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Dapsone-induced Neuropathy Compounds Hansen's Disease Nerve Damage: An Electrophysiological Study in Tuberculoid Patients[1]

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Although nerve damage is the most striking feature in all forms of Hansen's disease (HD), the action of anti-mycobacterial drugs on peripheral nerves has not been well investigated.

In two previous reports, the effect of dapsone (DDS) was controversial. According to Magora, *et al.* ([10]), in a prolonged study, DDS appeared not to be effective on lepromatous progressive neuropathy without erythema nodosum leprosum (ENL). In contrast, Naafs, *et al.* ([11]) showed that DDS can reverse nerve damage in borderline patients following "reversal reaction." Both of these studies used motor conduction velocities (MCV) to determine the condition of the nerves.

In a previous short-term study ([9]) performed on DDS-treated patients, we observed that the motor unit condition slowly deteriorated as shown by means of various electrophysiological recordings.

The impairment of peripheral nerve trunks in DDS-treated HD patients is currently related to the small amount of the drug penetrating the endoneurium ([1]) and to the presence of solid bacilli in the nerves of patients who had received continuous treatment for many years ([2, 7]). Another implicated mechanism could be an insidious immunological damage, insensitive to anti-mycobacterial drug action, as suggested by experimental animal models ([14, 15]).

We report here the results of electrophysiological recordings of motor unit parameters performed immediately after DDS withdrawal and repeated 4 months later in tuberculoid HD patients. These recordings strongly suggest that at least one quarter of the patients developed a DDS-induced neuropathy which compounded the nerve damage due to HD.

DDS neurotoxicity has been described in 17 cases of dermatological disorders different from HD (reviewed in [16]). Typically, a motor neuropathy, rather than a sensory one, affecting the hands and feet occurred within 5 years after the initiation of dapsone in therapy doses ranging from 100 to 600 mg/day. Slow acetylation of the drug with the resultant accumulation of toxic levels was suggested to explain this phenomenon. However, the mechanism of DDS-induced neuropathy is unknown, and the neuropathy was never observed in animals made toxic with the drug ([17]).

PATIENTS AND METHODS

Our investigations were carried out on a group of 39 western African tuberculoid HD patients (21 men and 19 women) ranging in age from 13–60 years (mean 30.2 ± 10.5). The patients were classified according to Ridley and Jopling ([13]) as: TT = 15, BT = 23, and BB = 10. The age at diagnosis of the disease ranged from 2–15 years (mean 5.7 ± 3.5) and the treatment period was from 1–10 years (mean 3.4 ± 2.2). All of the patients were placed on a monotherapy regimen of DDS 100–300 mg/day which was stopped on the basis of dermatological improvement. These patients never presented with reversal reaction during the time of care at the Institut Marchoux, Bamako,

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TABLE 1. *Electrophysiological parameters recorded in the right ulnar nerve of tuberculoid HD patients (N = 39) at the time of DDS withdrawal (control) and 4 months later (mean ± S.E.M.).*

Ulnar nerve	Control	4 mos. after control	Difference	Significance[a]	% Patients[b]
Motor distal latency (msec)	3.28 ± 0.99	2.80 ± 0.49	−0.48 ± 0.81	$p < 0.001$	23
Forearm motor conduction velocity (m/sec)	49.61 ± 6.57	54.46 ± 7.38	4.80 ± 5.51	$p < 0.001$	10
Elbow segmental motor conduction velocity (m/sec)	42.46 ± 8.99	54.38 ± 11.04	11.92 ± 8.64	$p < 0.001$	13
Integrated evoked potential of ADQ[c] muscle (mV × msec)	32.82 ± 20.35	27.43 ± 16.05	−5.39 ± 23.39	NS	13
Integrated Emg recording of ADQ muscle during full contraction (10 sec, a.u.)	10.74 ± 3.45	8.92 ± 3.21	−1.82 ± 4.52	$p = 0.01$	5
Emg recruitment of motor unit potentials in ADQ muscle (full contr., a.u.)	2.30 ± 0.65	2.33 ± 0.58	0.03 ± 0.62	NS	0

[a] Significance by mean of Student's paired *t* test except for Emg cotation (Wilcoxon test).
[b] Percent of patients showing abnormal values at control (i.e., out of the 95% confidence limits of the values of the recordings 4 months later).
[c] ADQ = abductor digiti quinti.

