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Alteration of Cytokines in Medication-Naive Adolescents with First-Episode Major Depressive Disorder 이 호 준 2019년 8월

박 사 학 위 논 문

Alteration of Cytokines in Medication-Naive Adolescents with First-Episode Major Depressive Disorder

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이 논문을 박사학위 논문으로 제출함

2019년 8월

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Acknowledgements

이 논문이 나오기까지 항상 따뜻한 격려와 배려로 논문 작성 시작과 끝까지 챙겨주시고, 지도해주셨던 김정범 교수님께 진심으로 감사드립니다. 본 논문을 세밀히 검토하고 소중한 조언을 주셨던 심사위원 정철호 교수님, 김희철 교수님, 정성원 교수님과 영남대학교 구본훈 교수님께도 감사의 말씀을 드립니다. 연구가 무엇인지도 모르고, 논문을 어떻게 써야할 지에 대해서도 막막해하던 저에게 연구 디자인부터 논문이 완성될 때까지 모든 지원을 아끼지 않고, 큰 가르침을 주신 고려대학교 이문수 교수님께 특히 감사드립니다.

부족한 영어 실력으로 도움을 청하였을 때, 당연하다는 듯 도움을 주었던 목영은 선생님과 멀리서 제 어려운 부탁에도 싫은 내색 없이 웃으며 도와주었던 정상협, 고시연, 정현경 선생님께도 감사의 말씀 전합니다. 전임의 생활의 큰 힘이 되어준 건엽, 지원, 승호, 지영 등등 소중한 벗들과 의국 선후배 여러분들, 주위에서 저에게 알게 모르게 도움주신 많은 분들께 감사의 말씀 드립니다.

언제나 아들을 무한 신뢰하고, 든든하다 얘기해주시는 아버지, 어머니께 존경과 사랑, 감사의 마음 전하며, 부족한 사위를 예뻐해 주시는 장인어른과 장모님께도 항상 감사하다는 마음 전하고 싶습니다. 지칠 때마다 힘이 되어주었던 누나를 비롯한 소중한 가족들에게도 감사드립니다.

마지막으로 그 무엇과도 바꿀 수 없는 소중한 나의 지후, 준후, 그리고 선영. 사랑한다.

2019년 8월

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1. Introduction

Major depressive disorder (MDD) is a leading cause of disability worldwide, creating significant burdens on individuals and families (1). This impact is challenging in childhood and adolescence, since the prevalence of MDD is about 1 to 7%, varying among countries (2). Depression in childhood and adolescence has a high incidence of recurrence through adulthood. It is commonly comorbid with other psychiatric disorders, such as anxiety disorder, substance misuse, and oppositional defiant disorder, as well as being associated with high risk of self-harm and suicidality unless properly treated (3-5). Given reports of differences in genetic predisposition to depression, hematologic test results, and medication responses in adults versus children and adolescents, the importance of studying the pathophysiology and etiology of depression in childhood and adolescence, specifically, has been emphasized (3, 6). Many studies have shown that depression, stress, and immune responses are interrelated, and inflammatory markers such as cytokines, a substance that mediates signals between immune cells, affect the development of depression (7-9).

Cytokine is a multifunctional, pleomorphic protein involved in immunological, physiological, and pathological reactions, that can be used as a measure for micro-inflammation (10). Cytokines can functionally be classified as proinflammatory and anti-inflammatory cytokines. Some cytokines can present both proinflammatory and anti-inflammatory properties, depending on the situation, so such classification may be overly simplified (11, 12). However, these classifications are commonly used in research seeking to identify the role of cytokines in depression. Proinflammatory cytokines include interleukin 1 beta (IL-1β), interleukin

