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Dapsone Neuropathy—Report of Three Cases and Pathologic Features of a Motor Nerve[1]

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Dapsone (4,4′ diaminodiphenylsulfone) is known to have caused peripheral nerve damage in some patients treated for dermatitis herpetiformis, cystic acne, pyoderma gangrenosum, and other skin disorders ([3–5, 9, 10, 13, 14]). The most important use of dapsone worldwide is in the therapy of leprosy, and there has been only one acceptably documented report of the occurrence of dapsone neuropathy in the context of leprosy ([15]). The pathological changes in this drug-induced neuropathy have never been reported.

The present communication concerns three young persons who, like the patient of Prayag, *et al.* ([15]), developed a motor neuropathy following ingestion of excessive doses of dapsone for hypopigmented skin lesions. In two of the three patients, the skin lesions were of maculoanesthetic leprosy; the other patient's lesions were nonleprous. None had any evidence of leprous nerve trunk involvement. We were fortunate in obtaining a motor nerve biopsy from one patient.

CASE HISTORIES AND FINDINGS

Patient I. S.J. was a 16-year-old female who had noted a solitary, almond-sized anesthetic macule on her right wrist. At the leprosy clinic of another hospital, she was diagnosed as having maculoanesthetic leprosy, and dapsone was prescribed in a dose of 100 mg daily. She misunderstood the instructions and consumed 200 mg daily. Two months later she developed progressive, painless, symmetrical weakness of both hands. On examination she had weak thumbs, weak grips, and clawing of both index fingers. The lower limbs, hips, shoulders, and face were normal. There was no anesthesia, no proprioceptive defects, no peripheral nerve enlargement, and no other skin lesions. The tendon reflexes were normal and the plantar response was flexor.

She was advised to discontinue dapsone. Having done so, her muscle strength returned to normal in the next 3 months. There was no neurologic deficit when last seen 2 years later, and the maculoanesthetic skin lesion had also healed.

Patient II. S.P. was an 18-year-old female who had noted two or three pale, coin-sized macules on her left shin. Her sister, a student of pharmacy, diagnosed leprosy and instructed her to take dapsone tablets. The patient took 50 mg daily for 5 months, then 100 mg daily for 1½ years, and because there was no change in the patches, she then took 200 mg daily until she was examined by us 5 months later.

Four months after ingesting dapsone 200 mg daily she developed weakness in both feet, the right foot more than the left, with frequent twisting of the ankles and pain on prolonged walking. Fifteen days prior to examination, she developed weakness in the right hand with clawing of the little finger. Eight days later similar symptoms were noted in the left hand.

Examination revealed that the macules on the shin were nonanesthetic and showed no loss of hair growth. No skin lesions of leprosy were present anywhere, and the peripheral nerves were not enlarged. Cutaneous and proprioceptive sensations were intact everywhere. There was mild wasting of both legs, the right leg more than the left, and muscle strength was graded as 3/5 in the hands and feet and normal in the hips and shoulders. The tendon reflexes were un-

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TABLE 1. *Dapsone excretion and isoniazid acetylation patterns of patients studied.*

	Patient		
	I	II	III
Dapsone excretion rate	Slow[a]	Slow	Slow
Isoniazid acetylation			
Rate[b]	Slow	Slow	Fast
% Acetylated	34%	35%	93%

[a] Slow = <40% excreted in 24 hr after 100 mg oral dose.

[b] WHO Bull. **49** (1973) 507–516. Slow = <70%; fast = >75%.

affected, and the plantar response was flexor.

Her cerebrospinal fluid (CSF) examination showed a protein of 20 mg%, sugar 70 mg%, chloride 650 mg%, and no cells.

Patient III. P.M.R. was a 26-year-old male who developed two small anesthetic macules on his leg. The dermatologist he consulted prescribed dapsone 100 mg daily, which he took for 2 years. He made an unsuccessful suicide attempt by swallowing 25 100-mg tablets of dapsone because the hypopigmentation persisted. After recovery from this episode, he independently increased the daily intake of dapsone to 400 mg. Two months later, he was unable to pick up small objects (he was a diamond sorter), especially with the left hand, and he then sought medical advice. On examination it was confirmed that he had two inactive anesthetic macules on his left leg. There was bilateral thumb and pinch weakness but no wasting. The feet were normal.

The sensory system was normal (except over the macules), and no peripheral nerve enlargement was present. Tendon reflexes were present, except for the right ankle jerk which was lost. The plantar response was flexor.

RESULTS

Table 1 shows the urinary dapsone excretion patterns and the isoniazid acetylation patterns of the three patients.