Mali. However, all of them presented with clinically detectable neuropathy of at least one nerve trunk.

Electrophysiological recordings. All of the electrophysiological recordings were made by the same investigator up to the 15th day following DDS withdrawal, and they were repeated exactly 4 months later. The ambient temperature of the laboratory was kept as constant as possible (25–30°C, currently 26°C). The cutaneous temperature of the patient was not monitored but was assumed identical for each patient in the two recording sessions.

Four electrophysiological methods were used to investigate the motor unit status of the right ulnar and popliteal nerves. 1) Distal motor latencies (DML) and motor conduction velocities (MCV) of the fastest fibers were calculated using the technique of Lamontagne and Buchthal ([8]). A supramaximal stimulus was applied through bipolar cutaneous electrodes, the cathode being located distally. For the ulnar nerve, the stimulation was applied: a) 3 cm above the wrist; b) 4 cm below and c) 10 cm above the epicondyle. For the popliteal nerve, the stimulation was applied: a) 3 cm above the ankle, b) 4 cm below and c) 6 cm above the neck of the fibula. Electrical stimulation consisted of a single rectangular pulse (0.5 msec–50 mA) delivered by a constant current stimulator at the rate of 0.5 Hz. The evoked muscle potentials were recorded with bipolar cutaneous electrodes (2 cm apart) applied above the end-plate zone of the abductor digiti quinti (ADQ) or the extensor digitorum brevis (EDB) muscles after preparation of the skin. Amplified muscle potentials were photographed on the oscilloscope. The latencies of the potentials were measured from the onset of the stimulus to the onset of the initial deflection of the base line. The distance between the cathode and the active recording electrode was measured over the skin on the course of the nerve.

2) The photographed ADQ and EDB potentials evoked by nerve stimulation at the wrist and ankle were digitized and integrated from the onset of the initial deflection to the return to the base line by means of a Hewlett Packard 9111A graphic tablet connected to a Hewlett Packard 85 calculator.

3) Electromyographical activity of the ADQ and tibialis anterior (TA) muscle was recorded during a 10-sec full contraction, using a DISA NC 13K80 needle positioned in the muscle to obtain the largest potentials

TABLE 2. *Electrophysiological parameters recorded in the right popliteal nerve of tuberculoid HD patients (N = 39) (mean ± S.E.M.).*

Popliteal nerve	Control	4 mos. after control	Difference	Significance[a]	% Patients[b]
Motor distal latency (msec)[c]	5.05 ± 1.19	4.38 ± 0.62	−0.66 ± 0.89	$p < 0.001$	25
Leg motor conduction velocity (m/sec)[c]	40.77 ± 4.92	44.11 ± 8.37	4.34 ± 5.66	$p < 0.05$	0
Popliteal segmental motor conduction velocity (m/sec)	35.37 ± 7.47	45.00 ± 12.66	9.63 ± 13.55	$p < 0.001$	5
Integrated evoked potential of EDB[d] muscle (mV × msec)[c]	19.59 ± 15.72	13.47 ± 9.39	−6.12 ± 13.19	$p < 0.01$	20
Integrated Emg recording of TA[e] muscle during full contraction (10 sec, a.u.)	9.31 ± 2.91	8.00 ± 3.77	−1.31 ± 3.85	$p < 0.05$	5
Emg recruitment of motor unit potentials of TA muscle (full contr., a.u.)	2.20 ± 0.47	2.15 ± 0.49	0.05 ± 0.53	NS	0

[a] Significance by mean of Student's paired *t* test except for Emg cotation (Wilcoxon test).
[b] Percent of patients showing abnormal values at control (i.e., out of the 95% confidence limits of the values of the recordings 4 months later).
[c] Due to total denervation of the EDB muscle in 3 patients, motor distal latency and motor conduction velocity in the leg were calculated on the basis of 36 values.
[d] EDB = extensor digitorum brevis.
[e] TA = tibialis anterior.

possible. This activity recorded on magnetic tape (2–20,000 Hz) with standardized amplification was integrated by means of a Grass 7P10A resetting integrator and visualized on paper. The results were expressed as the number of resets observed (arbitrary units).

