Indian J Lepr 2017, 89 : 139-150

http://www.ijl.org.in

Original Article

Study of Serum Interleukin-17 and Interleukin-4 Levels in South Indian Leprosy Patients across Clinico-Histopathological Spectrum

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Received : 05.02.2017 Accepted : 21.06.2017

Leprosy is a chronic granulomatous disorder of the skin and peripheral nervous system caused by *Mycobacterium leprae*. Tuberculoid leprosy (TT) has predominance of CD4+T cells and lepromatous leprosy (LL) of CD8+ and type 2 cytokines. In this study, clinico-histopathological profile of leprosy has been analyzed and correlated with serum Interleukin-17 and interleukin-4 levels. Thirty newly diagnosed leprosy cases fulfilling the inclusion criteria and thirty healthy controls constituted the study carried out over a period of one and half years. Clinical assessment, slit skin smear (SSS) and skin biopsy were done and classified according to Ridley Jopling. Serum IL-17 and IL-4 were estimated by ELISA. Among 30 cases, most were of 41-50 years (43.3%). Twelve (40%) were borderline leprosy who constituted majority. Four cases were in Type 1 reaction (T1R) and three in Type 2 reaction (T2R). Clinico-histopathological correlation was 100% TT/LL poles of spectrum, it varied in borderline leprosy. Serum IL-17 was significantly lower in leprosy cases (Mean = 3.8969 pg/mL), compared to controls (P = 0.001). Serum IL-4 was elevated in cases (Mean = 37.8346 = pg/mL) than controls (Mean = 6.1693 pg/mL) (P = 0.001), highest level being LL patients (Mean = 48.3403 pg/mL). Serum IL-4 had the highest level in type 2 reactions (T2R) (Mean = 48.5563 pg/ml) (P = 0.269). Defective secretion of IL-17 appears to correlate with disease acquisition and progression towards lepromatous pole. Overproduction of IL-4 in patients with lepromatous leprosy may predisposeto development of ENL. Further studies are required on a larger representative numbers to for better and definitive role of these cytokines in leprosy.

Key words : Leprosy, Interleukin-17, Interleukin-4

Introduction

Leprosy is a chronic granulomatous disorder chiefly involving the skin and peripheral nervous system caused by the organism *Mycobacterium leprae* (Prasad and Kaviarasan 2010). India achieved leprosy elimination as a public health

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problem in December 2005, however there are pockets of endemicity where the number of new case detection is still high (Evaluation NLEP Rajkot 2013-14). The prevalence rate of leprosy in India was 0.68 per 10,000 populations with 0.86 Lakh cases on record as on 1st April 2014 (de Souza et al 2016).

Leprosy is classified into paucibacillary (PB) and multibacillary (MB) types for treatment purposes (WHO 2017). However, for research and academic purposes using both clinical and histopathological features it is commonly classified into tuberculoid (TT), borderline tuberculoid (BT), midborderline (BB), borderline lepromatous (BL), and lepromatous (LL) leprosy (Ridley and Jopling 1962). A pressing need for the containment of the disease is establishing predictive diagnostic and prognostic biomarkers for the infection and its complications (reactional states). There has been a surge of research concerning the immune response of the host; it has focused on enlightening the immune patho-mechanisms with the hope that predictive diagnostic and prognostic parameters will emerge (de Souza et al 2016). CD4+T cells are the dominant players of both the induction and the effector phases of the immune response. On antigen engagement by their T-cell receptors (TCRs), they can differentiate into Th1 cells, secreting interleukins 2 (IL-2) and interferon (INF-) and resulting in macrophage activation; and Th2 cells secreting IL-4, IL-5, and IL-13, which stimulates the production of antibodies and inhibits macrophage activation; or Th17 cells that produce IL-17 and IL-22 are involved in inflammation and auto immunity (Lipscomb and Masten 2002). TT is characterized by predominance of CD4+ T cells and LL has predominance of CD8+ and type 2 cytokines. The borderline forms are known to be more prone for reactions (type 1), with predominant type 1 cytokines (Abdallah et al 2013). Hence there are significant immunopathological interactions between type 1 and type 2 cytokines in leprosy. T cells were shown to produce cytokines which couldn't be classified into Th1-Th2 scheme of which Interleukin (IL)-17 is one among them (Harrington et al 2005). Cell-mediated (Th1) immune response and humoral (Th2) immune response play different roles in leprosy infection and Interleukin 4 (IL-4) is a typical Th2 cytokine which is a critical mediator of the Th1/Th2 balance (Yang et al 2011). A regulated expression of CD209 on Schwann cells by the local cytokine environment can facilitate infection by *M. leprae*, perhaps leading to subsequent tissue injury. IL-4 has also been found to induce CD209 on macrophages, providing a common mechanism by which macrophages and Schwann cells can bind to and take up mycobacteria (Relloso et al 2002).

