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Clinical and electrophysiological evaluation of patients with thalidomide-induced neuropathy

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Abstract

Background: Whether thalidomide induces a sensory ganglionopathy or a length-dependent axonal neuropathy is disputed. Moreover no agreement exists concerning the effects of thalidomide dosage on the clinical and electrophysiological findings.

Objective: We examined the effect of age, gender, disease duration, total cumulative dose on the clinical and electrophysiologic parameters.

Methods: Fifteen patients who had previously received 100 mg/day of thalidomide for the treatment of multiple myeloma were evaluated retrospectively. Clinical findings and nerve conductions studies were evaluated using a modified total neuropathy scoring system.

Results: Sensory symptoms ($p = 0.033$, $r = 0.552$) and objective sensory findings ($p = 0.002$, $r = 0.730$) worsened with higher thalidomide doses. There was no effect of age, gender and disease duration, neither on clinical symptoms and objective findings, nor on electrophysiologic data. Twelve patients (%80) developed the electrophysiological findings of neuropathy. Six (40%) had pure sensory and 4 (26.6%) had sensori-motor peripheral neuropathy, while 4 (26.6%) had carpal tunnel syndrome. Sural sensory nerve action potential (SNAP) amplitudes were more prominently reduced compared to SNAPs obtained from the upper extremities. Sural SNAP amplitude showed a tendency toward reduction as the total cumulative dose, although it is not statistically significant (respectively; $p = 0.187$). Significantly reduced ulnar, peroneal and tibial compound muscle action potential amplitudes, slow motor nerve conduction velocities of the ulnar and peroneal nerves were found in the study group compared to reference norms ($p < 0.05$).

Conclusion: Our results suggest that thalidomide produces a dose dependent peripheral neuropathy, mainly localized to the peripheral nerves in a length dependent manner. The patient must be monitored closely to prevent irreversible consequences.

Key words: Thalidomide neuropathy; cumulative dose; neurotoxicity; electrophysiological findings; multiple myeloma.

Introduction

The glutamic acid derivative thalidomide was introduced in 1957, as a sedative, hypnotic, and antiemetic medication used during pregnancy. However, it was subsequently banned in 1961 as a result of its potent teratogenic effects (Apfel and Zochodne, 2004). Thalidomide is currently used as a treatment for discoid lupus erythematosus, prurigo nodularis, oral aphtosis ulcerations, sarcoidosis, Crohn's disease, graft-versus-host disease, rheumatoid arthritis, glioma, myelodysplastic diseases, prostate, breast, and colon cancers, as well as multiple myeloma that are resistant to other treatments (Ochonisky *et al.*, 1994; Chaudhry *et al.*, 2002). It has also been successfully administered as a first-line therapy in patients with newly diagnosed multiple myeloma (Cavo and Baccarani, 2006). Thalidomide inhibits activation of nuclear factor-kB (NF-kB), which is involved in the synthesis of neurotrophic factors that promote sensory neuron survival (Briani *et al.*, 2004; Umapathi and Chaudhry, 2005), and suppresses tumor necrosis factor (TNF) -a formation and integrin receptors, which are involved in leukocyte migration (Hausheer *et al.*, 2006).

Thalidomide-induced neuropathy was first reported in 1960s (Laguency *et al.*, 1986), with an incidence of peripheral neuropathy at 25-75% (Mileshkin *et al.*, 2006). Although it is hypothesized that thalidomide induces a dose-dependent sensorimotor length-dependent axonal neuropathy (Chaudhry *et al.*, 2002), lesion localization is disputed, as some claim that neurons in the spinal ganglia are involved (Giannini *et al.*, 2003). Furthermore, there is no consensus regarding the relationship between toxicity and total dosage (Apfel and Zochodne, 2004). We have examined the effect of age, gender, disease duration and total cumulative

dose on the clinical and electrophysiological parameters of thalidomide neuropathy.

Methods and materials

Patients

The charts of 15 patients who had previously received thalidomide treatment at a daily dosage of 100 mg were evaluated retrospectively. The patients who were referred to the neurologist with symptoms of peripheral neuropathy or who were followed up by haematologist had been selected for the study. There were 2 patients with myelodysplastic disease, 1 patient had Crohn's disease, and the remainder of the group was composed of individuals who underwent bone marrow transplantation for multiple myeloma. Patients with diabetes mellitus, vitamin B12 deficiency, amyloidosis, chronic renal failure, or monoclonal gammopathy were excluded from the study. None of the patients had previously taken medication with peripheral neurotoxic effects.

