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Chronic Immune Response Hypothesis for Chronic Fatigue Syndrome: Experimental Results and Literature Overview

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1. Introduction

Chronic fatigue is characterized by severe disabling fatigue associated with physical, mental, and immunological disturbances. Chronic fatigue lasting for more than 6 months is known as chronic fatigue syndrome (CFS). This condition has been known for at least two centuries under the names "neurasthenia", "post-viral fatigue", "myalgic encephalomyelitis" or "chronic mononucleosis". The estimated worldwide prevalence of CFS is about 1% and this number can be under estimated due to mild character of the symptoms which can be explained by normal reasons. No physical examination signs are specific to CFS; no diagnostic tests identify this syndrome; no definitive treatment for it exists. Pathophysiology of CFS is analyzed from various points of view among which a relation to chronic infections or/and hypothalamic-pituitary adrenal (HPA) axis disturbances seem to be the most important ones. Up to now there are no convincing evidences found to support any of the proposed hypothesis trying to explain its pathogenesis. The current concept is that chronic fatigue condition is multi-factorial where an unidentified infective agent causes an aberrant ongoing immune response which fails to be switched-off [Lorusso L et al, 2009]. Here we put forward a new hypothesis that this "unidentified" infective agent is mycobacteria, and protective response controlling mycobacterial infection exhausts immunity and total reserves of body leading to chronic fatigue [Roth J et al, 2011].

CFS is a long-lasting condition. Among 265 patients with established CFS diagnosis studied by Tirelli U et al. [1994] many patients reported profound fatigue, lasting from 6 months to 10 years, among them 102 (38%) patients had to stop their working activities for a period of time ranging from 3 months to 2 years. CFS affects all racial-ethnic groups and more often females than males [Dinos S et al, 2009]. The prevalence of women is estimated from 6 to 1 [Capelli E et al, 2010] to no difference [Ravindran MK et al, 2011]. CFS is rarely found in childhood and adolescence however often affects young adults from 20 to 40 years old.

The diagnosis of CFS is based on clinical criteria and depends on exclusion of other physical and psychiatric diseases. Besides significant, unexplained fatigue lasting more than 6 months, at least 4 of 8-11 additional symptoms should be present: 4-5 of immunological nature such as sore throat or lymph nodes; joint or muscle pain; irritable bowel syndrome; and 4-6 neurological ones: headaches, problems with concentration or memory; dizziness, impaired co-ordination, sleep disturbances; post-exertional exhaustion [Sharpe MC et al, 1991].

2. A review of literature

2.1 Immunological findings

A possible involvement of the immune system is supported by the observation that the onset of CFS is often preceded by virus infections and a 'flu-like' illness. Among immune disfunctions the decrease either in number or functional activity of natural killer (NK) cells, especially in the number or activation status of CD56+ cells was found by many groups [Brenu EW et al, 2011; Fletcher MA, et al, 2010; Brenu EW et al, 2010; Mihaylova I. et al, 2007; Maher KJ et al, 2005, Nas K, 2011]. Lorusso L. at al [2009] reported an increased number of CD8+ cytotoxic T lymphocytes; CD38 and HLA-DR activation markers and a decrease in CD11b expression associated with an increased expression of CD28+ T subsets. The reduction in CD16+ and CD57+/CD56+ NK lymphocytes along with an expansion of CD8+/CD56+ and CD16-/CD56+ NK subsets were found in the CFS group by [Tirelli et al, 1994]. Other works also found an increase in CD8+ T-cell numbers [Robertson MJ et al, 2005] while Barker E et al [1994] found no significant differences in the absolute numbers of circulating total T cells (CD3+) and of total helper/inducer (CD4+) or suppressor/cytotoxic (CD8+) T cells.

Some papers report a post-vaccination or post-infection onset of CFS. Exogenous insults, such as Lyme disease, infectious mononucleosis, Epstein-Barr virus, enteroviruses, parvovirus, gastric and other infections, vaccinations, exposure to toxins, some stressful life events can lead to CFS [Devanur LD et al, 2006, Ortega-Hernandez OD et al., 2009]. However a working group of the Canadian Laboratory Center for Disease Control that examined the suspected association between CFS and vaccinations did not find relation of CFS to vaccination [Appel S at al, 2007].

