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PURE NEURAL LEPROSY

Steroids prevent neuropathy progression

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ABSTRACT - Multidrug therapy (MDT), with rifampicin, dapsone, and clofazimine, treats leprosy infection but is insufficient in arresting or preventing the nerve damage that causes impairments and disabilities. This case-series study evaluates the benefits of the combined use of steroids and MDT in preventing nerve damage in patients with pure neural leprosy (PNL). In addition to MDT, 24 patients (88% male aged 20-79 years, median=41) received a daily morning dose of 60 mg prednisone (PDN) that was gradually reduced by 10 mg during each of the following 5 months. PNL was clinically diagnosed and confirmed by nerve histopathology or PCR. A low prevalence (8.3%) of reaction was observed after release from treatment. However, most of the clinical parameters showed significant improvement; and a reduction of nerve conduction block was observed in 42% of the patients. The administration of full-dose PDN improved the clinical and electrophysiological condition of the PNL patients, contributing to the prevention of further neurological damage.

KEY WORDS: peripheral neuropathy, pure neural leprosy, steroids.

Corticosteróides previnem a neuropatia na hanseníase

RESUMO - A poliquimioterapia (PQT), com rifampicina, dapsona, e clofazimina, trata a infecção na hanseníase, mas é insuficiente para interromper ou prevenir o comprometimento neurológico que causa as incapacidades e desabilidades, nesta enfermidade. Este estudo de série de casos avalia o benefício do uso combinado de prednisona e PQT na prevenção do dano neurológico em pacientes com a forma neural pura da hanseníase (FNP). Além do PQT, 24 pacientes (88% homens, com idade variando entre 20-79, mediana=41) receberam uma dose diária de 60 mg prednisona que foi reduzida gradualmente na dose de 10 mg durante cada um dos 5 meses subseqüentes. FNP foi diagnosticada clinicamente e confirmada através do estudo histopatológico ou PCR. Baixa prevalência de reação (8,3%) foi observada apenas após o final do tratamento. A maioria dos parâmetros clínicos mostrou melhora significativa e redução do bloqueio de condução foi observada em 42% dos pacientes. A administração de doses altas de prednisona melhora a evolução clínica e eletrofisiológica de pacientes com a FNP de hanseníase, contribuindo na prevenção de novos comprometimentos neurológicos.

PALAVRAS-CHAVE: neuropatia periférica, forma neural pura da hanseníase, corticosteróides.

Pure neural leprosy (PNL) presents a diagnostic challenge. PNL patients have nerve deficit or enlargement of peripheral nerves with or without tenderness in the absence of any sign of skin manifestation or history of skin patches. In India, it has been reported that from 5.5%-17.7% of all leprosy cases are PNL[1]. Leprosy neuropathy classically presents as acute neuritis characterized by nerve enlargement and pain that may be followed by neurological dysfunction[2]. Neurological alteration without nerve pain, known as "silent neuritis", has also been documented[3,4]. According to some authors, in PNL, *M. leprae* causes peripheral nerve damage leading to neuropathy, which may remain undiagnosed for an extended period of time, even years[5]. Furthermore, in all clinical forms of leprosy, the irreversible motor and sensory alterations may lead to increasingly severe secondary impairments long after the disease has been arrested as peripheral neuropathy may be present before the patient notices any symptoms of nerve function impairment[6]. Interventions that prevent, reverse, or limit leprosy-related nerve impairments are, therefore, of the highest priority. Early chemotherapy in new PNL patients is expected to prevent the development

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of nerve damage. Multidrug therapy (MDT) alone is aimed at treating the infection but is insufficient in arresting or preventing the nerve damage responsible for impairment and disabilities[4]. The deformities seen in patients who were diagnosed reasonably early and, so, received timely MDT[5], clearly indicate the need for using more intensive measures to recognize and treat recent nerve damage as expeditiously as possible.

Prednisone (PDN) remains the drug of choice for neuritis due to its ability to reduce nerve oedema, exert an immunosuppressive effect, and decrease post-inflammatory scar formation – all important for improving nerve function[3]. Moreover, when detected and treated in time with corticosteroids, peripheral neuropathy may not progress into deformity and may even reverse initial impairments[1].

