Original Article
Agomelatine enhances the therapeutic effect of venlafaxine on depression and improves the levels of S100B and GFAP

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Abstract: Objective: To determine the efficacy of venlafaxine combined with agomelatine in elderly patients with depression and observe the changes in S-100 calcium binding protein B (S-100B) and glial fibrillary acidic protein (GFAP) before and after treatment. Methods: The data of 142 elderly patients with depression treated in Affiliated Hospital of Gansu Medical College between January 2020 and January 2022 were retrospectively studied. Among the patients, 62 treated with venlafaxine were assigned to a control group, and 80 treated with agomelatine combined with venlafaxine were assigned to an observation group. In addition, 50 patients with suspected meningitis who were treated in Affiliated Hospital of Gansu Medical College over the same time span were enrolled into a normal group. The two groups of patients were compared in terms of clinical efficacy after treatment and the changes in S100B and GFAP before and after treatment. The diagnostic value of S100B and GFAP in patients with depression was explored. Additionally, the changes in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score before and after treatment were compared between the two groups, and the adverse drug reaction rate was also compared. Results: The patient group showed higher cerebrospinal fluid (CSF) levels of S100B and GFAP than the control group (P < 0.001). The areas under the curve (AUC) of CSF S100B and GFAP for diagnosing depression were 0.833 and 0.925, respectively, and the AUC of the combination of the two was 0.967, which was larger than that of CSF S100B or GFAP alone (P < 0.001). Additionally, the control group showed lower clinical efficacy than the observation group (P < 0.001). After treatment, the observation group exhibited lower CSF levels of S100B and GFAP than the control group (P < 0.001), and demonstrated higher RBANS score than the control group (P < 0.001). The difference in adverse drug reaction rate was not significant between the control group and the observation group (P > 0.05). Conclusion: S100B and GFAP can be used as diagnostic indicators of depression. Agomelatine plus venlafaxine are superior to venlafaxine alone in the treatment of depression. The combination can contribute to better S100B and GFAP levels, and take a more obvious role in alleviating disease symptoms, thereby improving the cognitive function and overall well-being of patients.

Keywords: Venlafaxine, agomelatine, depression, efficacy, S100B, GFAP

Introduction

Depression is currently recognized as one of the leading global diseases, ranking as the fourth most common condition worldwide and is often referred to as the main killer of mankind in the 21st century [1]. According to the statistics of the World Health Organization [2], depression has a global incidence of around 11%, with the number of affected individuals surpassing 340 million and continuing to increase. Unipolar depression is one type of depression. Compared to patients with bipolar depression, patients with unipolar depression complain of symptoms including dizziness, headache, cardialgia, and poor appetite, but the symptoms cannot be identified by examinations. In other words, the symptoms are more likely to be their subjective feelings, possibly caused by changes in the concentrations of neurotransmitters in their brains [3]. Patients with unipolar depression suffer great mental and even physical pain, which impacts on their social connections and professional functions, leading to a high risk of suicide [4].

Drug therapy is currently the main clinical treatment for depression. Venlafaxine, a multimodal antidepressant, can affect neurotransmitters through various mechanisms [5]. It can antagonize 5-HT3, 5-HT7 and 5-HT1D receptors, partially activate 5-HT1B receptors, fully activate 5-HT1A receptors, and inhibit 5-HT transporters [6]. Agomelatine, another unique antidepressant, can activate melatonin receptors (MT1 and MT2) and antagonize 5-HT2C receptors [7]. This mechanism can adjust the biological clock and improve sleep quality and biological rhythm of patients with depression.

Unlike many other diseases, the exact cause of depression is still under investigation, making it challenging to diagnose through a single test or a series of examinations. Some symptom assessment scales can help doctors to have a quantitative reference to the severity of depression symptoms, but they are not the basis for diagnosis [8]. The changes in microglial activity take a crucial part in the occurrence and development of nervous system diseases, and western medicine believes an involvement of microglia in the pathophysiological process of depression [9]. Glial fibrillary acidic protein (GFAP) and S-100 calcium binding protein B (S-100B) are regarded as microglia markers [10]. The research manly explored the role of GFAP and S100B in cerebrospinal fluid (CSF) and tissue materials.

Accordingly, this study analyzed the efficacy of venlafaxine combined with agomelatine in elderly patients with depression and its effects on S100B and GFAP to provide a reference for clinical treatment and outcome.