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2 (IL-2), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-ɣ). Anti-inflammatory cytokines include interleukin 1 receptor antagonist (IL-1Ra), interleukin 4 (IL-4), interleukin 10 (IL-10), transforming growth factor beta (TGF-β) (10, 13-16). The interest in discovering whether depression is affected by the immune response associated with cytokine stems from knowledge of the increased incidence of depression in medical diseases having increased cytokine levels, such as influenza infection, chronic hepatitis, rheumatoid arthritis, autoimmune disease, and cancer (17). The facts that depression was caused by interferon treatment in hepatitis patients, that depression like symptoms were caused by peripheral administration of TNF-α, and that depressive symptoms improved in psoriasis patients after the administration of an anti-TNF-α agent also support this hypothesis (18-20). Several meta-analyses of adult studies have reported increased levels of representative proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, and decreased levels of various cytokines, such as IL-1β, IL-4, IL-6, IL-10 and TNF-α, after antidepressant treatment, providing evidence of their associations with MDD and immune system dysregulation (21-26).

Based on these studies, hypotheses for pathophysiological mechanisms of depression have been suggested. Several factors have been identified that stimulate neuroinflammatory responses, such as lipopolysaccharide, chronic inflammatory diseases, and stresses. Some reports have stated that various stressors promote neuroinflammatory responses, and that increases in proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, result in activation of the hypothalamic-pituitary-adrenal (HPA) axis and increase of cortisol, known as the stress hormone. As a result, neurodegeneration occurs and a vicious cycle develops between the cytokines dysregulation and HPA-axis activation, eventually leading to

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depression (10, 14, 16, 20, 27). Further, in terms of the monoamine hypothesis, it has been suggested that cytokine increases the use of monoamines like serotonin and norepinephrine in the hypothalamus and amygdala, which eventually depletes these monoamines and leads to the development of depression (14, 28-30). A recent review explained that, in the interplay among the peripheral immune cells, the brain-blood barrier, and the microglia-astrocyte, homeostasis is normally maintained via neuroinflammation activation and anti-inflammatory responses, but when this balance is broken for some reason, mood disorder develops (31).

Some studies of children and adolescents have investigated the relationship between depression and inflammatory markers, such as cytokines. Henje et al. (32) reported that the levels of IL-2 were different in non-medicated depression patients compared to normal controls in a study of adolescent girls with depression. Gabbay et al. (33) reported a difference in INF-ɣ/IL-4 between patients and controls, suggesting an imbalance between proinflammatory and anti-inflammatory cytokines. In addition, a study of 76 adolescents with non-medicated internalizing disorders, such as depression and anxiety disorders, reported a difference in IL-6 levels compared to normal controls (34). A few longitudinal studies have also identified a relationship between depression and cytokines in children and adolescents. Copeland et al. (35) studied the progress of depressive symptoms and C-reactive protein (CRP) levels over time and reported that, although the CRP levels were not a predictor of depressive symptoms, depressive symptoms predicted subsequent increases of CRP levels. A study evaluated depressive symptoms in adolescent females weekly for 20 weeks, measuring IL-6 and CRP levels at the beginning and end points of the study. These levels were not correlated with trait levels, as measured using the

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Center for Epidemiologic Studies Depression (CES-D) scale, which measures depression severity, but they were correlated with state levels (36). Studies of cytokines have suggested that depression in adults may have different mechanisms than in children and adolescents. In one study, researchers compared and analyzed previous studies of the relationship between depression and cytokines in adults and adolescents, and they found similarities in increased IL-6 and decreased tryptophan, the precursor of serotonin, in both adults and adolescents. But they also found differences in that, whereas IL-1β levels were consistently increased in adults with depression, they varied in depressive children and adolescents without stress factors (16). Additionally, they reported that TNF-α levels were decreased in adolescents with depression and suicidality, whereas they were increased in adults with depression. Recently, a meta-analysis reported that results were not consistent except for increased TNF-α in studies of adolescents with depression, and even the TNF-α results were not statistically significant and differed from those in adult studies (37).