2.2 Immune cells activation

Cell associated adhesion molecules and the level of their soluble forms can be used as activation markers. CD56+ NK cells from CFS subjects were found to express an increased amount of cell adhesion molecules CD11b, CD11c, CD54; and activation antigen CD38 [Tirelli et al, 1994]. CD4+ T lymphocytes from CFS patients displayed an increased expression of the intercellular adhesion molecule-1 (ICAM-1/CD54). The total number of circulating (CD19+) B lymphocytes was higher in CFS patients than in controls [Tirelli U et al, 1994].

Another marker of activation is the production of pro-inflammatory cytokines. Brenu EW et al have studied Th1 and Th2 cytokine profile of CD4+T cells. Compared to healthy individuals, CFS patients displayed significantly increased levels of IL-10, IFN-γ, and TNF-α [Brenu EW et al, 2010]. An alteration in cytokine profile was found by many other groups [Patarca R, 2001; Carlo-Stella N et al, 2006; Tomoda A et al, 2005].

2.3 Genomics of CFS

Starting from 2005, a microarray analysis was applied to determine gene expression profiles of CFS patients. The results published differ significantly between research groups [Kaushik N et al, 2005; Fang H et al, 2006; Carmel L et al, 2006; Frampton D et al, 2011]. For example, upregulated expression of ABCD4, PRKCL1, MRPL23, CD2BP2, GSN, NTE, POLR2G, PEX16, EIF2B4, EIF4G1, ANAPC11, PDCD2, KHSRP, BRMS1, and GABARAPL1 was found by Kaushik N et al [2005]. A completely different gene set (PTPRR, DEFB1, FLJ, HSFY1, EST, HPRT1, GUCA1B, CACNG2, ESR2, MOG, DFFA, ACBD6 and 12 others) was identified by

Fang H et al [2006]. The most recent publication attempted and failed to predict the diagnosis basing on genomic data [Frampton D et al, 2011]. Thus, genes involved in CFS still to be found more accurately. However, most authors conclude that genes responsible for immune cell activation and perturbation of neuronal and mitochondrial functions are involved.

2.4 Treatment of CFS patients

In recent decades, many therapies for CFS have been examined including: psychological "cognitive behaviour therapy", gradual physical exercise, pharmacological therapies, which included antibiotics and anti-depressant drugs [Avellaneda FA et al, 2009]. Mild improvements were found in adolescent groups after cognitive behaviour therapy [Smith M et al, 2003]. Other approached were not effective [Alegre de Miquel C et al, 2005; Vermeulen&Scholte, 2004; Staud R, 2007, Romani A et al, 2008]. We want to emphasize that antidepressant medication has been found to have no beneficial effect on improving the symptoms of CFS showing that CFS does not have a dominant psychological aetiology as it was considered for many years [Friedberg & Jason 2001, Chambers et al. 2006].

2.5 Chronic immune response hypothesis

It can be hypothesized that CFS, at least at its early stages and at least in some CFS patients, results from immune system exhaustion induced by an excessive immune response against widely spread pathogens such as *M.tuberculosis* or *Herpes virus*. *Mycobacterium tuberculosis* (MBT) is the most successful pathogen of mankind and remains a leading cause of death due to a bacterial pathogen. It is estimated that every third person on the planet is infected with MBT. Yet 90-95% of those who are infected with MBT remain otherwise healthy. These people are classified as "latently infected". Mouse studies have shown that susceptibility or resistance to tuberculosis (TB) depends on genetic factors [Kondratieva et al, 2010]. It is also the case for humans. Epidemiological evidence points to a major role of human genetic factors in the development of TB. Numerous genetic studies were conducted with variable results. Some HLA class II alleles and variants of the natural resistance-associated macrophage protein 1 (NRAMP1) gene are most likely involved [Abel&Casanova, 2010, Stein CM, 2011].

We hypothesize that human population can be divided on genetic basis into three TB groups: i) resistant; ii) susceptible; and iii) intermediate ones. The susceptible group in low pathogen environment is a reservoir from which active TB cases emerge (reactivation TB). Resistant group can control MBT without any signs of infection or immune system activation. While the last one – intermediate group, is resistant to TB for the expanse of immune system exhaust leading to chronic fatigue as one possibility. Rheumatoid arthritis is a disease where cross reactivity to MBT and self heat shock proteins is considered as one of disease onset mechanisms [Adebajo AO et al, 1995]. The risk of tuberculosis is increased 2- to 10-fold in RA patients [Baronnet L et al, 2011]. Cases of joint/bone tuberculosis are reported [Yagi O et al, 2007]. Among pulmonary TB patients 72% show severe to moderate level of anxiety and depression according to Hospital Anxiety and Depression Scale (HADS) [Aamir&Aisha, 2010]. Sore throat or laryngopharyngitis can also be found in TB [Raza&Rahat, 2010; Huon et al, 2009]. The coincidence of major CFS signs and TB infection can be continued.

