Treatment effects of probiotics on cognitive function and regulatory role of cortisol, IL-1β in adolescent patients of major depressive disorder

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Article

Treatment Effects of Probiotics on Cognitive Function and Regulatory Role of Cortisol, IL-1β in Adolescent Patients of Major Depressive Disorder

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Abstract: To investigate effects of probiotics on cognitive function and regulation of cortisol and IL-1β in adolescents with depression. All 180 participants were randomly assigned into study group(treated by probiotics combined with sertraline hydrochloride) and control group(treated by sertraline hydrochloride). The repetitive Neuropsychological State Test (RBANS) and Hamilton Depression Scale (HAMD) were administered in MDD patients. The levels of serum cortisol and IL-1β were detected by ELISA kit. Except speech function, immediate memory, visual span, attention function, delayed memory and RBANS in the study group were significantly higher than those in the control group. The cortisol and interleukin1β in the study group were significantly downregulated than those in the control group. Except speech function, cortisol level was negatively correlated with RBANS total score and other factors in the study group. Interleukin-1β was negatively correlated with the total score of RBANS and each factor score. Cortisol and interleukin-1β were predictors of RBANS total score, which explained 46.80% of the variance. Cortisol had significant predictive effects on attention function and delayed memory, and interleukin-1β had significant predictive effects on visual span and speech function. It could concluded that probiotics can improve cognitive function in adolescents with depression by regulating cortisol and IL-1β levels.

Keywords: Adolescence; Major depressive disorder; Cognitive disorder; Cortisol; IL-1β; Probiotics

1. Introduction

Major depressive disorder(MDD) is a common mental disorder among adolescents. An epidemiological survey in Zhengzhou showed that 20.03% of middle school students have obvious depressive symptoms and 22.41% may have suspected depressive symptoms, the positive detection rate of depressive symptoms among high school students was significantly higher than that of middle school students. In Beijing, the prevalence rate of depressive disorder among students aged 6-16 was 2.29%(234/10 215 cases), which has an age effect. Along with the growth of the age, the prevalence rate of depressive disorder also increased, and the age of 12 is a key turning point and would reach a peak around the age of 15[1, 2]. Previous studies have found that patients with MDD have impaired cognitive functions such as the domains of information processing speed, attention or alertness, working memory, word learning, visual learning, reasoning and problem solving and social cognition. After conventional antidepressant treatment, negative emotion and sleep quality can be significantly improved, but there are still obvious cognitive impairments[3, 4]. Middle school students are at a crucial stage of development in academic performance. However, impaired cognitive function affects learning efficiency and correspondingly increases academic pressure, it may furtherly induce or aggravate depressive symptoms. On the other hand, Impaired cognitive function can affect treatment efficacy and raise the risk of relapse. This pathological process forms a vicious cycle so that the MDD patients could maintain their depressive state or become severer, so

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intervention and rehabilitation of cognitive function is still an unsolved problem in clinical practice of treatment program for MDD around the world.

Probiotics have been preliminarily verified the effects of improving cognitive function[5], In one study, Fei found that probiotic supplementation could enhances cognitive functions and benefitted sleep quality by increasing the abundance of intestinal flora in older adults with mild cognitive impairment[6]. Sanborn firstly enrolled 200 English-speaking, healthy middle-aged and older adults (aged 55–75), recruited from the community using social media and local advertisements. And then the participants will be randomized to either the probiotic or placebo group using random number generation, the results of this randomized clinical trial indicated that Lactobacillus GG (LGG) probiotic supplementation could promote anxiety and depression remission and enhance the cognitive domains of executive functioning and processing speed[7]. The researchers argued that it needed to translate preclinical data into clinical data where the evidence is more limited. Recent studies, to some degree, bridge the preclinical-clinical gap and suggest the role of infectious components in the pathogenesis of Alzheimer's disease(AD), there is lower abundance in the gut of E. rectale and B. fragilis in cognitively impaired elderly patients with brain amyloidosis, supplementation of Lactobacilli- and Bifidobacteria- based probiotics has improved cognitive, sensory and emotional functions and general life quality in subjects with AD[8]. In summary, probiotic supplementation was mainly utilized in improving cognitive function in patients of AD and MCI and healthy middle-aged and older adults in the present studies.