Due to the specific nature of child and adolescent studies, it is not easy to recruit appropriate samples in many cases. Some studies about this certain population have been conducted in patients with internalizing disorders, including both depressive and anxiety disorder, as well as those with or without antidepressant treatment. However, it would be important to control these factors. As far as we know, this is the first study conducted in this field on medication-naive adolescents with first-episode depression. Although some studies have reported differences in results between adolescent and adult studies, the reasons for those differences have not been clearly explained (for example, due to differences in the pathophysiology of depression between adolescents and adults, differences between depressive disorder and anxiety disorder, or

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differences in the number of episodes they experienced). Therefore, the current study investigates only medication-naive adolescents in first-episode MDD in an attempt to control for possibly confounding effects, such as chronicity, homogeneity of diagnosis, and history of exposure to psychiatric medications.

This study investigated alteration of cytokine and immune response in medication-naive adolescents with first-episode MDD. We hypothesized that these adolescents with MDD would differ significantly from healthy controls in inflammatory markers, such as cytokines, and that these differences would be altered by antidepressant treatments. We also examined the correlations between severity of depression and cytokine levels. We investigated the relationships between depression in adolescence and immune responses and compared our findings with those of existing studies.

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2. Materials and Methods

2.1. Participants:

We enrolled 25 adolescents with MDD and 25 adolescents without psychiatric disorders in this study. All participants were between 13 and 18 years of age at the time of enrollment. The patients with MDD visited the department of psychiatry at the Korea University Guro Hospital and were diagnosed with first-episode MDD. They had not taken any psychiatric medications and were confirmed to need antidepressant medications by child and adolescent psychiatrists. We included only medication-free patients, which we defined as "patients who discontinued their current medications during the study and for a washout period before the study began". The washout period varied for different drugs, from 1 week for methylphenidate to 3 weeks for fluoxetine. We included MDD patients who had not taken medication that affected the central nervous system for at least 3 weeks from the time of enrollment. Adolescents in the control group showed no psychiatric disorders through the semi-structured diagnotic assessments. They had no history of psychiatric diagnoses, psychiatric medications, or intellectual disability. We excluded participants who had neurological abnormalities or severe physical diseases (e.g., head trauma, multiple sclerosis, brain tumor, and neurovascular diseases). We also excluded from the study patients with intellectual disability. All participants were given a description of the study, and we obtained the written consent of both the adolescent and two guardians.

Participants were assessed using a psychiatric diagnostic test,

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intelligence test, and depression severity test. We collected blood samples at the time of enrollment to measure cytokine levels in participants. After the psychological test and blood sampling, the depressive adolescents were treated with antidepressant medications (e.g., escitalopram, sertraline or mirtazapine), and they underwent the psychological assessment test and blood sampling again after 12 weeks.

This study was approved by the Korea University Hospital Institutional Review Board (IRB No. 2017GR0135).

2.2. Assessment:

2.2.1. Diagnostic assessment: Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version - Korean version (K-SADS-PL-K)

This instrument was developed by Kaufman et al. (38). It is a semi-structured interview tool that takes about one and a half hours to perform. It is designed to assess the current and lifetime morbidity conditions and severity of the symptoms related to 32 psychiatric disorders, according to the DSM-IV diagnostic criteria. The K-SADS-PL Korean version was translated by Kim et al. (39) to confirm the reliability and validity for depressive disorder, anxiety disorder, attention deficit hyperactivity disorder, tic disorder, and oppositional disorder. Each question is scored 0 for no information, 1 for none, 2 for sub-threshold and 3 for above threshold. A sub-threshold diagnosis corresponds to a probable diagnosis, and a threshold diagnosis to a definite diagnosis.

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2.2.2. Intelligence test: Wechsler Intelligence Scale for Children-IV - Korean version (K-WISC-IV)

The K-WISC-IV is an intelligence test for children and adolescents. This instrument assesses cognitive ability (40). We excluded persons who had borderline intellectual functioning (below the score of 85 in the WISC-IV) from this study.