Clinical symptoms and signs, and electrophysiological parameters were rated using a modified total neuropathy scoring system defined by Chaudhry *et al.* (Chaudhry *et al.*, 2002). Pain and paresthesias, as well as hypoesthesia were graded as follows: normal (0), limited to toes or fingers (1), up to the ankle or wrist (2), reaching the knee or elbow (3), and spreading above the knee or elbow (4). Deep tendon reflexes were scaled as: normal (0), decreased Achilles reflex (1), absent Achilles reflex (2), hypoactive reflexes with unobtainable Achilles reflexes (3), or global areflexia (4). Motor strength was scored using the Medical Research Council (MRC) scale.

Electrophysiologic evaluation

All participants gave informed consent before inclusion in the study. Nerve conduction studies were performed using a Nihon Kohden-Neuropack (MEB-5504K) with a filter setting of 20 Hz to 10 KHz and a sweep speed of 5 ms/cm for motor and a bandpass filter of 20 Hz to 2 KHz, with a sweep speed of 1 ms/cm for sensory nerve conductions. Surface recordings with Dantec 13K60 disposable electrodes were obtained. Examination was performed in a warm room, with the skin temperature controlled at 32°C. Orthodromic nerve conduction velocities (NCV) of the digit II-wrist, palm-wrist segments of the median and digit V-wrist segment of the ulnar nerves were studied on the right upper extremity. Sensory NCV of the right sural nerve was also studied using the antidromic method. Latencies were measured to the negative peak. Peak to peak sensory nerve action potential (SNAP) amplitudes were measured. Terminal and F-wave latencies of the right median and ulnar nerves, motor nerve conduction velocities of the elbow-wrist segment of the right median and below elbow-wrist segment of the right ulnar nerve were performed. The patients did'nt have baseline EMG because the study was designed as retrospectively.

Compound muscle action potential (CMAP) amplitudes were measured from peak to peak. Motor NCV and CMAP amplitudes of the knee-ankle segments of the posterior tibial and peroneal nerves were measured in the right lower extremity. All nerve conduction studies were performed, according to the methods described by Oh (Oh, 1993). Electrophysiological function was summarized using a modified total neuropathy score. Neuropathy was scored relative to the lower limits of the sural SNAP and peroneal CMAP amplitudes: $< 5\%$ decrease (0), 76-95% of the lower normal limit (1), 51-75% (2), 26-50% (3), and 0-25% (4) (Chaudhry *et al.*, 2002). When there were only electrophysiologic findings without a clinical counterpart, the definition of subclinical neuropathy was used (Plasmati *et al.*, 2007). Nerve conduction studies were compared with the data obtained from 43 normal controls matched for age and sex ($p > 0.05$).

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL). A chi-square test was used to compare percentages across groups. Significance of differences between means of 2 groups showing non normal distribution was studied with the Mann-Whitney *U* test. The Kruskal-Wallis test was used for evaluation of more than two such groups. The correlation between nonparametric values was investigated using Spearman's test.

Results

Patients

Nine female (60%) and six male patients (40%) were studied with a mean age (range) of 52.46 ± 15.22 (18-73) years. Mean disease and thalidomide treatment duration was 22.60 ± 13.98 (5-52) and 9.60 ± 8.36 (1-31.5) months respectively. Mean total cumulative dosage was 26.78 ± 24.86 (2.8-94.5) g. In patients with neuropathic symptoms, the time elapsed to the onset of symptoms ranged from 2 days to 29.5 months. The demographic data, as well as the modified total neuropathy scores for sensory symp-

toms, objective sensory and reflex findings are demonstrated in Table 1. The electrophysiological grading is presented in Table 2.

