

## Physical Disabilities in Leprosy: Some Contemporary Basic Aspects

Glaucia G Mantellini<sup>1</sup>, Aguinaldo Goncalves<sup>2\*</sup> and Carlos Roberto Padovani<sup>3</sup>

<sup>1</sup>Physiotherapy Specialist Group of the Swiss Society of Gerontology (SGG), Switzerland

<sup>2</sup>Collective Health Area, Medicine College, Campinas Catholic University (PUC), Campinas, SP, Brazil

<sup>3</sup>Department of Biostatistics, Universidade Estadual Paulista (UNESP), Botucatu Campus, Botucatu, SP, Brazil

### Abstract

Leprosy consequences are huge regarding the psychological, social and economical aspects, although the rate of related lethality is low. The most important of them is the neuritis, which occurs associated with the leprosy reaction symptoms, triggered by delayed hyper sensibility, which determines and explains the therapeutic option based on immune suppressors combined with continuous antimicrobial chemotherapy. Mechanisms probably involved are explored at the same time as research perspectives worldwide are considered. In this context, it is pointed that the main challenge for the knowledge and intervention on Physical Disabilities in Leprosy is to overcome the semantic disagreements as well to understand the differences and traps protocols may provide.

**Keywords:** Leprosy; Physical disabilities; Neuritis

### Semantics and Protocols

As it is widely known, leprosy is an infect-contagious disease related to *Mycobacterium leprae*, whose spectrum of manifestations depends on the immune response from the infected people. The diversity of clinical signs and symptoms varies from simple dermatological lesion to peripheral nervous, ocular, bone damages and even damage of vital organs. These symptoms can come up a few months or many years after infection. Although the lethality rate of leprosy is not high enough to be ranked on the mortality causes of infectious diseases in Brazilian statistic figures [1], the occurrence of disabilities deriving from leprosy determines considerable consequences regarding not only physical but also psychological, social and economical aspects.

Leprosy neuropathy is clinically mixed; endangering sensitive, motor and autonomic nerve fibers and its anatomical distribution determines the diagnosis of a single or multiple mononeuritis, depending upon whether it lodges in one or several nerves. By the infectious process, the bacillary proliferation occurs in macrophages, which are infiltrated in the skin. The bacilli invade the nerves of the dermis and gather selectively on the laminar surface of Schwann's cells. The multiplication and death of those cells with the subsequent inflammatory response to the mycobacterium result into peripheral nerve lesion and functional impairments, especially loss of sensitivity to temperature, touch and pain. There are classical examples in the facial nerves, trigeminal, ulnar, common fibular nerve and posterior tibia [2].

The first challenge for the knowledge and intervention on the most frequent leprosy sequels, the Physical Disabilities of the Disease (PDL), consists of overcoming semantics disagreements. Regarding terminology standardization some international bibliographic references, mainly in the english language, do not seem to be clear enough. Words as "disabilities", "impairments", "dysfunctions" are frequently used and translated to other languages. For the purpose of this work we will use a unifying approach based on the International Classification of Functioning, Disability and Health [3].

So far it is important to explicit the existing difference between "impairment", "disability" and "handicap", conditions that decisively involve leprosy. The impairments correspond to changes in the organs, systems and body structures. Disabilities are characterized as consequences of impairments from the viewpoint of functional efficiency, that is, in the performance of personal activities and social participation [4,5]. Even though these disabilities are originally

impairments, they restrict daily life activities, which can be partially handled with physiotherapy, occupational therapy and surgery [6]. As a result of such limitations derived from visible changes or simply from the diagnosis of leprosy, many people with disabilities are segregated from their social life and have to adapt by themselves to an environment, in which they feel handicapped.

The PDLs have been assessed by different protocols, especially by the *Classification of Disabilities* in leprosy of the World Health Organization, WHO [7], in force since 1960. Since 2001, a three-level damage grade has been employed for the six body segments-eyes, hands and feet, as it follows:

- Grade 0: when there is no problem concerning leprosy.
- Grade I: when there is decrease or loss of sensitivity.
- Grade II: when the following is noticed:

+ in the eyes: Lagofalmo and/or ectropion; trichiasis; central corneal opacity; visual acuity less than 0.1 or inability at finger counting at a 6 meter-distance;

+ in the hands: Trophic lesions and/or traumatic lesions; clawed hands; reabsorption; "wrist drop" hands;

+ in the feet: Trophic lesions and/or traumatic lesions; clawed feet; reabsorption; "foot drop"; ankle contracture.

- Not evaluated, when there is no information on the subject or when physical examination was not really performed.

This protocol systematizes the PDLs in an increasing order, always showing the maximum grade of any spot evaluated, which is interpreted

**\*Corresponding author:** Aguinaldo Gonçalves, Rua Luverci Pereira de Souza 1151, Cidade Universitária, 13 083-730 Campinas, SP, Brasil, Tel: +55 19 3289 5022; E-mail: [aguinaldogon@uol.com.br](mailto:aguinaldogon@uol.com.br)

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as a general indicator of the individual condition. Such “quantified” information on sick people’s condition and their PDLs should be used:

I) To take a decision and to organize the patient’s rehabilitation in a more personalized way.