2.2.3. Depression severity assessment: Kovacs' Children's Depression Inventory (CDI) and Hamilton rating scale for Depression (HAMD)

The CDI is a self-report test developed by Kovac for assessing symptom severity of depression in children and adolescents. It is a version of the Beck depression inventory modified for childhood and adolescence (41). The CDI comprises 27 questions and requires the patients to self-report their symptoms severity. Item responses are presented as the statements of varying symptom severity.

The HAMD was developed by Hamilton (42) and comprises 17 questions. It is a tool that clinicians use to evaluate patients after observing their symptoms. It is widely used for objective evaluation of depression severity and is known as the gold standard.

For assessing the severity of depressive symptoms in all participants, we used Korean version of the CDI (43) and HAMD (44) that their reliability and validity have been verified, respectively.

2.3. Measurement of cytokines:

For the analysis of cytokines, blood samples of the patient and control groups were collected and separated into the plasma state through

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centrifugation. The blood samples were kept frozen at -50 °C. The collected blood samples were analyzed using the MILLIPLEX® MAP panel and the kit from the EMD Milipore Corporation. To calculate the cytokine concentrations in the samples, the median fluorescent intensity (MFI) data were saved and analyzed using the 5-parameter logistic or spline curve-fitting method. We analyzed 7 types of cytokines, IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ, which were the most investigated in previous studies.

2.4. Statistical analysis:

We performed statistical analysis using SPSS version 20. First, we calculated the means and standard deviations of the demographic and clinical data. To compare the levels of each cytokine between the depressive and healthy control groups, we performed a test of normality, and then we analyzed them using the Student's t test or the Mann-Whitney test, as appropriate according. We also performed paired t tests to measure the change in levels of each cytokine before and after treatment, within the depressive group after tests of normality. Finally, we analyzed the Pearson's correlation between each cytokine levels and the severity of depression. The statistical significance was set at $p<0.05$.

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3. Results

3.1. Demographic and clinical data:

Of the 25 first-episode depressive adolescents, 8 were males, and 17 were females, and their mean age ± standard deviation was 15.24 ± 1.79. The healthy control group had 6 males and 19 females, with a mean age of 16.00 ± 1.04. Of the 25 depressive patients, 7 adolescents had psychiatric comorbidities: 3 of attention deficit hyperactivity disorder (ADHD), 1 of persistent depressive disorder, 1 of obsessive compulsive disorder, 1 of anxiety disorder, and 1 of social phobia and ADHD. In the depressive adolescents, the mean period from onset of depressive symptoms to diagnosis of MDD (duration of episode) was 2.43 ± 1.65 months. Regarding the antidepressant treatment, 22 adolescents were treated with escitalopram, 2 were treated with sertraline, and 1 with mirtazapine.

In the depressive adolescent group, the scores for CDI and HAMD before treatment were 27.52 ± 8.53 and 19.68 ± 5.48, respectively, and after treatment, the scores were 17.92 ± 9.00 and 13.16 ± 5.57, respectively. The scores of CDI and HAMD after treatment were significantly decreased compared to those before treatment (Table 1).

3.2. Differences of cytokine level in plasma among depressive adolescents and normal controls:

We analyzed the differences between levels of plasma cytokines in the 25 depressive adolescent group and the 25 healthy control group. Of the

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7 cytokines initially examined, IL-1β and IL-6 were excluded from the analysis because they were below detectable values in the majority of patients and controls; therefore, we analyzed 5 cytokines, IL-2, INF-ɣ, TNF-α, IL-4, and IL-10. The levels of IL-2 ($p<0.01$), IFN-ɣ ($p<0.05$), TNF-α ($p<0.05$), and IL-10 ($p<0.05$), but not IL-4, were significantly lower in the depressive adolescent group than in the healthy control group (Table 2).

3.3. Changes of cytokine level after treatment of depressive symptoms in adolescents with major depressive disorder:

We examined the changes in levels of 5 cytokines from before treatment to after 12 weeks of antidepressant treatment in the 25 adolescents with MDD. Of the 5 cytokines we examined, IL-2 ($p<0.01$), INF-ɣ ($p<0.05$), and IL-10 ($p<0.05$) showed significant increases at 12 weeks post-treatment, compared to before treatment (Table 3). There were no significant differences between the depressive adolescent group and the healthy control group in posttreatment level of the IL-2, INF-ɣ, and IL-10.