Materials and methods

Sample collection

This study was performed with the approval from the Medical Ethics Committee of Affiliated Hospital of Gansu Medical College. The data of 188 elderly patients with depression treated in Affiliated Hospital of Gansu Medical College between January 2020 and January 2022 were retrospectively studied. In addition, 50 patients with suspected meningitis who were treated in Affiliated Hospital of Gansu Medical College over the same time spanning were enrolled into a control group. The enrolled depression patients showed no significant difference from the control group in age and gender (P > 0.05).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria of depression in the International Classification of Diseases 11th Revision [11]; (2) Patients whose Hamilton Depression Scale-24 score was over 17 points [12]; (3) Patients over 60 years old; (4) Patients with stable vital signs; (5) Patients who had their first onset and did not receive treatment before; (6) Patients with detailed clinical data.

Exclusion criteria: (1) Patients with a history of drug abuse; (2) Patients with impaired function of key organs such as heart, liver, and kidney; (3) Patients with immunodeficient pulmonary infection, infectious diseases, or organic diseases; (4) Patients with serious diseases, such as cerebrovascular diseases and tumors; (5) Patients with a suicidal tendency; (6) Patients allergic to the study drugs; (7) Patients with cognitive impairment, such as vascular dementia and Alzheimer's disease.

Sample screening

According to the inclusion and exclusion criteria, the samples were screened, and 142 patients who met the requirements were enrolled. Among them, 62 patients were treated with venlafaxine (control group) and 80 patients were treated with agomelatine combined with venlafaxine (observation group).

Clinical data collection

All the data were acquired from electronic medical records, including the baseline data and detection indicators. The baseline data included age, gender, body mass index (BMI), course of disease, education length, past medical history, smoking history and alcoholism history, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [13], and adverse drug reactions. Laboratory indexes included S100B and GFAP in CSF.

Evaluation criteria of efficacy

The reduction rate of Hamilton Depression Rating Scale (HAM-D) score = (HAM-D score before treatment - HAM-D score after 12 weeks of treatment)/HAMD score before treatment *100%. Cured: after 12 weeks of treatment, the reduction rate of HAM-D score was ≥ 75%, and clinical symptoms disappeared; markedly
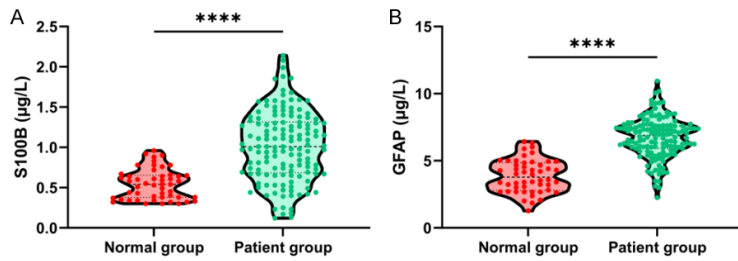
Figure 1. S100B and GFAP expression in control group and patient group. A: S100B expression; B: GFAP expression. Note: S-100B: S-100 calcium binding protein B; GFAP: Glial fibrillary acidic protein; ****P < 0.0001.

ing the clinical value of serum markers, and DeLong test was adopted for analyzing the difference in area under the ROC curve (AUC). P < 0.05 indicates a significant difference.

Results

Expression and diagnostic value of S100B and GFAP in CSF in patients with depression

effective: after 12 weeks of treatment, the reduction rate of HAM-D score was ≥ 50% and < 75%, and the clinical symptoms were obviously alleviated; effective: after 12 weeks of treatment, the reduction rate of HAMD score was ≥ 30% and < 50%, and the clinical symptoms were alleviated; ineffective: after 12 weeks of treatment, the reduction rate of HAMD score was less than 30%, and clinical symptoms were not alleviated or even worsened. Overall response rate = (the number of cured cases + the number of cases with markedly effective response + that of cases with effective response)/total number of cases *100%.

Outcome measures

Primary outcome measures: The two groups of patients were compared in terms of clinical efficacy after treatment and the changes in S100B and GFAP before and after treatment.

Secondary outcome measures: The diagnostic value of S100B and GFAP in patients with depression was explored. The changes in RBANS score before and after treatment were compared between the two groups of patients, and the adverse drug reaction rate was also compared.

