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Clinical Course of Uremic Neuropathy in Long-Term Hemodialysis

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A B S T R A C T

One hundred and thirty-one patients on long-term hemodialysis were examined for the presence of clinical symptoms and signs, and for the effects of dialytic age, age and sex on uremic neuropathy. According to dialysis age, the patients were divided into three subgroups: low dialysis age, <5 years of dialysis (n=58); intermediate dialysis age, 5-10 years of hemodialysis (n=39); and high dialysis age, >10 years of dialysis (n=34). Two patient subgroups were differentiated according to mean age of 53.2 years: younger (n=57) and older (n=74). Clinical grading of uremic neuropathy was based on Nielsen's criteria. The most common symptoms were restless legs syndrome (47%) and cramps (51%). Sensory symptoms were less common in patients on long-term hemodialysis, most common of them being paresthesia (29%) and burning feet syndrome (28%). Abnormal Achilles reflex (53%) and impaired vibration sense (59%) were the most common clinical signs. Clinically manifested uremic neuropathy was present in more than 80% of all study patients, i.e. mild in 41%, and moderate to severe forms of uremic neuropathy according to Nielsen's criteria in 39%. There was no evident effect of dialytic age and sex on the clinical course of uremic neuropathy, however, there was a clear impact of age. It is concluded that long-term hemodialysis does not influence the clinical course of uremic neuropathy unlike evident deterioration of electroneurophysiologic findings.

Key words: *uremic neuropathy, hemodialysis, uremia*

Introduction

A great number of patients on long-term hemodialysis have different forms of clinically manifested uremic neuropathy (60–75%). The incidence of uremic neuropathy, and the prevalence of some symptoms and signs mostly vary from study to study[1–6]. Most studies dealing with the issue included patients hemodialyzed for 1 to 2 years. Also, there is evidence for dissociation between the symptoms and signs of neuropathy as well as between the clinical signs and electrophysiologic findings[7–9]. Some of these studies emphasize that long-term dialytic treatment does not influence the clinical course as it does lead to worsening of electrophysiologic findings. The purpose of this study was to assess the effect of long-term dialysis on the clinical course of uremic neuropathy, to evaluate the impact of age and sex, and eventually to compare the clinical and electrophysiologic findings. With these aims in mind, a group of 131 patients dialyzed for more than 10 years were included in the study.

Subjects and Methods

One hundred and thirty-one patients on long-term hemodialysis at Department of Nephrology and Dialysis, General Hospital »Sveti Duh«, were included in the study. Patients with diabetes mellitus, chronic alcoholism, exposure to toxic drugs, collagen vascular disease, amyloidosis and sarcoidosis, patients previously treated with peritoneal dialysis and those who had rejected transplantation were excluded from the study. In the

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group of 131 hemodialyzed patients the mean age was 53.12 ± 13.2, and mean dialytic age 6.62 ± 5.0 years. Other features of the study patients are shown in Table 1.

Study patients were divided into two subgroups according to mean age (younger and older), and into three subgroups according to mean dialysis age: low dialysis age (LDA), <5 years on hemodialysis (n=58); intermediate dialysis age (IDA), 5–10 years on hemodialysis (n=39); and high dialysis age (HDA), >10 years on hemodialysis (n=34). There was no significant age difference between different dialysis age groups. Similarly, there was no significant difference in dialysis age between the two age subgroups of hemodyalized patients (Table 1).

Clinical bedside examination was performed in each individual patient. Symptoms and clinical signs relevant for uremic neuropathy were tested as previously described (Nielsen 1). Clinical grading of uremic neuropathy was established according to Nielsen's criteria: group I, no neuropathy; group II, mild neuropathy; and group III, moderate and severe neuropathy.

χ^2-test and t-test were used on statistical analysis.

