

주요 우울증에서 혈중 Cytokine과 임상적 호전과의 관계*

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The Relationship between the Serum Cytokine and Clinical Improvement in Major Depressive Disorder*

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ABSTRACT

Object : Currently, the alteration of cytokine system has been known to play an important role in regard to depressive symptom. We focused on the relationship between immunological parameters and clinical improvement in major depressive disorder.

Method : Data were collected on 26 patients with major depressive disorder using a 8-week prospective follow-up design. After 8-week treatment period with fluoxetine, patients were classified into a response group and a non-response group according to their psychopathological outcome as evaluated by Hamilton Depression Rating Scale. The differences of the immunological parameters between pre-treatment phase and post-treatment phase were compared among patients. The difference of those was also compared within each phase among them. The relationship between socio-demographic variables, depression, cytokine, mononuclear cells was examined by correlation analysis. Multiple regression analyses were performed to explore the predictors of clinical improvement of major depressive disorder.

Result : Pre-treatment levels of IL-1 in the response group were significantly higher than those in the non-response group. Pre-treatment levels of IL-1 of all patients and in the response group were positively correlated with pre-treatment monocyte counts. Patients with subsequent remission showed significantly lower IL-6 values at baseline than those with non-response. Post-treatment values of IL-6 did not differ significantly among the patients. The correlation test showed more frequent relations among cytokines and mononuclear cells in the response group than in the non-responder group. Especially, serum level of IL-6 in pre-treatment phase was only significantly correlated with HAMD score after 8-week treatment phase, while other cytokines and mononuclear cells were not. Pretreatment level of IL-6 was of paramount importance in predicting clinical improvement of depressive symptom.

Conclusion : The immune system of major depressive disorder patients might dichotomize the patients into subsequent responders and non-responders. Immune system might be of great influence on the clinical

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8 ELISA reader
492nm semi - log paper
Cytokine Cytokine
fluoxetine, 20mg
8
3. 자료분석
50% Chi - square test, Mann -
Whitney test
50% Cytokine Mann - Whitney
test 0 8
2. 면역학적 변수 Wilcoxon test
CRP, IL - 1, IL - 6, TNF - 8 가
level Cytokine 가
8 10ml 8
EDTA EDTA Spearman
1 correlation test 8
Cytokine - 70c 가 가
Cytokine R & D Stepwise
Human high sensitive IL - 1, IL - 6, TNF - , level) 0.05 (-
CRP ELISA test kit(R & D, USA) SPSS(vesion 10.0)
Cytokine 가
96 well plate 100 µl
Cytokine 500pg/ml 2 4
1. 사회인구학적 특성(1)
2 100 µl 26 가
가 2 6

Table 1. Demographic characteristics of the subjects with major depressive disorder

		RG(N=13)	NRG(N=7)	Total(N=20)	p-value
Sex ^a	Male	4	3	7	0.59
	Female	9	4	13	
Marital status ^b	Married	9	3	12	0.92
	Single	1	4	5	
	Divorced	3	0	3	
Total family income ^b	High	1	1	2	0.22
	Middle	9	6	15	
	Low	3	0	3	
Age mean(SD) ^c		42.30(7.73)	43.42(5.38)	42.70(6.87)	0.46
Education mean(SD) ^c		11.07(2.06)	10.28(1.70)	10.80(1.93)	0.59

a : Fisher's Exact test

b : Test for trend, linear by linear association

c : Mann-Whitney test

RG : Responders group, NRG : Non -Responders group, high : monthly income 3millions won, middle : between 1 and 3millions won, low : <1million won in total family income

20 가 (65.0%), 50% (NRG)
 , 7 (35.0%)
 (1). HAMD BDI 23.30
 2. 우울 증상의 비교 및 평가(2) ±4.94 27.23±5.30 HAMD
 (BDI) score 23.38±1.02
 HAMD 8 50% (26.62±2.40) 6.54±1.52(11.08±2.39)
 (RG) 13

Table 2. Depressive symptom data grouped according to the treatment response

		N	Pre-reatment Mean(SD)	Post-treatment Mean(SD)	p	% Reduction
HAMD						
	RG	13	23.38(1.02)	6.54(1.52)	<0.01	71.47
	NRG	7	22.57(2.26)	14.57(1.27)	0.02	33.32
BDI						
	RG	13	26.62(2.40)	11.08(2.39)	<0.01	67.41
	NRG	7	29.14(4.04)	16.67(1.63)	0.02	30.12