The acute symptoms of MDD are anhedonia, distress, insomnia, hopelessness, suicidal ideation and behavior, non-suicidal self-injury(NSSI), not including the cognitive impairment, therefore therapeutic strategies, especially effect of probiotic supplementation, for cognitive impairment in MDD patients are seldom explored. but another critical concern is that the mechanism of improvement effect is still unclear, meanwhile, the present research results are contradictory sometimes, in one study showed that kynurenine in serum of MDD patients was lower than that of health volunteers, nevertheless, another double-blind study indicated that kynurenine of MDD patients were higher than the health controls and treatment of selective serotonin reuptake inhibitors(SSRI) combined with probiotic bacteria Lactobacillus Plantarum 299v (LP299v) could decrease the decreased KYN concentration and improved cognitive performance[9, 10]. In recent years, the gut-microbiota-brain axis hypothesis of MDD have become an important field of pathological mechanism for MDD. There is two-pathway regulation between intestinal microbes and the central nervous system(CNS), and the disturbance of intestinal microflora can affect hippocampal neurogenesis and impair memory function in MDD patients, meanwhile, probiotics can regulate intestinal microecology and furtherly improve the cognitive function[11,12]. Gut microbiome disturbances have been widely implicated in MDD, one of previous study suggested bacteroides species enriched in the gut microbiome from MDD patients differentially impact the susceptibility to depressive behaviors and transplantation of fecal microbiome from MDD patients into antibiotic-treated mice could induce anxiety and despair-like behavior and impaire hippocampal neurogenesis[13]. Zhang, in one prospective study, proved that the abundance of fecal Streptococcus was highly correlated with both HAMD and HAMA scores. The patients with severe depression symptoms showed higher abundance of Phascolarctobacterium and Akkermansia, while enrichment of Akkermansia, Coprococcus and Streptococcus were observed with severe anxiety symptoms. Finally the researchers argued that fecal microbial metabolite indole-3-carboxyaldehyde proved useful to discriminate the severity of depression or anxiety symptoms in MDD patients[14]. So this study could proposed one hypothesis that probiotics can affect the brain function and improve cognitive performance in MDD patients.

Cortisol and IL-1β are considered as novel biomarkers of chronic stress which triggers impairment of intestinal mucosal barrier function associated with MDD and the aforementioned result could also be duplicated by animal models. Previous studies have verified that probiotics could regulate the process of human inflammatory reactions and stress hormone-releasing[15-19]. Therefore, it could hypothesize that cortisol, IL-1β are regulators between probiotics and improvement of cognitive function in MDD patients. This study aims to investigate the effect of

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probiotics on improving cognitive function in adolescents with MDD and the relationship between probiotics and cortisol, IL-1β.

2. Materials and Methods

2.1. Participants

This study was carried out in the clinics of 5th Affiliated Hospital in Science & Technology University of Henan and all clinical data were collected from Jan. 2019 to Dec. 2021, 160 adolescents with MDD, aged 17 ~ 19 years old, including 71 males and 79 females, were continuously enrolled by convenient sampling method. The patients were diagnosed with by 2 separate psychiatrist according to the diagnostic criteria of MDD in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition(DSM-V)[20]; Inclusion criteria: ①Senior high school students; ②All the patients were first diagnosed as MDD. Exclusion criteria: ①Patients who came from a divorced and parents died family; ②with personal history of left-behind; ③with severe medical diseases or disability; ④with history of brain injury, poisoning, asphyxia; ⑤who experienced major life events in the recent half year, such as lovelorn, unanticipated accident, bereavement, etc.

Using random number table, the experimenter randomly assigned the patients into two different room of Consulting room 1 as study group and Consulting room 2 as control group.

This study was approved by the Ethical Review Committee for medical research on May 31st, 2019(NO.2019-2019-6-4). Written informed consent was obtained from all participants.

2.2. Medical intervention

The study group was assigned to receive treatment of probiotics combined with Sertraline, while the control group was treated with Sertraline only. The initial dose of Sertraline(Pfizer) for adolescent MDD patients is usually 50mg/d, which will reach a fixed dose of 100mg per day after 4 to 7 days. All MDD patients have a dose range of 100 to 200mg per day, and it may be appropriately adjusted according to patient's tolerance and side effect. Probiotics(Enterococcus and Bacillus cereus capsules, Hangzhou Yuanda Biology) would be taken orally with 0.5g/ time, 2 times per day. The treatment period of this study was 2 months.