TABLE 1
CHARACTERISTICS OF HEMODIALYSED PATIENTS (N=131)

		Subjects		Age (yrs)	Dialysis age (yrs)
		(n)	(%)	(χ±SD)	(χ±SD)
Sex	Female	65	49.60		
	Male	66	50.40		
Age (yrs)	Younger (< 53.2)	57	44	40.3 ± 9.4	7.25 ± 5.1
	Older (≥ 53.2)	74	56	62.32 ± 5.9	6.18 ± 5.0
Dialysis age (yrs)	<5	58	44	54.34 ± 15.7	2.05 ± 1.3
	5–10	39	30	53.30 ± 11.5	7.08 ± 1.2
	≥ 10	34	26	51.06 ± 9.6	13.8 ± 2.4

Results

Many patients on long-term hemodialysis have some symptoms and signs of uremic neuropathy. More than

TABLE 2
CLINICAL FINDINGS IN PATIENTS ON LONG-TERM HEMODIALYSIS

Parameter	Total n=131 (%)	Female n=65 (%)	Malem n=66 (%)	p	Younger n=57 (%)	Older n=74 (%)	p
Symptom							
Restless legs	61 (47)	34 (53)	26 (39)	ns	21 (37)	54(54)	<0.05
Cramps (legs)	51 (39)	37 (58)	30 (45)	ns	26 (46)	57 (57)	ns
Cramps (arms)	21 (16)	13 (20)	8 (12)	ns	6 (10)	20 (20)	ns
Muscular weakness (legs)	83 (63)	45 (70)	38 (58)	ns	28 (49)	74 (74)	ns
Muscular weakness (arms)	24 (18)	17 (26)	7 (11)	ns	5 (9)	20 (20)	ns
Tiredness	78 (60)	43 (67)	35 (53)	ns	26 (36)	70(70)	<0.05
Paresthesia (legs)	38 (29)	26 (40)	12(18)	<0.05	13 (23)	35 (35)	ns
Paresthesia (arms)	18 (14)	12 (19)	6 (9)	ns	5 (9)	18 (18)	ns
Dysesthesia	12 (9)	9 (14)	4 (6)	ns	5 (9)	12 (12)	ns
Burning feet	37 (28)	22 (34)	14 (21)	ns	11 (19)	35(35)	<0.05
Pain:							
feet	11 (8)	8 (12)	3 (5)	ns	3 (5)	11 (11)	ns
legs	14 (11)	10 (16)	4 (6)	ns	3 (5)	15 (15)	ns
arms	6 (5)	5 (8)	1 (1)	ns	0 (0)	8 (8)	<0.05
Clinical sign							
Paresis	37 (28)	21 (33)	16 (24)	ns	9 (16)	28 (38)	ns
Stock area	17 (13)	12 (19)	5 (7)	ns	7 (12)	10 (13)	ns
Glove syndrome	3 (2)	3 (4)	0 (0)	ns	2 (3)	1 (1)	ns
Hypoesthesia (fingers)	6 (5)	4 (6)	2 (3)	ns	3 (5)	3 (4)	ns
Impaired vibratory perception:							
great toe	77 (59)	62 (55)	37 (56)	ns	23 (40)	54 (73)	ns
middle of tibia	54 (41)	27 (42)	26 (39)	ns	15 (26)	38 (51)	ns
thumb	16 (12)	9 (14)	7 (10)	ns	3 (5)	13 (18)	ns
Abnormal reflexes:							
Achilles	83 (63)	45 (70)	37 (56)	ns	30 (53)	53 (72)	ns
patellar	50 (49)	37 (58)	29 (44)	ns	27 (47)	38 (51)	ns
biceps	33 (25)	17 (27)	17 (26)	ns	13 (23)	20 (27)	ns
triceps	27 (21)	12 (19)	15 (23)	ns	9 (16)	17 (23)	ns

80% of the study group had clinically manifested neuropathy according to Nielsen's criteria, only 7% had no symptoms or clinical signs, and only 12% were without clinical signs of neuropathy. Motor symptoms were more common than sensory ones. In long-term dialysis patients, restless legs syndrome and cramps were the most common neuropathy symptoms, whereas paresthesia and burning feet syndrome were the most common sensory symptoms (Table 2).

The most common clinical signs were abnormal Achilles reflex and impaired vibration sense, followed by paresis of dorsiflexion of the great toe and stock area (Table 2). According to Nielsen's criteria, 20% of the study patients had no clinically manifested uremic neuropathy, 39% had mild, and 41% moderate to severe neuropathy. There was no statistically significant difference in the prevalence of any symptom or clinical sign among dialysis age subgroups, nor was any effect observed on the clinical severity of uremic neuropathy according to Nielsen ($p>0.05$, Tables 3 and 4).