2.6 Biomarkers predictive of susceptibility and resistance to TB

Recently whole-blood microarray gene expression analyses were performed in TB patients and in latently as well as uninfected healthy controls to define biomarkers predictive of

susceptibility and resistance [Maertzdorf J et al. 2011]. Fc gamma receptor 1B was identified as the most differentially expressed gene, and, in combination with four other markers, produced a high degree of accuracy in discriminating TB patients and latently infected donors. Elevated expression of innate immune-related genes in active TB and higher expression of particular gene clusters involved in apoptosis and natural killer cell activity in latently infected donors are likely to be the major distinctive factors determining failure or success in controlling TB. As it was shown above, a decrease in NK cell numbers or their functional activity is the major immune disturbances found in CFS patients. Could it be a connection to TB?

3. Experimental data

3.1 Methods

3.1.1 Individuals

We have collected retrospectively cases of 14 individuals who came as donors among other volunteers who took part in different clinical trials hold by our laboratory during 2003-2008 [Popova I et al, 2008; Svirshchevskaya E et al, 2008; Ertneeva I et al, 2008; Skripkina P et al, 2008]. These 14 patients were selected on the basis of their deviated immune status. They were asked to fill in two questionnaires: Multidimensional Fatigue Inventory (MFI) and Zung depression scale [Smets EM et al, 1995; Zung, 1971]. For comparison the questionnaires were also filled in by 18 donors with normal parameters of immune cells. MFI and Zung scores demonstrated an increased level of depression and fatigue in 10 out of 14 persons with deviated immune status. The rest 4 had immunodeficiency and chronic infections. All 14 were suggested to take part in a trial aimed to verify our hypothesis. Each patient signed the voluntary consent to take part in the trial. Immunological data of healthy donors were used as a control.

3.1.2 Flow cytometry analysis for surface markers

Peripheral blood lymphocytes (PBL) were isolated on density gradient and washed three times in phosphate buffered saline (PBS). For the fluorescence-activated cell sorter (FACS) analysis cells were transferred to FACS buffer (PBS, 1% bovine serum albumin, 0.05% NaN_3). Three-color flow cytometry was performed using FACScan instrument, CellQuest software (BD Biosciences) and the following antibodies: CD3-PE, CD19-FITC, CD4-FITC, CD8-PE, CD16-FITC, CD56-PE, HLA-DR-FITC (all from Sorbent, Moscow). Live events (5,000–10,000) were acquired with propidium iodide exclusion of dead cells.

3.1.3 Treatment

Volunteers with signs of chronic fatigue were suggested the treatment with isoniazid, 300 mg per day during 30 days. Immune status was estimated before and after treatment at days 0, 30, and 90.

4. Results

4.1 Abnormal immune status in some healthy volunteers

PBL were collected from 102 volunteers involved in 4 clinical trials (antiviral drug Panavir, itraconazole generic Rumicoz, topic steroid cream Akriderm, anti-histamine generic Klarotadin) conducted in our laboratory during 2003-2008. Invited volunteers were medical

students, health workers, graduate and Ph.D. students, friends and colleagues. Among them 8 persons took part in all four trials. So we were able to analyze the average parameters of immune cells for the whole population (Table 1) and variations with time for 8 persons (Fig.1). Among 8 volunteers 6 have normal CD4/CD8 ratio during all period of testing (Fig.1). Patient #5 showed a significant increase in this parameter while patient #8 demonstrated immunodeficiency at 3d and 4th testing. Patient #5, a young girl, suffered from seasonal allergy. Patient #8 was asymptomatic.

