Mesas Redondas / *Round Tables*

Epidemiologia da Reação / *Epidemiology of Reactions*

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Introduction

Reactions are a common phenomenon in patients with hanseniasis.

Hansen's disease causes disability through damage to peripheral nerves, resulting in loss of nerve functions which may seriously affect the future health and livelihood of the patients. Though nerve damage or impairment has been recognized as a serious complication of reactions for a long time, little is know about its natural history and risk factors.

Nerve impairment can occur across the entire spectrum of the disease, either as a chronic or as an acute phenomenon. Reversal reactions, or type 1 reactions, are generally the main cause of nerve damage in Hansen's disease. Erythema Nodosum Leprosum, or type 2 reaction, occurs mainly in lepromatous patients.

It is generally agreed that the severity of reversal reactions is related to the degree of nerve impairment. Nerve impairment can present itself very acute or it may be insidious and painless, the so called "silent neuritis". In case of silent neuritis, changes in sensory or motor functions are not readily apparent and can be detected only by repeated nerve function assessment through sensory and motor function testing.

In table 1 the definitions of commonly used terms are given.

Table 1 - Definitions

Nerve function	Motor, sensory and autonomic function of peripheral nerves
Impairment	Any loss of function
Nerve function	Clinical detectable impairment of motor, sensory or autonomic nerve function; the level of detectable impairment depends on the sensitivity of the testing instruments
Disability	Any restriction or lack of ability to perform an activity within the range considered normal
Deformity	Secondary structural changes of eyes, hands or feet resulting from nerve function impairment
Reaction	Appearance of symptoms and signs of acute inflammation. Clinical redness, swelling, pain and tenderness of nerves, often with loss of function (Hastings, 1985)

Incidence of reactions

Although a substantial percentage of patients develop a reaction during the course of the disease, few data on the frequency of occurrence of reactions and potential risk factors have been published in international journals. A major problem is the difficult of achieving a consistent and commonly agreed case-definition of especially reversal reactions.

Studies on the epidemiology of reactions, published in international literature are not comparable for the following reasons:

- the sensitivity of the testing instrument is not comparable, e.g. sensory testing with ballpen or with filaments,
- test results are not comparable, e.g. because of the use of different VMT scales and number of sensory points tested,
- some studies were done among field patients, others among hospital patients who are likely to have more serious disease,
- the type of study differs: retrospective,. prospective or cross-sectional,- diferent categories of patients are used: PB or MB, BT and BL,
- some studies include only severe reactions, others mild and severe reactions, some only acute reactions, others also silent neuritis,
- some include only self-reporting patients, others also actively detected cases,
- method of follow-up after stopping treatment is different: sometimes passive, sometimes active.

For the above reasons, it is difficult to provide accurate estimates of reaction incidences.

In this presentation, I will concentrate on results of studies on the occurrence of reactions during the MDT era. One of the effects of MDT is that reactions occur during treatment and after completion of MDT.

Table 2 shows the results of studies on the frequency of occurrence of reversal reactions in paucibacillary patients.

Table 2 - Reversal Reactions in Paucibacillary Patients

Study	Nº of Patients	Percentage of Reversal Reactions				Total
		Before	During	After		
Zaire						
PB	335	-	6	NS		6
Malawi						
PB	503	2.2	1.4	3	12 months	6.6
Self-rep	341	3.2	2.1	4.7	12 months	10.0
India						
PB	190	-	3.7	4.7	12 months	8.4
TT	77		3.8			3.8
BT	218		11.5			1..5
PB	295		9.5			9.5
Ethiopia						
BT-field	438	3.4	10.3	7.3	12 months	21.0
BT-study	128	10.2	7.0	3.9		21.1
Nepal						
BT	182	31.9	8.2	2.2	18 months	42.3

NS: Not Studied

- The study in Zaire was a prospective one. Most reactions were reported as mild, patients were only examined if they complained about skin and/or nerve symptoms.
- The study in Malawi was a prospective study. All reactions were reported as severe and occurred in self-reporting patients. No reactions were observed among patients who were after release from treatment was active.
- The first study in India was a prospective one, involving two groups of 95 PB patients treated with a different regimen. The second study in India was a retrospective study among all patients who attended a leprosy centre.
- The first study in Ethiopia was a retrospective study in a two-year cohort of patients in the ALERT field programme. The follow-up after release from treatment was passive, severe reactions and silent neuritis were included. The second study in Ethiopia was a prospective study in the ALERT field programme, using the same methods for classification of patients and diagnosis of reactions as in the routine field programme. The follow-up after release from treatment was active.

The study in Nepal was a hospital based prospective study, including mild and severe reactions.

Table 3 shows the frequency of occurrence of reversal reactions in multibacillary patients.

