ELECTRO-CLINICAL AND PROGNOSTIC PROFILE OF UREMIC POLYNEUROPATHY AMONG DIALYSIS PATIENTS

PROFIL ELECTRO-CLINIQUE ET PRONOSTIC DE LA POLYNEUROPATHIE UREMIQUE CHEZ LES PATIENTS DIALYSES

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Abstract

Background: Patients with ongoing dialysis are prone to damage in the peripheral nerve system. Our aim is to study clinical features, electrophysiological characteristics and severity of uremic polyneuropathy (PNP).
Methods: We included all dialysis chronic kidney disease patients over 12 months.
Results: Sixty-five patients were enrolled. We identified PNP in 31 patients (47.7%). The mean age was 49 ± 17,4 years old with a sex ratio of male to female 1.6. On examination, 54,8% of the patients were asymptomatic. Axonal PNP was the most frequent type (90%). The occurrence and the severity of PNP were significantly correlated with older age, increased "total neuropathy symptom score" and raised β2-microglobulinemia. Conclusion: Uremic PNP in patients under dialysis is frequently asymptomatic. It should be systematically identified. Assessment of predictive factors is crucial for an early and appropriate therapeutic approach.

Key Words: Chronic kidney disease; Dialysis; Electroneuromyography; Polyneuropathy

Résumé

Introduction : La neuropathie urémique est une complication fréquente de l'insuffisance rénale chronique (IRC). Notre objectif est d'étudier les caractéristiques électro-cliniques et la sévérité de la polyneuropathie urémique (PNP). Méthodes : Nous avons inclus les patients ayant une IRC terminale au stade de dialyse sur une période de 12 mois. Résultats : Soixante-cinq patients ont été recrutés. Une PNP a été identifiée chez 31 patients (47,7%). L'âge moyen était de 49 ± 17,4 ans avec un sex-ratio (H/F) de 1,6. A l'examen, 54,8% des patients étaient asymptomatiques. La PNP axonale était la plus fréquente (90 %). La survenue et la sévérité de la PNP étaient significativement corrélées à un âge avancé, un score "total neuropathy symptom" élevé et une augmentation de la β2-microglobulinémie. Conclusion : La PNP urémique chez les patients dialysés est fréquemment asymptomatique et doit être systématiquement détectée. L'identification des facteurs prédictifs est cruciale en vue d'une approche thérapeutique précoce et appropriée.

Mots Clés : Insuffisance rénale chronique ; Dialyse ; Electroneuromyogramme ; Polyneuropathie.

ملخص

مقدمة :اعتلال الأعصاب المتعدد هو أكثر المضاعفات العصبية شيوعًا للفشل الكلوي المزمن. هدفنا هو دراسة الخصائص السريرية والكهربائية وشدة اعتلال الأعصاب المتعدد. **أساليب**: قمنا بتجميع المرضى المصابين بمرض الكلى المزمن في مرحلة غسيل الكلى فى قسم أمراض الكلى في مستشفى الهادي شاكر في صفاقس والذين تمت إحالتهم إلى وحدة التخطيط العصبي لدينا على مدار 12 شهرًا. **نتائج** : تم تجميع خمسة وستين مريضا. حددنا اعتلال الأعصاب المتعدد عند 31 مريضًا (47.7٪). كان متوسط العمر 49 ± 17.4 سنة مع نسبة جنس (الذكور/الإناث) 1.6. عند الفحص، 54.8 ٪ من المرضى كانوا بدون أعراض. كان اعتلال الأعصاب المتعدد المحوري هو النوع الأكثر شيوعًا (90٪). ارتبط حدوث وشدة اعتلال الأعصاب المتعدد بشكل كبير مع تقدم العمر و زيادة نسبة β2 ميكروغلوبيلين في الدم وزيادة "مجموع أعراض الاعتلال العصبي"
استنتاج : غالبًا ما يكون اعتلال الأعصاب المتعدد عند المرضى الذين يخضعون لغسيل الكلى بدون أعراض. يجب تحديده بشكل مطلق. تقييم عوامل النذير أمر بالغ الأهمية للتشخيص المبكر في ضوء نهج علاجي مبكر ومناسب.

