of neuropathic pain, can be also administered in uremic pruritus, since pruritus and pain pathways seem to be similar. Fantini et al., suggested an involvement of terminal cutaneous fibers in uremic neuropathy, using immunofluorescence methods to search for the presence and the distribution of neuronal markers. They found a reduction in the number of cutaneous nerve terminals, assuming that altered skin innervations can be a possible consequence of neuropathy[8,9]. Furthermore, some groups investigated the possible influence of the autonomic nervous system on the emergence and persistence of pruritus, by using special tests, such as sympathetic skin response (SSR) and RR Interval Variation, in basal and profound breath conditions (RRIV), but concluded that pruritus is related to somatic neuropathy more than to autonomic dysfunction[10]. Finally, in uremic patients, pathophysiology of pruritus is explained by sensitive nervous fiber dismodulation, together with cutaneous deposition of irritative substances, as calcium salts and uremic toxins, provoking skin xerosis. Pruritus symptom is furthermore caused by many diseases, besides uremia, as irritative- allergic skin pathologies, systemic diseases, liver and endocrine, parasites, neoplastic, especially hematologic, infective,

psychiatric, psychogenic, physical photo-induced and iatrogenic diseases. Treatment of pruritus includes both local and an oral therapy. The first consists in the use of topical emollients as capsaicin. The second includes Gabapentin, opioid receptor antagonists, thalidomide, but Gabapentin is preferred for its minor side effects. For severe skin alterations, short wave UV treatment (UVB) is considered as treatment of choice[2]. More recent data showed that approximately 88.9 % of patients with uremic pruritus responded well to treatment with gabapentin at a dose of 300 mg daily, with mild and well tolerated adverse effects[11]. A review of the recent literature allowed us to realize that there is evidence that in uremic patients undergoing hemodialysis, the progression of pruritus is linked to the severity of neuropathy and that the more intense the pruritus in these patients, the more severe is their neuropathy.

Conclusions

Our study offers some interesting insights: firstly, we know that the peripheral neuropathy is a frequent complication in uremic patients and has a chronic course, presenting with clinical sensory-motor symptoms that are somewhat serious. Pruritus, on the other hand, is another frequent complication, but is less frequent than peripheral neuropathy. It is also known that the pathways carrying both neuropathic pain and pruritus are similar but not the same and this analogy allows a correlation between the two symptoms. We have found that severe pruritus is associated with a greater severity of neuropathy. Aggravation of pruritus, in our view, could be a marker of worsening peripheral neuropathy, helpful to monitoring uremic patients, mostly in terminal phase.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all the participants included in our study.

The article does not contain any data obtained by animals' studies performed by any of the authors.

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