3.4. Correlations of severity of depressive symptoms with levels of cytokines:

We analyzed the correlations between the severity of depressive symptoms and the levels of various cytokines in the depressive adolescents. For pre- and post-treatment, the CDI score was negatively correlated with the IFN-ɣ level ($r=-0.377$, $p<0.01$), and the HAMD score

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was negatively correlated with the INF-γ level ($r=-0.457$, $p<0.01$) and with the IL-10 level ($r=-0.216$, $p<0.05$) (Table 4).

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Table 1. Demographic and Clinical Data

	Depressive adolescents		Healthy controls
Gender : M / F	8 / 17		6 / 19
Age (years) : Mean ± SD	15.24 ± 1.79		16.00 ± 1.04
DOE (months) : Mean ± SD	2.43 ± 1.65		-
CDI : Mean ± SD	Before treatment 27.52 ± 8.52	After treatment 17.92 ± 9.00	5.56 ± 4.82
HAMD : Mean ± SD	Before treatment 19.68 ± 5.48	After treatment 13.16 ± 5.57	0.12 ± 0.44

CDI: Children's depression inventory; DOE: Duration of episode; F: Female; HAMD: Hamilton rating scale for depression; M: Male; N: Number of subjects; SD: Standard deviation.

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Table 2. Differences of Cytokine Levels in Plasma between Depressive Adolescents and Healthy Controls

		Depressive adolescents Mean (pg/ml) ± SD	Healthy controls Mean (pg/ml) ± SD	p-value
Proinflammatory cytokine	IL-2§	1.77 ± 0.33	2.20 ± 0.36	0.000**
	INF-γ§	6.07 ± 1.59	7.17 ± 1.87	0.034*
	TNF-α‖	10.25 ± 3.88	13.30 ± 4.25	0.021*
Anti-inflammatory cytokine	IL-4‖	32.51 ± 42.38	23.51 ± 13.40	0.794
	IL-10‖	7.39 ± 1.64	9.39 ± 3.14	0.015*

* $p<0.05$; ** $p<0.01$; § Student's t test; ‖ Mann-Whitney test

IFN: Interferon; IL: Interleukin; SD: Standard deviation; TNF: Tumor necrosis factor.

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Table 3. Changes of Cytokine Level after Treatment of Depressive Symptoms in Adolescents with Major Depressive Disorder

		Before AD treatment Mean (pg/ml) ± SD	After AD treatment Mean (pg/ml) ± SD	p-value
Proinflammatory cytokine	IL-2§	1.78 ± 0.35	2.26 ± 0.50	0.001**
	INF-γ§	6.17 ± 1.55	7.27 ± 1.84	0.024*
	TNF-α§	10.21 ± 3.06	9.90 ± 2.71	0.731
Anti-inflammatory cytokine	IL-4§	23.83 ± 12.08	23.00 ± 13.12	0.708
	IL-10§	7.39 ± 1.64	8.50 ± 2.01	0.033*

* $p<0.05$; ** $p<0.01$; § Paired t test

AD: Antidepressant; IFN: Interferon; IL: Interleukin; SD: Standard deviation; TNF: Tumor necrosis factor

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Table 4. Correlations of Severity of Depressive Symptoms with Levels of Cytokines

		CDI (r)	HAMD (r)
Proinflammatory cytokine	IL-2§	-0.189	-0.260
	INF-ɣ§	-0.377**	-0.457**
	TNF-α§	-0.167	-0.147
Anti-inflammatory cytokine	IL-4§	-0.035	0.086
	IL-10§	-0.028	-0.216*

* p<0.05; ** p<0.01; § Pearson's correlation analysis

CDI: Children's depression inventory; HAMD: Hamilton rating scale for depression; IFN: Interferon; IL: Interleukin; SD: Standard deviation; TNF: Tumor necrosis factor.