الكلمات المفاتيح:الفشل الكلوي المزمن; غسيل الكلى; تخطيط العضلات والأعصاب; اعتلال الأعصاب المتعدد.

INTRODUCTION

Chronic renal failure (CRF) is a complex disease and is recognized as a major health problem [1]. Number of prevalent CRF patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. End-stage renal failure (ESRF) is the last stage of CRF requiring extra-renal purification (by hemodialysis (HD) or peritoneal dialysis (PD)) and/or a renal transplantation. Patients with ongoing dialysis are prone to damage in the peripheral nerve system. Uremic neuropathy is one of the most common neurological complications of uremia [1,2] . Distal symmetrical sensorimotor peripheral polyneuropathy (PNP) is the most common pattern of neuropathy in CRF, and it predominantly affects the lower limbs when compared to the upper limbs [3] . Our aim is to identify and characterize uremic polyneuropathy (PNP) among ESRF dialysis patients, to compare the effects of different dialysis methods and to assess predictive factors of this neuropathy.

MATERIALS AND METHODS

Study procedure

The study involved outpatients with ESRF under dialysis at the neurophysiology unit of the Neurology Department, Habib Bourguiba Hospital, who had been referred from the Department of Renal Medicine, Hedi Chaker Hospital, for evaluation of uremic neuropathy. Patients with a history of peripheral neuropathy before the diagnosis of CRF, or suffering from diabetes, hypothyroidism or hepatitis were excluded from the study. This study has been undertaken over 12 months and was approved by the institutional ethics committee. Written informed consent was obtained from the patients for their participation in the study.

A detailed history was elicited about symptoms of peripheral neuropathy according to T-NSS score (Total Neuropathy Symptom Score)[4] . Detailed general physical examination and neurological examination were done and documented. Biochemical investigations including ionogram and creatinine level**,** urea reduction ratio (URR) after HD [5], parathormone (PTH) level (Normal range between 15 and 65 ng/L) and β2-microglobulinemia level (Normal range between 0.7 and 1.8 mg/L) were measured.

Nerve conduction studies

In all patients, we studied motor (median, cubital, peroneal, tibial) and sensory (median, cubital, sural) nerves of two sides.

All measurements were performed with the same operator according to standard techniques for surface electrodes. All patients had been in ambient room temperature for more than one hour before the recording. The HD and PD patients did not differ in skin temperatures over the nerves (all differences in mean values <0.2”C).

The following parameters were measured for the motor response: motor nerve conduction velocities, distal latency, F wave latency and distal amplitude according to the standardized normal adult values of motor nerve conduction studies in both upper and lower extremities. For the sensory response we measured sensory nerve conduction velocities and amplitude according to standardized normal adult values of sensory nerve conduction studies in both upper and lower extremities.

Based on electrophysiological parameters, peripheral neuropathy patterns were classified into axonal neuropathy, demyelinating neuropathy, and mixed neuropathy. In axonal neuropathy, compound muscle action potentials (CMAP) decrease, conduction velocities are normal or slightly decreased but never <75% of the lower limit of normal, and distal latencies are normal or slightly prolonged but never >130% of the upper limit of normal. Demyelinating neuropathy was defined according to the EFNS/PNS criteria [6] . It was classified as mixed neuropathy if it has features of both axonal neuropathy and demyelinating neuropathy. The severity of the PNP was graduated using Dyck’s classification for diabetic PNP [7] . For statistical analysis, we classified our patients into 2 groups according to the degree of involvement:

- Group A: stages 0 (no neuropathy) and 1 (asymptomatic neuropathy)
- Group B: stages 2 (symptomatic neuropathy) and 3 (disabling neuropathy).

Statistical analysis

Statistical analyses were performed using SPSS software (version 20). All the continuous variables were expressed as mean ± standard deviation (SD). All categorical variables were expressed as percentages. Independent t□test and ANOVA test were applied to compare nominal data between the groups. $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-five consecutive ESRF patients under dialysis, who consented to participate, were included in the study for one year. Forty-five patients were under HD while 20 patients were under PD.

