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Considerations for Erythema Nodosum Leprosum, with Emphasis on Its Oral Manifestations

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ABSTRACT

Leprosy is an infectious disease caused by *Mycobacterium leprae*, transmitted from person to person through contact among susceptible untreated patients. It presents a broad clinical spectrum which is related to the host's ability to mount a specific immune response. The lesions caused by the proliferation of *Mycobacterium leprae* (*M. leprae*) were significantly reduced in recent years with the early detection of new cases. Because they are less evident and/or study, maxillofacial injuries and the oral mucosa may reveal important details about the transmissibility and immunopathogenesis of leprosy. This article was based on a literature to verify an interrelation between oral manifestations in virchowian patients and immuno-pathological factors. Association between the infection of oral mucosa and some pathological findings as well as the participation of the local immune response in protection against the disease are research topics still not fully exploited.

Keywords: Leprosy; Hansen Disease; Oral Manifestation

1. Introduction

Leprosy is an infectious-contagious disease caused by *M. leprae*, transmitted from individual to individual through the contact with contagious patients without treatment. It presents a broad clinical spectrum that is related to the ability of the host to mount an immune response. The main local of entry of the Bacillus are the upper airways. There is still much to learn about the cellular and molecular mechanisms responsible for the ineffectiveness of the cellular immune response in leprosy. It is known, however, that there are changes in the processing of antigens and the production of some interleukins. Immune response in leprosy involves all major components of the immune response, such as macrophages, various interleukins, T lymphocytes and their subpopulations, NK cells, B lymphocytes and antibodies. The cytokines released by macrophages activated by *M. leprae*, perform various effects in cells of the immune system, helping to increase the effector mechanisms of the site of inflammation.

In leprosy, as well as in other infections where the macrophage is the main target of the parasite, the mechanism of immune response that determines cure or disease relates to types of cytokines produced by the immune system, where the predominance of Th1 profile determines the tuberculoid form, while Th2 profile leads to lepromatous form. So a great difficulty for the control and management of the disease is the occurrence of leprosy reactions. The cellular responses are related to the pathogenesis of reverse reactions. Several reactional stages are produced by a variety of immune mechanisms that give rise to severe tissue damage in the course of the clinical figure of the patient. Leprosy reactions are related to the exacerbation of cellular immunity, or demonstrate marked effects of immune-complex formation, called reaction type 1 and type 2, respectively [1].

The identification of specific lesions in the oral cavity in leprosy patients becomes of great importance, as well as the relevance of an imunopathology study, considering the scarcity on the subject in literature. There are many reports that discuss oral lesions, however there is a divergence about the region of the same.

Authors report that skin lesions are concomitant with oral lesions. Indeed so far not found. Furthermore, were found a few reports about the role of cytokines expressed in the oral mucosa.

2. Series of Problem

Leprosy is considered still today one of the biggest public health problems. The World Health Organization

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(WHO), after the introduction of multidrug therapy (MDT), had established the goal of elimination of the disease by the year 2005, *i.e.* the reduction of the prevalence rate of 1 for every 1000 inhabitants, unfortunately not met. Brazil continues occupying the second place in the world in prevalence of this disease, with an estimated, 6.72 patients/10,000 inhabitants and with prevision of 45,000 new cases annually. Although being as the second largest endemicity in the world, has contributed significantly to these statistical changes. In the State of Bahia, considered of an average prevalence in Brazil, was detected an increase in incidence, preocupating fact due to the difficulties for the low class inhabitants regarding the diagnosis and treatment of disease [2].

Brazil, according to a study by Penna [3], provides a downward trend statistically significant, in time for the time series of coefficients of detection.

However, in the period 1990-2008, this coefficient ranged from 20.0/100,000 inhabitants in 1990 and 29.4/ 100,000 inhabitants in 2003, presenting a "very high" classification according to the official parameters. However, the North, Northeast and Midwest still maintain rates at very high levels. Brazil, according to a second trend study, presents a decreasing tendency statistically significant downward trend, in time for the time series of coefficients of detection [4].

The State of Bahia, according some data, presents later decreasing trend, statistically significant in time to the time series of coefficients of detection. However, in the period from 1990 to 2008, this coefficient ranged from 7.52/100,000 inhabitants in 1991 and 29.32/100,000 inhabitants in 2003, showing a "high" rating for the second period, less than the official parameters found in Brazil [4] (**Tables 1** and **2**).