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4. Discussion

We found that the proinflammatory TNF-α level in the depression group was lower than in the healthy control group. Many previous studies have reported that increased levels of TNF-α were found in patients with depression (23, 26, 31, 37, 45), and that the levels decreased after antidepressant treatment (25). Amitai et al. (46) conducted a longitudinal study of cytokine changes before and after antidepressant treatment for children and adolescents diagnosed with depression and anxiety disorders, and reported that TNF-α decreased after antidepressant treatment. Similarly, Perez et al. (45) observed increases of TNF-α in youths with first-onset and recurrent-onset major depressive disorder, and reported decreased TNF-α after antidepressant treatment. Moreover, some studies reported that depressive symptoms were caused by a TNF-α injection and improved by an anti-TNF-α agent (18-20). However, Myung et al. (47) reported that some individual differences in TNF-α seem to exist, and Kohler et al. (25) described the mixed results of various studies. In a meta-analysis of child and adolescent study, D'Acunto et al. (37) reported that increases in TNF-α were not statistically significant. Also, some studies in children and adolescents reported decreased TNF-α in adolescents with suicidality or dysthymia, as seen in this study, while those studies did not cover only major depressive disorder adolescents (48, 49).

We found lower levels of IL-2 and IFN-ɣ in depressive adolescents. Kim et al. (50) similarly reported decreased levels of IL-2 in admitted adult patients with depression. A meta-analysis also reported decreased IL-2 in patients with history of suicide attempt or suicide ideation (51). Some studies have suggested that soluble IL-2 receptor (sIL-2R)

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increases and plasma IL-2 decreases. They also suggested the possibility of decreased production of IL-2 in depressive patients with suicidality (51-53). Mechanisms have been hypothesized whereby alteration of cytokines, such as decreases of IL-2, induce HPA-axis activation along with indoleamine-2,3 dioxygenase (IDO) activation, which then cause serotonin depletion and N-methyl-D-aspartate (NMDA) stimulation leading to increased risk of depression and suicide (51). In the current study, most of the 25 depressive adolescents had suicidality (i.e., 9 adolescents had a history of suicide attempt or self-harming behavior, and 14 adolescents had suicide ideation), supporting this mechanisms hypothesis. In addition, a recent meta-analysis reported that many studies have found decreased INF-ɣ levels in adult depressive patients (26), which is similar to our finding.

One of the anti-inflammatory cytokines we examined, IL-10, had lower levels in the depressive group than in the healthy group. In contrast, a number of previous studies reported higher IL-10 in depressive patients and decreased IL-10 after treatment of depression (25, 26, 54). However, in child and adolescent studies, IL-10 levels were inconsistent, with some showing nonsignificant increases (32, 45). One explanation for increased IL-10 is that it is an anti-inflammatory response to correct an activated inflammatory state due to high levels of proinflammatory cytokines (31). However, another proposed explanation is that reduced production of anti-inflammatory cytokines leads to inflammatory responses, and dysregulation between anti-inflammatory and neuroinflammatory responses can cause depression development (13, 15, 20, 27). In this way, IL-10 decreases, as seen in our study, may be associated with depression development. Other studies have reported decreased anti-inflammatory cytokine levels, such as transforming growth factor beta 1 (TGF-ß1) and IL-4 (50, 52, 55). Meanwhile, Clerici

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et al. (56) studied cytokine polymorphisms and found that lower genotypes of anti-inflammatory cytokines, such as IL-10, were often observed in MDD, raising the possibility that individuals who produce lower levels of anti-inflammatory cytokines may be susceptible to depression. Also, Laumet et al. (57) suggested that IL-10 decreases, as in the current study, may be part of the etiology of depression because a decreased capacity to induce IL-10 via T lymphocyte in meninges can negatively affect an individual's ability to resolve depression.