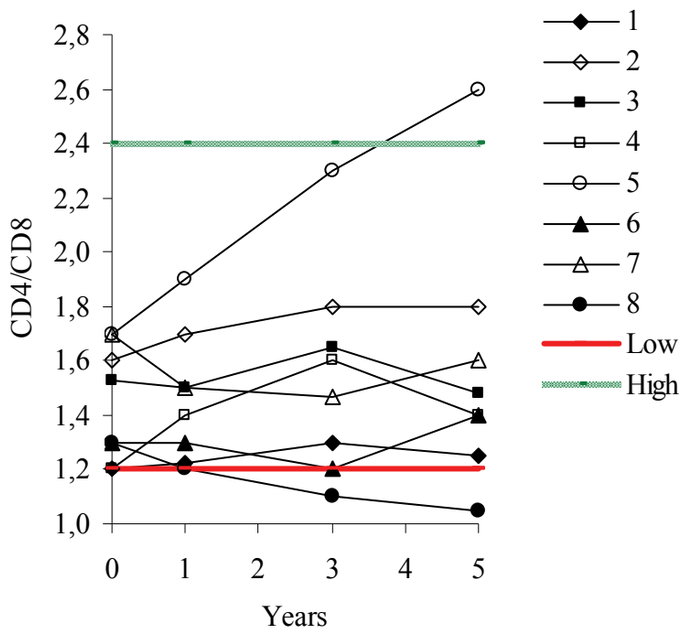


Fig. 1. Change in CD4/CD8 ratio in healthy volunteers with time. The percentage of CD4 and CD8 cells were estimated by cytofluorimetry. Normal range is shown as '"low-high" zone

CD	Trials				Average
	Panavir n=27	Rumicoz n=25	Akriderm n=28	Klarotadin n=22	n=102
CD3	72.5±7.2	70.8±5.2	75.1±4.3	74.3±8.2	**73.1**
CD4	39.0±5.3	37.6±8.1	38.3±5.8	39.2±7.3	**38.5**
CD8	23.9±4.9	25.1±6.2	29.3±4.6	26.3±5.4	**26.2**
CD16	12.2±4.5	10.6±4.6	12.9±3.5	12.8±6.6	**12.1**
CD56	14.5±5.5	11.3±5.5	13.1±5.6	10.0±4.3	**12.2**
CD19	9.0±6.2	7.5±3.2	10.1±5.3	8.7±6.3	**8.8**
HLA-DR	14.7±7.0	12.8±7.7	13.3±7.7	12.5±5.0	**13.3**
CD4/CD8	1.57±0.55	1.55±0.63	1.31±0.43	1.49±0.49	**1.47**
CD4/CD16	3.08±0.75	3.68±0.57	2.97±0.68	3.06±0.44	**3.18**
CD4/CD56	3.76±0.68	2.69±0.89	3.39±0.55	2.99±0.60	**3.15**

Table 1. Phenotype of lymphocytes in healthy donors

Among total group of donors we have found two types of immune deviations: decrease in CD4/CD8 ratios (≤1.2) or NK cell numbers (<5%) was found in 12 persons (12%) and a significant increase in CD4/CD8 (≥3) or NK numbers (>20%) was found in 11 volunteers (11%).

4.2 Clinical characteristics of fatigue group patients

All 23 individuals with deviated immune status were suggested to take part in the experimental trial. Fourteen persons agreed, while 9 refused. We asked 14 volunteers to fill in two questionnaires: Multidimensional Fatigue Inventory (MFI) and Zung depression scale. MFI estimates general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. Zung depression scale estimates the level of emotional depression. The summary of MFI for our patients varied from 15 to 35 with two cases 50 and 55. The summary of Zung scale was from 14 to 40. According to the work of Fang et al [2006] patients with MFI>54 and Zung scale >44 are considered as having CFS. With one exception all our patients cannot be classified as having CFS. Thus, we supposed that we worked with a group of patients with chronic fatigue induced by immune deviations. Most patients have various clinical symptoms shown in Table 2.

	Fatigue grade	Clinical symptoms	History of tuberculosis	Age
1	Severe, > 3 mo	none	10 year ago	52
2	Severe, > 12 mo	Prostatitis, herpes, sore throat, couth, phlegm	TB in family	24
3	Severe, > 5 mo	depression	none	24
4	Mild, > 3 mo	Sinusitis, pharyngitis, abnormalities with sleep	TB in family	47
5	Mild, > 6 mo	Depression, non refreshing sleep	none	55
6	Severe, > 12 mo	Depression, anxiety, non refreshing sleep, flu-like symptoms, often infections	none	56
7	Mild, > 3 mo	flu-like symptoms, often infections	none	22
8	Severe, > 12 mo	Depression, often infections, herpes	none	55
9	Mild or no	Reumathoid arthritis, hepatopathology, anxiety	25 years ago	67
10	Mild, > 6 mo	Depression, often infections, osteoarthrosis	none	52
11	Mild, > 12 mo	Lung inflammation	none	64
12	Mild, >12 mo	None	TB in family	53
13	Mild, > 3 mo	None	none	50
14	Mild, > 3 mo	Asthma	none	55