Considering this background, we have carried out this study to evaluate serum levels of IL-17 and IL-4 in untreated leprosy patients, compared to healthy controls so as to better comprehend the role of these cytokines in the immunopathogenesis of leprosy.

Materials and Methods

Thirty new clinically diagnosed and confirmed cases of leprosy after Slit skin smear and skin biopsy attending the outpatient department were studied. This was done over a period of one year & eight months, from October 2014 to June 2016. They were profiled according to Ridley Jopling classification. Patients on systemic steroids / immunomodulators, pregnant & lactating women, those on anti-leprosy medications and patients with other inflammatory diseases like psoriasis, rheumatoid arthritis, atopic dermatitis and contact dermatitis were excluded from the study. The study was approved by Institutional Ethical Committee.

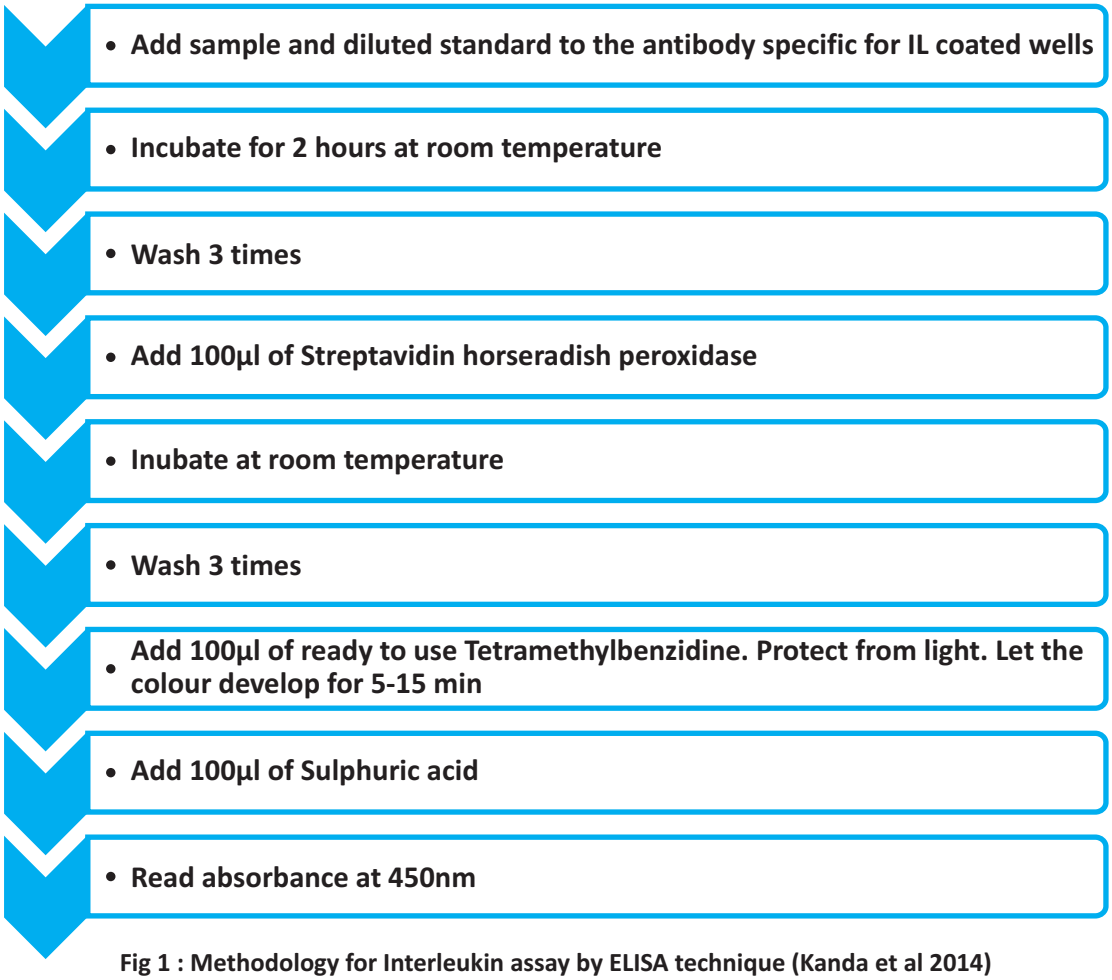

Fig 1 : Methodology for Interleukin assay by ELISA technique (Kanda et al 2014)

For comparing cytokine levels, 30 age and sex matched healthy controls were included. 5ml of venous blood was collected from the cases and controls, centrifuged and then serum was analysed as described by Kanda et al (2014) (Fig 1) for serum IL-4 and IL-17 by Diaclone Human ELISA kit (Diaclone SAS, France).

Statistical analysis was done by Chi-square test, one way ANOVA, T test-independent samples, Cramer's V test were carried out through the SPSS for Windows (version 20.0).P value less than 0.05 is significant.

Results

Out of the 30 cases, 18 (60%) were male and 12 (40%) were female among which majority (43.3%) were of the age group 41-50 years. After clinical assessment, the cases were subdivided of which 7 (23.3%) were tuberculoid leprosy (Fig 2), 12 (40%) borderline tuberculoid leprosy (BT,BB,BL) (Fig 3, Fig 4), 10 (33.3%) lepromatous leprosy and 1 (3.3%) Indeterminate leprosy. Majority were of the borderline spectrum. Four had type 1 reaction while three cases were in type 2 reaction. The slit skin smear (SSS) was negative in 7TT cases, 10

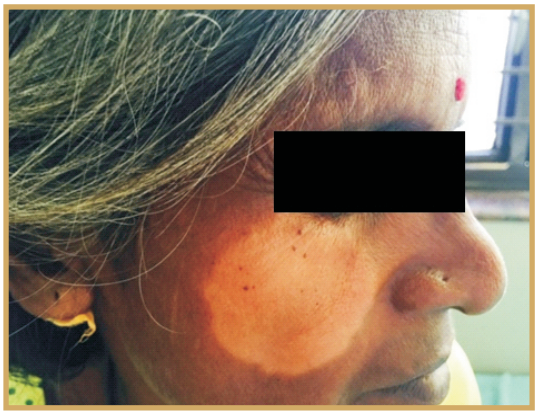

Fig 2 : Tuberculoid leprosy with a well defined hypopigmented patch over the right cheek