We compared cytokine levels before and after treatment of depression. After antidepressant treatment to improve of patients' symptoms, both the CDI and HAMD scores were reduced, showing improvement of depressive symptoms in most patients. Increases in cytokine levels after treatment were shown in IL-2, INF-ɣ, and IL-10. These cytokines were changed to the levels not significantly different from those of the healthy controls. In many of the previous studies, it has been consistently changed that the increased cytokine levels in depressed patients have decreased to levels similar to that of the healthy controls after treatment with antidepressants (25, 45, 54). These findings suggest that antidepressants have anti-inflammatory properties and immune modulating effects (54). In this respect, our findings suggest that the levels of cytokines, which were dysregulated, were then normalized through treatment due to the immune modulating effect of antidepressant treatment, given that immune dysregulation appears to be pathophysiology of depression.

Finally, we analyzed the cytokine levels and severity of depression based on CDI and HAMD scores in patients before and after treatment using Pearson's correlations analysis. We found that the CDI scores were correlated with IFN-ɣ levels, and the HAMD score were correlated with both IFN-ɣ and IL-10 levels.

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Our results have many similarities to those of previous studies of adults and youths, but also some differences as well. One hypothesis for pathophysiology in the relationship between depression and immunological response is that the etiology of depression is due to the activation of immune responses. Another hypothesis is that immunosuppression causes depression to develop (21, 58). Many studies have reported the relationship between depression and immune response, but it remains unclear whether a dysregulation of the immune response is a cause or a result of depression or stress reactions (31). Therefore, the increased or decreased cytokines associated with immune dysregulation seem to affect the development of depression. However, it is not clear whether the results in the current study are due to features of adolescence, features of first-episode depression, or features of racial, genetic characteristics of Koreans or Asians; thus, further studies are required.

There were several limitations in this study. The sample size was small, and the 12-week follow-up time after treatment was relatively short. Additionally, different antidepressant medications were administered: although almost all the adolescents with major depressive disorder in this study took escitalopram as an antidepressant medication, three of them took different antidepressants (i.e., 2 sertraline, 1 mirtazapine).

Studies of child and adolescent populations face challenge due to legal, ethical, individual, and familial limitations (59), so studies to identify the relationship between depression and immune imbalance in children and adolescents is insufficient compared to adult studies. We are the first to prospectively study medication-naive adolescents with first-episode MDD. We found relatively consistent results that several cytokine levels in adolescents with depression differed compared to normal healthy controls, and these differences were reduced after treatment of depression. Future studies need to increase sample size, and monitor the participants for a

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longer period of time, to better identify the impact of immune dysregulation on the etiology of depression. Further immunological studies and incorporating neuroimaging and genetic studies as well as new technologies like machine learning, could be helpful to find biomarkers of depression and subgroups of depression, elucidate its distinct etiology, and improve the treatment of depression.

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5. Summary

We investigated how immune inflammatory markers, such as cytokines, are expressed in adolescents with depression. Previous studies have reported that depression is related to immune responses and that, reciprocally, immune responses are involved in the development of depression. The subjects of this study were adolescents aged 13 to 18 years who had visited a psychiatric outpatient clinic at a university hospital and were medication-naïve patients with first-episode MDD. The patient group underwent blood sampling twice for analysis of cytokines, once before and once after treatment of depression. They were evaluated for depression severity using the CDI and the HAMD. The normal healthy group comprised adolescents with no psychiatric conditions, such as depression or anxiety disorders, and underwent blood sampling and assessed using the same depression severity scales. Analysis of cytokines found that levels of IL-2, INF-ɣ, TNF-α, and IL-10 in the depressed adolescents were lower than in normal adolescents. Further, after 12 weeks of treatment, the levels of IL-2, INF-ɣ, and IL-10 increased to levels similar to those of normal controls, where TNF-α did not. In addition, the correlations between depression severity and cytokine levels in the patient group showed that CDI scores were correlated with INF-ɣ, and HAMD scores with INF-ɣ and IL-10. These results show both similarities and differences with those of other studies, suggesting that the alterations of cytokines are associated with depression and that immune dysregulation affects the development of depression. To identify the etiology of depression and treat depression better, future research should be continued in this area, and collaboration with other fields of studies will be required.

