Effects of adjuvant folic acid + vitamin b12 therapy on Hcy metabolism, neurotrophy and nerve injury in patients with Alzheimer’s disease

Ping Han

Department of Neurology, 417 Hospital of Nuclear Industry in Lintong District Xi’an Shaanxi Province, Xi’an, Shaanxi Province 710600

ARTICLE INFO

Article history:
Received 8 Dec 2017
Accepted 22 Dec 2017
Available online 28 Dec 2017

Keywords:
Alzheimer’s disease
Folic acid
Vitamin b12
Hcy metabolism
Neurotrophy

ABSTRACT

Objective: To explore the effects of adjuvant folic acid + vitamin b12 therapy on Hcy metabolism, neurotrophy and nerve injury in patients with Alzheimer’s disease (AD). Methods: A total of 104 patients with Alzheimer’s disease were divided into control group (n=52) and study group (n=52) by random number table. Control group received clinical routine treatment, and study group received routine treatment combined with adjuvant folic acid and vitamin b12 therapy. The differences in Hcy metabolism, neurotrophy and nerve injury were compared between the two groups before and after treatment. Results: Before treatment, there was no statistically significant difference in serum contents of Hcy, neurotrophy indexes and nerve injury indexes between the two groups. After 3 months of treatment, serum Hcy of study group was lower than that of control group; serum neurotrophy indexes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) contents were higher than those of control group; serum nerve injury indexes myelin basic protein (MBP), neuron-specific enolase (NSE), neurofilament heavy (NfH) and S100 calcium-binding protein B (S100B) contents were lower than those of control group. Conclusion: Adjuvant folic acid and vitamin b12 therapy can effectively reduce Hcy content, increase neurotrophy and relieve nerve injury in patients with Alzheimer’s disease.

1. Introduction

Alzheimer’s disease (AD) is the degenerative nervous system disease commonly studied at present, which is insidious and progressively developed, and can be manifested as the impaired memory, executive dysfunction, personality changes, etc[1–3]. The cause of AD is not clear, some patients may show familial aggregation, and the self-care ability is lost in the later stage of the disease, which causes great pain to both patients themselves and their families. Adopting symptomatic treatment to improve concomitant disease and improve cognitive function is the basic principle of current AD treatment, but for large proportion of patients, the medication can only slow down disease progression to a certain extent and the drug treatment effect is limited. It is known that hyperhomocysteinemia is an independent risk factor for cardiovascular disease, and current scholars also think that abnormal Hcy metabolism is involved in the occurrence and development of AD, and the relative lack of plasma folate and vitamin b12 is the direct cause of elevated Hcy levels[4–6]. In this study, folic acid and vitamin b12 were used as adjuvant drugs for the overall treatment of patients with AD, and the change in neurotrophy indexes after Hcy metabolism was changed was explored to lay practice basis for discussing the implementation feasibility of subsequent such treatment in depth.

2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with Alzheimer’s disease; (2) diagnosed for the first time and receiving no other treatment outside the hospital; (3) the patients’ families signed informed consent; (4) cooperating with and completing the treatment and inspection.
Exclusion criteria: (1) with history of cerebral hemorrhage and cerebral infarction; (2) combined with cerebrovascular malformation, congenital mental retardation, etc.; (3) combined with serious cardiovascular diseases; (4) allergic to folic acid and vitamin b12.

2.2 Case information and groups

A total of 104 AD patients who were diagnosed and treated in this hospital between November 2011 and May 2017 were divided into control group (n=52) and study group (n=52) by random number table. Control group included 27 male cases and 25 female cases that were 67-79 years old; study group included 26 male cases and 26 female cases that were 65-78 years old. The differences in gender and age distribution were not significant between the two groups, and the follow-up study was approved by the hospital ethics committee.

2.3 Therapy

Control group received routine clinical treatment for Alzheimer’s disease, including the drugs that promoted neuronal metabolism, improved brain circulation and so on as well as proper diet and moderate exercise.

Study group received conventional treatment combined with adjuvant folic acid and vitamin b12 therapy, which was as follows: folate tablets 10 mg/d, vitamin b12 tablets 500 μg/d, for continuous 3 months of treatment.