Electrophysiologic studies were performed initially and at follow-up, and they are summarized in Table 2. All three patients were clinically asymptomatic within 3 months of stopping dapsone but, as seen in Figure 1, electropathologic features persisted even 2½ years later (Patient I).

Pathology. The most severely affected patient (Patient II) consented to a motor nerve biopsy. The nerve selected was the lateral division of the anterior tibial nerve supplying the extensor digitorum brevis muscle in the right foot. The nerve was divided into two segments and processed for light and electron microscopy, respectively. Hematoxylin and eosin- (H&E) and Fite-Faraco-stained sections of this motor and a nearby sensory nerve showed no inflammation and no bacilli. The superficial peroneal nerve, also biopsied, was normal on light microscopy. Toluidine blue-stained, semithin transverse sections of the motor nerve were generally unremarkable except for patches where myelinated fibers were sparse.

Abnormalities were visible at the ultrastructural level (Figs. 2–4). The initial occurrence appeared to be retraction and shrinkage of a myelinated axon from the adaxonal Schwann cell cytoplasm. Further axonal atrophy was associated with widening of intramyelin clefts and pressure from myelin whorls. The progressive disintegration of the neural elements left only debris occupying the attendant Schwann cell. The removal of the debris was effected by macrophages. Schwann cell processes budded into Bungner bands, but their repopulation by myelinated axonal outgrowths was not seen. The unmyelinated axons were generally well preserved, with occasional budded Schwann cell tongues embracing an axon, suggesting mild prior degeneration. Also occasionally seen was demyelination without associated axonal changes. The endoneurial connective tissue was moderately increased, and the blood vessels were normal.

DISCUSSION

Two of our patients had minor leprous skin lesions, and one had supposedly leprous skin lesions for which a higher (two to four times) than therapeutically indicated dose of dapsone was ingested, either deliberately or mistakenly. In all three, a purely motor (therefore nonleprous), predominantly distal neuropathy developed subacutely in the upper and/or lower limbs 2 to 4 months later.

TABLE 2. *Electrophysiologic findings (figures in parentheses indicate normal cut-off values).*

	Patient I	Patient II	Patient III
Ulnar nerve			
SAP[a]	a) 12 μV (>5 μV) b) 11 μV	a) 11 μV b) ND[e]	a) 13.6 μV b) 14.5 μV
DML[b]	a) 3.0 msec (<4.0 msec) b) 3.0 msec	a) ND b) ND	a) 3.0 msec b) ND
CMAP[c]	a) 8 mV disp.+ F wave N (<30 msec) b) 17 mV F wave 27 msec		a) 2.3 mV disp.+ F wave 28.2 msec
MNCV[d]	a) 51.8 m/sec b) 55.4 m/sec		a) 57.4 m/sec
Median nerve			
SAP	a) 15 μV (>10 μV) b) 19 μV	a) 15 μV b) 16 μV	a) 14.6 μV b) 16.3 μV
DML	a) 4.2 msec (<5 msec) b) 3.9 msec	a) 8.9 msec b) 6.8 msec	a) 4.5 msec b) 4.9 msec
CMAP	a) 9 mV disp.+ F wave—absent b) 17 mV F wave 28.6	a) Highly disp. F wave—absent b) 1.8 mV disp.++	a) Disp.+ F wave—absent b) 8 mV disp.+ F wave ?30 msec
MNCV	a) 50.0 m/sec b) 52.3 m/sec	a) 39.2 m/sec b) 42.0 m/sec	a) 55.6 m/sec b) 52.1 m/sec
Posterior tibial nerve			
Sural			
SAP	a) ND[e] b) ND	a) 23.4 μV (>5 μV) b) 18.0 μV	a) 13.8 μV b) ND
DML	a) ND b) ND	a) 17.0 msec (<6.0 msec) b) 6.0 msec	a) 4.4 msec b) 7.8 msec
CMAP		a) Disp.++ F wave—absent b) Disp.++ F wave 60.8 msec	a) 3.8 mV disp.+ F wave—abs. (<60 msec) b) 5.5 mV disp.+ F wave 49 msec
MNCV		a) 39.5 m/sec b) 52.7 m/sec	a) 38.7 m/sec b) 52.5 m/sec
Electromyography			
	a) Fibrillations and frequent long-duration polyphasics in hands and forearms	a) Fibrillations and highly polyphasic motor unit action potentials; single oscillations; quadriceps—N	a) Fibrillations, polyphasia in hands and feet; quadriceps, biceps—N
	b) Occ. polyphasia	b) Same as a)	b) Same as a)
Remarks			
	a) Motor axonopathy with myelinopathy	a) Distal motor myelin and axon degeneration with partial regeneration	a) Distal motor myelin and axon degeneration with partial regeneration
	b) Largely reversed	b) Same as a)	b) Same as a)

[a] SAP = sensory action potentials.
[b] DML = distal motor latency.
[c] CMAP = compound muscle action potential.
[d] MNCV = motor nerve conduction velocity.
[e] ND = not done.
a) = initial.
b) = follow-up.