2.3. Mental assessment

2.3.1. Repeatable Battery for the Assessment of Neuropsychological Status(RBANS) RBANS is utilized to evaluate the cognitive performance in patients of MDD, schizophrenia, bipolar disorder, stroke, Parkinson's disease with good property of reliability, validity, RBANS consists of 12 sub-tests(i.e., list learning, story memory, figure copy, line orientation, picture naming, semantic fluency, digit span, coding, list recall, list recognition, story recall, and figure recall), which are assigned into 5 factors of immediatememory, visuospatial, language, attention and delayed memory and a total scale score. Calculation method of Randolph Cortical-Subcortical Deviation Score is as follows: [(visuospatial-construction + attention)/2] − [(language + delayed memory)/2], where scores > 0 indicate a "subcortical" pattern and scores < 0 indicate a "cortical" pattern of performance. The scores from the five domains contribute to an overall total RBANS score and administration time is approximately 30 min [21].

2.3.2. Hamilton Depression Scale (HAMD) HAMD, consisting of 24 items, was employed to assess the severity of depressive symptoms in MDD patients, and all items can be assigned into 7 dimensions of anxiety/somatization, weight, cognitive disorder, diurnal variation, retardation, sleep disturbance and hopelessness. HAMD included a total of 24 items with 10 items were scaled from 0 to 2 and remaining 14 items were scaled from 0 to 4. Items of 0–2 points were valued as none(0), mild-moderate (1), and severe (2), while items of 0–4 points were valued as none(0), mild(1), moderate (2), severe (3), and very severe (4). the higher the score, the severer the degree of depression. The administration time is approximately 15 min[22].

The cognitive function and severity of depression in all MDD patients were anonymously rated before starting the medication and the demographical variables of gender, age were also registered.

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2.4. Cortisol and IL-1β test

Participants abstain from high-fat diet within 12 hours and sleep for 8 hours with overnight fast, at the time of 7:00 to 9:00 a.m., whole blood of 5 ml is collected in EDTA-containing anticoagulant tubes, which would be placed at room temperature for half an hour. The next step is to isolate the serum at a low temperature of 4 ℃ with 3000r/min for 10min, and then add the prepared species and standard product into the isolated serum for reacting of 30 minutes at 37 ℃, After the plate is washed 5 times, the TMB Chromogen Solution A, B is added for Color display at 37℃ within 10 minutes, the last step is to add termination solution and read opticaldensity(OD) value within 5 minutes. Cortisol, IL-1β are detected by Enzyme-Linked Immunosorbent Assay (ELISA kit, purchased from Shanghai Mingfeng Biological Co., LTD., Art. No. is M-10718, M-10083). A 10*96-well plate has been precoated with anti-Cortisol/ IL-1β IgG. Samples and the Cortisol/IL-1β-(Horseradish Peroxidase, HRP) conjugate are added to wells, where any Cortisol / IL-1β in the sample may competes with the added Cortisol/ IL-1β-HRP for antibody binding. The wells are washed for removing unbound material after incubation and then Tetramethylbenzidine(TMB) substrate is added which is catalyzed by HRP to produce blue coloration. The reaction is terminated by addition of Stop Solution which stops the color development and produces a color change from blue to yellow. The intensity of signal is inversely proportional to the amount of Cortisol/ IL-1β in the sample and the intensity is measured at 450 nm. All the operations procedure is carried out according to the instruction manual provided by manufacturer.

2.5. Statistical analysis

SPSS21.0 is used for data management and analysis, and χ2 for discrete variable, independent sample t-test for continuous variable, Pearson's correlation analysis, regression analysis were conducted for data processing[23]. $P< 0.05$ was considered statistically significant.

3. Results

3.1. Between-group comparison of demographic and clinical variables

There were no significant differences of gender, age and HAMD scores between the two groups ($P > 0.05$). (see Table1)

Table 1. Between-group comparison of demographic and clinical characteristics（%/ ±SD）.

Variables	Study group(N=80)	Control group(N=80)	χ^2/t	*P*
Gender				
Female	34	37	0.98	0.223
Male	46	43		
Age	17.86±0.67	17.68±0.79	0.26	0.794
HAMD score	31.08±5.96	30.84±5.52	1.62	0.108
RBANS score	281.43±37.90	271.18±41.35	1.63	0.104

3.2. Comparison of cognitive function between the study group and control group.

Independent sample t-test showed that factor scores of immediatememory, visuospatial, attention and delayed memory except language and total score of RBANS were significantly higher in the study group than those of in the control group ($P<0.05$ or 0.01)(see Table 2).

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Table 2. Comparison of cognitive function between the study group and control group (±SD).