2.4 Observation indexes

Immediately after inclusion (before treatment) and after 3 months of treatment, fasting cubital venous blood was collected from two groups of patients to isolate upper serum, which was cryopreserved for test. The content of Hcy in serum was determined by enzymatic transformation. RIA method was used to determine serum levels of neurotrophy indexes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2) as well as nerve injury indexes myelin basic protein (MBP), neuron-specific enolase (NSE), neurofilament heavy (NFL) and S100 calcium binding protein B (S100B), etc.

2.5 Statistical methods

Hcy, neurotrophy indexes and nerve injury indexes were all input in statistical software SPSS 25.0, t test was used to calculate statistics P and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Hcy metabolism

Comparison of serum Hcy contents between two groups of patients before and after treatment was as follows: before treatment, serum Hcy content of control group was (19.37±2.41) μmol/L and serum Hcy content of study group was (19.44±2.37) μmol/L; after 3 months of treatment, serum Hcy content of control group was (16.09±1.74) μmol/L and serum Hcy content of study group was (11.38±1.59) μmol/L. before treatment, serum Hcy contents were not significantly different between two groups of patients (P>0.05). After 3 months of treatment, serum Hcy contents of both groups were lower than those before treatment, and serum Hcy content of study group was lower than that of control group (P<0.05).

3.2 Neurotrophy indexes

Comparison of serum neurotrophy indexes NGF (ng/mL), BDNF (pg/mL), GDNF (pg/mL), IGF-1 (ng/mL) and IGF-2 (ng/mL) contents between two groups of patients before and after treatment was as follows: before treatment, serum NGF, BDNF, GDNF, IGF-1 and IGF-2 contents were not significantly different between the two groups (P>0.05). After 3 months of treatment, serum NGF, BDNF, GDNF, IGF-1 and IGF-2 contents of both groups were higher than those before treatment, and serum NGF, BDNF, GDNF, IGF-1 and IGF-2 contents of study group were higher than those of control group (P<0.05), shown in Table 1.

3.3 Nerve injury indexes

Comparison of serum nerve injury indexes MBP (pg/mL), NSE

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time point</th>
<th>NGF</th>
<th>BDNF</th>
<th>GDNF</th>
<th>IGF-1</th>
<th>IGF-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>52</td>
<td>Before treatment</td>
<td>14.28±1.75</td>
<td>30.29±3.76</td>
<td>27.38±3.05</td>
<td>5.36±0.57</td>
<td>9.18±1.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 3 months of treatment</td>
<td>18.73±2.05</td>
<td>39.81±4.53</td>
<td>34.52±4.29</td>
<td>6.52±0.73</td>
<td>14.57±1.61</td>
</tr>
<tr>
<td>Study</td>
<td>52</td>
<td>Before treatment</td>
<td>14.31±1.69</td>
<td>30.32±3.59</td>
<td>27.41±3.14</td>
<td>5.41±0.56</td>
<td>9.21±1.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 3 months of treatment</td>
<td>25.61±3.24</td>
<td>54.72±5.91</td>
<td>47.62±5.10</td>
<td>8.63±0.97</td>
<td>19.88±2.47</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, *P<0.05.
Comparison of serum nerve injury index contents between two groups of patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time point</th>
<th>MBP (ng/mL)</th>
<th>NSE (pg/mL)</th>
<th>NfH (pg/mL)</th>
<th>S100B (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>52</td>
<td>Before treatment</td>
<td>183.25±21.39</td>
<td>47.19±5.38</td>
<td>472.84±53.69</td>
<td>574.29±63.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 3 months of treatment</td>
<td>127.33±14.07</td>
<td>35.95±4.07</td>
<td>349.42±43.29</td>
<td>409.72±43.81</td>
</tr>
<tr>
<td>Study group</td>
<td>52</td>
<td>Before treatment</td>
<td>182.64±20.38</td>
<td>47.32±5.16</td>
<td>470.72±51.24</td>
<td>571.43±61.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 3 months of treatment</td>
<td>94.21±10.57</td>
<td>26.32±3.41</td>
<td>271.66±32.58</td>
<td>317.51±35.88</td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, *P*<0.05.