Clinical Findings

Eleven patients (73.3%) developed symptoms of peripheral neuropathy, 5 being grade 1, and the rest grade 2. Six patients (40%) had glove and stocking type of hypoesthesia on neurological examination (all grade 2), while the remainder of the group demonstrated no objective sensory abnormalities. Loss of deep tendon reflexes was found in 12 patients (80%). There were 5 grade 1, 4 grade 2, 2 grade 3 and 1 grade 4 changes, while in the remaining 3, no reflex changes were present. None had motor deficits.

There were four (26.6%) asymptomatic cases. Among the asymptomatic cases, two showed reflex abnormalities (grade 2 and grade 4) without objective sensory loss. The first, who showed sensory neuropathy in the lower extremities, was treated with a total dose of 8.4 g of thalidomide for 3 months. Electromyography (EMG) revealed a sensorimotor peripheral neuropathy, in the other patient, who was treated with 5.6 g of thalidomide for 2 months, sural SNAP amplitude was reduced by > 50% in both legs. In the two remaining asymptomatic individuals, no objective sensory, reflex or EMG abnormality was found.

The severity of sensory symptoms correlated well only with the total cumulative dose ($p = 0.033$, $r = 0.552$). In parallel with these findings, the degree of hypoesthesia was also related to the total cumulative dosage ($p = 0.002$, $r = 0.730$) (Fig. 1). No such relationship existed between the reflex abnormalities and total cumulative dosage of treatment ($p = 0.634$, $r = 0.134$). There was no statistically significant difference and correlation among the subjects classified into specific grades of symptom, hypoesthesia, reflex and electrophysiologic scoring, in terms of age, gender, disease duration and the time elapsed to the onset of symptoms ($p > 0.05$).

Electrophysiological Findings

Twelve patients (80%) showed nerve conduction abnormalities. Six (40%) had pure sensory neuropathies (4 diffuse and 2 confined to the lower extremities), four cases (26.6%) demonstrated a sensorimotor peripheral neuropathy (3 diffuse and in 1 restricted to the lower extremities). Four female subjects (26.6%) were found to have a carpal tunnel syndrome (CTS). Two of them had mild CTS as the sole neurophysiologic finding. The other 2 patients had CTS superimposed on a sensory neuropathy in the lower extremities. One of them had a unilateral moderate CTS, while the other had a mild bilateral CTS. There were 3 patients (20%) with normal electrophysiologic findings, without any neurological deficit. Two of them were asymptomatic. These asymptomatic patients were treated with a total dose of 5.25 and 19.6 g thalidomide for 3.5 and 7 months respectively. The third patient with normal nerve conduction studies that underwent treatment with a total dose of 30.8 g thalidomide for 11 months, had grade 2 sensory symptoms and hypoesthesia, accompanied by grade 3 reflex findings. In 2 patients (16.6%) the treatment had to be terminated because of peripheral neuropathy. The first patient, who had been treated with a total cumulative dose of 28 g thalidomide for 10 months, complained of grade 2 sensory symptoms, accompanied by hypoesthesia of the same grade. Deep tendon reflexes were normal. He had a unilateral CTS of moderate severity, superimposed on a sensory neuropathy in the lower extremities. EMG findings confirmed the diagnosis of a diffuse sensori-motor peripheral neuropathy in the second patient, who had been treated with 50.4 g of thalidomide for 18 months and showed grade 2 hypoesthesia and reflex abnormalities, in addition to grade 1 sensory symptoms. The decrease in sural SNAP amplitudes was greater than 50% in both cases.

Sural and median SNAP amplitudes showed a reduction greater than 50% of the lower limit of normal in 10 (66.6%) (dosage under 20 g in 4 and over 20 g in 6) and 2 (13.3%) (dosage over 20 g in both) of the cases respectively. On the other hand, peroneal CMAP amplitudes were reduced greater than 50% of the lower limit of normal in only 2 subjects (dosage over 20 g in both). Although not reaching statistical significance ($p = 0.187$), sural SNAP amplitudes showed a trend toward reduction, as thalidomide dosage increased. There were not any correlation between the total cumulative dose and peroneal CMAP amplidutes ($p = 0.444$). There was no statistically significant difference among the patients belonging to a specific electrophysiological category in regard to the total cumulative dose of thalidomide treatment ($p > 0.05$). The relationship of total thalidomide dose with clinical and electrophysiological findings according to modified total neuropathy score are shown in Table 3. Among the patients categorized according to the presence of normal nerve conduction findings, sensory, sensorimotor neuropathy or pure CTS, the total cumulative thalidomide dose did not differ significantly ($p > 0.05$).