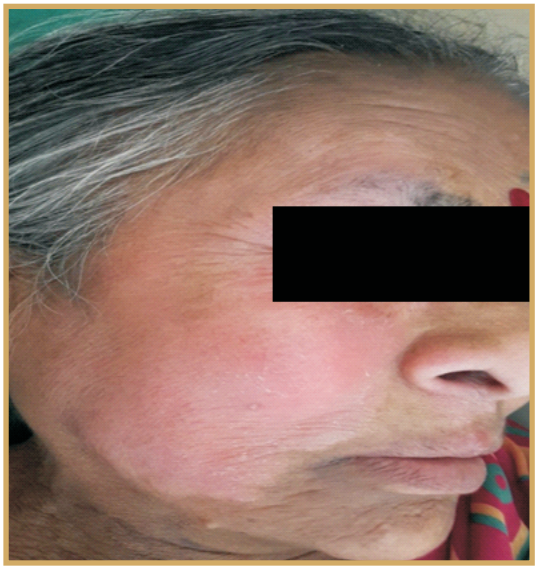

Fig 3 : Borderline tuberculoid leprosy with type 1 reaction presented with odema and erythema of the preexisting patch over right

cases showed BI 1+, others had 2 to 4+ BI (Table 1). Fifteen cases showed an MI of 21-80% (Table 2).

Clinico-histopathological correlation (Fig 5, Fig 6) showed variable findings in cases across the spectrum of leprosy. Concordance was 100% in TT, LL, BB but there was discordance in some BT and BL cases (Table 3).

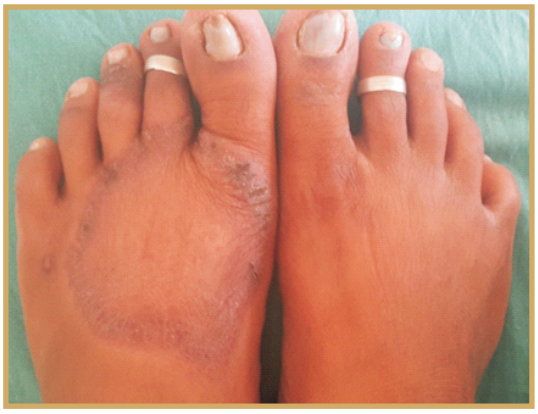

Fig 4 : Borderline tuberculoid leprosy with an asymmetrical plaque

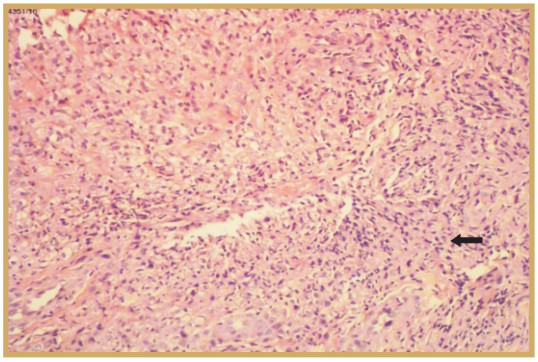

Fig 5 : Hematoxin and eosin stain (100x) Lepromatous leprosy showing extensive cellular infiltrate (Black arrow) and sheets of macrophages in the dermis

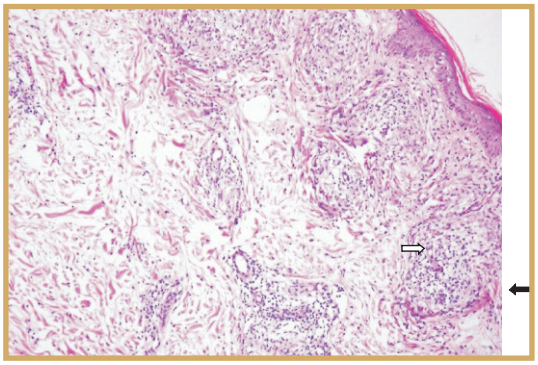

Fig 6 : Hematoxin and eosin stain (100x) Type 1 reaction showing intercellular edema (white arrow) and granulomas (Black arrow) in case diagnosed as Borderline Tuberculoid leprosy.