II) To evaluate the effectiveness of preventive programs on disabilities and dysfunctions, on the prevention of future PDLs and on the conduct of pre-existent ones.

III) To plan the resources which are necessary for the handling of those who present PDL before and after treatment.

The positive aspect of the present classification is the clear and concise lay out of the register form, easy to be filled in by the doctor. On the other hand, it fails to be sensitive to nosographic changes of the disabilities related to the characteristics of several lesions that were observed and that are relevant to a more personal monitoring of future patients. That means if a person, carrying various lesions with sensitivity alteration in several nervous sites (Grade I), and another with ulnar claw deriving from silent neuritis which was not properly treated (Grade II) are registered, the latter will have priority for the service, although it is also known the importance of adaptations and care for the people diagnosed with anesthetic alterations [8].

As a complement to the classification above, the clinical practice has elected the use of alternatives as the Eyes, Hands and Feet Index with a minimum rate of 0 and the maximum of 12, corresponding to the total amount of evidences related to the segments considered. In few services, “The Impairment Summary Form” for PDL prevention may still be found which tends to be more adequate in the activity supervision, but demands a longer time for the application as well as more dedication from the professionals involved.

Actually, recording of PDLs reflects more ample difficulties concerning their own characteristics. In studies performed in India, widely known as INFIR (ILEP Nerve Function Impairment and Reaction Study) some evidences of such complexity have been pointed out as neuritis definitions, silent neuropathy, paresthesia, reactions and their severity grades, articular proprioception and evaluation method, sensorial and motor deficiency, nervous thickening and respective grading [9]. The authors go beyond, pondering about the relevance of evaluation methods like: i) voluntary muscular tests; ii) nervous conduction measures (with Neurocare 2000 equipment for electromyography); iii) sensibility perception with the use of esthesiometer; iv) perception potentials for vibration (with Somedic® Vibrometer II); v) thermal detection (with TSA II, Thermal Sensory Analyzer) and vi) indicators of sensitive nervous conduction and questionnaire results upon daily life activities. They also call attention to predictive meanings of interesting semiological findings:

- Skin lesions that are found upon main nervous trunks would increase risk of nerve lesion, no matter if they show reaction signs.
- Absence of articular proprioception and deep tendinous reflexes would apparently indicate neuropathy progress.
- Neural thickening, pain on touching and paresthesia would be associated with risk of reaction or of neural function impairment in the diagnosis.

Thus, to check the reliability/safety of the PDL evaluation protocol by WHO, studies with pairs of examiners have been developed in India, using different methods for sensitivity-ball pen and a set of Semmes-Weinstein monofilaments and muscular straight test [10]. The results

of the analyses based on Kappa statistics in both situations indicate that the reliability reached was very good, with higher coefficients for Grades 0 and II and lower for Grade I, which shows that it is relatively easy to classify who has no disability or, on the contrary, someone who is severely disabled. The difficulties concerning Grade I would probably be found in operational definitions of PDL classification, as for instance:

- Variation of sites to be tested at the definition of sensitive and anesthetic limitation.
- Interpretation of other etiological impairments (decubitus, muscular atrophies or skin cuts), resulting in evaluation bias.
- Inclusion of impairments not related to leprosy and muscular weakness.
- Definition of muscular impairment.

It is important to mention that in field activities, time available for the evaluation, personal motivation, previous training and experience of the evaluator in field, as well as service organization conditions can alter how the protocol is filled in, and consequently, the PDL classification. The same authors reinforce this perspective, showing the need for trained and expert people in leprosy who may lead disability prevention programs, mainly in order to help dubious situations *in loco* and in real time.

## Neuritis and Reaction Symptoms

In general, it can be said that the pathogeneses of disabilities are neurogenic and inflammatory and they are responsible for primary lesions (straightly related to the presence of bacillus in the tissues or through inflammatory processes) and for secondary ones (deriving from the presence of tegument anesthesia or from alterations of motor paralyses). The chronic skin ulcers, very well known by multibacillar patients who have been sick for a long time, demand different kinds of treatment [11,12] and they become nervous lesion because they occur from a prolonged trauma in anesthetic areas and/or from secondary infections and not because of inadequate cellular traffic allied to immune response [13].

From the anatomo-physiological point of view, neuritis is considered as an important factor in PDL induction. They can be *obvious*, defined as those that present spontaneous pain or pain at touching in the peripheral nervous trunk; they can also be *silent*, with or without nervous swelling and/or functional impairment; or *frank* with pain at touching in peripheral nervous trunk, with or without functional impairment [14].

As authentic indicators and also as serious leprosy consequences, the neuritis is usually related to reaction symptoms of two different types [15].

- Type 1 or reversal neuritis, present in almost all forms of the disease (except the indeterminate) and especially on the borderline, it is triggered by delayed hyper sensibility to mycobacterial antigens. It is clinically observed through the reactivation of lesions in preexistent plaques with acute inflammation symptoms such as erythema; edema, and hyper sensibility; thickening of peripheral nerves; systemic disorders.