Statistical analyses

This study used SPSS 26.0 for data analysis, and Kolmogorov-Smirnov test for normality analysis. Normally distributed data were described by mean ± SD, using t-test for independent samples and paired t-test for within-group comparisons. Counted data were described by percentage, and analyzed using chi-square test. Receiver operating characteristic (ROC) curve and diagnostic indicators such as sensitivity and specificity were adopted for evaluat-

The CSF levels of S100B and GFAP in the patient group were higher than those in the control group (P < 0.001, **Figure 1A**, **1B**). The AUC of CSF S100B and GFAP in diagnosing depression was 0.833 and 0.925, respectively, and the AUC of the combination of the two was 0.967 (**Figure 2A-C**; **Table 1**). Further analysis by DeLong test showed that in diagnosing depression, the AUC of S100B combined with GFAP was notably greater than that of S100B or GFAP alone, and the AUC of GFAP was greater than that of S100B (**Table 2**, P < 0.01).

Comparison of baseline data

In terms of baseline data, the control group and observation group were not greatly different in age, gender, BMI, course of disease, education time, past medical history, smoking history, or alcoholism history (P > 0.05, **Table 3**).

Evaluation of clinical efficacy

The control group showed a notably lower overall response rate than the observation group (P < 0.001, **Table 4**).

Changes in S100B, GFAP, and RBANS score

After treatment, the patients showed decreased CSF levels of S100B and GFAP (P < 0.001, **Figure 3**), as well as increased RBANS scores (P < 0.001, **Figure 3**). Additionally, the observation group presented with lower CSF levels of S100B and GFAP (P < 0.001, **Figure 3**), as well as higher RBANS scores than the control group (P < 0.001, **Figure 3**).

Comparison of adverse drug reaction rate

No significant difference was identified between the control group and the observation
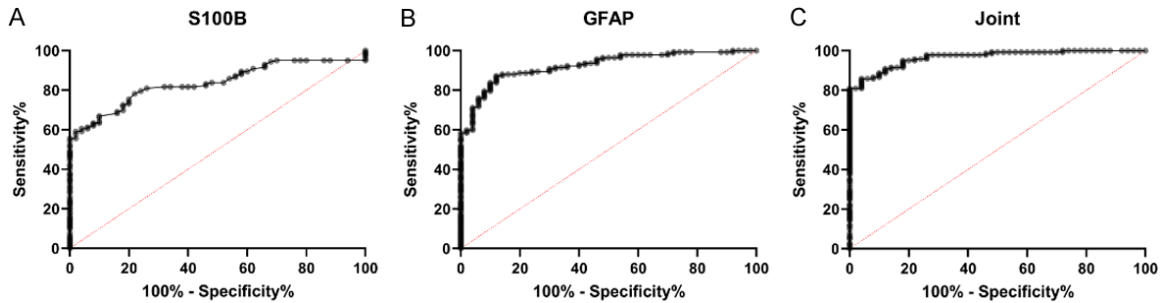
Figure 2. ROC curves of S100B and GFAP in diagnosing depression. A: ROC curve of S100B; B: ROC curve of GFAP; C: ROC curve of the combination of detection of S100B and GFAP; Notes: ROC: receiver operating characteristic; S-100B: S-100 calcium binding protein B; GFAP: Glial fibrillary acidic protein.

Table 1. ROC curve values

Predictor variable	Area under the curve	Confidence interval	Cut-off value	Sensitivity	Specificity	Youden index
S100B	0.833	0.777-0.889	0.93	59.16%	98.00%	57.16%
GFAP	0.925	0.888-0.962	5.1	87.32%	88.00%	75.32%
Join	0.967	0.946-0.988	0.77	85.92%	96.00%	81.92%

Note: ROC: receiver operating characteristic; S-100B: S-100 calcium binding protein B; GFAP: Glial fibrillary acidic protein.

Table 2. AUC-related values

Pair of test results	Z value	P value	AUC difference	Standard error value	95% CI	
					Lower limit	Upper limit
S100B - GFAP	-2.586	0.010	-0.092	0.218	-0.161	-0.022
S100B - Join	-5.019	< 0.001	-0.134	0.198	-0.186	-0.081
GFAP - Join	-3.056	0.002	-0.042	0.171	-0.068	-0.015

Note: AUC: area under the curve; S-100B: S-100 calcium binding protein B; GFAP: Glial fibrillary acidic protein.

group in adverse drug reaction rate during treatment (P > 0.05, **Table 5**).

Discussion

As a mental health issue, depression often manifests as low energy and decreased mobility, and in severe cases, patients may have suicidal intentions and behaviors [14]. The cause of depression remains unclear, and there is gold standard examination or laboratory method for the clinical diagnosis of depression [15]. Some symptom assessment scales can help doctors quantify the severity of depression, but they are not the basis for diagnosis.

