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Unexplained delayed nerve impairment in leprosy after treatment

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Summary The objective of this study was to examine the clinical signs, symptoms and course of neuropathies in patients with leprosy who after treatment developed nerve impairment, not explained by relapse or reversal reactions. We searched the case-records of leprosy patients, seen between 1985 and 2002 at the department of dermatology at our centre. Included in the study were patients who had developed nerve impairment after treatment of leprosy in the absence of relapse, erythema nodosum leprosum, or reversal reactions, and who were referred to a neurologist. In these patients, we recorded age, onset of leprosy, type of leprosy, treatment of leprosy, signs and symptoms of delayed nerve impairment, results of electrophysiological studies, responses to treatment and course. Included were 14 patients, of whom eight had a (sub)acute multiple mononeuropathy (group I); and six had a slowly progressive multiple mononeuropathy (group II). Patients in group I had limited improvement of nerve impairment after treatment with corticosteroids, and recurrence of symptoms and signs (usually of the motor nerves) when corticosteroids were tapered off. Patients in group II had slowly progressive predominantly sensory nerve impairment. Initially, they had only subjective symptoms, after at least 3 years objective signs became detectable. These patients were not treated with immunosuppressants. Two groups of patients with unexplained delayed nerve impairment could be distinguished. One group had a multiple mononeuropathy resembling reversal reactions with insufficient response to corticosteroids. In these patients, more aggressive and prolonged immunosuppressive treatment should be considered. The aetiology for the neuropathy in the other group remains unclear and further investigations are needed to understand the pathogenesis before treatment recommendations can be given.

Introduction

Leprosy is a leading cause of non-traumatic peripheral neuropathies world-wide.[1] Four types of nerve impairment can be distinguished: a) neuropathy with sensory deficit and skin lesions

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(in primary leprosy and relapse); b) distal symmetrical sensory (motor) neuropathies (in primary leprosy and relapse); c) mono-neuropathies with thickening of the nerves (in primary leprosy and relapse), and d) neuropathies in reversal reaction (RR) (with a beneficial response to corticosteroids) and in erythema nodosum leprosum (ENL) reaction.[2,3]

Relapses can be recognized by reappearance of skin lesions, an increase of bacterial load by means of skin smears or biopsy and/or an increase of antibodies to phenolic glycolipid (PGL)-I. Reversal reactions (RR) are characterized by increased inflammatory activity in skin and/or nerves in patients in the borderline part of the leprosy spectrum.[4–8] The RR is supposed to be a delayed type hypersensitivity reaction to *Mycobacterium leprae* antigens. Severe RR should be treated with corticosteroids: initial dose 40–60 mg/day and after a clinical response (decrease of symptoms and signs of inflammation in skin and nerves), followed by a gradually tapering-off phase. This needs to be continued for several months.[9–11] ENL is another type of reaction, and is associated with borderline lepromatous and lepromatous leprosy. This is characterized by leucocytosis and fever, together with multiple erythematous tender nodules and to varying degrees, neuropathy, oedema, arthralgias, iridocyclitis, orchitis and nephritis. Elevated levels of tumour necrosis factor-alpha and circulating immune complexes may play a role in the pathogenesis of ENL and nerve injury, but do not appear to be the only contributing factor.[12–17] ENL can also be treated with corticosteroids, especially when patients are suffering from neuropathy.

Another type of neuropathy that is described in the literature is the so-called 'silent neuritis'. This neuropathy is 'silent' in onset in that the patient is unaware of anything being wrong until very late. Although the term 'silent neuritis', also named 'quiet nerve paralysis' and 'silent neuropathy', is used often, details are scarce in the literature on the aetiology, natural history or clinical course.

At the Academic Medical Centre of the University of Amsterdam, we evaluated patients with leprosy who had a delayed progressive nerve impairment, which could not be explained by relapse or regular reaction, and without another reasonable explanation for the deterioration. The aim of the present study was to study the clinical signs, symptoms and course of these neuropathies.

Materials and methods

SELECTION OF PATIENTS

A dermatologist with special expertise in leprosy (W.R.F.) at the Academic Medical Centre of Amsterdam referred patients with leprosy, who were suffering from neurological impairment in the period between 1985 and 2002. In some cases, the diagnosis of leprosy had been made before 1985. A neurologist with special expertise in neuropathies (M.V.) and a resident in neurology (N.R.R.) collected the following data from the medical records of these patients: age, onset of leprosy, type of leprosy, treatment of leprosy, signs and symptoms of delayed nerve impairment, results of electrophysiological studies, course, responses to treatment, and anti-PGL-I.

We investigated patients with leprosy who after treatment developed progressive nerve impairment that could not be explained by relapse or reaction and without another obvious explanation for the deterioration. Evaluated were patients with leprosy in a period of progressive nerve impairment.