The active record of the coefficient of prevalence per 10,000 inhabitants in 2000 was 1.5 (in the State) and 1.3(in the capital), increasing to 2.4 and 4.0, respectively, in the year 2002. While the coefficient of incidence in this same period ranged from 1.3 to 1.2 in the State, and from 1.2 to 0.8 in the capital [5].

Table 1. Leprosy situation in countries that have not yet reached the goal of elimination of disease-prevalence and incidence recorded during 2004, 2005 and 2006.

	Prevalence (per 10,000 inhabitants)			Incidence (per 100,000 inhabitants)		
Country	2004	2005	2006	2004	2005	2006
Brazil	79.908 (4.6)	30.693 (1.7)	27.313 (1.5)	49.206 (28.6)	49.384 (26.9)	38.410 (20.6)

Source: Marzliak, 2006.

Table 2. Situation in Brazil early 2005.

Country	Prevalence	Incidence	New Cases—Children (absolute numbers)	Relapse (absolute numbers)
Brazil	1.7	26.9	4193	1606

Source: BRAZIL. The Ministry of health. National Leprosy Control Programme. Available in: http://portal.saude.gov.br/portal/saúde/visualizar_texto.cfm?idtxt=21149. Access in: Dec. 20, 2008.

The reduction of cases in children under age 15 is the priority of the National Leprosy Control Programme (PNCH), being an indicator of leprosy in the PAC—More Health. The detection of cases in this age group has to do with recent disease outbreaks and transmission assets and its epidemiological monitoring are relevant to the control of leprosy [6].

The detection coefficient in Bahia in this age group in the period from 2001 to 2008, presented a "high" rating (**Table 3**). The spatial distribution of cases in children under 15 years old in 2008 shows that there has been notification of children in 65 (15.6%) counties of the State, which are surrounded by silent areas or without cases. It is worth noting that the municipalities of this State are entered in ten areas of increased risk of detection of leprosy cases, defined by the study of clusters.The parameters in Priority Actions of health Surveillance Programme (PAV) it is observed that the average percentage when assessed the degree of disability (GIF) in

Table 3. Epidemiological and operational indicator of leprosy in Brazil, 2001 to 2008.

2001	3.555	6.96	45.874	26.61	84.7	6.0	64.7	67.9	81.6
2002	3.862	7.47	49.438	28.33	84.2	5.9	63.1	68.0	75.8
2003	4.181	7.98	51.900	29.37	84.9	5.6	60.9	52.7	69.3
2004	4.075	7.68	50.565	28.24	84.8	5.8	60.4	43.9	67.3
2005	4.010	7.34	49.448	26.86	85.5	5.8	58.9	45.5	69.2
2006	3.444	6.22	43.642	23.37	86.6	5.7	60.6	49.7	85.5
2007	3.048	6.07	40.126	21.19	83.0	9.4	55.1	49.8	81.1
2008	2.910	5.88	38.992	20.56	88.2	7.7	67.8	54.3	79.4

Source: BRAZIL. The Ministry of health. National Leprosy Control Programme. Available in: http://portal.saude.gov.br/portal/saúde/visualizar_texto.cfm?idtxt=21149. Access in: Dec. 20, 2008.

the diagnosis was 87.3% for this period, considered as "regular". GIF 2, important indicator of early detection, fluctuated between 3.1% and 8.5%, showing rating of "low" to "medium" in the period, according to parameters. The evaluation of the GIF in healing was considered "pre-carious" in the period, with an average of 47.7% evaluated. The proportion of the examined contacts showed an average of 40%, varying from 69.7% in 2001 and 30.2% in 2008, keeping up with the classification "precarious". The percentage of healing in cohorts showed an average of 68.7%, considered "precarious", oscillating between 60% in 2003 and 80.2% in 2006 (**Table 4**).

3. Clinical Manifestations in Leprosy

Few diseases present a broad spectrum of pathological and clinical forms regarding leprosy, where we can find patients with a single injury that heal spontaneously, as well as individuals with generalized injuries configuring a severe and extensive form of the disease. The classification of Madrid divided the leprosy in two polar groups: tuberculoid and lepromatous, and other classified as indeterminate and borderline.