4) The recruitment of the muscle unit potentials (MUP) was also studied using conventional electromyography in the ADQ and TA muscles. The intensity of the recruitment of the MUP during the strongest contraction was graded as follows: interference pattern = 3, loss of the MUP = 2, single MUP = 1, and electrical silence = 0.

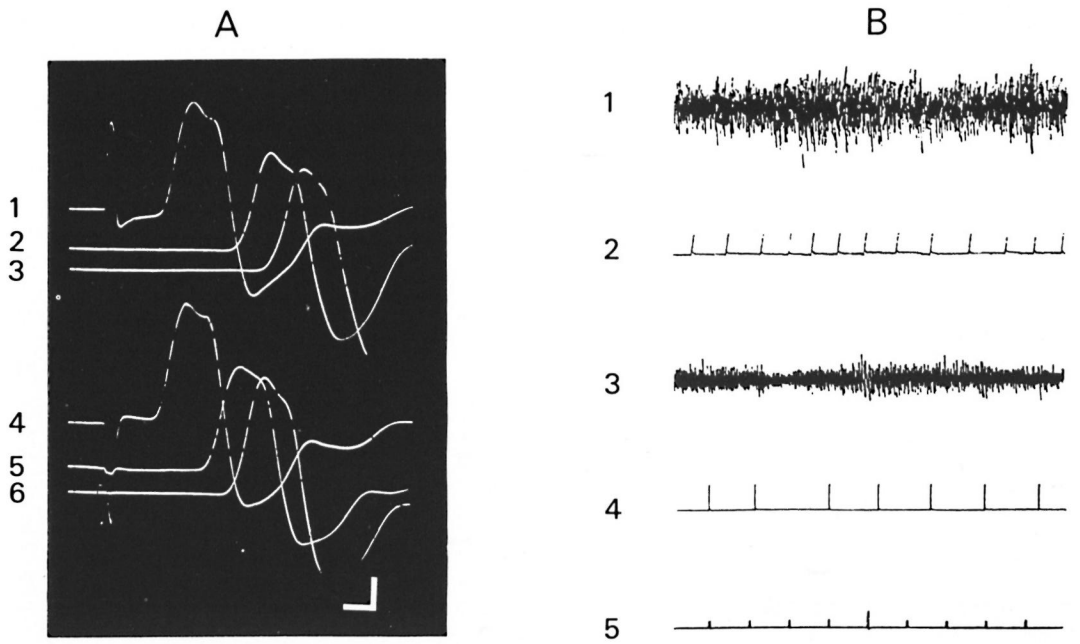
Statistical analysis. All of the values are indicated as the standard deviation around the mean. Emg recruitment presents a nonparametric distribution, and the difference between the results of the two recording sessions was evaluated by means of a Wilcoxon paired test. Assuming that all other results were normally distributed around their mean, the Student paired *t* test was applied to compare the mean results at the time of DDS withdrawal and 4 months later.

To appraise the prevalence of DDS-induced neuropathy in our patient population, we calculated the percentage of the values obtained at the first recording session, which was out of the 95% confidence interval (mean + 2 standard deviations), of the mean results observed during the second recording session.

RESULTS

The results for the ulnar nerve are shown in Table 1; for the popliteal nerve, in Table 2. Parameters concerned with MCV were improved at a highly significant level. The most sensitive of them were the DML decrease of the ulnar and popliteal nerves since 23%–25% of the patients presented abnormal values at the first recording session. For the ulnar nerve, the motor distal latency decreased from 3.28 ± 0.99 msec to 2.80 ± 0.49 msec during the 4-month interval ($p < 0.001$); for the popliteal nerve, from 5.05 ± 1.19 msec to 4.38 ± 0.62 msec ($p < 0.001$).

In HD neuropathy, ulnar motor conduction slowing at the elbow, as well as at the knee for the popliteal nerve, is common. These abnormalities were observed at the



THE FIGURE. Electrophysiological recordings.