This study evaluates the benefits of the combined use of steroids and MDT in preventing and arresting nerve damage in PNL patients.

METHOD

A prospective longitudinal study was performed in a group of 24 PNL patients, of whom 88% were male ranging from 20-79 years of age (median=41), diagnosed at the Leprosy Outpatient Clinic, Oswaldo Cruz Institute, Rio de Janeiro RJ, Brazil, between 1998 and 2000. PNL was clinically diagnosed and confirmed by nerve histopathology or PCR, as described by Jardim et al[7]. All patients received MDT (rifampicin, dapsone, clofazimine) for paucibacillary (PB) leprosy for 6 consecutive months in accordance with WHO recommendations[8] plus a daily morning dose of 1 mg/kg of PDN for one month followed by a progressive 10 mg/monthly reduction over the remaining five months. Clinical and electrophysiological examinations were performed at diagnosis and 12 months after beginning MDT. The research was carried out in strict compliance with the International Norms on Ethics in Human Research; and all patients were duly informed prior to providing their written consent.

Neurological examination – Pain and paraesthesia were evaluated by way of visual analogue scales (VAS). Sensory impairment, motor deficit, and disability status were assessed by standard methods. Values were given to thermal and pain sensations (0=anaesthesia, 1=hypoaesthesia, 2=normal) including the monofilament force as subjectively felt by the patients (0=no sensation, 1=300g, 2=4g, 3=2g, 4=0.2g, and 5=0.05g). The bilateral grades of 13 nerves were added to form the sensory score (normal=234). Individual muscle strength was graded according to the Medical Research Council of London[9] recommendations and added to the motor score (normal score=80, since 8 nerves were evaluated bilaterally).

Electrophysiological examination – All nerve conduction assessments were performed by the same specialist on a Nihon-Koden–Neuropack 2. Standard nerve conduction techniques were utilized[10] to evaluate the median, radial, ulnar, and sural sensory nerves as well as the median, ulnar, and peroneal motor nerves (total of 14 nerves). Partial conduction block (CB) (with or without temporal dispersion) was defined as a 50% or more reduction of the proximal as compared to the distal amplitudes. Abnormal temporal dispersion (TD) was defined as a proximal distal compound muscle action potential (CMAP) duration increase of more than 30%. A prolonged latency and/or 85% reduction in sensory conduction velocity (SCV) or motor conduction velocity (MCV) was considered as a demyelinating lesion; and an axonal lesion was defined as >30% reduction in amplitude with/without a <30% reduction in conduction velocity[11]. All other patterns of amplitude, latency, and velocity not corresponding to any of these definitions were considered non-classifiable, as suggested by Tankisi et al.[12]

Statistical analysis – Data were analyzed using SPSS for Windows™ v. 11.5. Unless stated otherwise, all results were expressed as median because of the non-gaussian distribution of variables. Maximum and minimum values are in parentheses. McNemar and Wilcoxon tests were used to compare variables and *p* values of less than 0.05 were considered statistically significant.

RESULTS

Findings at diagnosis – The referred patients had been symptomatic for a period of 2-120 (median=14) months before diagnosis clinical and laboratory data are shown in Table 1. The frequency of the signs and symptoms are shown in Tables 2 and 3. Disability grade 2, i.e., eye, hand or foot deformities such as ulcers, claw fingers/toes, foot or hand drop, lagophthalmos, or amyotrophy, was conferred on 18 (75%) patients. In the sensory evaluation, the median nerve was the most frequently impaired (42%) while motor dysfunction occurred predominantly in the ulnar nerve (38%).

CB always accompanied by TD was observed in 10% of the patients, most often in the ulnar nerve. All patients demonstrated demyelinating nerve lesions in a varying number of nerves ranging from 1 to a maximum of 10 (median=4.5). Axonal lesions were present in 46% of the patients at a maximum of 2 affected nerves out of the 14 assessed in each patient. A combined pattern (simultaneous axonal and demyelinating findings in the same nerve) was found in 38% of the patients, with a maximum of 2 affected nerves. Furthermore, the nerves of 83% of the patients was found to have non-classifiable lesions.