Table 1 : Bacteriological index (BI) of cases included in the study

Bacteriological index	Frequency	Percentage (%)
No AFB	7	23.3
1+	10	33.3
2+	8	26.7
3+	3	10
4+	2	6.7
Total	30	100.0

Table 2 : Morphological index of bacilli in slit skin smears

Morphological index	Frequency	Percentage (%)
No AFB	7	23.3
1-20%	5	16.7
21-40%	6	20
41-60%	4	13.3
61-80%	5	16.7
81-100%	3	10
Total	30	100.0

Table 3 : Comparison of Clinico-histopathological classification of cases included in the study

Clinico-Histopathological Crosstabulation									
			Histopathology						Total=30
			TT	BT	BB	BL	LL	I	
Clinical diagnosis	TT	Count	7	0	0	0	0	0	7
		% within HPE	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
	BT	Count	0	5/6	1/6	0	0	0	6
		% within HPE	0.0%	83.3%	16.6%	0.0%	0.0%	0.0%	
	BB	Count	0	0	2/2	0	0	0	2
		% within HPE	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	
	BL	Count	0	0	1/4	¾	0	0	4
		% within HPE	0.0%	0.0%	25.0%	75.0%	0.0%	0.0%	
	LL	Count	0	0	0	0	10/10	0	10
		% within HPE	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%	
	I	Count	0	0	0	0	0	1	1
		% within HPE	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	
Total		**Count**	**7**	**5**	**4**	**3**	**10**	**1**	**30**