Population characteristics

The mean age in the present study was 49 ± 17.4 years. Male to female ratio was 1.6. Mean duration of CRF was 85 ± 61.65 months. Eighty percent of patients had residual diuresis. The mean duration of dialysis was 51.6±36.5 months for HD group and 40.9±32 months for PD group respectively. For HD patients, the number of hours per week was 10.42±2.37 hours. The Polysulfone and Polyamide filters (synthetic membranes) were the most used (67% and 20% respectively) followed by cellulosic membrane filter (13%). Demographic, clinical and biological features according to the type of dialysis are shown in **Table I**. On comparing the two groups of HD and PD patients, patients with PD showed statistically significant reduced serum potassium and β2-microglobulinemia levels (P < 0.001 and 0.002 respectively).

Table I: Summary table of demographic, clinical and biological features

		All patients	HD group	PD group	P
Age (years)		49±17.4	49.2±19.2	49.4±12.9	NS
Sex-ratio (M/F)		1.6	1.36	2.33	NS
Dialysis duration (months)		46.2±34.3	51.6±36.5	40.9±32	NS
Motor system examination	• Motor weakness (Lower limbs)	4	4	0	-
	• Distal amyotrophy (Lower limbs)	1	1	0	-
	• Decreased deep tendon reflexes (Lower limbs)	7	5	2	-
Sensory system examination	**Subjective signs (n):**				
	• Pain	1	1	0	-
	• Paresthesia	22	17	5	NS
	Objective signs (n):	7	5	2	-
	• Impaired pain and temperature sensation (Upper and lower limbs)				
	• Impaired vibration and joint position sense (Lower limbs)	12	8	4	-
Serum Potassium (mmol/l)		4.9±1	5.3±0.9	4.1±0.6	**$<10^{-3}$**
Creatinine level (µmol/L)		885.2± 297.6	947.8± 344.2	857.4±274	NS
PTH level (ng/L)		398.2± 242.9	433.2±260.2	319.5±18.3	NS
β2-microglobulinemia (mg/L)		35.1±8.9	37.4±8.7	30±7.1	**0.002**

NS : not significant; PTH: parathormone

Electrophysiological parameters

The prevalence of PNP in the present study was 47.7% (n=31) based on electrophysiological parameters (23 HD patients (74.2%); 8 PD patients (25.8%)). PNP was associated with carpal tunnel syndrome (CTS) in 9 cases (13.8%). The most common patterns of peripheral neuropathy were pure axonal neuropathy pattern (90%) followed by mixed neuropathy pattern (10%).

Sensory neuropathy type was notified in 14 cases (9HD group; 5 PD group), while sensory-motor type was seen in 17 cases (14 HD group; 3 PD group). The uremic PNP was asymptomatic among 54.8% of cases. Most common nerves Involved were the sural nerve, posterior tibial nerve, and common peroneal nerve (96.7%, 46.8% and 43.6% respectively). On comparing demographic, clinical and biological characteristics of patients with PNP (Group 1) and patients without PNP (Group 2) **Table II**, patients with PNP showed statistically significant older age, more sensory signs, raised T-NSS score and higher β2-microglobulinemia level. A Comparison of electrophysiological parameters of 65 dialysis patients, 31 patients with PNP, and 34 patients without PNP is shown in **Table III**. On comparing demographic, clinical and biological features of patients according to PNP severity **Table IV**, Group A showed statistically significant older age, raised T-NSS score and β2-microglobulinemia.

Table II: Demographic, clinical and biological characteristics of patients with and without PNP

		Patient with PNP	Patient without PNP	P
Age (years)		55.5±16	43.6±16.9	**0.005**
Sex-ratio (H/F)		20/11	20/14	NS
Anuria (n)		9	4	-
Type of dialysis:				
• **HD**		23	22	NS
• **PD**		8	12	
Dialysis duration (months)		59.8±44.5	50.3±34.3	NS
Hours of HD per week (n)		10.5±2.1	10.3±1.8	NS
Type of HD filter:				
• **Synthetic membrane**		20	19	NS
• **Cellulosic membrane**		3	3	
URR (%)		70±14.1	72.7±7.5	NS
Sensory signs	Subjectives (n)	17	6	**0.04**
	Objectives (n)	19	0	-
T-NSS		1.4±1.6	0.4 ± 0.6	**10^{-3}**
Serum Potassium (mmol/L)		5.1± 1	4.8±1	NS
Creatinine level (µmol/L)		905.5±322	862.9±271.8	NS
PTH level (ng/L)		419.2±216.7	375.2±270.4	NS
β2-microglobulinemia (mg/L)		37.6±9.4	32.8±7.9	**0.03**