HAMD : Hamilton depression rating scale, BDI : Beck's Depression Inventory, RG : Responders group, NRG : Non-Responders group

Table 3. Numbers of Lymphocytes, Monocytes(A), levels of CRP, TNF- (B), levels of IL-1 , IL-6 (C) with regard to treatment response

(A)

	N	Lymphocyte		Monocyte	
		Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)
Total patients	20	2.03(0.78)	1.77(0.57)	0.37(0.15)	0.38(0.11)
Responders	13	1.83(0.85)	1.77(0.69)	0.39(0.17)	0.36(0.12)
Non-responders	7	2.40(0.49)*	1.76(0.30)*	0.38(0.11)	0.39(0.17)

* : p<0.05 in Wilcoxon test

(B)

	N	CRP		TNF-	
		Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)
Total patients	20	2.03(0.78)	1.77(0.57)	0.94(0.50)	0.82(0.42)
Responders	13	1.83(0.85)	1.77(0.69)	0.86(0.39)	0.73(0.32)
Non responders	7	2.40(0.49)	1.76(0.30)	1.10(0.66)	0.99(0.56)

(C)

	N	IL-1			
		Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)	Pre-treatment Mean(SD)
Total patients	20	0.23(0.22)**	0.10(0.37)**	1.36(1.17)*	2.19(0.84)*
Responders	13	0.27(0.27)**	0.10(0.41)**	0.64(0.39)**	2.08(0.97)**
Non responders	7	0.15(0.54)	0.09(0.02)	2.70(0.88)	2.38(0.54)

** : p<0.01 in Wilcoxon test

** : p<0.05 in Wilcoxon test

(N=13). 22.57 ± 2.26(29.14 ± 4.04)
 14.57 ± 1.27(16.64 ± 1.63)
 (N=7), 8
 (2).

(HAMD : mean rank, 10.96 vs. 9.64 ; p>0.05 ;
 BDI : mean rank, 9.77 vs. 11.86 ; p>0.05).

3. 혈중 면역학적 변수

1) 면역 혈구

0 , 8
 (3A).
 가 (p<0.05 : 3A).

2) CRP

CRP
 가 (3B).
 가 (r = - 0.65 ; p<0.05 : Data not shown in Table),

3) IL-1 β

IL - 1 (mean rank, 12.84 vs. 8.10 ; p<0.05),
 8 IL - 1 (p<0.01 : 3C, 1A). IL -

1 가 (r=0.47 ; p<0.05 in total patients : r=0.53 ; 0.05<p<0.1 in responders : 4, 2).

IL - 1 CRP 가 (r=0.61 ; p<0.05 : 4).

8 IL - 1 IL - 6 4). 가 (r=0.59 ; p<0.01 in total patients : r=0.60 ; p<0.05 in responders : 4), TNF - (r= 0.61 ; p<0.01 in total patients : r=0.68 ; p<0.05 in responders :

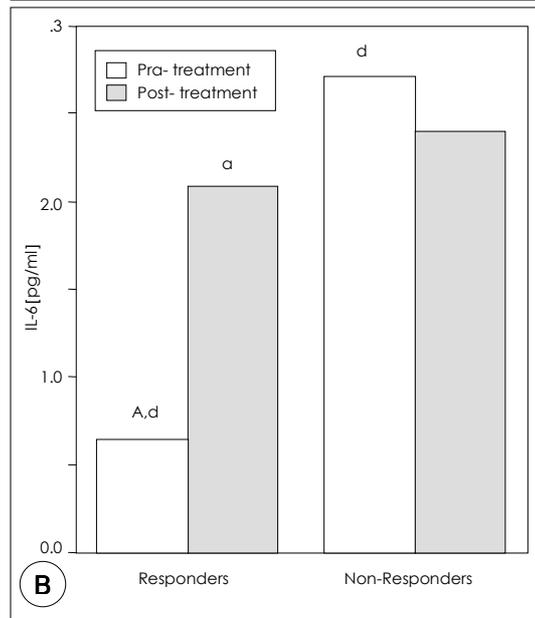
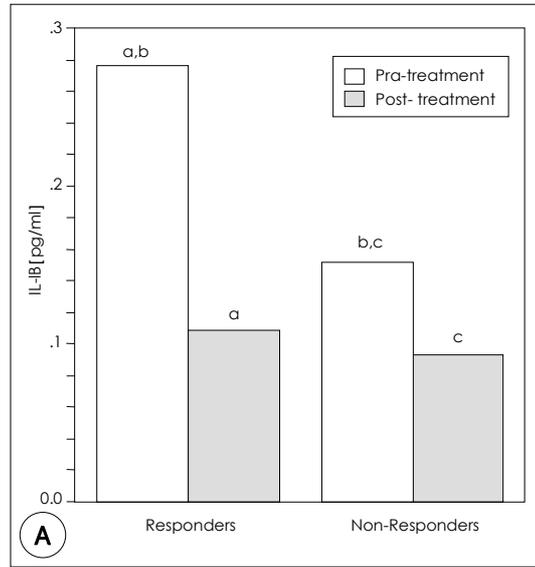