In 1966, Ridley and Jopling divided the spectrum into five groups based on clinical, pathological and immunological factors, such as being: Tuberculoid (TT), borderline Tuberculoid (BT), borderline-borderline (BB), borderline Lepromatous (BL) and lepromatous-Lepromatous (LL). The indefinite and neural forms are off this classification.

For outpatient work purposes in the field, WHO simplified the classification of patients into paucibacillary (PB), to individuals who presented negative baciloscopy and/or up to 5, skin lesions, and multibacillary (MB) for individuals with positive baciloscopy and widespread injuries [1].

According to these authors neural lesions usually precede the skin lesions. Occur exclusively in the peripheral nervous system (PNS). The first manifestations are the sensitive, being the first anatomical structures committed the neural "ramuscles" (distal components of PNS), progressing to proximal direction, affecting secondary nerves, and, finally, the peripheral nerve trunks. These become swollen, painful to palpation or percussion.

Classification as indeterminate refers to the initial state in which the histologic and clinical form is uncertain. The cutaneous lesion presents as poorly defined macules, hypopigmented and thermal hypoaesthesia region, can occur changes of sensibility tactile sensitivity and painful. The patient's immune potential is not evident in the lesions in this form of leprosy.

At this stage of the disease the patient, according to the potential of immune response can progress to the various forms of the spectrum, but can also occur spontaneously cure.

In tuberculoid form, lesions are isolated or infrequent, macular or infiltrated. Patients present hypopigmented lesions distributed asymmetrically.

On the face, due to the rich innervation, hypoesthesia can be difficult to be detected.

In borderline or dimorphic, we find a mixture of elements of the two poles of the disease, *i.e.* the lepromatous or tuberculoid form.

Antibodies are in low concentrations, when detected, whereas the cellular immunity remains or is exacerbated.

Most patients with Hansen's disease develop the form borderline, which is immunologically unstable. According to the clinical data, the bacteriological test among others, these patients tend to present themselves as dimorfotuberculides or borderline-lepromatous.

In lepromatous leprosy or *wirchovian* in the characteristic form of dissemination, the lesions show no defined

Table 4. The detection coefficient in Bahia in this age group in the period 2001 to 2008.

Indicators/ Year	New cases 0 - 14 age	Detection Coefficient 0 - 14 years/100 milinhabitants	New cases total	Coefficient Detection General by 100,000/inhabitants	% evaluated as to GIF in diagnosis	% of patients with GIF 2 in diagnosis	% Evaluate as GIF in healing	% of Contacts Examined
2001	3.555	6.96	45.874	26.61	84.7	6.0	64.7	67.9
2002	3.862	7.47	49.438	28.33	84.2	5.9	63.1	68.0
2003	4.181	7.98	51.900	29.37	84.9	5.6	60.9	52.7
2004	4.075	7,68	50.565	28.24	84.8	5.8	60.4	43.9
2005	4.010	7.34	49.448	26.86	85.5	5.8	58.9	45.5
2006	3.444	6.22	43.642	23.37	86.6	5.7	60.6	49.7
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Source: BRAZIL. The Ministry of Health. National Leprosy Control Programme. Available in: Disponível em: http://portal.saude.gov.br/portal/saúde/visualizar_texto.cfm?idtxt=21149. Access: Dec. 20 2008.

boundaries. Even in this form of the disease we can observe that, in particular, rhinitis occurs early and specific, by diffuse infiltration, sometimes with "hansenomas", later, ulceration and perforation can occur and collapse of the nasal septum.

4. Oral Manifestations

Little emphasis was given to Oral lesions in leprosy. A greater interest started in 1930 with Pavloff [7]. This author published papers regarding lesions in the nose and mouth, followed by other papers drew attention of localized lesions in the mucous membrane of the lips, cheek and neck [8-10].

Pavloff shows a higher frequency of lesions in the soft palate, uvula and pillars of the fauces. There were no elements of prominence observed in the cheek and gum. On the lips and tongue nodules were detected in skin and mucous board. This author also reported several isolated tubers at the end and sides of the tongue, and sclerotic glossitis, geographic tongue and increase in fungiform papillae.

In most published papers there was always a higher incidence of injury in the hard palate, soft palate and uvula, in descending [7,9,11-16].

Most of these works refers to lepromatous patients, or patients in the intermediate form tending to lepromatous pole.

The most frequent types of lesions observed in these studies were: infiltration, hansenomas and exulcerations. Some studies did not correlate these lesions with *M. leprae*, and do not cite specific lesions of leprosy patients.

