GLOBAL SCIENCE LIBRARY

CASE REPORT

Journal of Clinical Case Reports & Reviews

Dysbalance of cytokines in schizophrenia and strategies for restoration of immune functions

Dimitre H Dimitrov

South Texas Veterans Health Care System, 7400 Merton Minter, San Antonio, Texas, USA

Abstract

We discuss the cumulative effect of different cytokines in veterans with schizophrenia. Previously we reported that the chemoattractant G-CSF, MCP, MDC and GRO, which activates human macrophages, monocytes, neutrophils and basophils that these factors were significantly increased compared to control subjects and also that levels NF-γ and IL-17 and Il-2 were significantly decreased as compared to controls. Based on these results we hypothesize that the immune system with schizophrenia is trying to restore the balance of their immune system by reducing the amounts of pro-inflammatory cytokines and increasing the amounts of anti-inflammatory and regulating cytokines. We decided to use an unorthodox approach by clustering the cytokines in four groups according to their predominant functions and analyzing the effect of cumulative amounts of cytokines in each group. This hypothetical approach provided theoretical explanation about the changes of cytokines in patients with schizophrenia.

We suggest an individualized approach for treatment of psychosis in patients with schizophrenia by augmenting psychotropic medications with the help of monoclonal antibodies which block the excessive amounts of specific proinflammatory cytokines.

Keywords: *schizophrenia, cytokines, monoclonal antibodies, immune system*

Introduction

Cytokines play an important role in inflammatory processes and immunopathology [1]. The cytokine model of schizophrenia leads to the conclusions that immunological immunotherapy leading to opposing the effect of cytokines may represent an useful strategy for treatment in autoimmune diseases and such treatment may also lead to reduction of psychotic symptoms. Currently the available monoclonal antibodies cannot be used as a first line in treatment in schizophrenia but may become useful in patients with high levels of certain serum cytokines coinciding with severe psychotic presentations [2,3].

Cases

Cytokines In our previous studies we demonstrated that the chemoattractant cytokines Granulocyte-macrophage colony-stimulating factor (G-CSF), Monocyte chemotactic protein-1 (MCP-1), Human macrophage-derived chemokine (MDC) and the chemotactic cytokine GRO (historic abbreviation for Growth related oncogene) which activates human neutrophils and basophils. These factors were significantly increased compared to control subjects [4]. We also described decreased levels of Interferon-gamma (INF-γ) and IL-17 which are mainly proinflammatory and decreased levels of Il-2 which is regulating the immune T cells. Based on these previously published results we hypothesize that the immune system of patients in the schizophrenia group is trying to restore the balance by reducing the amounts of pro-inflammatory cytokines and increasing the amounts of anti-inflammatory and regulating cytokines. To explore this we decided to use an unorthodox approach by clustering the cytokines in four groups according to their predominant functions and analyzing the effect of cumulative amounts of cytokines in each group. Selected data from previously published results, with the mean value in picograms of the cytokines in each group, were analyzed by using this approach (Table 1). The results presented in Table one show that the amounts of chemoattracting chemokines, ati-inflammatory and regulating cytokines are increased compared to the control group and the amounts of proinflammatory cytokines are decreased.

Although in the group of schizophrenia the patients as a whole had reduced proinflammatory cytokines some patients with severe psychotic symptoms had increased amounts of certaine cytokines. The levels of these cytokies were at least three times above the mean values for the group described previously [4]. When we examined the specific levels of cytokines for each patient we found that one of the veterans had high levels of IFN-

γ, Interleukin 1 receptor antagonist with Il-1RA and Il-4, one veteran had high levels of Il-17. Two veterans had high levels of Il-6 (mainly anti-inflammatory properties), one veteran had high levels of Il-1β (mainly proinflammatory cytokine), Il-4 and Il-2, and one veteran had high levels of Il-1RA. The severity of symptoms of veterans were evaluated using the Positive and Negative Syndrome Scale (PANSS). We had had a group of 12 veterans with PANSS >100 and high levels of cytokines. The dysbalance of cytokines in veterans with severe psychosis compared to controls is represented in Table 2. The results indicate higher amounts of chemokines, antii-inflammatory and regulating cytokines and lower amount of proinflammatory cytokines as compared to controls.

