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Peripheral Motor Neuropathy Caused by Excessive Intake of Dapsone (Avlosulfon)

Ingmar Rosén[1] and Rune Sörnäs[2]

[1] Department of Clinical Neurophysiology, University Hospital, S-22185, Lund
[2] Department of Neurology, the Hospital of Halmstad, Halmstad, Sweden

Summary. A case of selective peripheral motor polyneuropathy caused by excessive intake of dapsone is described. The condition was characterized by a peripheral muscle weakness in all limbs, normal sensitivity and present, although weak, muscle reflexes. Neurophysiologically, low amplitude muscle responses, prolonged distal latencies and reduced motor conduction velocities were found together with electromyographic signs of denervation. Sensory neurography was normal. The patient showed a complete clinical recovery and a marked neurophysiological restitution after termination of the excessive drug intake. The patient was found to acetylate dapsone at a slow rate. The case is compared with those previously reported in the literature.

Key words: Polyneurophathy — Dapsone — Neurophysiology

Introduction

Although mainly used for treatment of leprosy, dapsone is also used for treatment of dermatitis herpetiformis and related skin disorders. The drug may cause anaemia, anorexia, allergical dermatitis and hepatitis (Graham 1975; Letter Lancet 1981). Amongst complications involving the nervous system psychotic reactions have been reported. We recently had the opportunity to study one further untoward effect on the nervous system, i.e. a selective peripheral motor polyneuropathy.

Case History

A 30-year-old concrete worker, previosly well developed an acute itching eczema during military service in 1965 and, an allergic reaction to iodine was found. The patient has since then avoided exposure to iodine but has occasionally experienced allergic skin reactions.

Offprint requests to: I. Rosén at the above address

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In 1966 treatment with dapsone (Avlosulfon ICI) was initiated at a dose of 50 mg/day, later increased to 150 mg/day. The patient's skin condition was significantly improved.

Since the early 1970's the patient increased his intake of the drug without consulting his doctor. For several years he took as much as 400 mg/day on average. As soon as he felt symptoms of itching he immediately took 400–500 mg and later the same day a further 200–300 mg. When the itching ceased the patient did not take any dapsone for some days until new symptoms appeared. At the end of 1974 the patient noticed pain in his calves after jogging. Gradually his legs became weaker and he noticed difficulty in walking. From the beginning of 1975 his condition gradually deteriorated and the patient also noticed a decreasing circumference of his leg muscles.

From the early part of 1975 the patient noticed weakness of his hands which became considerably worse towards the end of the year. When first seen by a neurologist in November 1975 he had difficulty in writing his name, picking up small items and buttoning his clothes. He reported moderate paresthesias in his hands but no sensory symptoms in his feet.

The neurological examination in November 1975 showed marked atrophy of the intermetacarpal spaces and a moderate atrophy of the leg muscles. There was also a reduced strength of dorsiflexion of wrists and feet. However, tests of sensitivity to vibration, touch and pin-prick were fully normal. The tendon jerks were somewhat weak but present and symmetrical. The plantar reflexes were normal.

The patient was persuaded to reduce his intake of dapsone considerably over the next year down to 300 mg/week at the maximum. His condition improved significantly during this time. He was again able to hold a nail between his fingers and to hit it forcefully and had no difficulty in managing his work. The atrophy of the hand muscles had disappeared. No further symptoms emerged during a 4-year follow-up period.

The patient's capacity to acetylate isoniazid by N-acetyl transferase was estimated by determining acetylisoniacid in urine (Varughese et al. 1974). The proportion of acetylisoniazid to total hydroazides in urine was 54%, clearly showing that he belonged to the group of slow acetylators.

Neurophysiological Examinations

The patient was first examined neurophysiologically in April 1976, i.e. a few months after reduction of the excessive dapsone intake. The results are listed in Table 1 and illustrated in Fig. 1. The amplitudes of the compound muscle action potentials recorded with surface electrodes from distal muscles were generally lower than normal. The motor conduction velocities of the median, fibular and posterior tibial nerves were reduced. There was also a pathological temporal dispersion of the muscle responses, especially after a long nerve conduction distance (upper records on Fig. 1 A, B and C).