However, there are few studies that included an immunohistochemical study of the oral mucosa.

The study of positive bacilloscopy in oral mucosa in material apparently healthy has been cited by authors in 1939, reviewing 456 lepromatous patients and other clinical forms, found an overall frequency in the lepromatous, 19.1% of lesions in the oral cavity, and 2.09% on the lips, 1.4% tongue, 11.7% in the hard palate, 5.9% soft palate and 3.2% in the uvula.

The changes that MH may present in the oral cavity were described in 1970 from the form of the disease and its time evolution. A study conducted in 1973 found the MH lesions in the oral mucosa, reporting that they only occur in later stages of the disease, inexisting in tuberculoid and indeterminate forms. The majority of the authors mention the nasal mucosa as the main site of contamination and elimination of Hansen bacilli. With the advent of specific medication initiated at the sulphonis time, has been admitted to the disappearance of the early disappearance of these manifestations in the duration of therapy. Few researchers gave emphasis on leprosy lesions in the oral cavity, a reason why, in the prophylactic sense, little has been done in the field of dentistry.

Regarding the involvement of the oral mucosa in leprosy, few studies have been conducted on the specific lesions in this area and, although scarce, the work focused on the field have attracted the attention of researchers.

The authors call the attention of health professionals who work with leprosy, as well as dentists, for the specific lesions of the disease in the oral mucosa [17].

5. Aspects of the Immune Response in Leprosy

5.1. General Aspects

Little is known of these factors that defend against infection and disease after exposure to m. leprae, however, complement activation promotes phagocytosis of m. leprae [18]. When the bacillus is in contact with phagocytic cells of the host, it is phagocytosed and initiate to conduct mechanisms of intracellular changes acting in elimination of the parasite. The nonspecific cellular immunity has been evaluated by several tests in leprosy patients, however, some authors report that these results are unconformity.

Other researchers [19] by evaluating a set of tests, consider there is a nonspecific impairment of cellular immunity in lepromatous patient. Work undertaken by using parameters such as counting T and B lymphocytes in peripheral blood blast transformation of lymphocytes, macrophage inhibition test (MIF) and prolonged allograft survival, according to these authors, is not totally discordant, thus emphasizing the cellular immune deficiency in lepromatous patients. Evidence suggests that the system is mycobacterial oxygen-dependent, however, other methods of intracellular killing such as the oxygen-independent system probably involved in the killing of *M. leprae in vivo* [20]. There is no evidence for defects in natural barriers skin or mucous membranes in leprosy-susceptible individuals, and there is no established role for IgA in the defense against *M. leprae* [21].

Macrophages from tuberculoid and lepromatous patients may be inefficient in the recognition and presentation of some mycobacterial antigens [22]. The cellular hypersensitivity depends on specific T lymphocyte associated to the macrophage. This is responsible for resistance to infection by *M. leprae*.

The main parameter for the evaluation of cellular immunity is the Mitsuda test. The author of this test (1919) found that after intradermal injection with a suspension of ground fenicated hansenomas, presented in tuberculoid patients a positive reaction among the first three weeks, whereas it was negative in wirchovian patients.

According to Modlin *et al.* [23], the inverse correlation between cellular immunity and humoral immunity was initially investigated in terms of the adaptive im-

mune response. Different sub-populations of T-cells correlated with the response against M. leprae, including CD4 and CD8 cells and the pattern of cytokines they produce. CD4 cells produce the pattern type 1 or Th1 cytokines, including IFN-γ predominantly in tuberculoid lepromatous lesions, whereas CD8 T-cells that produce the pattern type 2 or Th2 cytokines, including IL-4, also prevalent in L-lep. In this way the leprosy provides an excellent model for the investigation of mechanisms through which the innate immune system determines, in man, the beginning of infectious disease.

5.2. Aspects of Innate Immunity

The innate immune system cells are provided with a coding sequence of pattern recognition receptors (PRRs), which recognizes the molecular receptors associated to the pathogen (PAMPs), which are shared between groups of pathogens.

Several toll-like receptors (TLRs) mediate the innate immune recognition of M. tuberculosis and related species. Basically, the activation of the heterodimer TLR2/1 by lipopeptides *M. leprae* induce the production of cytokines such as TNF-α, as part of the acute inflammatory response and IL-12, which mediates the role of the innate immune response to instruct the adaptive type 1 response or production of Th1 cytokines [24].