CSF is a colorless and transparent liquid circulating in the ventricles and spinal cavity of the central nervous system, with functions of protection, nutrition and removal of metabolic wastes [16]. Over the past years, researchers have found that some biomarkers in CSF are

closely associated with the pathogenesis of depression. These biomarkers hold promise as indicators for the diagnosis, evaluation of disease progression and treatment of depression [17]. S100B is a calcium-binding protein, which is primarily produced by astrocytes. It affects many biologic processes in cells, like cell proliferation, differentiation, and calcium signal transduction [18]. Reportedly, elevated S100B levels usually can be found in the serum and CSF of patients with depression, which may be due to the activation of astrocytes, neuroinflammation, and changes in neurotransmitters [19]. GFAP is a specific intermediate filament protein of astrocytes, which is mainly implicated in the maintenance of cytoskeleton and the regulation of cell function [20]. Patients with depression usually present with increased GFAP levels in serum and CSF, which may be associated with neuroinflammation, changes in neurotransmitters, and reduction of nerve

Table 3. Baseline data

Factors	Control group (n=62)	Observation group (n=80)	χ^2 value	*P* value
Age			1.797	0.180
≥ 60 years old	31	49		
< 60 years old	31	31		
Gender			1.928	0.164
Male	39	41		
Female	23	39		
BMI			0.030	0.861
≥ 25 kg/m^2	17	23		
< 25 kg/m^2	45	57		
Course of disease			0.498	0.480
≥ 3 years	37	43		
< 3 years	25	37		
Education length			1.111	0.291
≥ 8 years	23	23		
< 8 years	39	57		
Past medical history				
Hypertension	22	27	0.004	0.829
Diabetes mellitus	17	20	0.106	0.744
Smoking history			1.928	0.164
Yes	39	41		
No	23	39		
Alcoholism history			0.157	0.691
Yes	5	8		
No	57	72		

Note: BMI: body mass index.

Table 4. Comparison of efficacy between the control group and the observation group

Group	Cured	Markedly effective	Effective	Ineffective	Total response rate
Control group (n=62)	2 (3.23)	18 (29.03)	28 (45.16)	14 (22.58)	48 (77.42)
Observation group (n=80)	5 (6.25)	44 (55.00)	26 (32.50)	5 (6.25%)	75 (93.75%)
χ^2 value		14.477			8.037
P value		0.002			0.046

growth factors [21]. However, whether S100B and GFAP in CSF have diagnostic value in depression is still under exploration. In this study, we found that S100B and GFAP were increased in patients with depression. This indicates a correlation of S100B and GFAP with the onset of depression. Similarly, Michel et al. [10] revealed a significant increase in serum GFAP in patients with unipolar depression, and Arora et al. [22] found a lower S100B level in healthy individuals than in patients with depression. In this study, the CSF levels of S100B and GFAP were increased in patients with depression, suggesting a possible diagnostic value of

S100B and GFAP for depression. BFurther, we analyzed the AUCs of S100B and GFAP by ROC curves. According to the results, the AUCs of S100B and GFAP in diagnosing depression were both greater than 0.8, and the AUC of their combination was greater than 0.9. De-Long test showed that the AUC of S100B combined with GFAP in CSF was greater than that of S100B or GFAP alone. This suggests that the joint detection result of S100B and GFAP in CSF might be a marker for depression.

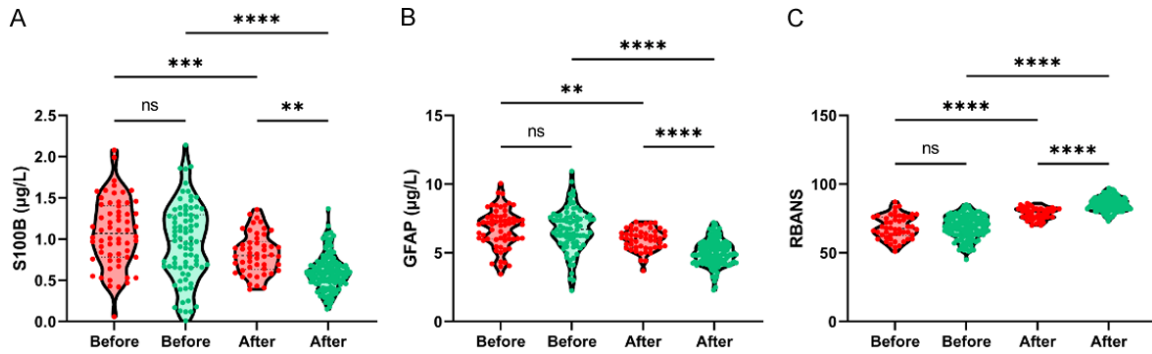Depression causes changes in the emotional state of patients, and also brings sleep disor-