There was a significant slowing of the motor NCV of the below elbow-wrist segment of the ulnar

Table 1

Modified total neuropathy symptoms scores; objective sensory and reflex findings

Patient	Age (years)	Sex	Duration of disease (months)	Total Cumulative Dose (g)	Duration of treatment (months)	Time elapsed to the onset of sensory symptoms	Sensory Symptoms	Objective Sensory Findings	Reflex Findings
1	35	M	14	8.4	3	1 months	1	0	1
2	65	F	36	50.4	18	6 months	2	2	0
3	59	F	6	16.8	6	3 months	1	0	1
4	60	M	5	11.2	4	2 months	2	2	1
5	54	F	17	8.4	3	asymptomatic	0	0	2
6	51	M	26	28	10	15 days	1	2	2
7	66	E	13	5.6	2	asymptomatic	0	0	4
8	61	F	24	30.8	11	7 months	2	2	3
9	55	F	11	28	12	10 months	1	0	2
10	18	F	36	19.6	7	asymptomatic	0	0	0
11	73	M	52	56	20	6 months	2	2	2
12	47	F	12	2.8	1	2 days	1	0	1
13	26	F	19	5.25	3.5	asymptomatic	0	0	0
14	60	F	44	94.5	31.5	29.5 months	2	0	1
15	57	M	24	36	12	7 months	2	2	3

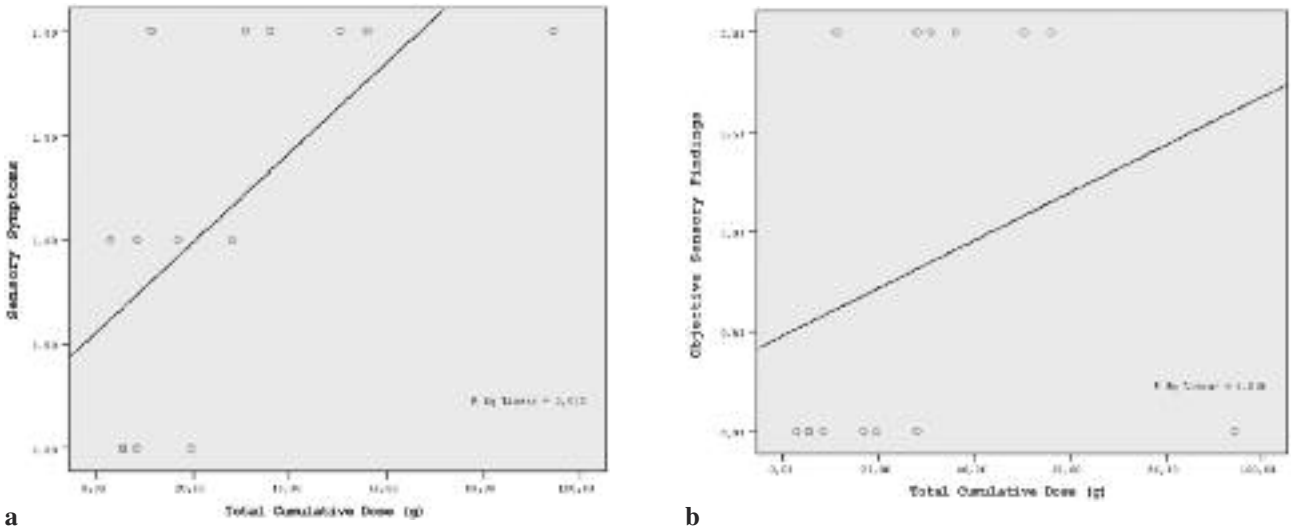
* Pain, paresthesias and hypoesthesia were graded as follows: normal (0), limited to toes or fingers (1), up to the ankle or wrist (2), reaching the knee or elbow (3), and spreading above the knee or elbow (4).

* Deep tendon reflexes were scaled as: normal (0), decreased Achilles reflex (1), absent Achilles reflex (2), hypoactive reflexes with unobtainable Achilles reflexes (3), or global areflexia (4).