A number of mechanisms that regulates the function of TLR in leprosy has been identified. Besides ability to IL-4 downregulate the expression of TLR2/1, it also inhibits cytokine responses induced by TLR2/1. The IL-10 has no effect on the expression of TLR2/1 but inhibits, intensely, the secretion of cytokine induced by TLR2/1 [24].

The polymorphism in TLR1 and TLR2 genes have been investigated in patients with leprosy, but there is no convincing data to suggest that TLR1 gene polymerphisms may contribute to the response TLR2/1 against lipopeptides, and the pathogenesis of the disease [25-28].

The ability of TLRs to induce an antimicrobial activity is the main aspect of their role in innate immunity. There is evidence to suggest that the microbial action of vitamin D may contribute to the onset of the disease in leprosy.

Analysis of gene expression profiling in leprosy lesions indicated that the genes coding for the key components in microbial pathway of vitamin D were differenttially expressed in T-lep lesions compared to L-lep [29].

Leprosy has provided an interesting model to investtigate the key role of human innate immune system in host defense in relation to the susceptibility to microbial infection, the expectation that this knowledge may contribute to new therapeutic interventions for leprosy and other infectious diseases of connotation worldwide.

6. Cytokines and T-Cell Subsets

Cytokines are mediators of mechanisms which main function is to modulate cellular interactions and which are peptides synthesized by cells with the potential response after activation. Cytokines are soluble by-products that are T-cells which are important in mycobacterial infection. The immune response of T-cells plays an important role in Hansen disease.

Today we know that human CD4 have functionally distinct subpopulations which differ in the pattern of production of Th1 and Th2, cellular and humoral immunity, respectively.

TNF-α is the principal mediator of host responses to Gram-bacteria, and may also have an influence on the response of other infectious organisms. Its main source is the LPS-activated mononuclear phagocytes, although the T-cell of antigen-stimulated, activated NK-cells and activated mast cells can also secrete this protein.

The biological actions of TNF, such as the LPS, are best understood as a function of quantity. The main actions of TNF in low concentrations range from the induction of vascular endothelial cells to express new surface receptors (adhesion molecules) that causes the endothelial cell surface to become adhesive to leukocytes, initially neutrophils, subsequently to monocytes and lymphocytes as well as acting on neutrophils to increase its adhesion to endothelial cells. These actions contribute to the accumulation of leukocytes at sites of inflammation, and physiologically, are the most important local effects of TNF [30].

TNF activates inflammatory leukocytes to kill the microbes, stimulates mononuclear phagocytes and other cells to produce cytokines, including IL-1, IL-6, more TNF and chemokines.

Interleukin 10, produced by the T lymphocyte, Th-1 and TH-2, Langerhans cells, macrophages and keratinocytes are immunosuppressors and immunostimulators. In lymphocyte Th-1, suppresses the synthesis of their cytokines, decreasing cell-mediated responses, while in B lymphocytes, increases the proliferation and antibody production. The antigen-presenting function and the production of TNF-α, IL-1, IL-6, IL-8 and GM-CSF is presented decreased in macrophages.

In addition to the lymphokines produced by lymphocytes, there are many other cytokines that participate in cell interactions of immune substrates [31]. According to the same author, the two major activities of IL-10 is to inhibit the production of cytokines (eg. TNF, IL-1, chemokine and IL-12) by macrophages and inhibit the fringe function of macrophages in the T-cell activation. This latter effect is due to reduced expression of MHC II CL molecules and reduced expression of certain costimulatory (eg. B7). The net effect of these actions is to inhibit immune mediated inflammation by T-cells In addition to

its inhibitory effects on macrophages, IL-10 has a stimulatory action on B cells. On the other hand, there are interleukin-4 which has as its main physiological function the regulation of immune responses mediated by IgE and mast cells/eosinophils. The main sources of IL-4 are T CD4+ lymphocytes, especially those pertaining to subpopulation Th-2.

Some T CD8 cells are also capable of producing IL-4 as well as activated mast cells and basophils. IL-4 is a factor of growth and differentiation for T-cells, particularly for cells of Th-2 subpopulation, and growth factor for mast cell, acting synergistically with IL-3 in stimulating the proliferation of these cells.