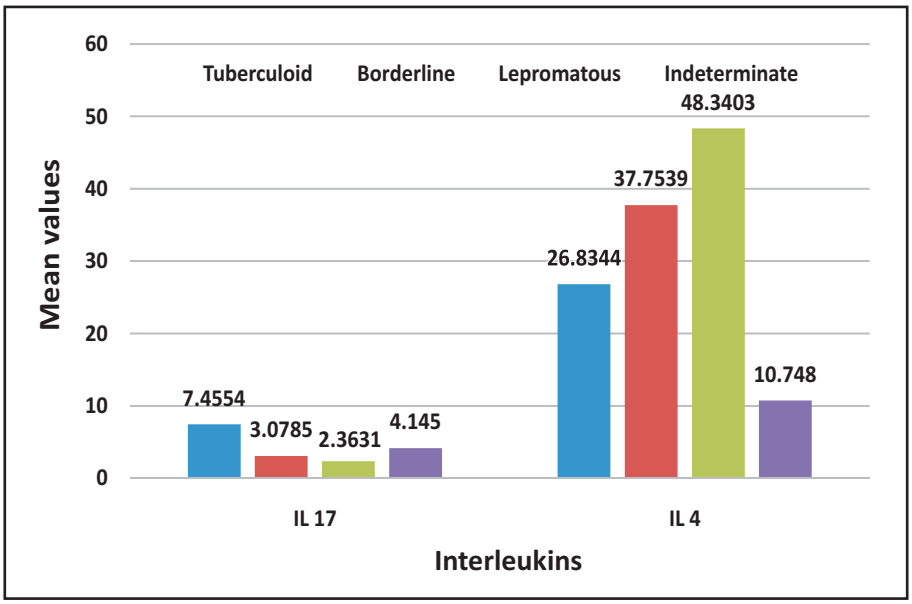

Fig 7 : Interleukin levels in leprosy cases included in the study

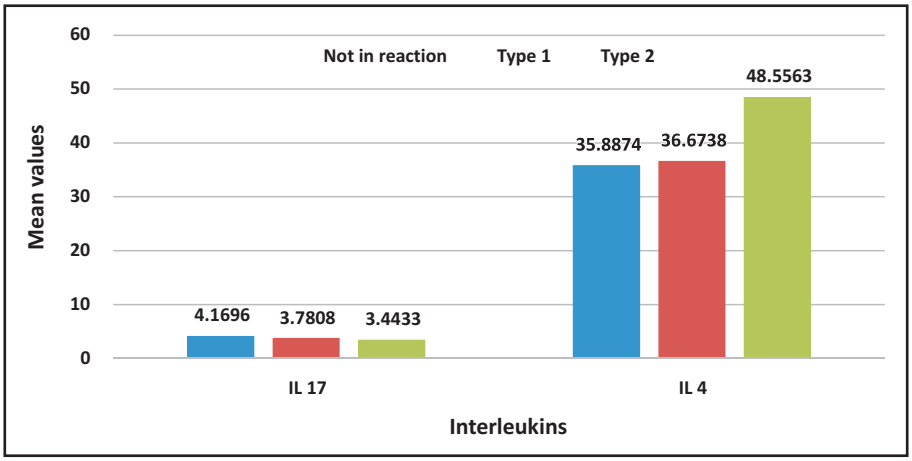

Fig 8 : Interleukin levels in in leprosy cases in reactions

Table 4 : IL levels in leprosy cases and controls

Interleukins	Group	Number	Mean (pg/ml)	Std. Deviation
IL- 17	Cases	30	3.8969	2.35135
	Controls	30	34.4736	20.08977
IL- 4	Cases	30	37.8346	11.91886
	Controls	30	6.1693	3.35330

Table 5 : IL 17 and IL 4 levels in leprosy cases across the spectrum

Interleukins	Type of leprosy	Number	Mean (pg/ml)	Std. Deviation	F value	P value
1L- 17	Tuberculoid	7	7.4554	1.11005	26.012	0.001
	Borderline	12	3.0785	1.05545		
	Lepromatous	10	2.3631	1.50641		
	Indeterminate	1	4.1450	–		
	Total	**30**	**3.8969**	**2.35135**		
1L-4	Tuberculoid	7	26.8344	11.79755	16.210	0.001
	Borderline	12	37.7539	6.26149		
	Lepromatous	10	48.3403	4.33170		
	Indeterminate	1	10.7480	–		
	Total	**30**	**37.8346**	**11.91886**		

Table 6 : IL 17 and IL 4 levels in leprosy cases with and without reactions

Interleukins	Reaction status	Number	Mean	Std. Deviation	F value	P value
IL-17	Not in reaction	23	4.1696	2.43483	0.132	0.877
	Type 1	4	3.7808	3.00623		
	Type 2	3	3.4433	2.49078		
	Total	**30**	**4.0313**	**2.43240**		
Il-4	Not in reaction	23	35.8874	13.56918	1.388	0.269