Electromyographic needle recording demonstrated profuse denervation activity (fibrillations and positive sharp waves) in the distal muscles (first interosseos muscle of the hand, abductor pollicis brevis, anterior tibial and triceps surae muscles). In these muscles the number of motor unit potentials recruited at maximal voluntary effort was reduced. The motor unit potentials also showed a marked increase of amplitude, duration and complexity. The electromyographic findings in more proximal muscles (biceps brachii and quadriceps) were normal.

The patient was again examined in October 1977, i.e. almost 2 years after the reduction of dapsone. In the arm the motor conduction velocities and response amplitudes were normal. In the leg there was still a reduction of velocites and response amplitudes although the response amplitudes had increased. The posterior tibial nerve especially showed a marked remaining temporal dispersion of

Table 1. Neurographic values obtained immediately after, 2 and 4 years after reduction of dapsone intake and compared with the normal range. Left side examined on all occasions. Recording sites for motor neurography: hypothenar, thenar, extensor digitorum brevis and abductor hallucis muscles

	Normal	1976-04-27	1977-10-23	1979-09-25
Ulnar nerve				
Motor conduction velocity	>50 m/s	59.5	61.0	56.5
Distal latency	< 3 ms	3.3	3.1	2.8
Motor response amplitude	>7 mV	4.0	7.5	7.5
Sensory conduction velocity	>40 m/s	46.0	48.0	56.0
Sensory response amplitude	> 7 uV	0.7.0	12.0	12.0
Median nerve				
Motor conduction velocity	>50 m/s	42.0	52.5	53.0
Distal latency	<4.0 ms	4.6	4.4	3.6
Motor response amplitude	>4.0 ms	2.0	8.	10.0
Sensory conduction velocity				
dig I	>40 m/s	49.0	48.0	55.0
dig III	>40 m/s	50.0	54.0	57.0
Sensory response amplitude				
dig I	>15 uV	33.0	35.0	42.0
dig III	>10 uV	29.0	25.0	23.0
Fibular nerve				
Motor conduction velocity	>40 m/s	37.5	36.5	35.0
Distal latency	<4.5 ms	6.4	6.2	4.0
Motor response amplitude	> 3 mV	1.8	3.0	3.2
Posterior tibial nerve				
Motor conduction velocity	>40 m/s	36.5	28.5	32.0
Distal latency	< 7 ms	8.8	4.7	6.2
Motor response amplitude	> 5 mV	0.4	0.5	0.5

the muscle response. Sensory neurography was normal on both occasions.

The electromyographic examination did not demonstrate any remaining denervation activity in the hand muscles. In these muscles the motor unit potential size was even larger than on the previous occasions, presumably due to axonal sprouting.

In the leg the anterior tibial and triceps surae muscles showed very large motor unit potentials and occasional fasciculations. In the latter muscle sparse fibrillation potentials were also recorded. In proximal muscles (vastus medialis and biceps brachii) electromyography was normal as on the previous occasion.

The patient was again examined in September 1979. There was a further decrease of the distal motor latency values for the ulnar and median nerves. Other neurographic values as well as the electromyographic examination were unchanged as compared with the second test.