Factors	Study group(N=80)	Control group(N=80)	*t*	*P*
immediatememory	65.93±17.26	60.16±15.79	2.20	0.029
visuospatial	90.69±21.30	83.70±19.62	2.16	0.032
language	79.89±11.12	82.18±11.48	−1.28	0.202
attention	87.44±11.00	81.70±15.57	2.69	0.008
delayed memory	64.61±19.75	56.73±12.94	2.99	0.003
total score of RBANS	388.55±46.72	364.46±44.43	3.34	0.001

3.2. Comparison of cortisol and IL-1β between the study group and control group.

Independent sample t-test revealed that the levels of cortisol and interleukin1β in the study group were significantly lower than the control group (P<0.05 or 0.01) (see Table 3).

Table 3. Comparison of cortisol and interleukin1β between the study group and control group (±SD).

indices	Study group	Control group	*t*	*P*
cortisol	234.22±32.01	633.44±70.23	−5.23	0.000
IL-1β	86.82±25.61	130.11±55.80	−2.45	0.015

3.3. Correlation analysis of cognitive function and cortisol and IL-1β in study group.

Pearson's correlation analysis was performed for cognitive function and cortisol and IL-1β in MDD patients, Besides factor of language, cortisol level in study group negatively correlated with total score of RBANS and other factor scores (P<0.01); IL-1β negatively correlated with the total score and factor scores of RBANS (P<0.05 or 0.01) (see Table 4).

Table 4. Correlation analysis of cognitive function and cortisol and IL-1β in study group（r）.

indices	immediatememory	visuospatial	language	attention	delayed memory	total score of RBANS
cotisol	−0.293**	−0.378**	−0.106	−0.376**	−0.519**	−0.614**
IL-1β	−0.257*	−0.451**	−0.311**	−0.380**	−0.240*	−0.565**

Note: * is P＜0.05, ** is P＜0.01.

3.4. Regression analysis of associated factors of cognitive function in the study group.

Multiple regression analysis was employed for data analysis with facor scores and total score of RBANS as dependent variables and cortisol and IL-1β as independent variables. The results found that cortisol and IL-1β were predictors of RBANS total scores (P=0.000), which accounting for 46.80% of the variance. Cortisol significantly predicted attention and delayed memory and IL-1β significantly predicted visuospatial and language(P<0.05 or 0.01) (see Table 5).

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Table 5. Regression analysis of associated factors of cognitive function in the study group.

dependent variable	independent variable	regression coefficient	standard error	*t*	*P*	R^2
immediatememory	cotisol	−0.029	0.016	−1.78	0.080	0.103
	IL-1β	−0.100	0.084	−1.20	0.235	
visuospatial	cotisol	−0.033	0.018	−1.81	0.075	0.236
	IL-1β	−0.291	0.095	−3.05	0.003	
language	cotisol	0.005	0.010	0.51	0.615	0.100
	IL-1β	−0.149	0.054	−2.76	0.007	
attention	cotisol	−0.021	0.010	−2.13	0.037	0.192
	IL-1β	−0.110	0.051	−2.18	0.032	
delayed memory	cotisol	−0.079	0.017	−4.73	0.000	0.269
	IL-1β	0.016	0.086	0.18	0.857	
total score of RBANS	cotisol	−0.157	0.034	−4.64	0.000	0.468
	IL-1β	−0.634	0.174	−3.64	0.000	

4. Discussion

Development and health maintenance in has a meaning of transition and milestone in all adolescents' life, and the adolescents are commonly susceptible to various kinds of stress. Yang et al. in one survey found that adolescents tend to have stress response to the epidemic of COVID-19 which associates with their depressive symptoms. Fu et al. in another study argued that traditional confucianism and examination culture resulted Chinese families into high expectation for teenager in academic performance. The previous study showed that parent-child communication and interaction style could affect teenagers' perceptions of academic pressure, which combined with too many learning tasks led to inadequate exercise time and weight gain, and overweight may furtherly augment teenagers' susceptibility to stress response. It has been verified that academic pressure of junior high school students in China associated with school burnout and eventually induced depressive symptoms[24-26]. Conventional therapeutic response on cognitive impairment which is usually considered as the core symptom of MDD is poor. In present clinical practice, improvement of treatment efficacy and prognosis for cognitive impairment is an urgent task.

This study found that immediatememory, visuospatial, attention and delayed memory and total score of RBANS were higher, the levels of cortisol and IL-1β were lower in the study group than those of in the control group. Cortisol and IL-1β negatively correlated with the total score and factor scores of RBANS; Multiple regression analysis showed cortisol and interleukin1β were predictors of the total score of RBANS and accounting for 46.80% of its variance; cortisol is a significant predictor of attentional and delayed memory and IL-1β had predictive effect on visuospatial and language. These results indicate that probiotics can improve cognitive function in adolescents with depression by regulating levels of cortisol and IL-1β.

