

CASE REPORT

DAPSONE INDUCED MOTOR POLYNEUROPATHY

Auburn JW Jacob, A Rajendran, Jeewan Menezes and Mario Vaz*

Emmaus-Swiss Leprosy Project and Referral Hospital, Palamaner 517408, Chittoor Dt, AP, India.

Dapsone induced neuropathy has been documented during the management of a variety of skin disorders requiring a high dose of dapsone. In leprosy however, the diagnosis is complicated by the occurrence of nerve deficits as a part of the disease process. While dapsone-induced neuropathy is clearly not the major cause for neurological damage in leprosy, the importance of diagnosing it is underscored by the often dramatic recovery of nerve function which occurs after stopping the drug. It is likely that this side-effect is under-diagnosed in leprosy patients and is mistaken for a neural deficit related to reactional states. The present paper reports the occurrence of dapsone-induced neuropathy during the treatment regimen for leprosy, and outlines certain criteria which will aid in its diagnosis.

A 17 year old male patient was referred to us from a nearby leprosy control unit with a diagnosis of silent neuritis for further management. He had been clinically classified as having borderline-borderline leprosy. On admission the patient had already completed 3 pulse doses of the WHO multibacillary, multidrug regimen (rifampicin 600 mg, clofazamine 300 mg and dapsone 100 mg supervised once a month, followed by dapsone 100 mg and clofazamine 50 mg daily, unsupervised) which had been preceded by 14 days of intensive therapy consisting of rifampicin 600 mg, clofazamine 100 mg and dapsone 100 mg daily, supervised (National Leprosy Eradication Program, 1987). Three days following the third pulse dose the patient complained of weakness in both the lower limbs, at which point he was brought to the hospital. Our own examination showed that the patient had multiple, ill-defined, flat, non-anesthetic, hypopigmented patches on the trunk.

Peripheral nerves were not thickened or tender and skin smears were negative at routine sites as well as over the patches. Detailed muscle assessment showed a decrease in muscle power in the anterior and lateral compartments of both legs as well as the intrinsic muscles of both feet (MRC grade 0-1). There was no sensory loss.

The patient was started on prednisolone 30 mg twice daily and the anti-leprosy treatment was continued. After 2 weeks the muscle assessment was repeated and showed no improvement with the oral steroid course. At this stage the patient's case was reviewed and in the absence of any cardinal signs of leprosy on our own examination, the possibility that the patient had been wrongly diagnosed as having leprosy was entertained. The patient was therefore referred to the National Institute of Mental Health and Neurosciences, Bangalore, for further investigations. A sural nerve biopsy showed no evidence of inflammation and ENMG studies indicated severe axonal neuropathy of motor fibers in the lower limbs and possibly mild axonal motor neuropathy in the upper limbs. A final diagnosis of bilaterally symmetrical motor axonal neuropathy induced by dapsone was made.

On his return to our hospital all anti-leprosy treatment and corticosteroids were stopped. The patient was given placebos and advised to follow up at regular intervals. Over the next 6 months there was a gradual recovery of muscle power in both the lower limbs till near complete recovery at the end of the 6 months follow up period. At this point a detailed examination was done. There were no new skin lesions and all peripheral nerves remained unthickened and non-tender.

Dapsone induced peripheral neuropathy during the treatment of leprosy has been documented as early as the 1950s (Allday and Barnes, 1951).

* Current address : Nutrition Research Centre, Department of Physiology, St John's Medical College, Bangalore 560034, India.

Most reported cases of this adverse effect however, are documented in dermatological conditions where involvement of nerves is not a part of the natural course of the disease, such as dermatitis herpetiformis (Waldinger *et al*, 1984; Arhens *et al*, 1986; Hubler and Solomon, 1972; du Vivier and Fowler, 1974), Pyoderma gangrenosum (Saqueton *et al*, 1969), acne conglobata (Saqueton *et al*, 1969), sub corneal pustular dermatosis (Fredricks *et al*, 1976), cystic acne vulgaris (Gehlman *et al*, 1977) and alopecia mucinosa (Rapoport and Guss, 1972).

In these cases a majority of patients were males and ranged from 17 to 57 years in age. Onset of neurological symptoms following the use of dapsone was extremely variable, between 10 days (Homeida *et al*, 1980) and 18 years (du Vivier and Fowler, 1974). The daily dose of dapsone ingested in most cases was > 300 mg (Hubler and Solomon, 1972; du Vivier and Fowler, 1974; Saqueton *et al*, 1969; Fredricks *et al*, 1976; Rapoport and Guss, 1972; Homeida *et al*, 1980), the cumulative dose showing a wide range dependent on the duration of treatment. The neurological manifestations described, were usually in the form of a distal bilateral motor weakness of the extremities (Waldinger *et al*, 1984; Arhens *et al*, 1986; Hubler and Solomon, 1972; du Vivier and Fowler, 1974; Saqueton *et al*, 1969; Fredricks *et al*, 1976; Gehlman *et al*, 1977), proximal muscle weakness however, also being recorded as the major presentation (Rapoport and Guss, 1972). There was usually no sensory impairment and when present this was restricted to a mild sensory loss, usually involving a single modality of sensation (Waldinger *et al*, 1984; Gehlman *et al*, 1977). Much more severe sensory loss has however also been described (Arhens *et al*, 1986; du Vivier and Fowler, 1974). In a single case the motor neuropathy was accompanied by optic nerve atrophy (Homeida *et al*, 1980). Cessation or reduction in dose of the drug resulted in complete or partial recovery (Hubler and Solomon, 1972; Gehlman *et al*, 1977; Rapoport and Guss, 1972), however a complete absence of recovery has also been documented (Homeida *et al*, 1980).