Table 2. Clinical characteristics of patients

4.3 Immunological characteristics of fatigue group patients

Blood from all patients was collected before the treatment and total numbers and percentages of T, B and NK subsets were analyzed. The results are shown in Tables 3-4. All these patients have different disturbances in immune parameters: either a deviation in CD4,

CD8 subsets or in CD16, CD56 cells. So, we divided the patients into two groups basing on CD4/CD8 ratio. Group 1 included patients with CD4/CD8≤1.2 and was designated "immunodeficiency group" (IDG) (Table 3). Group 2 included patients with ≥2.1 and was designated as "hyperstatus group" (HSG) (Table 4). We also included CD4/CD16 and CD4/CD56 ratios for comparison. Table 5 shows in the same way as Tables 3-4 summary from Table 1 for healthy controls. The statistical difference between IDG and HSG is significant for the CD4, CD8 percentage and their ratios only because we have selected patients using CD4/CD8 criteria for division. If we do the same using CD16 differences (low group <12, high group >12) we will also get significant difference, in this case for CD16, CD56 percentage and ratios (Tables 6 and 7).

	CD4	**CD8**	**CD16**	**CD56**	**CD4/CD8**	**CD4/CD16**	**CD4/CD56**
1	32	29	30	12	1.1	1.1	2.7
3	32	35	8.5	7.2	0.9	3.8	4.4
4	40	33	8.2	6.8	1.2	4.9	5.9
6	38	39	11	9.3	1.0	3.5	4.1
7	30	38	14	6.3	0.8	2.1	4.8
13	38	35	15	18	1.1	2.5	2.1
AV	**36**	**35**	**14**	**10**	**1.0**	**3.0**	**3.9**
SD	**4.2**	**3.4**	**7.4**	**4.2**	**0.2**	**1.2**	**1.3**

AV –Average meaning
SD – Standard deviation

Table 3. Immunological characteristics of fatigue patients with CD4/CD8 immunodeficiency

	CD4	**CD8**	**CD16**	**CD56**	**CD4/CD8**	**CD4/CD16**	**CD4/CD56**
2	38	18	28	6.1	2.1	1.4	6.2
5	61	20	16	18	3.1	3.8	3.4
8	58	12	8.0	5.9	4.8	7.3	9.8
9	65	8.9	11	4.1	7.4	5.9	16
10	58	10	18	16	5.8	3.2	3.6
11	40	12	10	14	3.3	4.0	2.9
12	61	23	4.4	5.3	2.7	14	12
14	38	11	6.9	5.1	3.5	5.5	7.5
AV	**52**	**14**	13	9,3	**4.1**	**5.6**	**7.6**
SD	**11.6**	**5.2**	**7.6**	**5.7**	**1.8**	**3.8**	**4.6**
t-test	**0.00**	**0.00**	0.34	0.37	**0.00**	**0.05**	**0.03**

t-test – probability estimated by Student' t-test between data shown in Tables 3 and 4.

Table 4. Immunological characteristics of fatigue patients with CD4/CD8 hyperstatus

There was no correlation between T and NK cell deviations. There results show that there are two non-related mechanisms of immune disturbances in these patients. Heterogeneity in

immune parameters of fatigue patients can at least partially explain why no significant difference in comparison with healthy subjects was found by previously published studies. As our patients cannot be diagnosed strictly as CFS patients, we may only hypothesize that either immune abnormalities in CFS patients are overseen or they can be less pronounced during disease progression.