In recent years, the microbial-gut-brain axis theory, which indicates the continuous bidirectional-regulation model between central nervous system(CNS) and gastrointestinal tract(GT), has become a hot field of pathological mechanism for MDD, Changes of intestinal microbial composition can increase the permeability of intestinal barrier and activate inflammation and immune response of whole body, this aforementioned process, which furtherly regulate the release of monoamine neurotransmitters by alerting the activity of hypothalamic-pituitary-adrenal axis(HPA axis) and abundance of brain-derived neurotrophic factor(BDNF), eventually leads to MDD[27-29]. Cortisol is a kind of steroid hormone produced by adrenal gland for stress response, while IL-1β is a cytokine that activates and regulates function of immune cells and participates in the regulation of human inflammatory response. Both cortisol and IL-1β are sensitive to environmental stress, which is of great effect for individuals to maintain normal physiological function and adapt to environment. Heavy learning tasks, high academic competition pressure and common sleep debt increase the levels of cortisol and IL-1β, the previous studies have confirmed that cortisol can interact with testosterone to reduce the volume of the hippocampus and impair episodic memory, meanwhile, interleukin-1β,

known as the "cytokine storm", can induce secretion of other inflammatory cytokines and result in neuron reduction of hippocampal pyramidal cell and weakening of neural regeneration in the dentate gyrus. At the same time, High level of IL-1β can decrease BDNF and trigger the atrophy and ultimately death of hippocampal neurons[30-32]. In addition, some other studies have found that volume of the prefrontal lobe in individuals who experiencing chronic and stable stress is smaller than the controls. Meanwhile, the decrease of hippocampus volume, caused by chronic stress that consistent with upregulation of cortisol and IL-1β, is considered to be one of the neural basis of MDD[33-36]. It can furtherly affect cognitive functions of reasoning, problem solving, planning and strategy, analysis, behavioral decision-making and inhibition, memory, etc. in patients with MDD.

Long-term chronic stress can cause disorder of intestinal flora composition. Appropriate supplementation of probiotics can promote the balance-restoration and function-improvement of intestinal flora. Based on bidirectional-regulation model between CNS and GT, probiotics, which is benefit for mature of intestinal epithelial cells and maintenance of intestinal barrier function, can induce the change and expression of the circulation level of pro-inflammatory and anti-inflammatory cytokines, and this pathway can directly affect brain function. Otherwise, probiotics may limit the invasion of endotoxin by changing intestinal permeability and abate inflammatory response that inhibiting the hyperactivity of HPA axis[37, 38]. In a word, descending of cortisol and IL-1β can ultimately improve the cognitive function of adolescents with MDD.

One limitation of the present study is that the small sample size may make the results susceptible to type II errors, so it needs to be very cautious for applicate the data into another MDD patients group. Another limitation is that the life quality and psychosocial function were not assessed. It is necessary to furtherly verify the results of this study in a large sample and conduct a longitudinal study for observing the life quality, psychosocial function, rehabilitation rate, academic performance of the MDD patients in future research. Based on the finding in this study, it may be hopeful to efficiently improve the cognitive function of MDD patients in clinical settings.

5. Conclusions

The present study verifies that probiotics improve cognitive function in adolescents with MDD by regulating levels of cortisol and IL-1β on a microbial-gut-brain axis mechanism. It is indicated that the probiotics combined with antidepressants should be emphasized in the clinical practice to improve MDD prognosis.

6. Patents

Author Contributions: Shi SL performed conceptualization, formal analysis, original draft preparation, investigation, data curation X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis; Zhang SY and Kong LM contributed to experimental design, supervision, manuscript review and editing, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Ethical Review Committee for medical research (NO.2019-2019-6-4).

Informed Consent Statement: Written informed consent was obtained from all participants.

Data Availability Statement: The data and trial protocol can by requested from the corresponding author.

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Conflicts of Interest: The authors declare that there have no conflict of interest.

Appendix A

Major depressive disorder, MDD; interleukin-1β, IL-1β; Repeatable Battery for the Assessment of Neuropsychological Status, RBANS; Hamilton Depression Scale, HAMD; central nervous system; CNS; gastrointestinal tract, GT; hypothalamic-pituitary-adrenal axis, HPA axis; brain-derived neurotrophic factor, BDNF

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