Table 3 - Reversal Reactions in Multibacillary Patients

Study	Nº of Patients	Percentage of Reversal Reactions			Total
		Before	During	After	
Zaire					
MB	280	6.4	41.1	NS	6
India					
BL	67		14.9	NS	6.6
LL	123		2.4	NS	10.0
MB	190		6.8		
Ethiopia					8.4
BL-field	266	4.9	38.7	NS	3.8
L-field	109	-	19.2	NS	1..5
MB	375	3.5	33.1	NS	9.5
MB-study	158	10.1	27.9	2.5	
					21.0
Nepal					21.1
BL	106	29.2	16.8	NS	
LL	31	6.5	-	NS	
MB	137	24.1	13.1	NS	42.3

NS: Not Studied

It involved the same centres as the studies on reversal reactions in paubacillary patients. The first study in Ethiopia concerned a two-year cohort of patients who were treated with MDT until skin smear negativity. However, the study on reactions was limited to the first 2 years of MDT.

In table 4 the findings of studies on the frequency of occurrence of ENL reactions in multibacillary patients are presented in some of the same centres as the studies about reversal reactions.

The findings in the above studies confirm that reactions occur prior to treatment, during MDT and after release from MDT.

Table 4 - Erythema Nodosum Leprosum Reactions in Multibacillary Patients

Study	Nº of Patients	Percentage of ENL Reactions Before	During	After	Total
Zaire					
MB	280	6.4	12.1		
Ethiopia					
BL-field	266	0.8	1.9	24 months	2.7
LL-field	109	2.8	8.3	24 months	11.1
MB-field	375	1.3	3.7		5.0
MB-study	158		1.3		1.3
Nepal					
BL	106	1.9	0.9		2.8
LL	31	16.1	16.1		32.2
MB	137	5.1	4.4		9.5

Point in time of occurrence of reactions

The point in time of occurrence of reactions was studied in the ALERT field programme. Table 5 presents the point in time of occurrence of 183 reversal reactions which were diagnosed in paucibacillary patients during a 3 1/2 year period.

Most reactions occurred during MDT. The reactions after release from treatment were diagnosed among self-reporting patients and are most likely an underestimate. In patients diagnosed with a reaction one year or more after release from treatment, the possibiltiy of a relapse was ruled out. Of the 26 patients, 21 responded to prednisolone treatment within a few weeks. This and the observation that these patients did not develop recurrent signs of activity after stopping prednisolone, favours the diagnosis of reversal reaction. Of the reamaining five patients the data were incomplete.

Table 6 gives the point in time of occurrence of 307 reversal reactions in BL patients and 58 in LL patients which were also diagnosed during a 3 1/2 year period in the ALERT field programme. All reactions were diagnosed in patients who were on MDT.

The risk of reversal reaction among multibacillary patients appears to be highest during the first six months of MDT, after which there is a steady decline. However, reactions still occurred more than 2 years after the start of MDT.

Table 7 presents the point of occurrence of 15 ENL reactions in BL patients and 25 in LL patients. The data suggest that during the first 2 years of MDT the risk of ENL reaction appears constant. However, the number of reactions are too small to draw definite conclusions.

Table 5 - Point in time of occurrence of reversal reactions in 183 paucibacillary patients in ALERT Leprosy Control Programme in Ethiopia

Time of occurrence of reversal reaction	No. of Patients	Percentage
Diagnosis	30	16
During MDT	76	42
After release from MDT		
6 months	29	16
07-12 months	12	7
13-18 months	8	4
19-24 months	9	5
25-30 months	4	2
31-36 months	3	2
37-42 months	1	0.5
43-48 months	1	0.5
Not specified	10	5
Total	183	

Table 6 - Point in time of occurrence of reversal reactions in 307 BL patients and 58 LL patients in ALERT Leprosy Control Programme in Ethiopia

Time of occurrence of reversal reaction	BL Patients		LL Patients	
	No.	%	No.	%
Diagnosis	32	10	2	3
During MDT				
6 months	109	36	14	24
7-12 months	45	15	14	24
13-18 months	47	15	7	12
19-24 months	21	7	6	10
25-30 months	20	7	5	9
31-36 months	11	4	5	9
37-42 months	9	3	2	3
43-48 months	7	2	1	2
49-54 months	2	1	1	2
55-60 months	3	1	1	2
60 +	1			
Total	307		58	

Table 7 - Point in time of occurrence of ENL reeactions in 15 BL and 25 LL patients in ALERT Leprosy Control Programme in Ethiopia

Time of occurrence of reversal reaction	BL Patients No.	%	LL Patients No.	%
Diagnosis During MDT	4	27	5	20
6 months	2	13	5	20
7-12 months	4	27	4	16
13-18 months	2	13	4	16
19-24 months	2	13	3	12
25-30 months	1	7	2	8
31-36 months	0		1	4
37-42 months	0		0	
43-48 months	0		1	4
Total	15		25	

Table 8- Distribution of nerve function impairment in 161 patients with a reversal reaction