A = Conduction velocities in the ulnar nerve: 1, 2, 3 = stimulation at the wrist, below and above the epicondyle immediately after DDS withdrawal; 4, 5, 6 = 4 months later. The digitization and integration of potentials recorded subcutaneously in the ADQ muscle (1, 2) gave an approximation of the amount of innervated muscle fibers.

B = Full contraction activity in the ADQ muscle during 10 seconds recorded by needle on magnetic tape and off-line visualized on chart paper: 1 = Emg activity after DDS withdrawal; 2 = reseting integration of line 1; 3 = Emg activity 4 months later; 4 = integration of line 3; 5 = time base: 1 second.

time of drug withdrawal (ulnar = 42.46 ± 8.99 m/sec; popliteal = 35.37 ± 7.47 m/sec). Four months later these segmental conduction velocities were significantly increased ($p < 0.001$) (ulnar = 54.38 ± 11.04 m/sec; popliteal = 45.00 ± 12.66 m/sec), returning to near-normal values. Moreover, the MCV of the ulnar nerve at the forearm and of the popliteal nerve at the leg, scarcely affected in HD neuropathy, also showed a significant increase.

In contrast, parameters exploring the degree of innervation of distal muscles were impaired at the second recording session. If the Emg recruitment, coarsely graded, was not modified, the integration of the full contraction activity of the ADQ and TA muscles decreased significantly and 5% of the patients showed abnormal values at the first recording session. However, the integrated potential of the ADQ and EDB muscles evoked by nerve stimulation was more sensitive; 13% of the patients presented abnormal ADQ values at the first recording session, although the mean value of the group did not present significant variation due to the great dispersion of the results around the mean. The difference was significant ($p < 0.01$) in EDB and 20% of the patients were affected.

We attempted to correlate those electrophysiological parameters showing significant variations with the total dose of DDS given to each patient, but no correlations were found.

DISCUSSION

The 17 previously published cases ([16]) of dapsone-induced neuropathy lead us to delineate the main characteristics of the side effects of this drug.

In 16 of the 17 cases (94%), a motor neuropathy was present, affecting upper and/or lower extremities. A sensory component to the neuropathy was present in seven cases (41%). The neuropathy occurred within 1

year of DDS therapy in 8 cases (47%), within 1 to 5 years in 5 cases (29%), and after 10 years of DDS use in 4 cases (23%). DDS-induced clinical neuropathy usually improved within 1 year after discontinuation of the therapy.

Electromyographic examinations disclosed an axonal motor neuropathy in 14 of the 17 patients. Sensory conduction velocities were normal when calculated except for one patient in whom a sprue was associated with DDS-induced neuropathy ([4]). The slowing of MCV and the increase of MDL were only observed in association with a strong muscle denervation ([6]).

In our patients, the mean values of distal MCV and MDL both in ulnar and popliteal nerves were significantly improved following DDS withdrawal, as quickly as 4 months. The initial mild slowing of the terminal segment of the nerves could reflect a loss of the fastest conducting axons and/or a mild degree of secondary demyelination, as observed in uremic neuropathy ([5]). Occurring in parts of the nerve classically not affected in human HD neuropathy ([3]), these abnormalities would only be dapsone-dependent. More surprising is the MCV improvement of the ulnar elbow segment and of the popliteal nerve above the neck of the fibula. In HD neuropathy, these segmental MCV are known to be strongly reduced ([9, 10]), particularly when the nerves are enlarged in relation to a possible entrapment of nerve fibers. A 28% MCV increase was recorded in the two nerves, suggesting that DDS might further impair focal demyelination resulting from the entrapment ([12]).

In contrast, the distal innervation of both upper and lower limbs showed a significant deterioration following DDS withdrawal. The integrated muscle potential evoked by distal stimulation of the nerve trunk gave a numerical reflection of the amount of innervated muscle fibers. The integration of the maximal voluntary contraction recorded by needle electromyography during a fixed period gave a reflection of the number of functional motor units. A discrepancy between these two values exists when a block of conduction occurs in some nerve fibers proximal to the site of stimulation.