NS : not significant; **HD:** hemodialysis; **PD:** peritoneal dialysis; **URR:** urea reduction ratio; **T-NSS:** Total Neuropathy Symptom Score; **PTH:** parathormone

Table III: Comparison of electrophysiological parameters of 65 dialysis ESRF patients who participated in the study

	Mean ±SD			P
	Dialysis patients (n=65)	**Patients with PNP (n=31)**	**Patients without PNP (n=34)**	
Right median nerve				
dL (ms)	3.4± 0.7	3.6±0.9	3.3±0.5	NS
CV (m/s)	52.1±4.4	50.4±3.9	53.8±4.3	**0.002**
Amplitude (mV)	7.2±2	6.2±1.8	8±1.9	**$<10^{-3}$**
F wave latency (m/s)	28.8±3.9	29.4±3.5	28.4±4.2	NS
Left median nerve				
dL (ms)	3.5± 0.8	3.7±1	3.3±0.5	**0.017**
CV (m/s)	52.9± 4.9	51.7±5	54±4.7	NS
Amplitude (mV)	7.5± 2.5	6.6±2.4	8.3±2.4	**0.006**
F wave latency (m/s)	28.2± 3.6	29.4±4.3	27.3±2.6	**0.021**
Right ulnar nerve				
dL (ms)	2.8± 0.4	2.9±0.4	2.7±0.4	**0.04**
CV (m/s)	59.1±5.4	56.9±4.8	60±5.3	**0.019**
Amplitude (mV)	8.3±2.5	7.7±2	8.8±2.3	NS
F wave latency (m/s)	28.9±2.9	29.9±3	28.1±2.6	**0.019**
Left ulnar nerve				
dL (ms)	2.7±0.5	2.9±0.5	2.6±0.5	NS
CV (m/s)	57.5±4.2	55.1±5	57.1±5	NS
Amplitude (mV)	8±2.3	7.2±1.9	8.8±2.5	**0.005**
F wave latency (m/s)	29±3.2	29.9±3.6	28.5±2.7	NS
Right CP nerve				
dL (ms)	3.9±0.9	4±1.1	3.8±4	NS
CV (m/s)	47.5±8.9	41.5±5.8	47.6±6.8	**$<10^{-3}$**
Amplitude (mV)	4±1.7	3.1±1.5	4.7±1.5	**$<10^{-3}$**
F wave latency (m/s)	52.8± 5.9	54.6±6.5	51.1±4.7	**0.034**
Left CP nerve				
dL (ms)	4±1.1	4.1±1.4	3.8±0.8	NS
CV (m/s)	44.1±4.5	41.9±8.5	46.6±7.2	**<10 -3**
Amplitude (mV)	3.8±1.6	3±1.5	4.6±1.5	**$<10^{-3}$**
F wave latency (m/s)	52.5± 6	53.2±6.6	51.8±5.4	NS
Right posterior tibial				
nerve	4.8±1.7	5.5±2.1	4.2±1	**0.002**
dL (ms)	41.2±3.5	40.7±6	43.3±3.6	**0.034**
CV (m/s)	5.6± 3	4±2.6	6.9±2	**$<10^{-3}$**
Amplitude (mV)	54.8± 6.9	57.7±5.9	52.2±6.7	**0.001**
F wave latency (m/s)				
Left posterior tibial				
nerve	5±2.4	5.8±3.2	4.3±0.9	**0.012**
dL (ms)	41±3.7	39.6±5.6	43.1±3.2	**0.005**
CV (m/s)	5.7± 3	4±2.4	7.2±2.7	**$<10^{-3}$**
Amplitude (mV)	55.1±6.1	57.9±5.7	52.8±5.6	**0.001**
F wave latency (m/s)				
Right median nerve				
(sensory)				
CV (m/s)	50±7.2	46.8±6.9	52.8±6.1	**0.034**
Amplitude (mV)	14.9±8.2	12.9±8.9	16.8±7.3	NS
Left median nerve				
(sensory)	52.5±6.8	50.2±6.6	54.4±6.3	**0.02**
CV (m/s)	14±6.8	12.4±5.9	15.2±7.4	NS
Amplitude (mV)				
Right ulnar nerve				
(sensory)	54.5±7.7	52±8.7	56.8±6.1	**0.013**
CV (m/s)	10.2±4.9	8.8±4.6	11.6±5	**0.028**
Amplitude (mV)				
Left ulnar nerve				
(sensory)	54.7 ±6.9	52.4±7.7	56.7±5.6	**0.015**
CV (m/s)	9.6±4.6	8.7±4.4	10.4±4.7	NS
Amplitude (mV)				
Right sural nerve				
CV (m/s)	45 ±7.2	42.4±7.6	47.5±6	**0.004**
Amplitude (mV)	8.1±5.2	4.9±4.5	11±4	**$<10^{-3}$**
Left sural nerve				
CV (m/s)	44.7±6.5	42±6.6	47.1±5.4	**10^{-3}**
Amplitude (mV)	8± 4.9	4.9±4	10.9±3.8	**$<10^{-3}$**