Interferon-gamma, also called immune interferon or type II is produced by células T CD4+ aand activated CD8+ and by NK cells. IFN is a potent activator of mononuclear phagocytes. Indirectly induces the synthesis of enzymes that mediate the respiratory effort, allowing human macrophages kill phagocytosed microbes, it is the main activating factor of Macrophage.

Among many functions performed by IFN-γ, we know that amplify the recognition phase of immune response by promoting the activation of T CD4+ helper cells restricted to Class II, promotes the differentiation of T lymphocytes and stimulates the cytolytic activity of NK cells.

The immune system cells (eg. T-cells and monocytes) synthesize mainly TGF-β1. Both the T-cells activated by antigens such as mononuclear phagocytes activated by LPS, secrete biologically active TGF-β1.

TGF-β inhibits the growth of many cell types and stimulates others. Many times, it may inhibit or stimulate the growth of the same cell type. As a cytokine, TGF-β is potentially important because it antagonizes many lymphocyte responses [32].

6.1. Cytokines of the Tuberculoid Type

In tuberculoid leprosy, displays manifestations related to exacerbation of the immune response that leads to granuloma formation well defined, limiting injuries and tendencies for the complete destruction of the bacilli.

Many laboratories have analyzed cytokines produced by T-cells of tuberculous patients and healthy individuals exposed, *i.e.* for those with cellular immunity to *M. leprae*.

A consistent finding is that the T-cells reactivated from M. leprae from tuberculous patients are predominantly Th-1 phenotype. They produce high levels of IFN-γ and reduced or non-detectable levels of IL-4 [33].

Gilka Kaplin [13], 1989, injected type cytokines IFN-γ and IL-2 in lepromatous lesions and observed evident signs and significant increase in degradation of *M. leprae*, suggesting a possible association among the Th-1 cytokines and bacterial elimination.

6.2. Cytokines in Tuberculoid Type

The lepromatous type is characterized by a deficiency in its imunecelular response, excessive bacillary multiplication and dissemination of bacilli to the viscera and nervous tissue.

The results are still not so evident on the release of cytokines by T-cells in this type of leprosy. The question of whether cytokines are involved in non-responsiveness in lepromatous is important and should be examined.

Some researchers [23] studied cytokine patterns in situ lesions through PCR test in and found that in lepromatous lesions for mRNAs, Th-2 cytokine were enriched by IL-4, IL-5 and IL-10, whereas IFN-γ and IL-12 were absent.

Padmini Salgami [34] studied the production of cytokines by T-cells in lepromatous leprosy, as well as Tuna Mutis [35] and many other researchers, saying that there may be other sources which originated T-cells, the mechanisms of non-responsiveness, and perhaps other unknown variables that may give rise to differences observed in relation to the role of certain cytokines studied.

6.3. Correlation among Cytokines and Clinical Manifestations

In addition to the clinical features, lepromatous leprosy patients presented during a specific treatment, lepra reactions, erythematous nodules, fever, asthenia, arthralgia and other typical findings of acute inflammatory reaction [36].

The reaction type 2—ENH—common in HIV is an acute inflammatory reaction, systemic, involving the formation of immune complexes that circulate in the peripheral blood and shows its most frequent clinical manifestation on erythema nodosum leprosum. It affects multibacillary patients, becoming worse when related to leprosy, being responsible for considerable morbidity, particularly erythema nodosum recurrent. The pathology of ENL involves deposition of immune complexes and change in cell-mediated immune response. The episode of ENL is triggered by the deposition of immune complexes in tissues [37].

There is an increase in TNF-α which is associated with destruction of *M. leprae*, granuloma formation, elevated C-reactive protein (CRP), stimulation of acute inflamematory reaction, and is involved in defense, in macrophage activity, and the reaction of ENL, compromising the patient's general condition (FOSS, 1993).

In an acute inflammatory response occurs an increase in IL-1, IL-6 and TNF-α, where IL-1 and IL-6 will act on the hepatocyte stimulating the production of proteins of acute inflammation. Levels of IL-1 and TNF-α increase in HT and DT, and decrease in HD and DV patients [1]. It was also observed an increase of IL-4 in lepromatous

patients. In bacillary forms there was an increase in the concentration of antibody anti-PGL1 [30] being associated with increased IL-4 and decreased IL-1 and TNF-α.