Table 2

Modified total neuropathy scores of the electrophysiological findings

Patients	Median SNAP amplitude	Median CMAP amplitude	Ulnar SNAP amplitude	Ulnar CMAP amplitude	Peroneal CMAP amplitude	Posterior tibial CMAP amplitude	Sural SNAP amplitude
1	0	0	0	0	2	0	4
2	0	0	0	0	0	0	4
3	0	0	0	0	0	0	0
4	2	0	2	1	4	4	4
5	0	0	0	0	0	0	4
6	3	0	2	0	0	0	4
7	2	0	0	1	3	0	4
8	0	0	0	0	0	0	0
9	2	0	1	0	0	0	4
10	0	0	0	0	0	0	0
11	2	0	1	0	0	0	4
12	1	0	0	0	0	0	0
13	0	0	0	0	0	0	0
14	2	0	4	0	0	0	4
15	4	0	4	1	3	0	4



a b

FIG. 1. — The correlation between (a) sensory symptoms (b) objective sensory findings and total cumulative dose

Table 3

The effect of total thalidomide dosage on clinical and electrophysiological findings according to modified total neuropathy score

	Total Cumulative Dose (g)	p value (Kruskal-Wallis)
Sensory symptoms		
0	9.71 ± 6.74	
1	16.80 ± 11.37	p = 0.020
2	46.48 ± 28.32	
Objective Sensory findings		
0	21.03 ± 28.73	p = 0.039
2	35.40 ± 16.19	
Reflex findings		
0	25.08 ± 23.06	
1	26.74 ± 38.21	p > 0.05
2	30.10 ± 19.58	
Sural SNAP amplitude		
Normal	15.05 ± 11.37	p > 0.05
> 50% decrease	32.65 ± 28.10	
Peroneal CMAP amplitude		
Normal	30.95 ± 27.11	p > 0.05
> 50% decrease	11.20 ± 3.2	
Median SNAP amplitude		
Normal	19.95 ± 16.0	p > 0.05
> 50% decrease	36.00 ± 19.9	
Ulnar SNAP amplitude		
Normal	16.45 ± 15.52	p > 0.05
> 50% decrease	65.25 ± 41.36	

(56.80 ± 8.28 m/s) and the knee-ankle segment of the peroneal nerves (45.12 ± 6.28 m/s) in the study group compared to normal subjects (61.73 ± 6.06 m/s, p = 0.012 and 59.93 ± 6.9 m/s, p = 0.000, respectively). Ulnar (11.19 ± 3.52 mV), peroneal (3.89 ± 1.66 mV) and tibial (8.07 ± 4.39) CMAP amplitudes of the patients were also significantly reduced when compared with the reference norms (13.68 ± 2.45 mV, p = 0.020, 8.03 ± 4.28 mV, p = 0.000 and 14.90 ± 8.19 mV, p = 0.001, respectively). No significant difference was present in terms of F wave latency (27.27 ± 2.83), motor nerve conduction of elbow-wrist segment (55.30 ± 6.59), or CMAP amplitudes (10.79 ± 0.36) of the median nerve when compared to control subjects (26.32 ± 1.69, p = 0.398, 57.50 ± 4.96, p = 0.356 and 11.72 ± 0.42, p = 0.461, respectively). On the other hand, median (2.81 ± 0.53 ms) and ulnar (2.11 ± 0.24 ms) terminal latencies were shorter than the controls (3.18 ± 0.41 ms and 2.52 ± 0.40 ms respectively). There were no significant differences between peroneal and tibial terminal latencies or F-wave latencies of the upper and lower extremity motor nerves (p > 0.05) of the study group compared to control values. The SNAP amplitudes of digit II-wrist (15.04 ± 12.48 μV), palm-wrist (35.50 ± 17.75 μV) segments of the median and the digit V-wrist (11.54 ± 8.00 μV) segment of the ulnar nerve showed a significant reduction comparing with those of normal subjects (21.37 ± 7.64 μV, 128.7 ± 61.52 μV, 16.54 ± 7.13 μV; p = 0.005, p = 0.000, p = 0.014 respectively). Although the sural SNAPs were absent in 10 cases, in the remaining 5 patients they (15.56 ± 11.93 μV) did not differ from the control population (19.37 ± 11.11 μV, p = 0.179). Sensory NCV of the finger-wrist (43.89 ± 4.60 m/s) and palm-wrist (38.86 ± 5.86 m/s) segments of the median and sural nerves (34.76 ± 11.07 m/s) were significantly slow when compared with normal values (48.59 ± 4.83, 44.93 ± 5.48 and 42.04 ± 3.92 m/s; p = 0.002, p = 0.014 and p = 0.031 respectively). No significant slowing of the digit V-wrist segment of the ulnar nerve (43.03 ± 4.16 m/s) was detected compared with the reference norms (46.31 ± 4.46 m/s, p > 0.05).