All three patients were slow excretors of dapsone ([6]). Two showed slow and one showed rapid acetylation of isoniazid. Since leprosy neuropathy was excluded by the clinically, electrophysiologically, and histologically normal sensory nerves, the differential diagnosis of Guillain-Barré syndrome was considered, but the historical data, the preservation of the tendon reflexes, the normal CSF picture, and the pathologic findings ruled out an immunologically mediated peripheral neuropathy.

The electrophysiologic findings, similar to those reported by others ([8, 9, 15]), pointed to a distal axonopathy with myelinopathic conduction defects proximally in the long motor nerves. The electron microscopic features, as revealed in a long motor nerve biopsied near its termination, also pointed to primary degeneration of the myelinated axons, and regenerative activity was conspicuously absent. After dapsone was stopped, presumably vigorous myelin and axon regrowth resulted in excellent clinical improvement.

The existence of dapsone-induced neuropathy raises some questions: a) Is the paucity of reports in the leprosy literature and their frequency in the dermatology literature due to a dose relation ([13, 14]) and/or the difficulty of proving a causal relationship in the presence of leprous neuropathy? The present communication and that of Prayag, *et al.* ([15]) suggest the former, but some lep-

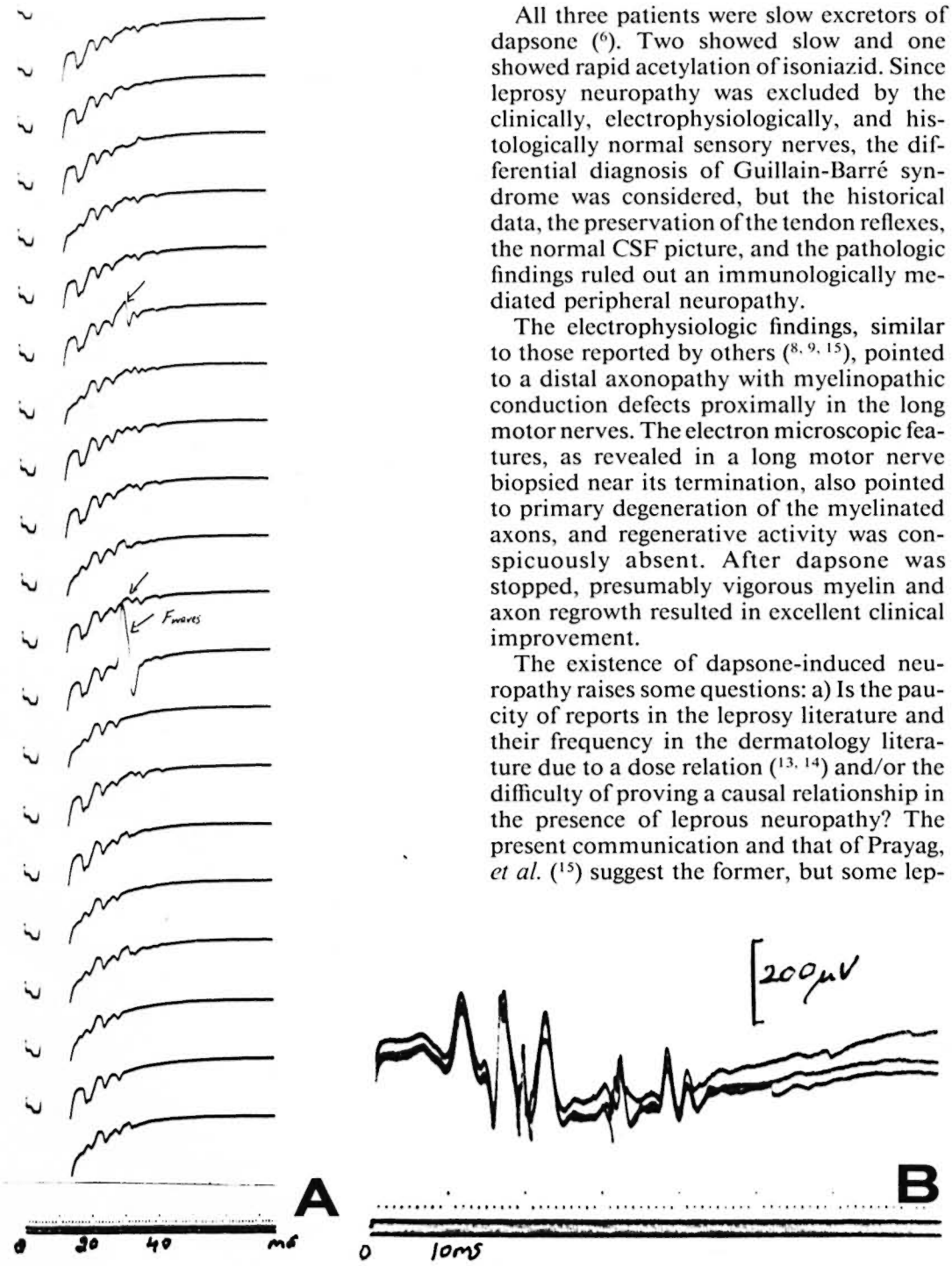

FIG. 1. A = Patient I. Follow-up at 2½ years. Although completely recovered clinically, electrophysiologic abnormalities persist in the form of a dispersed CMAP and infrequent F waves in a thenar muscle.

B = Patient III. A markedly delayed, dispersed, and attenuated evoked potential was recorded from abductor hallucis muscle 3 months after stopping dapsone, although he was much improved clinically.

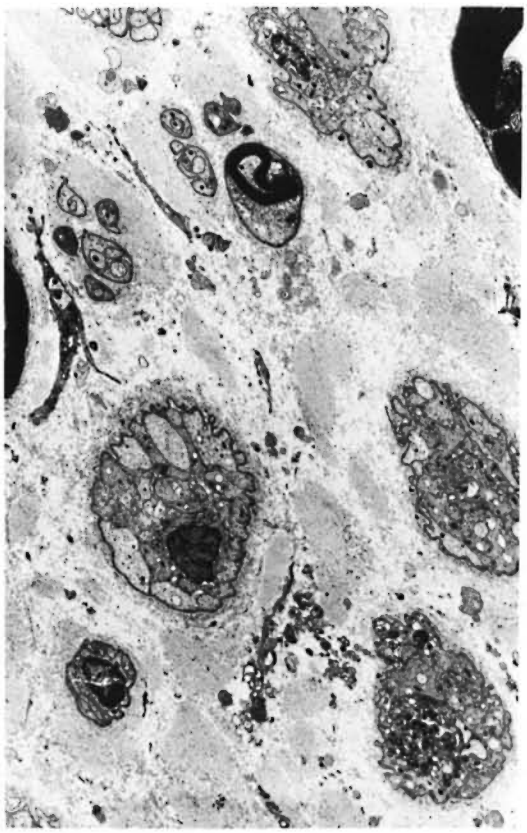

FIG. 2. Proliferated Schwann cell processes forming Bungner bands are seen; also a few intact unmyelinated axons and a myelinated axon (×5000).

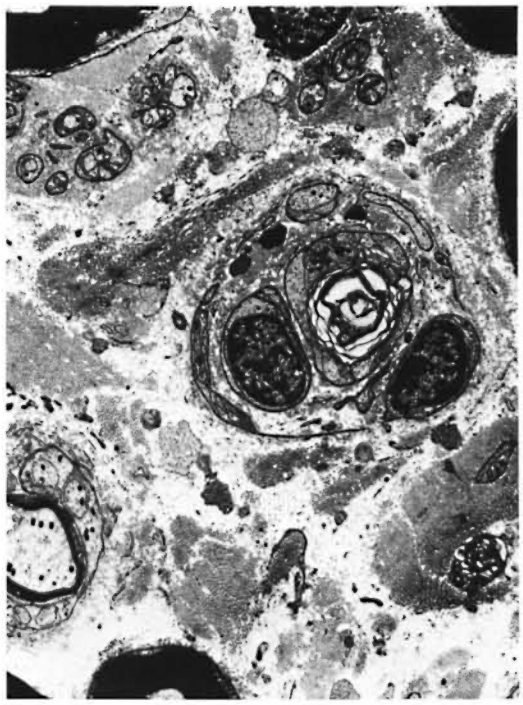

FIG. 3. A degenerating myelinated nerve fiber surrounded by Schwann cells and their processes simulating an onion bulb. The endoneurial collagen is increased (×5000).