The dysregulation of the cytokines probably is influenced by the substance abuse history of the patients with PANSS>100. In this group we had six patients with documented substance abuse history and six patients without documented substance abuse history. The amounts of cytokines in each group are presented in Table 3. The veterans with history of substance abuse had higher amounts of chemokines, anti-inflammatory and regulating cytokines. All veterans had prolonged treatment with antipsychotic medications and the changes of cytokines could be secondary to treatment.

We hypothesize that the dysregulation and increase of chemo-attracting cytokines leads to wide adverse effects in the brain and may lead to mood and psychotic symptoms [5-7]. The recruitment and enhanced survival of phagocytic cells, macrophages and monocytes may be causing synaptic destruction and neuronal damage [5]. We propose that the veterans with increased levels of Il-6 might show reduced psychotic symptoms if they receive therapy with Tocilizumab (Actemra), monoclonal antibody blocking the effect of Il-6. The veterans with increased levels of Il-1, may show improvement with Canacuminab (Ilaris), the veterans with increased Il-17 may improve with Secukinumab (Cosentyx) and the veterans with increased levels of TNF - may benefit from treatment with Adalimumab (Humira). If this approach is successful it will be a step forward towards personalized treatment of schizophrenia. Our analysis showed that use of illicit substances is associated with higher amounts of chemoattracting cytokines with potential for worsening of psychopathology.

		Schizophrenia	**Controls**
Chemokines	G-CSF	56.6	37.4
	MCP-1	540	287
	MDC	1360	650
	CRO	759	78.9
	Fractalkine	141	133
	Total	2,856.00	1,186.00
Proinflammatoty	Il-17	3.2	23.4
	IFN-γ	10.9	76.9
	IL-1β	1.5	2.4
	TN F-β	4.1	5.2
	IL-6	2.8	9.6
	IL-12 p70	2.9	36.6
	Total	22.2	154.1
Anti-inflammatory	IL-4	9.2	6.8
	IL-10	5.9	3.3
	IL-13	5	9.2
	Il-1RA	33.8	36.3
	Total	53.9	55.6
Regulating	Il-2	5.5	18.1
	IL-9	1.1	1.5
	Il-3	0.23	0.59
	Total	6.83	21.9

Table 1. Amounts in picograms of representative cytokines from each group.

	Inflammatory	Anti-inflammatory	Regulating	Chemo-attracting
Shizophrenia >100 PANSS	129.9	258.7	33.9	3,094
Controls	154	55.6	7.6	1,186

Table 2. Comparison between amount of cytokines in patients with schizophrenia with PANSS >100 and controls.

Substance use	Chemokines	Proinflammatory	Anti-inflammatory	Regulating
No use	386	21.7	43.1	5.7
Substance use	553	15.7	9.8	25.3
Controls	197	225.7	9.3	1.3

Table 3. Comparison of amounts of cytokines in picograms according to substance abuse history.

Discussion and conclusion

In our pathway analyses of the cytokines described in our previous publications we showed that the four groups of cytokines are part of the Il-17 pathway and in our results based on the genome-wide expression of these veterans with schizophrenia we showed that Il-17 is linked to immune/inflammatory mechanisms [8,9].

IL-17 is a pleiotropic protein. Quite often it has a modest activity on its own, but most probably it's final impact on immunity has a result of a synergistic action with other cytokines. Although Il-17 is not a potent inducer of inflammation by itself it is capable of recruiting immune cells via chemokine expression. IL-17 is considered to be a chief orchestrator of immunity and is strongly associated with immunopathology [10]. Il-17 was discovered in T cells as a homolog of Herpes virus protein from the T cell lymphotropic virus herpes virus saimiri. IL-17 activates the NF-kB pathway which controls inflammatory processes and cytokine production [11]. This raises questions whether a viral protein with cytokine activity was advantageous to the original virus infecting squirrel monkeys Saimiri sciureus? How did it evolve to be advantageous to humans and is it possible that when there is a great dysbalance of cytokines it can become "wolf in sheep's clothing" causing extensive pathology? The advantages for humans may be that Il-17 is important in initial host defense. IL-17 expression in synergy with TNF leads to rapid recruitment and enhanced survival of phagocytic cell, macrophages and monocytes through production of G-CSF, MCP, MDC and GRO [10].