ENMG studies have suggested that dapsone induced neuropathy is a primary axonal neuropathy (Waldinger *et al*, 1984; Arhens *et al*, 1986). Attempts to demonstrate this adverse effect in experimental animal models (Kamala *et al*, 1984)

and in tissue cultures (Irani *et al*, 1986) have however been unsuccessful. Slow acetylation of dapsone with resultant accumulation of toxic blood and tissue levels has been suggested as a cause of neurotoxicity. This is true for isoniazid, and the same enzyme N-acetyl transferase acetylates both dapsone and isoniazid. Slow dapsone acetylators have been demonstrated in some of the aforementioned studies (Waldinger *et al*, 1984; Gehlman *et al*, 1977).

The diagnosis of dapsone induced neuropathy is rarely entertained during the treatment of leprosy patients. While our own suspicions in this case were aroused by the absence of cardinal signs in the patient, this side effect is likely to occur in leprosy patients as well and is highlighted by a recent report of dapsone neuropathy in three leprosy patients (Sirsat *et al*, 1987). While a great majority of the neurological deficits in leprosy can be accounted for by the disease itself, the paucity of literature on neuropathy induced by dapsone during the course of treatment of leprosy is probably not due to the infrequent occurrence of this side effect but rather is a reflection of under-diagnosis. The importance of correctly diagnosing this adverse effect is underscored by the diametrically opposite steps that must be taken if the neurological deficit is due to a reactional state or whether it is dapsone induced. Whereas in the former case, anti-leprosy treatment of which dapsone is the mainstay must be continued together with the institution of anti-reactional therapy, the primary step that must be taken in the latter is the withdrawal of dapsone. Such a measure in dapsone induced neuropathy in leprosy patients, has been associated with encouraging results: complete clinical recovery being reported within 3 months of stopping dapsone, although electrophysiological changes in the nerves may persist for longer (Sirsat *et al*, 1987). The implementation of multi-drug regimens allows for the use of alternate anti-leprosy regimens once dapsone is stopped.

Like the diagnosis of leprosy itself, a high index of suspicion is possibly the major requirement for a diagnosis of dapsone induced neuropathy, which must be included as part of the differential diagnosis of patients on treatment who develop recent, bilaterally symmetrical, largely motor deficits in the absence of tender nerves and which is not responsive to treatment with corticosteroids. While it is possible that these clinical

DAPSONE INDUCED POLYNEUROPATHY

features may fit the diagnosis of several neurological disorders, they form the basis on which leprosy workers in the periphery could refer patients for a confirmation of diagnosis to larger centers equipped with histopathological and ENMG facilities.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Gourie Devi of the National Institute of Mental Health and Neurosciences, for her advice and help.

REFERENCES

- Allday EJ, Barnes J. Toxic effects of diamino diphenyl sulphone in the treatment of leprosy. *Lancet* 1951; 2 : 205-6.
- Arhens EM, Meckler RJ, Callen JP. Dapsone induced peripheral neuropathy. *Int J Dermatol* 1986; 25 : 314-6.
- du Vivier A, Fowler T. Possible dapsone induced peripheral neuropathy in dermatitis herpetiformis. *Proc R Soc Med* 1974; 67 : 439-40.
- Fredricks EJ, Kungelman TP, Kirsch N. Dapsone induced motor polyneuropathy : A complication of prolonged treatment of subcorneal pustular dermatosis. *Arch Dermatol* 1976; 112 : 1158-60.
- Gehlman LK, Koller WC, Malkinson FD. Dapsone induced neuropathy. *Arch Neurol* 1977; 34 : 644-6.
- Homeida M, Babikr A, Daneshmend TK. Dapsone induced optic atrophy and motor neuropathy. *Br Med J* 1980; 281 : 1180.
- Hubler WR, Solomon H. Neurotoxicity of sulphones. *Arch Dermatol* 1972; 106 : 598.
- Irani S, Mukerjee R, Jaganathan R, Antia NH. In vitro study of the effect of dapsone on the components of peripheral nerve in organized nerve culture model. *Ind J Med Res* 1986; 83 : 449-52.
- Kamala AN, Shetty VP, Antia HN. Evaluation of neurotoxicity of dapsone in the mouse model. *Ind J Lepr* 1984; 56 : 251-6.
- National Leprosy Eradication Program in India. Guidelines for multidrug treatment in endemic districts. Leprosy Division, Directorate General of Health Services. DGHS-33-9/86, 1987.
- Rapoport AM, Guss SB. Dapsone induced neuropathy. *Arch Neurol* 1972; 27 : 184-5.
- Saqueton AC, Lorinez AL, Vick NA, Hamer RD. Dapsone and peripheral motor neuropathy. *Arch Dermatol* 1969; 100 : 214-7.
- Sirsat AM, Lalitha VS, Pandya SS. Dapsone neuropathy-report of three cases and pathologic features of a motor nerve. *Int J Lepr* 1987; 55 : 23-9.
- Waldinger TP, Siegle RJ, Wendell W, Voorhees JJ. Dapsone induced peripheral neuropathy. *Arch Dermatol* 1984; 120 : 356-9.