	CD4	CD8	CD16	CD56	CD4/CD8	CD4/CD16	CD4/CD56
AV	39	26	12	12	1.47	3.18	3.15
SD	5.0	4.5	4.9	4.3	0.52	0.77	0.60

Table 5. Immunological pattern of the control group (n=102)

	CD4	CD8	CD16	CD56	CD4/CD8	CD4/CD16	CD4/CD56
3	32	35	8.5	7.2	0.9	3.8	4.4
4	40	33	8.2	6.8	1.2	4.9	5.9
6	38	39	11	9.3	1.0	3.5	4.1
8	58	12	8	5.9	4.8	7.3	9.8
9	65	8.8	11	4.1	7.4	5.9	15.9
12	61	23	4.4	5.3	2.7	13.9	11.5
14	38	11	6.9	5.1	3.5	5.5	7.5
AV	**47**	**23**	**8.3**	**6.2**	**3.1**	**6.4**	**8.4**
SD	**12**	**11**	**7.5**	**5.1**	**1.8**	**1.1**	**1.4**

Table 6. Immunological characteristics of fatigue patients with NK immunodeficiency

	CD4	CD8	CD16	CD56	CD4/CD8	CD4/CD16	CD4/CD56
1	32	29	30	12	1.1	1.1	2.7
2	38	18	28	6.1	2.1	1.4	6.2
5	61	20	16	18	3.1	3.8	3.4
7	30	38	14	6.3	0.8	2.1	4.8
11	40	12	10	14	3.3	4.0	2.9
10	58	10	18	16	5.8	3.2	3.6
13	38	35	15	18	1.1	2.5	2.1
AV	**43**	**25**	**20**	**13**	**2.3**	**2.4**	**3.8**
SD	**13**	**13**	**2.3**	**1.7**	**2.4**	**3.5**	**4.3**
t-test	0.30	0.31	**0.00**	**0.02**	0.26	**0.01**	**0.03**

t-test – probability estimated by Student' t-test between data shown in Tables 6 and 7.

Table 7. Immunological characteristics of fatigue patients with NK hyperstatus

4.4 Clinical effect of izoniazid treatment on fatigue

Three patients reported nausea during first 2-5 days. No other side effects of this treatment were reported. Among 14 patients one (#7) discontinued the treatment. All patients were asked to fill in again MFI and Zung questionnaire (ZQ). Patients with severe forms of fatigue (##1, 2, 3, 8) found that they started feeling "better and more energetic" after 2-3 weeks of treatment. Their MFI and ZQ scores were significantly improved. Patient 6 described the effect as "relaxing" and "sleep impoving". Other patients self-rated the effect as neutral however the MFI and ZQ scores on average were better for 8 of 9 patients.

Clinical symptoms of other associated pathologies (prostatitis, sore throat, couth, phlegm, flu-like symptoms) subsided to the end of treatment in those patients who had them at the time of the trial. We monitored 8 of 14 patients for 1 year. Two months post-treatment all of them felt significantly better than before with no signs of fatigue. At 6 mo post treatment 2 persons who earlier suffered severe fatigue, again had sings of it and were recommended the second course. The results were the same: quick elimination of fatigue symptoms and slow improvement in somatic symptoms.

4.5 Immunological effects of izoniazid treatment

We analyzed parameters of lymphocytes in treated patients before the treatment and at days 30 and 90. The results are shown in Fig.2. All parameters of immune status were better than before the treatment showing that the therapy was effective.