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Alteration of Cytokines in Medication-Naive Adolescents with First-Episode Major Depressive Disorder

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(Abstract)

Evidence suggests that depression is correlated with stress and with immune inflammatory responses, and efforts have been made to identify the relationships between depression and inflammatory markers, such as cytokines. This study investigates cytokines, comparing medication-naive adolescents with first-episode major depressive disorder (MDD) to normal adolescents, examining changes in cytokine levels before and after treatment of MDD adolescents, and exploring the relationship between cytokine levels and severity of depressive symptoms. The participants in this study were 25 adolescents with MDD and 25 healthy adolescents without psychiatric disorders, aged from 13 to 18 years. We took blood samples and assessed depression severities twice in the depressive patient group, before and after treatment, and once in the

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normal control group. Our analysis of the cytokines shows that, compared to healthy controls, the adolescents with depression had lower levels of interleukin 2 (IL-2), interferon gamma (INF-ɣ), tumor necrosis factor alpha (TNF-α), and IL-10 before treatment, and increased levels of IL-2, INF-ɣ, and IL-10 after treatment. In addition, the IFN-ɣ levels were correlated with depressive symptom scores on both the Children's Depression Inventory (CDI) and Hamilton Rating Scale for Depression (HAMD), whereas the IL-10 level were correlated only with the HAMD scores. We expect to identify the role of immune responses involved in the development of depression with a prospective analysis of the changes in cytokines in medication-naive adolescents with first-episode MDD.

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약물에 노출되지 않은 초발 우울증 청소년 환자의 사이토카인 변화

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(초록)

우울증이 스트레스 및 면역 염증 반응과 서로 관련성을 가지고 있다는 증거들이 밝혀지고 있으며, 특히 우울증과 cytokine 등의 염증 지표들과의 관련성을 밝히기 위한 노력들이 있어왔다. 본 연구에서는 이전에 정신과적 약물에 노출된 적이 없는 청소년 우울증 환아들이 정상 청소년들과 비교하여 사이토카인의 어떤 차이가 있으며, 우울증 치료 전후의 사이토카인의 변화는 어떠한지 알아보고, 우울증 증상의 심각도와 사이토카인 수치와의 어떠한 상관관계를 보이는지에 대해서 알아보고자 하였다. 연구 대상은 13-18세의 청소년들 중 이전에 정신과적 약물치료를 받은 적이 없는 주요 우울장애 환아 25명과 정신과적 질환이 없는 정상 대조군 25명이었다. 연구 대상자들 중 우울증 환자군은 우울증 치료 전과 우울증 치료 12주 후 각 2회에 걸쳐 혈액 채취 및 우울증 심각도 평가를 시행하였고, 정상 대조군은 1회 혈액 채취 및 우울증 심각도 평가를 시행하였다. 사이토카인의 분석 결

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과, 청소년 우울증 환자군은 정상 대조군과 비교하여 Interleukin 2(IL-2), Interferon gamma(IFN-ɣ), Tumor necrosis factor alpha(TNF-α)와 IL-10이 더 감소되어 있었고, 우울증 환자군 내에서 치료 후 IL-2, INF-ɣ, IL-10의 증가가 관찰되었다. 또한 IFN-ɣ가 우울 증상 심각도 평가 척도인 Children's depression inventory(CDI) 및 Hamilton rating scale for depression(HAMD)과 상관관계를 나타내었고, IL-10은 HAMD 점수와 서로 상관관계를 나타내었다. 본 연구에서는 정신과적 약물에 노출되지 않은 초발의 청소년 우울증 환아의 사이토카인 변화를 전향적으로 분석함으로써 우울증 발병에 관여하는 면역반응의 역할을 밝히는데 도움을 줄 것으로 기대한다.

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□ 논문 및 저서

「소아 청소년 불안장애에 동반된 신체증상」 석사학위논문 2008. 12.