Fig. 1. The difference and change of serum IL-1 (A) and IL-6 (B) according to treatment response. a : p<0.01 in Wilcoxon test in both (A) and (B) b : p<0.01 in Mann-Whitney Test(A) c : p<0.05 in Wilcoxon test(A) d : p<0.01 in Mann-Whitney Test(B).

4). TNF - 가 (r=0.82 ; p<0.05 : 4).

3) IL-6

IL - 6 , IL - 6

Table 4. Correlation between immunologic parameters and IL-1 (A) and IL-6(B)

(A)

	Lymphocyte		Monocyte		CRP		IL-6		TNF-	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Total patients	-0.31	-0.14	0.47*	-0.11	0.16	0.03	-0.29	0.59**	0.07	0.61**
Responders	-0.16	-0.11	0.53 ^α	-0.30	0.61*	0.03	0.01	0.60*	0.22	0.68*
Non responders	-0.61	-0.12	0.23	0.36	0.47	-0.62	-0.23	0.71	-0.14	0.82*

(B)

	Lymphocyte		Monocyte		CRP		IL-1		TNF-	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Total patients	0.22	0.07	-0.35	-0.02	0.07	-0.02	-0.29	0.59**	0.32	0.54*
Responders	-0.59*	-0.10	-0.36	-0.32	0.22	0.19	0.01	0.60*	0.25	0.30
Non responders	-0.09	0.48	0.49	0.63	-0.01	-0.51	-0.23	0.71	0.45	0.80*

Pre : pre-treatment, Post : post-treatment
 * : $p < 0.05$ in Spearman correlation test
 ** : $p < 0.01$ in Spearman correlation test
 α : $0.05 < p < 0.1$ in Spearman correlation test

Table 5. (A) Correlation between immunologic parameters and FHAMD and (B) Stepwise multiple regression Analysis for the factor affecting the clinical improvement(FHAMD)

(A)

Lymphocyte	Monocyte	CRP	IL-1	IL-6	TNF-
0.424	-0.32	-0.03	-0.20	0.59**	0.28

** : $p < 0.01$

(B)

Equation : $FHAMD = 6.159 + 2.337 \times IL-6$
 $R^2 = 0.352$ Adjusted $R^2 = 0.316$ $p = 0.006$
 FHAMD : HAMD score after 8-week Treatment

(mean rank, 7.08 vs. 16.86 ; $p < 0.01$: 1B).
 IL - 6 가 ($p < 0.05$ in total patients, $p < 0.01$ in responders : 3C, 1B).
 IL - 6 가 (1B).
 가 ($r = -0.59$; $p < 0.05$: 4).
 IL - 6 TNF - 가 ($r = 0.54$; $p < 0.05$ in total patients, $r = 0.80$; $p < 0.05$ in non - responders : 4).
 4) TNF- α TNF - 가 (0.05<

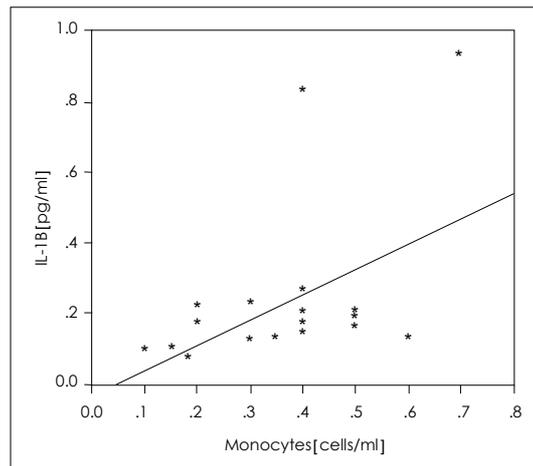


Fig. 2. The correlation of serum monocyte count and the level of IL-1 in patients with major depressive disorder before treatment (spearman correlation coefficient ; $r = 0.470$; $p = 0.04$).