Hcy has been recognized as an independent risk factor for coronary heart disease. At present, some scholars have pointed out that hyperhomocysteinemia is also an independent risk factor for AD, and if the plasma Hcy content increases by 5 μmol/L, the occurrence risk of AD will increase by 40%[7,8]. Hcy has the following two metabolic pathways: (1) methylated into methionine from methionine synthase; (2) catalyzed into cysteine and adenosine by cystathionine beta-synthase[4]. In these pathways, the role of methionine synthetase is vitamin B12-dependent, the function of cystathionine beta-synthase requires donors from folic acid decomposition, and therefore, the addition of exogenous folic acid and vitamin B12 can effectively promote Hcy metabolism and reduce plasma Hcy levels. There is no clear conclusion whether reducing the Hcy levels can become the effective means for AD treatment, adjuvant folic acid and vitamin b12 therapy was added in the overall treatment of AD in this study, the changes in Hcy levels were compared at first, and it was found that compared with those before treatment, serum Hcy levels of both groups decreased to different extent after 3 months of treatment; further compared with that of control group, serum Hcy content of study group was lower after 3 months of treatment, indicating that folic acid and vitamin b12 can effectively accelerate the Hcy metabolism and reduce the Hcy content in the body. The effect of Hcy content change on the patient's condition will be further elaborated.

The cognitive dysfunction of AD patients is directly related to the repair dysfunction of injured neurons, and the expression deletion of many neurotrophy factors is involved in the occurrence and development of AD[9,10]. Both NGF and BDNF can maintain the growth and survival of neurons, it is combined with neuron surface receptor Trk and activate the MAPK/ERK signaling pathway to be involved in the regulation of damage neuron proliferation and differentiation, and their expression reduction can directly inhibit the damaged nerve repair and affect the patients' cognitive function[11,12]. GDNF is secreted by neuroglial cells, which is similar to BDNF, and also has important roles such as promoting nerve injury repair. Both IGF-1 and IGF-2 belong to the IGFs family, they exert growth hormone and other biological effects and can also promote the growth of a variety of nerve cells, and researches have shown that IGF-1 and IGF-2 expression reduce in a variety of brain injury diseases (cerebral hemorrhage, schizophrenia, etc.)[13–15]. The study results showed that compared with those before treatment, serum NGF, BDNF, GDNF, IGF-1 and IGF-2 levels of both groups increased after 3 months of treatment, indicating that both therapies can optimize the neurotrophy status in patients with AD to different extent; further compared with those of control group, serum NGF, BDNF, GDNF, IGF-1 and IGF-2 levels of study group were higher after 3 months of treatment, it confirms that after accelerating the decomposition of Hcy, folic acid and vitamin b12 can further improve the neurotrophy status in patients with AD, and it clarifies the significance of reducing Hcy for AD improvement.

There is β amyloid deposit out of nerve cells in patients with AD, the peripheral nerve cell membrane and mitochondrial membrane are damaged and provide less energy, so the synthesis of relevant neurotransmitters reduces, and the nerve cell damage and a series of dysfunctions occur[16,17]. After nerve cell injury, the specific factors in the cells can be released out of the cells and enter into the blood through the blood brain barrier, so the nerve injury-related indicators in peripheral blood can specifically reflect the severity of AD and measure the clinical therapeutic effect. MBP is an important part of the myelin sheath, the continuous myelin destruction can cause the MBP to fall into blood, and the increase of serum MBP content is a specific marker of myelin sheath injury[18]. Numerous studies have confirmed that serum NSE content increases in most patients with AD, and the specific content is positively correlated with the degree of brain injury. NfH is a multimer composed of three subunits with different molecular weight, and its high expression is found in both cerebrospinal fluid and serum of patients with optic neuritis, which is possibly related to nerve cell and spinal cord injury[19]. S100B is a typical neurobiochemical marker, its expression trend in human cerebrospinal fluid and serum is basically similar to that of
NSE, and the high expression of S100B is also an important symbol of nerve injury[20]. This study showed that compared with those before treatment, serum MBP, NSE, NIH and S100B contents of both groups reduced after 3 months of treatment; further compared with those of control group, serum MBP, NSE, NIH and S100B contents of study group were lower after 3 months of treatment, confirming that reducing Hcy content can effectively reduce the degree of nerve injury in AD patients.

Routine therapy combined with auxiliary folate and vitamin B12 therapy can effectively reduce the Hcy levels, improve the neurotrophy state and inhibit the nerve injury in patients with AD, it is expected to relieve the AD condition and improve the treatment outcome, and it is worthy of popularization and application in clinical practice in the future.

References