	Type 1	4	36.6738	4.79206		
	Type 2	3	48.5563	6.12617		
	Total	**30**	**37.4115**	**12.50160**		

Serum IL-17 was significantly lower in cases (Table 4) (Mean = 3.8969 pg/mL), compared to controls (Mean = 34.4736 pg/mL) (P = 0.001) and the lowest level in lepromatous leprosy (mean = 2.3631 pg/mL) (Table 5). Serum IL-4 was significantly higher in cases (Table 4) (Mean = 37.8346 pg/mL) compared to controls (Mean = 6.1693 pg/mL) (P = 0.001), with the highest level being lepromatous leprosy cases. (Table 5) (Mean = 48.3403 pg/mL) (Fig 7) Serum IL-17 showed no significant differences in reactional states (Table 6) while serum IL-4 levels were highest in Type 2 reaction (Mean = 48.5563 pg/ml) (P = 0.269). (Fig 8)

Discussion

A total of 30 newly diagnosed leprosy cases were evaluated. Parameters like age, sex, duration of the disease were comparable with other studies in the country (Sehgal et al 1982). The male to female ratio was 3:2 which coincides with a study which showed male preponderance (Rao 2006). An increase in their number may be due to cultural and sociological changes, which generate greater exposure for men. After clinical examination, SSS and biopsy of 30 cases, they were classified as indeterminate leprosy, tuberculoid, borderline (BT+BB+BL) and lepromatous leprosy.