Figure 3. Changes in S100B, GFAP, and RBANS score. A: Changes in S100B before and after treatment; B: Changes in GFAP before and after treatment; C: Changes in RBANS score before and after treatment. Notes: S-100B: S-100 calcium binding protein B; GFAP: Glial fibrillary acidic protein; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; nsP > 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Table 5. Incidence of adverse drug reactions

Group	Nausea and vomiting	Dizzy	Palpitation	Constipation	Somnolence	Total incidence
Control group (n=62)	3	2	2	4	3	14 (22.58)
Observation group (n=80)	2	1	2	2	2	9 (11.25)
χ^2/Z value						3.304
P value						0.069

ders, cognitive dysfunction, other physiologic dysfunctions, and nerve injury-related symptoms as it aggravates, seriously compromising patients' quality of life [23]. Currently, drug therapy is the primary treatment for depression in clinical practice. As an agonist of melatonin receptor and an antagonist of 5-hydroxytryptamine receptor, agomelatine can regulate patients' sleep cycle and optimize their night sleep structure to improve sleep quality and can adjust circadian rhythm to restore normal sleep and activity patterns, thus stabilizing their physiologic functions and improving their endocrine status [24, 25]. Venlafaxine is a phenylethylamine compound. It acts on the presynaptic membrane of nerve after oral administration, inhibiting the reuptake of 5-hydroxytryptamine and norepinephrine by neurons, thus prolonging the action time in synaptic cleft, rapidly reducing the sensitivity of B-receptor, improving patients' persistent depression and maintaining emotional stability [26, 27]. However, the effect of the combined treatment with both drugs in depression is still controversial. In this study, the observation group showed lower CSF levels of S100B and GFAP, as well as higher RBANS scores than the control group after treatment. Additionally, the observation group exhibited a higher efficacy

than the control group. These results imply that the combined therapy can improve the therapeutic effect in patients with depression. There are some possible reasons: Agomelatine alone can improve the sleep rhythm of patients with depression and promote the stable recovery of endocrine and overall physiological state. Moreover, by enhancing neuronal plasticity and promoting neuronal regeneration, the symptoms of cognitive impairment can be alleviated to some extent. However, agomelatine alone has difficulty in improving the overall emotional state of patients. Combined adoption of venlafaxine can shorten the duration of depression, improve their negative emotional states, and keep their emotional stability by prolonging the action time of 5-hydroxytryptamine and norepinephrine and enhancing the action time of dopamine. The main advantage of the combination of the two drugs is that they can improve the emotional state and neurologic function of patients in various ways, which are beneficial to patients' clinical symptoms and physiologic function. In addition, by alleviating the symptoms of patients with depression, agomelatine may indirectly pose a positive effect on neuroinflammation and neurodegenerative changes, thereby affecting the levels of S100B and GFAP. We also found that the combination of the two

drugs did not increase the incidence of adverse events in patients, showing a comparable safety profile with the single drug treatment.

This study has verified the efficacy of venlafaxine combined with agomelatine in elderly patients with depression and its effects on S100B and GFAP through retrospective analysis. However, the study has some limitations. First, S100B and GFAP are expressed in many disease cases. In this study, although patients were selected based on inclusion and exclusion criteria, further comparison of S100B and GFAP in CSF with S100B and GFAP in other disease cases is still needed to further accurately assess their influenceB. Second, since this is a retrospective study, it is impossible to obtain the long-term prognosis of patients. As a result, whether the treatment plan has long-term efficacy still needs analysis by more data. Therefore, we hope to carry out prospective studies in the future to improve the conclusions.

To sum up, S100B and GFAP can be adopted as diagnostic indicators for depression. Agomelatine plus venlafaxine are superior to venlafaxine alone in the treatment of depression. The combination can contribute to better S100B and GFAP levels, and take a more obvious role in alleviating disease symptoms, thereby improving the cognitive function and overall well-being of patients.

Acknowledgements

Disclosure of conflict of interest

None.

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