- Type 2 neuritis, which is characterized by leprous or nodosum erythema and/or its equivalent, thriving in the multibacillar forms of the spectrum. Recognized as a paradigm of the immunological system disease, it is triggered by local deposition of immune complexes and it is identified due to the appearing of dermal or erythematous

subcutaneous nodules, which are warm, movable and sometimes very painful; erythematous lesions with vesicles or blisters that may develop into ulcerations, such as systemic symptoms (fever, adenomegaly, weight loss, arthralgia, myalgia; nerve thickening, pain and nerve sensibility).

The main characteristic of leprosy neural lesion is the unique capacity of *M. leprae* to invade the peripheral nervous system. The comprehension of how the neural lesion happens is very challenging and controversial. The discovery of delayed hyper sensibility induction determined by antigens present in Schwann's cells as well as clinical observations strongly influenced the introduction of new therapeutic principles based on immune-suppression combined with long-term antimicrobial chemotherapy [16].

This very same therapeutics that destroys the bacilli, "healing" people, may trigger neuritis after medication treatment is ended. That is because, even when resistant alcohol-acid material in microbiological observation cannot be traced anymore, immune-histochemistry exams still reveal presence of *M. leprae* antigens—the lipoarabinomannan—which remains in lesions for a long period, increasing the risk of (re) stimulation of the immunological system and the corresponding reaction symptoms even if most bacilli are dead [17,18].

## Mechanisms and Perspectives

The polemic aspect concerning neural lesion is whether the disease is stable or not in its forms and types. In all observable nuances, result of bacillary interaction seems to lead with infection followed by the reaction of cytokines IL-12, IL-18, TNF $\alpha$  and IFN $\gamma$ . However, for some individuals genetic constitution would enable the initial low response scenario (congenital and/or specific immunity), allowing posterior bacillary multiplication and establishing different levels of non-response, present in the clinical spectrum of the disease. In other words, leprosy presents a particular immunity pattern which results from complex dynamics between cells and factors including: i) subperineural edema; ii) axon atrophy with secondary Desmielinization; iii) non-mielinized fibers loss and iv) resistant macrophages activation and fibroblasts in the endoneural space [19,20].

The mechanisms involved with TNF $\alpha$  and TNF2 after bacillary invasion into Schwann's cells are still not very clear, but it is already known that before that there is direct interaction of multiple surface molecules present in *M. leprae* with basal lamina of axonal unities of Schwann's cells, causing bacillary infection [21,22]. Such discoveries open perspectives towards new drugs and vaccines that are able to block up the connection of microorganisms to the basal surface avoiding neural lesions before the actions mediated immunologically worsen the disease.

Another possibility of intervention (a little later, though) is the pursuit of new and effective therapeutic interactions that are able to foster axonal regeneration, for instance, the stimulation of inhibitors as MMP, TNF $\alpha$  and adhesins [23], since after bacteriologic removal (done through multidrug therapy), reactive responses bring about neural and tissue inflammations, which may precede permanent lesion and disabilities if they are not treated adequately.

Although teeming with so many questions and few precise answers, the field of analyses for etiopathogenic comprehension of the disease and of the nerve lesion has many current research perspectives. From the IDEAL – "Initiative for Diagnostic and Epidemiological Assays for Leprosy" [24], some important themes are being topped in many scientific centers worldwide:

- Identification of antigenic T cells specific to *M. leprae* which would provide specificity recognized by antibodies.
- Deeper comprehension of the composition and organization of *M. leprae* genome.
- Investigation into molecular epidemiology of the bacillus aiming at a better comprehension of transmission and intervention strategies.
- Ethical procedures for sample collection.
- Standardization of work definitions and laboratory methods.
- Validation of analysis tools.

Once applied, such laboratory progresses can contribute for the elucidation of diagnosis as well as serve as indicator of therapeutic adequacy. This is the case of DNA detection of *M. leprae* (by Polymerase Chain Reaction–PCR) in paucibacillary patient, years after the end of the multidrug therapy, suggesting the presence of live bacilli during longer time than expected [25] or in communicants, showing subclinical bacillar infection [26]. As far as the first circumstance is concerned, it is worth mentioning that the application was on "pure" neuritis, which can help outline precocious therapeutic intervention and prevention of deformities when there is absence of the most frequent leprosy signs and symptoms [27].

In relation to therapeutics of reactions, there is also a kind of restlessness for the discovery of new possibilities for recovery of neural function after the reaction process is uncertain, occurring only in around 60% of the cases [28]. Studies *in vivo* on the action of corticoids in the production of cytokines in neural lesions, suggested that this production could be decreased if the medication acted more rapidly on cellular reactions and on the lesion profile of cytokines as immune-suppressor element, avoiding local inflammatory process.

## Author Contributions

Glaucia G Mantellini was responsible for information gathering and exploratory writing.

Aguinaldo Goncalves was responsible for technical discussion and editorial formulation.

Carlos Roberto Padovani was the institutional advisor and over all reviser.

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