dL: Distal latency, **CV:** conduction velocity, **SD:** standard deviation, **CP:** common peroneal, **NS :** not significant

Table IV: Demographic, clinical and biological characteristics of patients according to PNP severity

	All patients	Group A	Group B	P
Age (years)	48.1±17.4	44.1±17.2	52.7±16.7	**0.05**
Sex-ratio (M/F)	1.6	1.46	2.11	NS
Dialysis duration (months)	51.8±46	52.1±45.3	51.5±33.4	NS
Type of dialysis				
• **HD**	45	23	21	NS
• **PD**	20	11	9	NS
Hours of HD per week (n)	10.4±2	10.3±1.9	10.6±2	NS
T-NSS	0.6±0.8	0.3±0.6	0.9±1	**0.006**
URR (%)	72.7±9.6	72.9±7.9	72.4±11.5	NS
Serum Potassium (mmol/l)	4.9±1	4.8±1.1	4.9±1	NS
Creatinine level (µmol/L)	893.4±307.7	888±320	900±298	NS
PTH level (ng/L)	404.6±250.8	398.7±206.4	411.4±297.4	NS
β2-microglobulinemia (mg/L)	34.5±8.6	32.2±7.6	37.3±9	**0.021**

NS : not significant; **HD:** hemodialysis; **PD:** peritoneal dialysis; **T-NSS:** Total Neuropathy Symptom Score; **URR:** urea reduction ratio; **PTH:** parathormone

DISCUSSION

Multiple neurological complications are seen in CRF, of which uremic neuropathy is the most frequent and disabling. It is regarded as the most reliable indicator of insufficient dialysis treatment. The prevalence of peripheral neuropathy was established in ESRF in various international studies, but the prevalence in dialysis patients as well as the different effects of each method are not well established [8–12] . The prevalence of PNP in the present study was 47,7% based on electrophysiological parameters which were lower when compared to other published studies such as Jasti et al (90%), Aggarwal et al. (70%) and Babu et al. (65%) [4,13,14] . This can be explained by the potential beneficial effect of dialysis on uremic peripheral neuropathy. In our sample, uremic neuropathy was more frequent in men than than in females probably representing the same distribution as seen in CRF patients. A positive correlation was noted between the occurrence of PNP and old patients, with a more severe form (P=0.005 and 0.05). PNP may appear at any age [15] . However, nerve structural abnormalities begin mainly after the age of 40 years and were histologically confirmed among old patients [16,17] .

In our study, the electrophysiological findings confirmed the results of previous studies [10,18].

Even in patients without clinical evidence of peripheral neuropathy, many studies through nerve conduction studies have disclosed evidence of a high prevalence of subclinical peripheral neuropathy [19] . About 54.8% of patients had asymptomatic peripheral neuropathy in the present study. The absence of clinical findings may delay the diagnosis of peripheral neuropathy. Thereafter a multidisciplinary approach including regular nerve conduction studies for diagnosis and treatment by increasing dialysis may delay or improve this type of complication.