Currently we have not used monoclonal antibody therapy in the treatment with veteran with schizophrenia but we have the capacity to evaluate the mental health of patients with autoimmune diseases and psychotic symptoms. Such patients have regular appointments in Dermatology and Rheumatology clinics and in these clinics they receive monoclonal therapy for their medical problems. Some of these patients also have mental health problems and we can evaluate the effect of monoclonal antibodies on their psychiatric symptoms.

We would like to illustrate our suggestions with the following clinical report:

A 36-years old male with prior history of ADHD, HLA B27 positive was hospitalized under emergency detention for psychotic and bizarre behavior and paranoid delusions. At the time of admission his UDS was positive for cannabis and amphetamines. He responded to treatment with Haloperidol 5 mg po q 4 hrs and Lorazepam 2 mg IM q hrs prn. His psychotic symptoms resolved quickly, the mood stabilized and he was discharged on Risperdal 1 mg po bid with a diagnosis of Bipolar Disorder, current episode manic with severe psychotic features. After the discharge from the hospital the veteran had pain issues. On consult with Rheumatology he was diagnosed with Ankylosing spondylitis, lateral and medial epicondylitis, lumbosacral spondylosis, rotator cuff syndrome, carpal tunnel syndrome and uveitis and had pain issues. Treatment with Adalimumab was started in July 2015. The dose of Adalimumab was increased to 40 mg SC q week. His pain and stiffness improved greatly. The veteran has stopped the use of cannabis and did not have any psychotic symptoms. He continued to have some racing thoughts which were well controlled with Lamotrigine and the veteran requested to discontinue Risperidone which was causing somnolence and fatigue. During the next three years his pain issues were well controlled with Adalimumab. He had regular follow up appointments with psychiatry and remained free of delusions, paranoia and hallucinations. During a routine psychiatry follow up his score on the Positive and Negative Syndrome Scale was 42 with mildly elevated symptoms of anxiety and hostility. The veteran had symptoms of inattention which responded well to Wellbutrin and Lamotrigine has stabilized his mood.

We conclude that the suppression of cytokines by Adalimumab could lead to a reduction of psychotic symptoms. In this case with autoimmune diseas the immunological medications might have been beneficial for the resolution and progression of the psychotic symptoms.

In 2019 the veteran had Rheumatology appointment and reported that Adalimumab is losing its efficiency and requested medications for pain. He was switched to Certlizumab which did not have any significant effect and later was started on Etanrecept. His pain worsened gradually, the veteran resumed the use of cannabis, became psychotic and was hospitalized again.

Alongside of using monoclonal antibodies as anti-inflammatory drugs new studies in psychosis were initiated with monoclonal antibodies against cell adhesion molecules such as Tysabri

(Natalizumab, Biogen) which interacts with alpha-4 integrin; Actemra (Tosilizumab, Genentch) and Sylvant (Siltuximab, Jansen) which target the cytokine IL-6 as well as Ilaris (Canakinumab, Novartis) which targets IL-1.

A trial of treatment of schizophrenia with Natalizumab was initiated in Great Britain [12]. This monoclonal antibody targets the overactive microglial cells in people with multiple sclerosis and is nvestigated for the treatment of schizophrenia. Patients with TRAP syndrome (TNF-receptor associated periodic syndrome) responded to IL-1 inhibition and this medication has already been approved for the treatment of TRAPS patients [13].

The limitations of the proposed results include the small sample size, which limit the power to obtain statistically significant data. The observations in the serum may not represent corresponding accurate changes in the CSF and furthermore the levels of serum cytokines may represent an inflammatory process in other systems and organs and not only the brain.