In our study, the amount of innervated muscle fibers decreased in ADQ and EDB, suggesting that motor axons degenerated after DDS withdrawal. Identically, the number of functional motor units in ADQ and TA decreased despite the amelioration of MCV usually observed when nerve conduction blocks disappear. Increasing muscle denervation was not described in previous cases of DDS-induced neuropathy after therapy was stopped, but axonal regeneration was always observed after more than 4 months.

In conclusion, 39 tuberculoid HD patients treated with DDS monotherapy showed a highly significant improvement of their ulnar and popliteal motor conduction velocities 4 months after DDS withdrawal. Twenty-five percent of them showed abnormal values at the time the drug was stopped. In contrast, the distal muscles presented electrophysiological abnormalities, indicating a persistent denervation. The open question is the occurrence of muscle re-innervation later than 4 months after withdrawal in this disabling disease.

SUMMARY

In 17 previous cases of dermatological disorders, an axonal motor neuropathy was described as a dapsone (DDS) therapy side effect. In this study, we attempted to assess DDS-induced neuropathy in the ulnar and popliteal nerves of 39 tuberculoid Hansen's disease patients using electrophysiological recordings at the time of DDS withdrawal, owing to dermatological improvement, and 4 months after. Distal motor latencies, conduction velocities at forearm and leg and above the epicondyle and the neck of the fibula were improved at a highly significant level. Twenty-five percent of the patients presented abnormal values (outside of the 95% confidence interval) at the first recording session compared to those at the second session. By contrast, parameters exploring the degree of innervation of distal muscles showed a progressive denervation. These results lead to an impairment of Hansen's disease neuropathy during DDS therapy affecting the motor conduction velocities of one quarter of the patients, and are discussed in terms of physiopathological mechanisms.

RESUMEN

Se describió una neuropatía axonal motora como efecto colateral de la terapia con dapsona (DDS) en 17 casos de desórdenes dermatológicos. En este estudio, intentamos medir la neuropatía inducida con DDS en los nervios ulnar y poplíteo de 39 pacientes con la enfermedad de Hansen tuberculoide, usando registros electrofisiológicos al momento de suspender el DDS (debido a la mejoría dermatológica) y 4 meses después. Las latencias distales motoras, las velocidades de conducción al antebrazo y pierna y arriba del epicóndilo y cuello de la fíbula, mejoraron todas a un nivel altamente significativo. Comparando con los datos del segundo registro, 25% de los pacientes presentaron valores anormales (fuera del intervalo de 95% de confianza) en el primero. En contraste, los parámetros que exploran el grado de innervación de los músculos distales mostraron una denervación progresiva. Estos resultados sugieren una afectación de la neuropatía en la enfermedad de Hansen durante la terpia con DDS capaz de alterar las velocidades de conducción motora en un cuarto de los pacientes. Los hallazgos se discuten en base a los mecanismos fisiopatológicos.

RÉSUMÉ

Dans 17 cas déjà rapportés de troubles dermatologiques, on a décrit une névropathie motrice des axones, comme effet secondaire de la thérapeutique à la dapsone (DDS). Dans cette étude, on a tenté d'évaluer cette névropathie induite par la DDS, au niveau des nerfs cubitaux et poplités de 39 malades atteints de lèpre tuberculoïde, au moyen d'enregistrements électro-physiologiques effectués au moment de l'interruption du traitement par la dapsone, suite à une amélioration biologique, et 4 mois plus tard. Les temps de latence moteurs distaux, les vitesses de conduction au niveau de l'avant-bras et de la jambe, de même qu'au niveau de l'épicondyle et de la tête du radius, ont été améliorés d'une manière très significative. Vingt-cinq pour cent des malades présentaient des valeurs anormales (en-dehors de l'intervalle de confiance à 95%) lors de la première séance d'enregistrement, par rapport aux résultats notés à la seconde séance. Par contre, les paramètres qui traduisent le degré d'innervation des muscles distaux, ont montré une dénervation progressive. Ces résultats mènent à penser que la maladie de Hansen entraîne une aggravation de la névropathie au cours de la thérapeutique sulfonée, qui affecte les vitesses de conduction motrice, et ceci chez un quart des malades. Ces résultats sont discutés quant aux mécanismes physiopathologiques impliqués.

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