Negative slit skin smear (SSS) values correlated with clinical diagnosis in 7 cases of tuberculoid leprosy. In others BI ranged from 1 to 4+ (Table 1). MI in 15/23 (68%) of smear positive cases ranged from 41-80% (Table 2). This shows higher than usually reported bacteriological positivity in the cases included in our study and thus would limit the scope of extrapolation and generalization of findings of this study.

In our study clinico-histopathological correlation was 100% TT and LL leprosy, it varied in borderline leprosy (Table 3). Moorthy et al (2001) in a histopathological correlation study on 372 leprosy patients using Ridley Jopling classification showed 62% correlation.

The immunopathology of leprosy is primarily due to immune interaction between subsets of T-cells, antigen presenting cells and *Mycobacterium leprae* antigens. Such interactions produce type 1/type2 cytokines (Reja et al 2013). These cytokines communicates signals between immune response and tissue damage (Manandhar et al 2002). During the chronic course of leprosy, sudden increase in immune activity may occur which are called reactions. They are type I (reversal reaction, RR) due to acute increase in cell mediated response, or type II (erythema nodosum leprosum, ENL), described as an immune mediated disease (Murr et al 2002) with respect to T-cell cytokine response in leprosy, it was demonstrated that *Mycobacterium leprae* responsive T-cell clones from RR lesions were polarized to a type 1-like cytokine profile (Naafs 2000). Similarly peripheral blood mononuclear cells (PBMC) from ENL patients also displayed a type 1 cytokine secretion profile (Faber et al 2004). These approaches have been useful in understanding the immunopathology of the different disease states of leprosy. However, they are difficult for routine monitoring of clinical states of patients and in aiding diagnosis (Verhagen et al 1998). Research has focused on the association of differential cytokine profiles with the spectral pathology; however, results from such studies have been varied and conflicting, and in retrospect, it is difficult to associate distinct cytokine patterns with different spectral forms of leprosy or its reactions (Moubasher et al 1998). IFN- and TNF were elevated in TT compared with LL patients with a significant negative correlation with bacillary index (Salgame et al 1991). With *in vitro* stimulation with *M. leprae* or its antigens, a vast majority of the T cells recruited in TT are CD4+ with Th1 phenotype producing IFN- , IL-2, and TNF but little or no IL-4, IL-5, and IL-6, (Haanen et al 1991, Mutis et al 1993 and Yamamura et al 1991) furthermore, *in vivo* analyses evidenced mRNA for IFN- , IL-2, lymphotoxin, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (Lockwood 2005). LL patients, on the other hand, had higher serum levels of IL-10 and IL-1 13 compared with TT patients (Haanen et al 1991). *In vivo* studies have found predominance of IL-4, IL-5, and IL-10 in LL lesions previously (Miossec et al 2009) and also a positive correlation between IL-10 levels and bacillary index (Haanen et al 1991).

In our study, serum IL-4 was found to be elevated in cases compared to controls with the highest level among lepromatous leprosy patients and Type 2 reaction and the lowest in borderline leprosy. The hypothesis is that the spectrum of leprosy reflects the balance between Th1 and Th2 populations is indeed exciting. In TT, there is good evidence of predominant IL-2 and IFN- production, while LL patients have mainly cytokines of a Th2 type, including IL-4 (Rojas

et al 1997). Type 1 Reaction is associated with an overproduction of Th1-type cytokines (Sarno et al 1991). Since Th1 and Th2 cells can cross-regulate one another; IFN- directly suppresses IL-4 secretion and Th2 polarization, (Lockwood 2005) which is evident in type 1 RL. On the contrary, type 2 reactions occur in patients with poor CMI to *M. leprae*, abundant bacilli, and a strong polyclonal antibody response. In addition, increased IL-8 and IL-10, and sustained expression of IL-4 and IL-5; all cytokines associated with neutrophil chemotaxis and antibody production were observed in ENL lesions (Sarno et al 1991). However, there is also evidence of enhanced production of TNFα and IL-6, and increased circulating IL-2 receptors in acute ENL episodes causing nerve destruction (Rojas et al 1997). Since IL-4 inhibits CMI responses and favors humoral immunity, IL-4 might contribute to high antibody levels and unrestricted replication of bacilli in such patients. Studying this cytokine profile in both sera and tissues of larger leprosy population is recommended to clarify these points. Surprisingly, our TT patients had elevated IL-4 compared to controls. This discrepancy may be due to the difference between lesional and circulating cytokine profile, particularly toward the tuberculoid pole, the well-known of localized neurocutaneous disease, rather than being systemic disease, for further investigations.