The cumulative analyses of groups of cytokines clustered in four different main groups has also limitations. The cytokines in various amounts may have different functions in different combinations. Therefore the findings in this report should be considered preliminary and could be used only as a hypothesis for designation of tailored therapy for schizophrenia.

Acknowledgements

The results discussed in this manuscript are based on previous publications in co-authorship with Walss-Bass, C, Fries G, Braida, N, Lee, S, Yantis J., Honaker C, Valdez C, Paredes RM, Velligan, D., Coelho R, and Cueller, J.

Funding

The research has been supported by a New Investigator Award Grant to Dimitre Dimitrov, MD, from VISN 17 of the Department of Veterans Affairs.

Disclaimer

The views expressed herein are those of the author and do not necessarily represent the views of the US Department of Veterans Affairs.

References

1. Dimitrov DH, Braida N, Walss-Bass C. The link between immune system dysregulation and Schizophrenia. PsychiatrTimes. 2011, 27: 23-27.
2. Dimitrov DH, Lee S, Yantis J, Honaker C, Braida N. Cytokine serum levels as potential biological markers for the psychopathology in schizophrenia. Adv Psychiatr. 2014: 493505.
3. Girgis RR, Kumar SS, Brown AS. The cytokine model of schizophrenia: emerging therapeutic strategies. Biolog Psychiatr. 2014; 75: 292-299.
4. Dimitrov, DH, Lee, SW, Yantis J, Valdez C Paredes RM, et al. Differential correlation between inflammatory cytokines and psychopathology in veterans with schizophrenia: potential role of IL-17 pathway. Schizopr Res. 2013; 151: 29-35.
5. Dimitrov DH. Correlation or coincidence between monocytosis and worsening of psychotic symptoms in veterans with schizophrenia. Schizophr Res. 2011; 126: 306-307.
6. Dimitrov DH, Lee S, Yantis J, Honaker C, Braida N, et al. Elevated serum levels of high sensitivity C-reactive protein are associated with severe delusional symptoms in a subgroup of patients with schizophrenia. J Clin Psychiatr. 2015; 17: 1-4.
7. Dimitrov DH, Lee S, Yantis J, Honaker C, Roberta C, et al. Dysequilibrium of cytokine serum levels in veterans with chronic schizophrenia medicated with antipsychotics: association with measures of excitement and hostility. Prim Care Companion CNS Disord. 2015; 77: 131-132.
8. Fries RG, Dimitrov, DH, Lee S, Braida N, Yantis J, et al. Genome-wide expression in veterans with schizophrenia further validates the immune hypothesis for schizophrenia. Schizophr Res. 2018; 192: 255-261.
9. Gardiner EJ, Cairns MJ, Liu B, Beveridge NJ, Carr V, et al. Gene expression analysis reveals schizophrenia-associated dysregulation of immune pathways in peripheral blood mononuclear cells. J Psychiatr Res. 2013; 47: 425-437.
10. Veldhoen M. Interleukin 17 is a chief orchestrator of immunity. Nature Immunol. 2017; 8: 612-621.
11. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, et al. Herpes virus saimiri encodes a new cytokine, Il-17,which binds to a novel cytokine receptor. Immmunity. 1995; 3: 811-821.
12. Robinson J. Trial begins to investigate efficacy of monoclonal antibody against schizophrenia. Pharmaceuti J. 2017.
13. La Torre F, Caparello, MC, Cimaz R. Canakinumab for the treatment of TNF-receptor associated periodic syndrome. Expert Rev Clin Immunol. 2017; 13: 513-523.

Correspondence: Dimitre H Dimitrov, South Texas Veterans Health Care System, 7400 Merton Minter, San Antonio, Texas, USA, Tel: (210) 275 1090; E-mail: dhdimitre@yahoo.com

Rec: May 08, 2020; Acc: May 22, 2020; Pub: May 25, 2020

J Clin Case Rep Rev. 2020;3(3):153
DOI: 10.36879/JCCRR.20.000153