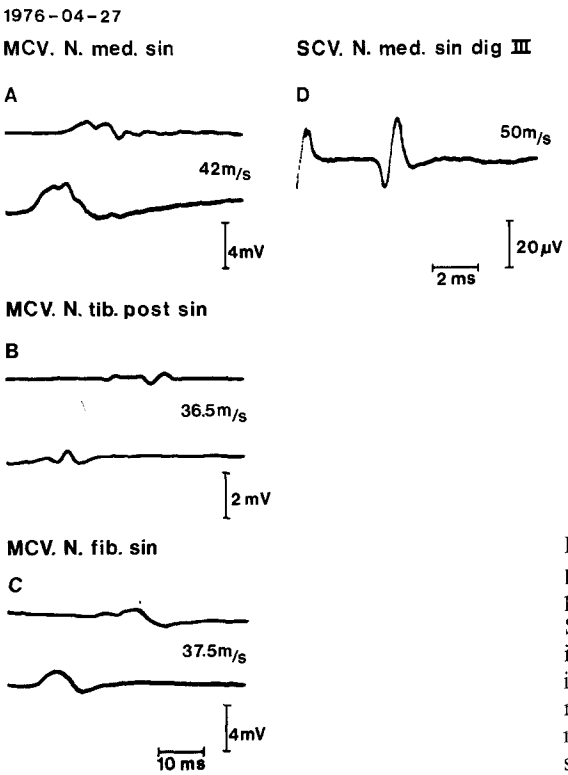

Fig. 1 A–D Oscilloscope traces photographed at the initial neurophysiological examination. Stimulation sites: wrist and elbow in *A*, ankle and knee in *B* and *C*, in *D* the recording was made with a needle electrode close to the median nerve at the wrist at stimulation of the third finger

Discussion

Although our patient started to show signs of a peripheral motor neuropathy a long time after the initiation of dapson treatment, the connection between the drug treatment and the neurological disorder seems very likely. The symptoms presented at a time when the patient had increased his drug intake considerably. According to our information he has not been in touch with substances known to cause motor neuropathy (e.g. lead) (Dyck et al. 1975). The very marked improvement clinically and neurophysiologically after the dose was reduced makes the connection even more likely. The fact that the neuropathy markedly improved despite a continuing low dose intake indicates that the toxic effect on the nervous system is dose related.

The amount of dapsone given in total and as daily dosages are listed in Table 2 for ten reported cases exhibiting signs of motor neuropathy as a result of dapsone intake. Our case had by far the largest total intake of the drug and presumably also the largest daily intake preceding the onset of neurological symptoms.

Dapsone is metabolized by acetylation by the same enzyme, N-acetyltransferase, as isoniazid (Gelber et al. 1971). The neurotoxicity of isoniazid is due to slow acetylation with accumulation of toxic drug levels (Devadatta and Gangudharam 1960). The severity of the neuropathy is determined by both the rate of acetylation and the total dose ingested. The conditions are presumably similar for dapsone (Koller et al. 1977). There is a genetically determined polymorphic

Table 2. Summary of dapsone intake and neurophysiological findings in reported cases of dapsone-induced polyneuropathy

Author	Amount dapsone given	Maximal daily dose	Motor conduction	Sensory conduction	EMG	Acetylation
Saqueton et al. (1969)	1/26 g – 3 months 2/48 g – 5 months	400 mg/d 350 mg/d	Slow Normal	--- ---	--- ---	--- ---
Wyatt and Stevens (1972)	36 g – 5 months symptoms 8.6 g	200 mg/d	Normal	Normal (paresthesia)	Denervation	---
Hubler and Solomon (1972)	91 g – 9 months	300 mg/d	---	---	---	---
Rapoport and Guss (1972)	58 g – 7.5 months symptoms: 4 g	500 mg/d	Normal	---	Denervation	---
Gutmann et al. (1976)	144 g – 17 months	400 mg/d	Normal (distal latencies prolonged)	Normal	Denervation	---
Epstein and Bohm (1976)	216 g – 24 months	300 mg/d	Normal	---	Denervation	---
Fredericks et al. (1976)	>300 g – 5 years	600 mg/d	Slow	Normal	Denervation	---
Koller et al. (1977)	7.7 g – 6.5 weeks	200 mg/d	Normal (distal latencies prolonged)	Normal (vibration threshold increased)	Denervation	Slow
Rosén and Sörnäs (present case)	>1500 g – 8 years	400 mg/d up to 800 mg/d	Slow (distal latencies prolonged)	Normal (paresthesia)	Denervation	Slow

metabolism of isoniazid (La Du 1972) as well as for dapsone (Gelber et al. 1971) with a subdivision into slow and fast acetylators. The proportion of fast acetylators in a Swedish population is 32% (Hanngren et al. 1970). There is a close correlation between the rate of acetylation of isoniazide and dapsone (Hanson et al. 1981). The case of Koller et al. (1977), a slow acetylator, developed neuropathy after as low dose as 200 mg/day for 6.5 weeks. Our case, also a slow acetylator, developed neurological signs of polyneurophaty after a much larger intake. For the future it seems advisable to determine the capacity for acetylation before starting long-term dapsone treatment.