The most common nerves involved were the sural nerve, posterior tibial nerve, and common peroneal nerve. This finding was similar to other published studies [14] . Lower limbs were more commonly affected than upper limbs, which indicates a length-dependent pattern of peripheral neuropathy [20,21] .Sensory-motor type was identified in 54.83 % of our patients. These results were similar to other published international studies [22,23] . Axonal PNP pattern was the most frequent form in our study corresponding to the previous series. This axonal loss was confirmed histologically by Thomas and al, on sural nerve biopsies, demyelination is rather due to axonal loss [24] .

Literature comparing electrophysiological features of ESRF patients with and without PNP is sparse. According to Aggarwal *et al*.[4] mean nerve conduction velocities (m/s) of right median, ulnar, common peroneal, and posterior tibial nerves were 51.34 ± 6.07, 53.04 ± 5.91, 44.72 ± 6.14, and 44.2 ± 5.17, respectively, which were almost similar to our results. PNP was associated with CTS in 9 cases (13.8%). In fact, 20% to 50% of the patients dialyzed for 10 years or longer are reported to have CTS [25] .

The effect of PD and HD on peripheral neuropathy remains a subject of controversy. We did not find any correlation between dialysis methods and the occurrence of PNP. However, in comparing the two groups of HD and PD patients in our study, patients with PD showed statistically significant reduced serum potassium and β2-microglobulinemia levels ($P < 0.001$ and 0.002 respectively). Former studies showed that patients under PD had less risk of developing PNP because of its superiority in the removal of uremic toxins [26,27] . Besides, regarding etiopathogenic factors of PNP and the implication of β2-microglobulin and PTH levels, we could explain that a long duration of dialysis increased the risk of PNP by increasing the accumulation of these 2 molecules. In fact, the risk of accumulation of these two molecules has been reported among 66% in dialyzed patients within 4 years and could reach 100% after 20 years of dialysis [28–31] . However, in a study comparing the different effects of HD and PD on uremic PNP outcome, the difference in outcome of the clinical signs during HD and PD was not of such a magnitude that one of these dialysis forms should be preferred before the other as regards neuropathy [11] . Peripheral neuropathy may deteriorate during both HD and PD, but in significantly different ways, indicating that several pathogenetic mechanisms are probably involved in uremic neuropathy. However, adequate dialysis may delay the occurrence and the deterioration of neuropathy and may even induce a slow improvement [12] . In our study, we didn't find a statistically significant difference between the 2 types of filters concerning the occurrence of the PNP probably because of the reduced number of cellulosic membranes used. However, dialysis with synthetic membranes may improve electrophysiological features more than dialysis with cellulosic membrane [32] .

According to former studies, a *risk* factor that may predispose to develop severe PNP is a reduced number of hours per week of HD [26,33], which wasn't confirmed in our study. According to Krishnan et al., the standard rhythm of three sessions per week may stop PNP progression, but without total regression. Whereas, daily HD may have a significant improvement [34] , which is explained by a better removal of uremic toxins. In patients regularly controlled, signs of neuropathy are generally lacking as long as the creatinine level is reduced and creatinine clearance exceeds 60 mL/minute [25] . Besides, nerves of uremic patients have been shown to exist in a chronically depolarized state prior to dialysis, with subsequent improvement and normalization of resting membrane potential after dialysis. The degree of depolarization correlates with serum potassium, suggesting that chronic hyperkalemic depolarization plays an important role in the development of nerve dysfunction [35] . On another hand, raised β2-microglobulinemia and parathyroid hormone (PTH) blood levels in uremic patients may cause neuropathy, as secondary hyperparathyroidism is a universal complication of CRF [36] .

In our study, we noted that the risk and the severity of PNP were correlated with raised β2-microglobulinemia (P=0.03 and 0.021 respectively). It was also associated with increased serum potassium, creatinine and PTH levels

without statistical significance, probably due to the small number of our sample.

CONCLUSION

We conclude that uremic PNP in patients with ESRF under dialysis is a common but underestimated complication. It is usually asymptomatic stressing the need for regular nerve conduction studies. The knowledge of predictive factors is crucial for early diagnosis in view of early and appropriate management.

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