Follow-up – All patients were clinically re-evaluated after release from MDT. However, five patients who had a minimally-altered neurophysiological examination upon diagnosis were lost for nerve conduction re-testing. Acute neuritis occurred in only 2 (8%) patients in the 27th and 30th months after treatment.

Table 1. Clinical and laboratory data.

ID	Age (years)	Gender	SS	DG	Lepromin	Histopathological findings	Reaction	Presentation symptom (months)
3193	46	F	0.00	3	8	UII/F	N	Paresthesia (60)
3197	55	M	0.00	2	5	EG/Fibrosis	N	Paresthesia (6)
3214	25	M	0.00	2	9	EG	N	Paresthesia (2)
3233	55	M	0.00	2	0	UII/Fibrosis	N	Sensory impairment (8)
3244	28	M	0.00	0	11	UII/Fibrosis	N	Paresthesia (12)
3262	55	M	0.00	2	0	Fibrosis	N	Paresthesia (30)
3285	45	F	0.00	2	0	Normal*	N	Paresthesia (6)
3291	61	M	0.00	2	4	UII	N	Paresthesia (7)
3316	66	M	0.00	2	5	UII/Fibrosis	N	Paresthesia (8)
3369	39	M	0.00	2	0	UII	N	Paresthesia (23)
3374	23	M	0.00	2	12	UII/Fibrosis	N	Paresthesia (6)
3386	25	M	0.00	2	0	AFB	N	Paresthesia (58)
3401	79	M	0.00	0	9	Fibrosis	N	Paresthesia (84)
3418	20	M	0.00	2	9	UII/Fibrosis	N	Amiotrophy (72)
3432	29	M	0.00	2	9	UII/Fibrosis	N	Paresthesia (8)
3435	61	M	0.00	0	0	EG	N	Paresia?? (12)
3436	22	M	0.00	0	5	Normal	N	Sensory impairment (24)
3441	56	M	0.00	2	7	Normal	N	Motor impairment (12)
3450	42	M	0.00	0	6	Fibrosis	N	Paresthesia (24)
3467	25	M	0.00	2	9	EG	N	Paresthesia (14)
3469	37	M	0.00	2	6	Fibrosis	N	Pain (120)
3476	28	M	0.00	0	3	Fibrosis	N	Pain (20)
3275	66	F	0.00	2	6	Normal	Y(N) 21m	Paresthesia (24)
3382	24	M	0.00	2	5	UII/Fibrosis	Y(N) 24m	Paresthesia (20)

ID, identification; F, female; M, male; SS, slit skin smears; DG, disability grade; UII, unspecific inflammatory infiltration; EG, epitelioid granuloma; AFB, acid fast bacilli.

Table 2. Variations in clinical parameters.

	Initial	After MDT	p value
Signs and symptoms [n (percentage or minimum-maximum)]			
Patients w/paresthesia	22 (92%)	10 (42%)	0.000
Patients w/erithrocyanosis	17 (71%)	8 (33%)	0.022
Patients w/nerve enlargement	21 (88%)	17 (71%)	NS
No. of enlarged nerves	2 (0-6)	1 (0-6)	0.007
Patients w/neural pain	9 (38%)	5 (21%)	NS
Patients w/ muscle weakness	21 (88%)	16 (68%)	NS
No. of muscles w/weakness	2 (0-6)	1 (0-2)	0.000
Patients w/ sensory impairment	20 (83%)	19 (79%)	NS
No. of nerves w/ sensory impairment	4 (0-16)	3 (0-11)	0.033

Table 3. Nerve conduction parameters: percentage of patients with altered amplitude, velocity, and latency.

		Initial	After MDT	p value
CMAP	AMP	79%	79%	0.673
	MCV	92%	79%	0.306
	ML	92%	79%	0.306
SNAP	AMP	92%	90%	0.602
	SCV	71%	90%	0.132
CB		38%	11%	0.046

CMAP, compound muscle action potential; AMP, amplitude; MCV, motor conduction velocity; ML, motor latency; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; CB, conduction block.