Excluded were patients with neuropathies of one of the following categories: a) neuropathy with sensory deficit and skin lesions in primary leprosy and relapse; b) sistal symmetrical mainly sensory neuropathies in primary leprosy and relapse; c) mono-neuropathies with thickening of the nerves in primary leprosy and relapse; d) neuropathies as part of a RR or ENL with good response to corticosteroids.

In addition, we excluded patients suffering from complications, such as ulcers and osteomyelitis. Furthermore, patients with progressive nerve impairment were excluded if they had not been seen by a neurologist from our centre.

ELECTROPHYSIOLOGY

Electrodiagnostic studies were performed using standard techniques. Skin temperature was maintained between 32° and 35°C. The electrophysiological studies included motor and sensory conduction velocities in at least two arm nerves and one leg nerve, F-responses of the ulnar nerve and peroneal nerve, H-reflex of the soleus muscle and electromyography of distal arm and leg muscles.

Polyneuropathy was classified as demyelinating when fulfilling the neurophysiological criteria for demyelination as defined by the ad hoc subcommittee. If these criteria were not fulfilled, but there was neurophysiological evidence of polyneuropathy, the polyneuropathy was classified as axonal.[18,19]

ANTI-PGL-I

An enzyme-linked immunoassay-test for the detection of circulating IgM antibodies against 3,6-di-O-methyl glucopyranosyl residue of the trisacharid part of the phenolic glycolipid antigen PGL-I of *M. leprae* was performed. The test result is defined in optical density (OD). Values above OD = 0·150 were defined as positive.[20]

Results

Included in this study were 14 patients with leprosy, who had developed after treatment nerve impairment not explained by relapse or reaction.

Based on signs and symptoms, electrophysiological examinations and follow-up over the years, two groups could be distinguished. The first group consisted of patients with a (sub)acute multiple mononeuropathy, with an unsatisfactory response to corticosteroids. The second group consisted of patients with a slowly progressive multiple mononeuropathy.

In the first group ($n = 8$) (Table 1), all patients had been treated with multiple drug therapy (MDT) in the past, according to the standard regimen introduced by the WHO in 1982.[21,22] All patients who were diagnosed before 1982, had also MDT, although some patients received medication for a longer period than recommended. Over the years, all but one patient had one or two reversal reactions with complete improvement after treatment with corticosteroids. Between 1 and 22 years after the diagnosis of leprosy, a (sub)acute multiple mononeuropathy developed, with progressive sensory and/or motor deficits of hands and/or feet, and in two patients with painful and swollen hands. In these patients, all kinds of sensory disturbances were reported: sensory loss, dysaesthesia, allodynia and pain.

Electrophysiological examinations showed small sensory nerve action potentials (SNAP)

Table 1. (Sub)acute multiple mononeuropathy: no or slow recovery on corticosteroids. M = male/F = female, A = age in 2002, D = year of diagnosis leprosy, MDT = multiple drug therapy, RR = reversal reaction: years after diagnosis leprosy, with good response to corticosteroids, SMM = subacute multiple mononeuropathy: years after diagnosis leprosy, SER = serology: anti-PGL-I, positive = OD > 0·150

Patient no.	MF	A	D	MDT	RR	SMM	Period of prednisone schedule	Dosage prednisone (mg/daily)	Type of leprosy	SER +/−
1	M	40	1989	1989–1991	1	13	2002, continuing	45 ↓	BT-BB-BL	OD = 0·923 +
2	M	44	1975	1996–1998	21	22	1997–2000 (? left Holland)	25 ↓/↑ (7·5–20)	BT-BB	OD = 0·300 +
3	M	33	1993	1993–1995	0·5	2	1995–1999	40-20-15-20 ↓	BT	OD = 0·099 −
4	M	48	1984	1991–1993	7	13	1997–2001	60 ↓/↑ (30–40)	BT	OD = 0·283 +
5	F	39	1978	1980–1988	2	4	1982–1988	40–30 ↓/↑ ↓	BL-BT	OD = 0·078 −
6	F	71	2001	2001–2002	–	1	2002–continuing	60-40-20 ↓/↑ ↓	BL	OD = 0·213 +
7	F	67	1971	< 1983	9 and 18	19	1990–1993 (? left Holland)	40 ↓	BL	OD = 0·065 −
8	M	41	1996	1996–1998	1	2	1998–2002	30 ↓ (17·5)-50-60 ↓, cyclosporin	BL	OD = 1·143 +

Table 2. Electrophysiological results: most affected nerve. MCV = motor conduction velocity, SCV = sensory conduction velocity, CMAP = compound muscle action potential, SNAP = sensory nerve action potential