Type of impairment	Affected nerves No.	%
Ulnar sensation	142	18
Median sensation	115	15
Tibial sensation	218	28
Facial sensation	92	12
Ulnar muscle strength	124	16
Median muscle strength	48	6
Peroneal muscle strength	37	5
Total nerves impaired	776	

Table 9 - Risk factors for the development of reactions

Classification of the disease
Extent of clinical disease
Disability grade at diagnosis in BT patients
Mode of detection
Chemotherapy
Pregnancy and puerperium
BCG vaccination
Others: intercurrent infections. , s, trauma, oral contraception

The nerves most at risk

The nerves which are reported most commonly at risk in a reversal reaction are the ulnar, facial and common peroneal nerve. Others report that the tibial nerve is most commonly affected. In a study in Ethiopia among 161 patients with a reversal reaction, it was found that in 51 patiens (32%) only one nerve was affected. Sensation loss of the foot soles was in almost half of these patients the most common single problem. In the remaining 110 patients (68%) more than one nerve was impaired. In 161 patients, in total 776 nerve functions were impaired. The distribution of the nerve functions impairment which is presented in table 8 shows that impairment of foot sole sensation was the major problem, followed by impairment of ulnar sensation and ulnar motor function.

Possible risk factors for the development of reactions

In 1985 the WHO identified prevention of disability as one of the three main objectives of hanseniasis control, in addition to treatment and reahabilitation of patients. Because reversal reactions are the main cause of disability and deformity, early detection and appropriate treatment of these reactions and appropiate treatment of these reactions are the corner stones in the prevention of these conditions. In this respect, identification of factors which may predict the occurrence of reactions, is very important. Several risk factors have been identified, mostly based on case reports. Studies on immunological and molelcular aspects have not yet identified specific mediators and simple tests which confidently predict the risk of development of a reaction. The following risk factors have been reported (table 9):

- Classification of the disease.

Borderline patients, BT, BB and BL, the immunological unstable forms of hanseniasis, have a much higher risk of developing a reversal reaction than TT and LL patients. The WHO-recommended categorization into pauci - and multibacillary patients does not allow identification of and special attention to these high risk groups. LL patients have the highest chance of developing ENL reactions.

- Extent of clinical disease

In the study in Nepal, it was shown that patients with extensive disease, which was defined as three or more body areas out of a total of nine involved, have a tenfold higher risk of developing a reversal reaction than patients with less than three areas affected.

- Disability grade at the time of diagnosis

In a study In Ethiopia it was observed that the risk of development of a reversal reaction is significantly higher in BT patients with disability grade 1 or 2 at the time of diagnosis of the disease than in those without disability.

- Mode of detection of patients

In Malawi it was found that the incidence of reversal reactions was significantly higher in self-reporting patients than those detected actively. The most likely explanation for this, is that self-reporting patients have more advanced disease than patients detected through an active case-finding approach (of whom part will be self-healing).

- Chemotherapy

In patients treated with MDT, ENL reactions appear to be relatively rare. In studies carried out during the dapsone monotherapy era, 25% or more of the multibacillary patients were reported to develop an ENL reaction during the course of the treatment. A possible explanation for the decline in ENL reactions is the daily dose of clofazimine. The anti-inflammatory activity of this dose may be adequate to prevent ENL reactions in many patients.

Treatment as a risk factor for reversal reactions has been and still is a subject for debate. The available data on occurrence of reversal reactions after starting MDT clearly show that the risk of developing the reaction is highest during MDT (paucibacillary patients) and during the first year of MDT (Multibacillary patients). As no studies have been carried out in which the occurrence of reversal reactions was compared in patients treated with dapsone and patients treated with MDT, there is no information on reaction incidence in relation to different regimens. In Nepal, it was observed that in several patients a reversal reaction or an

ENL reaction that existed at the time of diagnosis of hanseniasis got worse after the patient received the first dose of rifampicin.

- Pregnancy and puerperium

In several publications, an increased risk of reversal reaction during pregnancy and puerperium has been reported. In a study in Ethiopia during the dapsone monotherapy era, 44% of 119 women with hanseniasis presented 85 episodes of reversal reactions during pregnancy and the first 12 months after delivery. Becasue there were no non-pregnant women followed-up in the studies, the relative risk of reversal reaction associated with pregnancy is not known.

- BCG vaccination

Reactions after BCG vaccinations have been observed in hanseniasis patients.

- Other factors

In the literature, several other factors have been mentioned: intercurrent infection, especially tuberculosis, HIV, dual infection, stress, trauma, and oral contraception. However, the evidence is anecdotal to a large extent.

Final remark

There is no doubt that a substantial part of disability and deformity in hanseniasis patients is the result of missed diagnosis or improper management of reactions. It is estimated by the WHO, that there are beween one and two million disabled (ex) - patients with disability grade 2 worldwide. This estimate will be much higher, probably at least double, if patients with sensory loss or disability grade 1 are also included. These patients are potentially at risk of developing deformities. Early detection and treatment of nerve impairment is the first and most important measure for successful prevention of disabilities in hanseniasis.

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