It was also observed that during the MDT decreased in IL-4 and anti-PGL1 (flow bacillar) and increase in TNF-α. Immunological changes assessed in peripheral blood, or supernatants culture compared to immunohistochemical results showed that in patients DV and VV increased TGF-β1 and CD8+ cells in the infiltrate and the absence of TGF-β1 and increase of CD4+ cells in patients with TD and TT.

6.4. Reactional States

Perhaps the biggest problem in handling and controlling leprosy is the occurrence of leprosy reactions. The immune-cellular responses have been questioned regarding to be involved in pathogenesis of reverse reactions [38]. Robert Modlin [39] analyzed the cytokine patterns in lesions type 1 and type 2, and basically, found that the signs of cytokines, similar the type Th-1, tended to predominate in reverse reactions, whereas those of type Th-2 were exacerbated in erythema nodosum leprosum.

Kaplan Gilda shows that TNF-α and IL-6 increases a lot in ENL patients [35]. However, according to Ottenhoff [38], the immunopathology of the reactions type 1 and type 2 is associated with many different cytokine patterns.

According to Ottenhoff studies [38], cytokines Th-1 inhibit Th-2, and vice versa. Due to cytokines are important regulators, they can provide a new form of immunotherapy for leprosy reactions.

The reactional episodes are acute intercurrences that may occur in leprosy, as manifestations of the patient's immune system [40] and can be of two types. Reaction Type 1, also called Reverse, more frequent in HD and HT, which is characterized by erythema and edema of the lesions and/or thickening of the nerves (neuritis). And the reaction type 2, or ENL, where the most affected patients are lepromatous. They have painful erythematous nodes anywhere in the body. It can progress to neuritis.

The reaction type 2 is of humoral hypersensitivity and occurs in DV and VV. It can occur in treatment-naïve patients, but usually occurs during treatment or after leaving the hospital [31].

In the reaction type 2 occurs: increase in the level of PCR; increase ROI (reactive intermediate of oxygen) andcytokines TNF-α, IFN-γ, IL-1, IL-5 and anti-PGL-1, and IL-4 and TGF-β are reduced [4].

The Ministry of Health [41] calls attention to a very important issue related to immune response in lepromatous leprosy, because it was found that patients with this type of leprosy had an extremely small amount of T-cells responsible for production and generation of anti-*Mycobacterium leprae* clones. This change is not yet completely understood, but it is believed that there is a malfunction in the mechanism of presentation of *Mycobacterium leprae* to lymphocytes or even the absence of lymphocytes reactive to the bacillus.

7. Final Comments

Besides the epidemiological differences and knowledge still precarious, particularly on the parasite-host relationship, particularly when the generation of oral manifestations, the information presented enable you to view operational problems that reveal the need for more engagement of situations in the implementation of strategic actions provided in the Pact for Life, PAVS and PAC-More Health, to improve the integral attention to people with leprosy, or consequences of the disease [3].

The National Program to Combat Leprosy in Brazil was developed in response to the commitment of the country to eliminate the disease as a public health problem, as explained by the Ministry of Health [6]. The program is outlined in three fundamental points: the updating of data from monitoring of patients for reliable interpretation of the magnitude of the problem in Brazil, the idea that reducing the prevalence rate and interrupt the chain of transmission of the disease depends on early diagnosis and treatment MDT standard and that the reduction of social carrying depends on early detection and assessment of physical disability, and treatment of disabilities already.

The campaign to combat leprosy is from the federal government provides equipping Brazilians with as much information so they can be active in prevention. The sooner the disease is identified, the less likely consequences. Every year, Brazil has 47,000 new cases of the disease. In the first half of this year were registered 201 cases in Salvador, less than the number recorded in the same [6].

"Leprosy is still a public health problem in the country, but a new survey by the Ministry of Health reveals a reduction of 27.5% in total new cases between 2003 and 2009, going from 51,941 to 37,610. In the same period, the number of services to patients in treatment increased by 45.9%. Between days 25 and 31 January, the ministry conveys the media campaign "Health is Good to Know", with the focus on disease. The aim is to encourage the population to find units that makes the diagnosis and treatment. The sooner you identify leprosy, the lower the chances of sequelae" [21].

"Despite the significant reduction in the prevalence coefficient of leprosy in Bahia, which currently is 1.9 cases/10 thousand inhabitants, the state demands intensified action to eliminate the disease, justified by a standard medium endemicity according to the parameters of prevalence" [2].

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