The following symptoms and clinical signs were more common in the older subgroup: restless legs syndrome, tiredness, burning feet syndrome, and pain ($p<0.05$), paresis and atrophy of dorsiflexion of great toe ($p<0.05$), and impaired vibration sense in the tarsal and tibial region ($p<0.01$). Older patients had a statistically significantly higher rate of the severe forms of uremic neuropathy than younger ones according to Nielsen ($p<0.01$) (Table 4). There was no sex difference in any particular symptom or sign except for paresthesia ($p<0.05$), and no statistically significant difference in the clinical forms of neuropathy according to Nielsen ($p>0.05$, Table 4).

Discussion

The symptoms and signs of uremic neuropathy are very common in long-term hemodialysis patients. In our patients, two motor symptoms were most common: cramps and restless legs syndrome. Similar results have been reported in the literature[6], however, their importance in

TABLE 3
EFFECT OF DIALYSIS AGE ON THE CLINICAL COURSE OF UREMIC NEUROPATHY

	Dialysis age (yrs)		
Symptoms and signs of neuropathy	<5 n=58 (%)	5–10 n=39 (%)	≥ 10 n=34 (%)
Symptom			
Restless legs	26 (45)	17 (43)	18 (53)
Cramps (legs)	28 (48)	22 (56)	18 (53)
Cramps (arms)	12 (21)	3 (8)	6 (18)
Muscular weakness (legs)	36 (62)	28 (72)	19 (56)
Muscular weakness (arms)	12 (21)	5 (13)	6 (18)
Tiredness	38 (65)	26 (66)	14 (41)
Paresthesia (legs)	18 (31)	11 (28)	10 (29)
Paresthesia (arms)	6 (10)	7 (18)	5 (15)
Dysesthesia	5 (8)	6 (14)	2 (8)
Burning feet	19 (32)	8 (20)	10 (29)
Pain			
feet	5 (8)	5 (13)	1 (3)
legs	6 (10)	5 (13)	3 (9)
arms	2 (3)	3 (8)	1 (3)
Clinical sign			
Paresis	16 (27)	10 (26)	11 (32)
Stock area	6 (10)	8 (20)	3 (9)
Glove syndrome	1 (2)	0 (0)	2 (6)
Hypoesthesia (fingers)	1 (2)	1 (3)	4 (11)
Impaired vibratory perception:			
great toe	33 (57)	23 (59)	21 (62)
middle of tibia	25 (43)	15 (38)	13 (38)
thumb	11 (19)	5 (13)	0 (0)
Abnormal reflexes:			
Achilles	33 (57)	24 (61)	26 (76)
patellar	24 (41)	19 (48)	22 (64)
biceps	14 (24)	9 (23)	11 (32)
triceps	11 (19)	9 (23)	7 (20)

TABLE 4
EFFECT OF PATIENT AGE ON THE CLINICAL COURSE OF UREMIC NEUROPATHY ACCORDING TO NIELSEN

		Clinical grade of neuropathy after Nielsen					
		A		B		C	
		(n)	(%)	(n)	(%)	(n)	(%)
Age (yrs)	Younger (<53.2)	15	26	28	49	14	25
	Older (≥53.2)	10	14	27	36	37	50

χ^2-test, S=0.0093

the assessment of uremic neuropathy is not completely clear because of unknown pathophysiological background.