rologists ([17, 18, 20]) speculate that dapsone aggravates nerve damage in some multibacillary patients ingesting even therapeutic doses for prolonged periods. b) Does a slow acetylation rate of isoniazid identify the dapsone-neuropathy-prone individual ([14]) (as it does the individual at risk for isoniazid neuropathy [11])? The data in Table 1 show that one of our three patients was a rapid acetylator of isoniazid (and presumably also of dapsone). It is possible that mechanisms other than slow acetylation are predisposing factors. The additional finding (Table 1) that all patients were slow excretors of dapsone ([6]) is also interesting, although its importance is unclear. c) Where does dapsone enter (and influence) the nervous system? A peripheral nerve location is unlikely for two reasons: the purely motor neuropathy and the distal neuropathy that has developed in the vast majority of reported cases ([4, 5, 9, 10, 15, 17, 22]). Further, Boddingius, *et al.* ([2]), working with dapsone-fed normal mice, were unable to detect the drug in the Schwann cells or in peripheral nerves. Rather, it appears that dapsone exerts its deleterious effect directly on the spinal motor neuron or emerging rootlets. The (largely reversible) metabolic derangement is manifested in the farthest regions of the longest fibers as a "distal motor axonopathy."

Our ignorance about these aspects of the problem is compounded by the lack of an animal model. Rodents such as guinea pigs ([21]), rats ([8]), and mice ([12]) have not developed neuropathy when dosed (or overdosed) with dapsone.

SUMMARY

We report the clinical features, electrophysiologic findings, and dapsone and isoniazid excretion studies in three young people who ingested excessive amounts (2–4 times the prescribed dose) of dapsone for hypopigmented macules and who developed, subacutely, progressive motor neuropathy a few months later. Pathologic studies on a biopsied motor nerve confirmed the

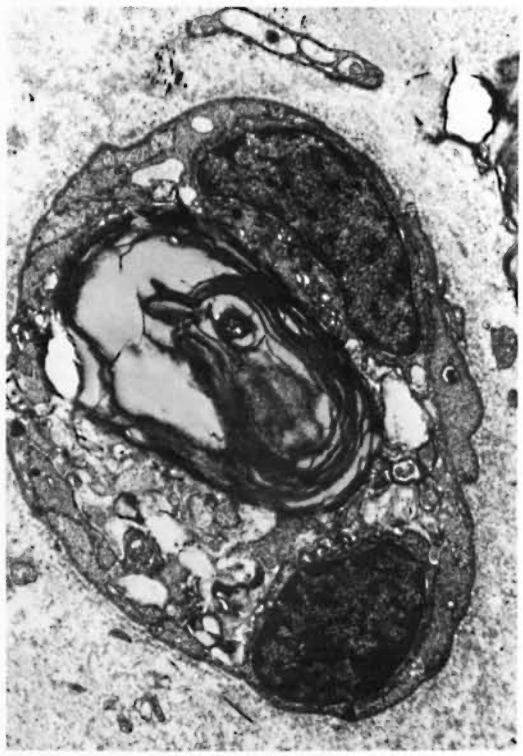

FIG. 4. A myelinated nerve fiber undergoing advanced degeneration within the Schwann cell cytoplasm which shows myelin debris (×12, 500).

electrophysiologic conclusion of distal motor axonopathy. All made a rapid recovery in a few months after dapsone was stopped, although electrical abnormalities persisted. One patient was a rapid acetylator of isoniazid.

RESUMEN

Se describen las características clínicas, los hallazgos electrofisiológicos y los datos de excreción de dapsona y de isoniazida en 3 jóvenes que ingirieron cantidades excesivas (2 a 4 veces la dosis prescrita) de dapsona debido a la presencia de máculas hipopigmentadas y quienes unos meses después desarrollaron una neuropatía motora subaguda y progresiva. Los estudios patológicos en biopsias de nervios motores confirmaron la conclusión electrofisiológica de axonopatía motora distal. Todos los pacientes se recuperaron pocos meses después de haber suspendido la dapsona aunque persistieron las anormalidades eléctricas. Un paciente fue un acetilador rápido de la isoniazida.

RÉSUMÉ

On relate ici les caractéristiques cliniques, les observations électrophysiologiques et les résultats d'études d'excrétion de la dapsone et de l'isoniazide chez trois sujets jeunes, présentant des macules hypopigmentées, qui avaient ingéré des quantités excessives de dapsone (jusqu'à 2 et 4 fois la dose prescrite). Ces sujets avaient développé quelques mois plus tard, une nevropathie motrice progressive sub-aiguë. Des études pathologiques menées sur une biopsie de nerf moteur ont confirmé les observations électrophysiologiques qui concluaient à une axonopathie motrice distale. Tous les sujets ont guéri rapidement, en quelques mois, après interruption du traitement par la dapsone; les anomalies électriques ont cependant persisté. Un des malades s'est révélé un acetylateur rapide de l'isoniazide.

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