Discussion

Lesion level is disputed in thalidomide-induced neuropathy. Either spinal ganglion or the peripheral sensory axons may be involved. Degeneration of the spinal ganglia neurons has been detected in fetal phocomelic rabbits and in cultures treated with the serum of the patients with thalidomide neuropathy (Giannini *et al.*, 2003). Hyperintense lesions found in the posterior columns of the spinal cord, in addition to absent spinal and cortical somatosensory evoked potentials (SEP) suggest that the primary site of neurotoxicity may be the dorsal root ganglion (Giannini *et al.*, 2003; Isoardo *et al.*, 2004). On the other hand, sensory nerve conduction studies reveal a more marked reduction of amplitudes in the lower extremity nerves, compared to the SNAPs of the upper extremity, in addition to a reduction of CMAP amplitudes (Chaudhry *et al.*, 2002), supporting the hypothesis of a length dependent axonopathy. Our findings were similar, showing greater affection of sural SNAPs compared to median SNAP. Absent sural SNAPs in two-thirds of our patients, as well as significant SNAP amplitude reductions of the upper extremity nerves demonstrate that sensory axons are primarily affected. The slowing of ulnar and peroneal motor NCV, as well as CMAP amplitude reductions of upper and lower extremity nerves were also noted. Plasmati *et al.* recently demonstrated that the reduction in CMAP amplitude of the peroneal nerve occurred almost simultaneously with the sural nerve SNAP amplitude reductions, providing further evidence for an axonopathy (Plasmati *et al.*, 2007), supported by our findings. The high incidence of CTS (26.6%) may be explained by the greater number of females in our study group or due to the effects of acquired amyloidosis. Apparently, due to primary affection of sensory nerve conductions in the majority of these cases, the terminal latency of the median nerve was not prolonged, but surprisingly shorter in our study group compared to normals. Slow sensory NCV of the digit II-wrist and palm-wrist segments of the median nerve is most likely due to high incidence of CTS in our study group.

The effect of total cumulative dose and the duration of exposure on peripheral nerve toxicity are not very clear: Numerous studies have reported a good correlation between total cumulative dose over 20 g (Chaudhry *et al.*, 2002; Plasmati *et al.*, 2007; Cavaletti *et al.*, 2004) and neuropathic signs and symptoms, as well as reduction of the sural SNAP amplitude. Some reports also indicate that the duration of treatment over 6 months to 1 year have similar significant associations (Mileshkin *et al.*, 2006; Tosi *et al.*, 2005). However, other studies found no relationship between these parameters (Ochonisky *et al.*, 1994; Cavo *et al.*, 2006; Plasmati *et al.*, 2007; Clemmensen *et al.*, 1984). In our study, higher total cumulative doses were directly correlated with objective sensory findings. Severity of sensory symptoms was also dose related. Sural SNAP amplitude showed a trend towards reduction as the total dosage increased. Age, sex and disease duration do not have an effect on the severity of

clinical and electrophysiological findings, which was not studied before. The occurrence of a peripheral neuropathy in association with multiple myeloma due to monoclonal gammopathy is common (Vital, 2001), so we excluded the patients with monoclonal gammopathy from our study. Myelodysplastic disease and Crohn's disease are not accepted as a cause of peripheral neuropathy.

Despite cessation of treatment, clinical and electrophysiological findings may continue to deteriorate over the subsequent 3-4 months and may be irreversible (Chaudhry *et al.*, 2002; Tosi *et al.*, 2005). Patients must be closely monitored before neuropathic symptoms affect their quality of life.

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