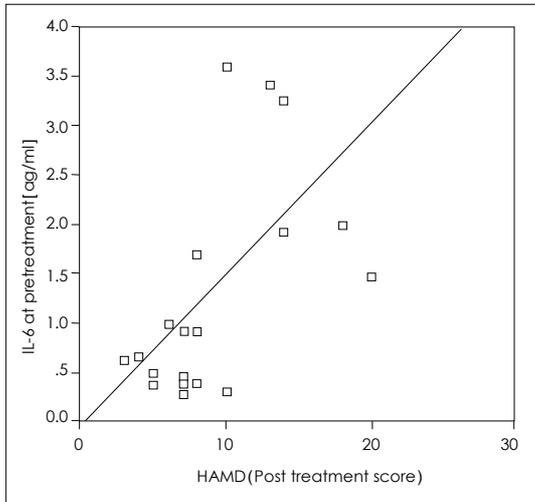


Fig. 3. The Correlation of clinical improvement (Post treatment HAMD score) and serum levels of IL-6 before treatment. Equation : FHAMD = 6.159 + 2.337 x IL-6. Abbreviation ; FHAMD = HAMD score after 8-week Treatment.

p < 0.1 ; 3B).

5) 예측 인자

(FHAMD score)
 Cytokine
 IL - 6 (p < 0.01 :
 5A, 3). IL - 6
 가
 , 8 HAMD score 31%
 (= 0.59 : 5B).

고 찰

CRP, IL - 1 , IL - 6, TNF -
 가
 가
 가 ¹²⁾¹⁶⁾

가
 , 가 .
 (blast)
 가 ,
 가
 .
 가 (Monocyte hypothesis)
 가 ¹⁷⁾¹⁸⁾
 CRP
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 CRP
 IL - 1
 Cytokine
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 CRP가
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 Cortisol 가
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 IL - 1 가 IL - 1
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 IL - 1
 11) IL - 1
 IL - 1 가 ²¹⁾²²⁾

IL - 1 가 HPA
가 . Dobbin
IL - 1 가 가
가 가 ,²³⁾
IL - 1 가 TNF -
가 ,
가 가 IL - 6
IL - 1 가
. IL - 1 Corticotropin IL - 6 가
Releasing Factor(CRF)²⁴⁾ IL - 1
가 HPA axis . TNF -
glucocorticoid receptor transport . IL - 6 ,
glucocorticoid resistance 가
.²⁵⁾ IL - 1 HPA , IL - 6 가
axis cortisol 가 가
cortisol IL - 6 가
가 ,
가
IL - 1 가 IL - 1 IL - 6 8
, 가 SSRI fluoxetine 8 가 IL - 6
, Serotonin IL - 6가
. IL - 1²⁶⁾ IL - 1¹²⁾
5 - HT tryptophan 가²⁸⁾
indolamine - 2, 3 - dioxygenase(IDO) . IL - 6 pro - and anti - inflammatory
가 5 - HT seroronin system 가 Cytokine
(highly pleotropic)Cytokine
.²⁷⁾ IL - 1 IL - 6가 Cytokine
serotonin system HPA axis , Schindler IL - 6가 IL - 1 TNF -
cortisol 가 , IL - 6 IL - 6
(e.g. IL - 4, IL - 10, TNF - 1)³⁰⁾ cortisol
가 IL - 1 가 가 HPA
serotonin system 가 가 cortisol 가 ,
, CRH IL - 6 가 ,
glucocorticoid receptor HPA 가 cortisol
가 glucocorticoid receptor IL - 6가 가 IL - 1 , TNF -
, 가 , Cytokine 가 .³¹⁾³²⁾

HPA
 cortisol 가 Cytokine
 가 , corticotropine
 releasing factor(CRF) cortisol 가
 가 glucocorticoid 가
 Cytokine
 가 ³³⁾
 IL - 6 가
 , Cytokine
 , glucocorticoid Cytokine
 가 Glucocorticoid receptor
 HPA axis
 가
 IL - 6 가
 IL - 6가 ³⁴⁾
 Maes
¹⁴⁾
³³⁾
 가
 가
 가
 가
 가 Cytokine system
 Cytokine
 가
 Dexamethasone suppression test(DST)
 HPA axis
 cortisol study Cytokine,
 , 가 HPA axis 가
 , IL - 6가
 가 , 40%

Cytokine 가
 가 가
 Cytokine
 ,
 2
 가
 fluoxetine 20mg
 ,
 Cytokine 가
 중심 단어 : Cytokine
 CRP · IL - 1 · IL - 6 · TNF -

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