	Patients	Normal	Units
Group I			
1 Right peroneal nerve			
MCV	37	> 40	m/s
CMAP	2·0	> 2·5	mV
F-wave latency	59	< 56	ms
2 Left ulnar nerve			
MCV	43	> 40	m/s
CMAP	–	> 10	mV
F-wave latency	34	< 32	ms
3 Left peroneal nerve			
MCV	33	> 40	m/s
CMAP	0·3	> 2·5	mV
4 Right ulnar nerve			
MCV	43	> 50	m/s
SNAP	–	> 10	μV
5 Right ulnar nerve			
MCV	42	> 50	m/s
CMAP	1·5	> 3·5	mV
SNAP	6·0	> 10	μV
6 Left median nerve			
MCV	37	> 50	m/s
CMAP	1·5	> 5·4	mV
SNAP	1·3	> 10	μV
7 Left peroneal nerve			
MCV	34	> 40	m/s
CMAP	1·1	> 2·5	mV
8 Left peroneal nerve/sural nerve			
CMAP	1·9	> 2·5	mV
SNAP	1·9	> 5	μV
Group II			
1 Left ulnar nerve			
MCV	27	> 50	m/s
F-wave latency	52·8	< 32	ms
2 Left ulnar nerve			
MCV	38	> 50	m/s
CMAP	2·1	> 3·5	mV
SCV	48	> 53	m/s
SNAP	2·0	> 10	μV
3 Left peroneal nerve			
MCV	35	> 40	m/s
CMAP	1·8	> 2·5	mV
4 Right ulnar nerve			
MCV	48	> 50	m/s
SNAP	–	> 10	μV
F-wave latency	35	< 32	ms
5 Right ulnar nerve			
MCV	40	> 50	m/s
CMAP	1·8	> 3·5	mV
SCV	48	> 53	m/s
SNAP	3·4	> 10	μV
6 Right post-tibial nerve			
MCV	41	> 45	m/s

and compound muscle action potentials (CMAP), with normal or slowed conduction velocities of the affected nerves (Table 2). None of the slowed conduction velocities was in the demyelinating range.

All patients were treated with corticosteroids in a schedule of 25–60 mg prednisone for 3 weeks, followed firstly by a period of a steady dosage (20–40 mg), and secondly by a tapering-off phase. Initially, all patients had some improvement of symptoms and signs, but none recovered completely, and in the tapering off phase of prednisone, the symptoms and signs deteriorated. In some patients, improvement of nerve function during steroid treatment was accompanied by impairment in another nerve. This nerve impairment with poor response to steroids was observed in all patients. It appeared in all borderline-types of leprosy: BT (borderline tuberculoid leprosy), BB [borderline (borderline) leprosy], BL (borderline lepromatous leprosy). Anti-PGL-I could be positive ($n = 5$) or negative ($n = 3$). Skin lesions were still present in two patients at the onset of the neuropathy.

Patients in the second group ($n = 6$) (Table 3) had a slowly progressive multiple mononeuropathy. Initially, they had progressive sensory symptoms in the distribution of one or more nerves. They had no signs of activity of leprosy, although in some cases the serology remained positive. At neurological examination, no new signs of nerve impairment could be detected. The sensory disturbances included, apart from the sensory loss, dysaesthesia and paraesthesia in patients 1 and 4, and dysaesthesia with allodynia in patient 6. Patients 2, 3 and 5 had solely sensory loss. After at least 7 years the first signs of nerve impairment were detected clinically, confirmed by electrophysiological examination (Table 2). However, there were no signs of leprosy activity. This type of neuropathy appeared in all borderline types of leprosy, and all, but one, had been treated with multiple drug therapy (MDT) in the past, according to the standard regimen introduced by the WHO in 1982.

Discussion

In this study, we evaluated patients who developed delayed nerve impairment after treatment for leprosy, which could not be explained by relapse or regular reaction. We could distinguish two groups. The first group of patients had a (sub)acute multiple mononeuropathy resembling

Table 3. Slowly progressive multiple mononeuropathy. M = male/F = female, A = age in 2002, D = year of diagnosis of leprosy, SER = serology: anti-PGL-I, positive = OD > 0·150, SUB = subjective symptoms: years after diagnosis of leprosy, OBJ = objective signs (neurological examination/electrophysiological examination): years after diagnosis of leprosy, B = nerve biopsy, ND = not done, No* = no signs of inflammation