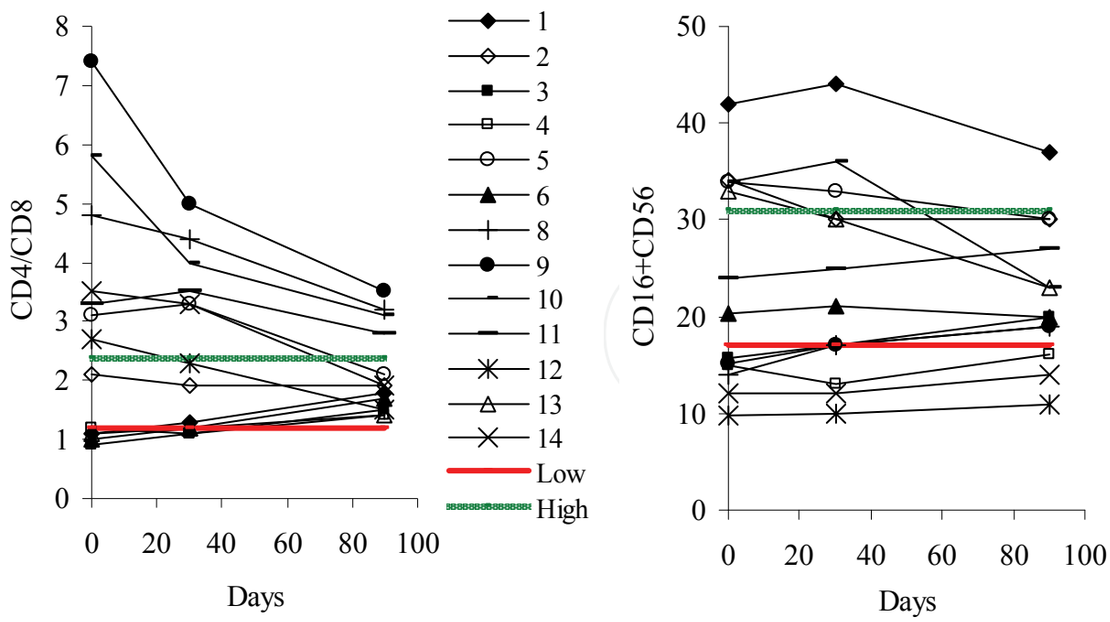


Fig. 2. Changes in CD4/CD8 ratio (left panel) or number of CD16+CD56 NK cells (right panel) before and after izoniazid treatment of patients with chronic fatigue.
Normal range is shown as '"low-high" zone

5. Discussion

MTB, the causative agent of tuberculosis remains a major threat to global health as the leading cause of death due to a bacterial pathogen. Every third person on the planet is infected with MBT. However, only 10% among infected individuals develop TB while others remain otherwise healthy. These people are classified as "latently infected," but remain a reservoir of MBT. Latent TB has traditionally been defined as infection with MBT in foci within granuloma that remain in nonreplicating state but retain their ability to induce TB when a disruption of the immune response occurs. However, recent experimental data support a dynamic model of latent TB where endogenous reactivation as well as damage response occur constantly in immunocompetent individuals [Cardona PJ, 2009, Ahmad S, 2011]. This model suggests that some type of macrophages (foamy macrophages) phagocytose extracellular nonreplicating MBT; however, the bacilli do not grow in the intracellular environment of activated macrophages but are also not killed due to the nonreplicating state of the bacilli. The nonreplicating bacilli-loaded foamy macrophages drain from lung granuloma towards the bronchial tree and return to a different region of lungs and begin the infection process at a new location once again [See review Ahmad S, 2011]. It can be speculated that activated foamy macrophages can enter not only the lungs but also other organs as TB is known in many forms of localization [Horsburgh&Rubin, 2011; Russell, 2011; Dorhoi et al, 2011, Galimi R, 2011]. These new locations of MBT can attract immune cells inducing all the symptoms characteristic for CFS patients.

Here we put forward a new hypothesis that at least in some patients chronic fatigue can be induced by ongoing immune response against MBT. We have chosen patients from a large cohort of individuals basing on two criteria: i) they have signs of fatigue and depression; and ii) their immune status was deviated from a normal one. Selected patients have various medical problems (prostatitis, herpes, sore throat, couth, phlegm, sinusitis, pharyngitis, mild reumathoid arthritis). The aims of the trial were: i) to estimate whether anti-tuberculosis treatment can help in resolving fatigue and depression; and ii) if the treatment affects immune status of the patients. The results were encouraging as most patients felt a decrease in fatigue symptoms. This effect was not long-lasting as in severe cases 6 mo later some patients again complained the signs of fatigue. The remittance of the disease can again be explained in terms of “chronic interaction between MBT and immune cells”. Izoniazid treatment hypothetically removed some active foci inducing a following decrease in immune response. However, new locations of MBT were formed with time due to a genetic susceptibility to TB. This means that anti-tuberculosis treatment could possible be needed for a longer time or for repeated courses during several years.

We have also shown that parameters of immunity were improved after anti-tuberculosis treatment. These results showed that immune status can be used as a parameter to monitor. In our trial only persons with deviated immunity were included. Possibly among CFS patients also individuals with immune disturbances can be considered as candidates for izoniazid therapy.

Finally I want to emphasize that the effect of izoniazid on fatigue could be a by-stander to MBT infection and be connected to some other targets in brains of immune system. However, new studies are required to clarify this matter.

6. Acknowledgments

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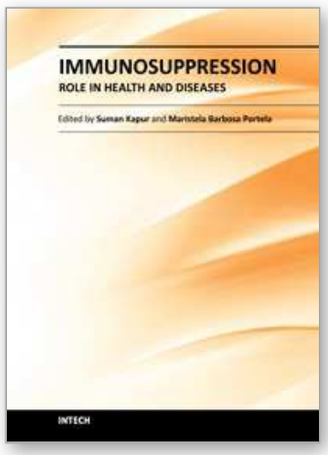
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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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