Th17 cells produce IL-17 and IL-22 which are involved in inflammation and auto immunity (Davey and Rees 1974). Serum IL-17 was significantly lower in leprosy cases compared to controls and the lowest levels were observed in lepromatous leprosy. There showed no significant differences in reactional states. Another study by Abdalla et al (2013) has also reported lower IL-17 in leprosy cases than controls with lowest being in lepromatous pole. Th17 mechanism of induction and their effector function is nowadays the focus of important studies in immunology (Lim et al 2010). Studies on infection models, described significant role of IL-17 level in mycobacterial infections, namely *M. tuberculosis* (Wozniak et al 2010). Susceptibility to pulmonary *M. avium* - intra cellulare complex may be associated with biases in Th1/Th2/Th17 immunity (Khader and Cooper 2008). Moreover, Th17 cells can provide interferon IFN- independent protection against *M. tuberculosis* (Novoa et al 2011). In accordance, in patients with tuberculosis disease, IL-17 was not detected in bronchoalveolar lavage fluid, which may be due to suppression by Th1 cytokines, including IFN- (Park et al 2005). Thus, Th1 and Th17 responses cross-regulate each other during mycobacterial infection (Park et al 2005). Another infection with similar pathology is leishmaniasis. The weak type 1 immune response observed in *L. braziliensis* infection may be mediated by poor innate immune response with impaired IL-17 (Yamamura et al 1992). Therefore, it is speculated that such an inherent deficiency can also contribute to the development of leprosy and even to disease progression toward the lepromatous pole.

The Egyptian study which assessed both IL-4 and IL-17 showed similar results. The only difference in our study was a slightly higher value of IL-4 in ENL unlike theirs where the IL-4 was higher in LL than in ENL (Abdulla et al 2013). This explains how universal immunolopathology of leprosy is across the globe. Studies to assess the validity of measuring serum cytokines for diagnosing and monitoring the leprosy spectrum and reactions have presented contradictory results with respect to the predominant cytokines involved. This may be due to the different assay conditions, samples,

and populations examined (Rane et al 2011). Since IL-17 is related to protective mechanisms against disease progression, while IL-4 could be related to disease progression, with Th2 activation; further, follow up studies on larger number of patients can obviate a significant negative correlation between them.

Conclusion

There is a good clinico-histopathological correlation in the entire spectrum except some cases of borderline spectrum. Defective secretion of IL-17 observed in the present study can be related to disease acquisition as well as progression toward lepromatous pole in leprosy patients. The overproduction of IL-4 in patients with lepromatous leprosy increases the liability to develop ENL. Since ENL management is a difficult issue, IL-4 may be investigated further to predict the reactional state in leprosy. The role of IL-17 in leprosy isn't clear and has not been studied extensively. This indicates infection may be acquired by poor innate immune response with impaired IL-17. While the findings of present study are interesting and would be useful in planning more studies, further research in leprosy on inherent deficiency of interleukin-17 is required to help in the better understanding of the immunopathology of leprosy.

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How to cite this article : Poovamma AS, Ashwini PK, Veeranna S and Jayadev B (2017). Study of Serum Interleukin-17 and Interleukin-4 Levels in South Indian Leprosy Patients across Clinico-Histopathological Spectrum. *Indian J Lepr.* **89** : 139-150.