Literature reports and our own experience indicate that clonazepam is very effective in the management of restless legs and cramps. It seems that these symptoms may have a central origin. Muscle weakness in legs is also a common symptom but is not specific enough. Paresthesia and burning feet syndrome are the most common sensory symptoms but their prevalence is considerably lower than the prevalence of cramps and restless legs syndrome. Paresthesia is an early symptom of uremic neuropathy. It is believed to result from an early lesion of peripheral nerve fiber. The prevalence of these symptoms in different studies varies from 6% to 32%[6,10–14]. Late sensory symptoms such as pain and dysesthesia have a lower prevalence and often come in combination with other symptoms and clinical signs of neuropathy. The most common signs of uremic neuropathy in patients on long-term hemodialysis are abnormal Achilles reflex (motor sign) and impaired vibration sense on the pulp of great toe (sensory sign). There is no clear predominance of motor over sensory clinical signs of neuropathy. Paresis of large toe dorsiflexion is the most frequent late clinical sign. Sensory symptoms such as hypesthesia and hypalgesia are less common. According to Nielsen's criteria, clinical signs are most important for clinical grading of uremic neuropathy. There are great differences in the frequency of clinical signs among different studies, ranging from 11% to 75%[4,6,14–18]. Our study revealed a high prevalence of the symptoms and clinical signs of neuropathy in hemodialysis patients, especially a higher frequency of motor than sensory symptoms and clinical signs. More than 80% of all study patients had clinically manifested uremic neuropathy according to Nielsen. The number of patients with mild, moderate and severe uremic neuropathy was almost equal. There was no significant effect of dialytic age on the clinical course of uremic neuropathy. Unlike clinical course, there was evident electrophysiological deterioration due to long-term hemodialysis. Our previous electrophysiological study of uremic neuropathy in long-term dialysis patients showed the patients with more than 10 years of dialytic treatment to have 11 of 16 electrophysiological parameters tested significantly worsened as compared with a group of patients with <5 years on hemodialysis ($p<0.01$). All but one of these 11 parameters were related to motoricity. The electrophysiological deterioration during long-term hemodialysis is best seen through worsening of the H-wave of tibial and F-waves of peroneal and tibial nerves[19]. The results of our study are consistent with those reported by other authors who have demonstrated that hemodialysis does not influence the clinical course of uremic neuropathy, whereas electrophysiological findings showed a tendency to worsening. However, most of these studies considered only 1 to 2 years of hemodialysis. Unlike dialytic age, there was a clear impact of age on both the clinical course and electrophysiological findings of uremic neuropathy. It seems that many of the symptoms and signs are related to age. The clinical and electrophysiological findings of uremic neuropathy showed no sex difference.

In conclusion, there is a high incidence of clinically manifested uremic neuropathy in patients on long-term hemodialysis. Prolonged hemodialytic treatment does not influence the clinical course of uremic neuropathy but leads to evident deterioration of electrophysiological findings. Older patients are burdened with more symptoms and clinical signs, and have more severe forms of neuropathy than younger ones.

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KLINIČKI TIJEK UREMIČKE NEUROPATIJE U BOLESNIKA NA DUGOTRAJNOJ HEMODIJALIZI

S A Ž E T A K

U 131 bolesnika na dugotrajnoj hemodijalizi ispitivana je prisutnost kliničkih simptoma i znakova uremijske neuropatije kao i utjecaj dijalizne i životne dobi te spola na istu. Prema dužini dijalize bolesnici su podijeljeni u 3 podskupine: kratka dijalizna dob, <5 godina dijalize (n=58); srednja dijalizna dob, 5–10 godina dijalize (n=39); visoka dijalizna dob, >10 godina dijalize (n=34). U odnosu na srednju životnu dob ispitanika koja je iznosila 53,2 godine, bolesnici su podijeljeni u dvije dobne skupine: mlađe (n=57) i starije (n=74). Kliničko stupnjevanje uremijske neuropatije izvršeno je na temelju Nielsenovih kriterija. Najučestaliji simptomi u bolesnika bili su sindrom nemirnih nogu (47%) i grčevi (51%). Senzorički poremećaji imali su nižu prevalenciju, a najčešće su bile prisutne parestezije (29%) i sindrom užarenih stopala (28%). Promijenjen refleks Ahilove tetive (53%) i poremećaj osjeta vibracije (59%) bili su najčešći klinički znaci neuropatije. Klinički manifestna uremijska neuropatija zabilježena je u 80% ispitanika: blaga forma u 41%, umjerena do teška, prema Nielsenovim kriterijima, u 39% bolesnika. Nije zabilježen jasan utjecaj dijalizne dobi i spola na klinički tijek uremijske neuropatije, a evidentan je utjecaj životne dobi. Možemo zaključiti da dugotrajna hemodijaliza ne utječe na klinički tijek uremijske neuropatije, dok je taj utjecaj jasan kod ispitivanja elektrofizioloških parametara.