The patients significantly improved in most clinical parameters evaluated. In 65% (n=7) of the patients, an over-50% reduction in VAS for Pain was recorded. Even though the number of patients with sensory impairment remained constant, in 71% of the patients, the sensory scores significantly improved, worsened in 21%, and remained unchanged in 8%. The muscle strength of 63% of the patients also showed significant improvement, including a reduction in the number of affected nerves and muscles and no cases of worsening.

The nerve conduction evaluation did not show significant differences in the combined nerve amplitudes, latencies, or velocities of the 19 patients assessed (Tables 2 and 3). However, CB significantly decreased in 42% (8/19). Although the demyelinating lesions of all patients remained, the number of affected nerves (median=6, maximum of 12 nerves) actually decreased. Moreover, 94.7% of the patients ended treatment with at least one normal nerve and 1 patient tested normal for all 14.

DISCUSSION

PLN is a form of the disease that presents as an inflammatory neuropathy (neuritis) with secondary nerve dysfunction in the absence of skin lesions. Very few PNL patients show any nerve damage improvement at the end of treatment. Consequently, it would appear that antibacterial therapy alone does not prevent new nerve damage either during or after chemotherapy. Clearly, in leprosy, the permanent disabilities that often accompany nerve damage are the major concern[13]. Thus, new treatments and prophylactics are urgently needed.

The use of corticosteroids was initiated at least fifty years ago[14] but continues to be the drug of choice in treating reaction. In one report, six-month steroid therapy had a satisfactory effect in reversing motor paralysis caused by neuritis in about 75% of the affected nerves[3]. In a PNL case study, treatment with the previous scheme in conjunction with MDT prevented the establishment of nerve trunk paralysis[5]. In the present study, full-dose prednisone and MDT were administered to a group of PNL patients with positive results.

Steroids appear to act as treatment and prophylactics at the same time. Van Brakel et al.[15], who administered 40 mg/kg prednisone to patients with various clinical forms of leprosy for four consecutive months, detected a reduced risk of reaction and nerve function impairment solely within this period. The present results, however, indicated that higher doses of prednisone were necessary to recover nerve function.

During neuritis, either isolated or associated with reversal reaction or *erythema nodosum leprosum,* there is an induction or worsening of disabilities[3]. In this study, the patients receiving steroids developed fewer reactions, even long after MDT had ended.

After treatment, all the parameters of patients receiving corticosteroids showed improvement. Steroids prevented progressive nerve damage by interrupting the inflammatory process that is produced in PNL. In addition, steroids protected other nerves from being damaged by new episodes of neuritis. Corticosteroids may be acting as both prophylactics and treatment at the same time. Van Brakel et al.[15] administered prednisolone (40 mg/daily) for four months but found no improvement of tactile sensation or reduction in risk of leprosy reaction or nerve function impairment beyond the initial four-month treatment phase. The present results indicated that higher doses of prednisone were necessary to recover nerve function.

Electrophysiological examination provides invaluable information for diagnosing and recommending the most appropriate therapeutic treatment for neuropathies. Naafs has reported that, during reversal reaction with neuritis, immunosuppressive therapy with corticosteroids led to a biphasic response[3]. Initially (within days), the oedema regressed and, after several months, remyelination and nerve regeneration took place. Since recovery time usually takes more than six months (especially recovery from axonal lesions), nerve conduction testing should be performed not less than one year after follow-up has begun.

In this study, the most outstanding electrophysiological finding was the reduction in conduction block / temporal dispersion. Although demyelinating lesions predominated when analyzing each nerve separately, the observed conduction block reduction is indicative of the regeneration of demyelinating lesions. This event has the same physiopathological significance as that reported about MVC improvement when using corticosteroids[16].

Although demyelinating lesions remained in most patients, the significant reduction of CB seen was probably related to a reduction of inflammatory edema. The worsening of nerve conduction velocity was unreal because the nerve conduction study on the five lost patients demonstrated minimal changes.

The improvement observed in this group of patients indicated that the administration of full-dose PDN together with MDT was both safe and useful for PN patients. It is clear, however, that to define the most appropriate use of steroids as a prophylactic drug for leprosy neuropathy, further evaluations need to be performed on a larger number of patients in a double-blind placebo study for longer follow-up time periods

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