The motor conduction velocities were reported to be decreased in two previously reported cases (Table 2) (Saqueton et al. 1969; Fredericks et al. 1976). Distal motor latencies have been reported to be prolonged in two additional cases (Gutmann et al. 1976; Koller et al. 1977). In a number of other cases loss of motor responses in some distal limb muscles have been reported. In all cases investigated electromyography has shown signs of denervation. These findings are all compatible with an axonal degenerative disorder of motor axons. However, the slowing of impulse conduction in proximal parts of motor nerve fibres as well as the clear temporal dispersion of muscle response after conduction over large segments of the nerves, as shown in the present case, clearly indicates an interference with nerve impulse conduction in motor axons not undergoing axonal degeneration (Fig. 1).

Both clinically and neurophysiologically the selective reaction of motor neurons in contrast to the sensory neurons is noteworthy. Although paresthesias have been reported in one previous case (Wyatt and Stevens 1972) as well as our case and increased thresholds to vibration have been reported in a third case (Koller et al. 1977) most patients with dapsone induced polyneuropathy did not exhibit any sensory signs or symptoms and the sensory neurography was normal in all cases tested (Wyatt and Stevens 1972; Gutmann et al. 1976; Fredericks et al. 1976; Koller et al. 1977). One would therefore have to look for signs of distal muscle weakness or appearance of electromyographic signs of denervation in order to detect an early appearance of dapsone-induced neuropathy.

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References

Devadatta S, Gangudharam PR, Andrew (1960) Peripheral neuritis due to isoniazid. Bull WHO 23 : 587-

Dyck PJ, Thomas PK, Lambert EH (1975) Peripheral neuropathy, vol 1, Saunders Company, London

Epstein FW, Bohm M (1976) Dapsone-induced peripheral neuropathy. Arch Dermatol 112 : 1761–1762

Fredericks ED, Kugelman TP, Kirsch N (1976) Dapsoneinduced motor polyneuropathy. Arch Dermatol 112 : 1158–1160

Gelber R, Peters JH, Gordon GR (1971) The polymorphic acetylation of dapsone in man. Clin Pharmacol Ther 12 : 225–238

Graham WR (1975) Adverse effects of dapsone. Int J Dermatol 14 : 494–500
Gutmann L, Martin JD, Welton W (1976) Dapsone motor neuropathy axonal disease. Neurology 26 : 514–517
Hanngren Å, Borga O, Sjöqvist F (1970) Inactivation of isoniazid (INH) in Swedish tuberculous patients before and during treatment with para-aminosalicylic acis (PAS). Scand J Respir Dis 51 : 61–69
Hanson A, Melander A, Wahlin-Boll E (1981) Acetylator phenotyping: A comparison of the isoniazid and dapsone tests. Eur J Clin Pharmacol 20 : 233–234
Hubler Jr WR, Solomon H, Wichita K (1972) Letter to the Editor. Arch Dermatol 106 : 598
Koller WC, Gehlmann LK, Malkinson FD, Davis FA (1977) Dapsone-induced peripheral neuropathy. Arch Neuro 34 : 644–646
La Du BN (1972) Isoniazid and pseudocholinesterase polypolymorphisms. Fed Proc 31 : 1276–1285
Lancet, letter (1981) Adverse reactions to dapsone. Lancet II, pp 184–185
Rapoport AM, Guss SB (1972) Dapsone-induced peripheral neuropathy. Arch Neurol 27 : 184–185
Saqueton AC, Lorincz AL, Vick NA (1969) Dapsone and peripheral motor neuropathy. Arch Dermatol 100 : 214–217
Varughese P, Hamilton EJ, Eidus L (1974) Mass phenotyping of isoniazid inactivators by automated determination of acetylisoniazid in urine. Clin Chem 20 : 6, 639–641
Wyatt EH, Stevens JC (1972) Dapsone induced peripheral neuropathy. Br J Dermatol 86 : 521–523

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