	M/F	A	D	Type of leprosy	Clinical features	SUB	OBJ	SER +/−	B
1	M	39	1990	BT	Patchy sensory signs/symptoms	4	8	OD = 0·789 +	ND
2	F	53	< 1981	BL	First sensory signs/symptoms, later motor signs; hands	> 12	> 21	OD = 0·174 +	ND
3	M	39	1979	BT	Sensory > motor signs/symptoms; feet > hands	9	12	OD = 0·012 −	ND
4	F	50	1971	BT	Sensory signs/symptoms; hands	14	22	OD = 0·034 −	ND
5	F	42	1974	BT	Sensory signs/symptoms; hands	14	21	OD = 0·167 +	No*
6	M	43	< 1988	BL	Sensory signs/symptoms; feet	> 3	> 7	OD = 0·365 +	No*

reversal reactions. However, when these patients were treated with corticosteroids, there was incomplete response and when the corticosteroids were tapered off, the nerve impairment became worse. This course is unusual in regular reversal reactions. The second group consisted of patients with a chronic and slowly progressive form of a multiple mononeuropathy. There was no activity of leprosy and anti-PGL-I was positive or negative. Initially there were only subjective symptoms, but over the years nerve impairment became detectable.

All patients, in both groups, belong to the borderline area of the leprosy spectrum.

The first group comprised patients with subacute, delayed nerve impairment, initially, resembling a normal reversal reaction. However, almost all these patients had this delayed nerve impairment years after the MDT. Furthermore, it is remarkable that these patients showed no optimal response to corticosteroids and had progressive nerve impairment when the corticosteroids were tapered off. We postulate that this nerve impairment is caused by an immune mediated process, as in regular reversal reactions. However, it is probably not the same mechanism as in regular reversal reaction. It seems that this group of patients is suffering from a more chronic immune mediated process. This is not an unknown phenomenon in the immune mediated neuropathies. For instance, Guillain–Barre syndrome (GBS) is an acute form of an inflammatory neuropathy, in which the inflammatory reaction is of short duration. There is also a chronic form, chronic inflammatory demyelinating polyneuropathy, in which the inflammatory process goes on for many months to several years. We suggest that the group of patients we identified is a chronic variant of a regular reversal reaction. This type of nerve impairment should probably be treated more aggressively, and for longer, than is usual in regular reversal reactions. We do not think that limited improvement to corticosteroids is due to the fact that these patients were treated too late, when nerve damage had become permanent.[15] All patients were started on corticosteroids soon after deterioration of nerve function. None of the patients had a good response on corticosteroids and some patients even showed an increase in nerve impairment during the initial period of high dosages of corticosteroids.

In group II, the aetiology remains unclear. It is possible that fibrosis of the nerves plays a role. In leprosy, endoneurial fluid pressure might increase, resulting in obstruction of the venous outflow through the epineurium and consequently oedema. This may be to such an extent that it leads to microvascular insufficiency (ischaemia) and loss of nerve function. When the cause of oedema is eliminated at an early stage, these effects may be rapidly reversible, but when the oedema is long lasting the nerve tissue will be invaded by connective tissue cells, leading to a fibrous scar.[23]

Another explanation could be that fascicles in a nerve are irreversibly destroyed by the acute granulomatous reaction and this destruction may still go on after the acute phase, initially silently (subjective complaints of the patient), later with objective signs. This neuronopathy may be compared with the post-polio syndrome, in which there is also a progressive loss of neurons late after the initial infection. Therefore we postulate that this type of impairment is a post-leprosy syndrome, in which the sensory and motor neurons become exhausted.

Vasculitic neuropathy may develop late after treatment of leprosy. Bowen *et al*. described a patient who had a stepwise multifocal sensory disturbances 25 years after treatment.[24] Vasculitis in patients in group II seems unlikely, since the symptoms developed slowly over much longer periods than has been described by Bowen *et al*.

Does either of these groups demonstrate ‘silent neuritis’, ‘silent neuropathy’ or ‘quiet

nerve paralysis' (QNP)? All studies examining patients with a possible QNP that we could find lack details on the course, mode of onset and initial impairment. It is not clear whether or not these patients were suffering from the outcome of a more or less 'silent' reaction or relapse, from a side effect of treatment or other causes of nerve impairment or from a slowly progressive neuropathy as described in our study.[25–27]

In conclusion, we could distinguish two forms of neuropathies in patients with leprosy, not explained by relapse or regular reversal reaction. The first group of patients is suffering from a sub-acute multiple mononeuropathy that becomes chronic, probably immune mediated, with an incomplete response to corticosteroids. We postulate that this is different type of reaction from the regular RR, although the initial signs and symptoms are the same. These patients do not respond sufficiently to corticosteroids and may even deteriorate during the therapy. We suggest that these patients should be treated with a more aggressive schedule of corticosteroids: a higher dose and a longer duration, or perhaps in combination with another immunosuppressive medication, such as cyclosporin. The other group of patients is suffering from a slowly progressive neuropathy, with initially subjective symptoms, but objective signs at a later stage. The aetiology for this neuropathy remains unclear, and further investigations are needed to understand the pathogenesis, before treatment recommendations can be given.

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