Correlation of serum Tau and 8-iso-PGF2α levels with nerve injury and oxidative stress in patients with traumatic brain injury
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Objective: To study the correlation of serum Tau and 8-iso-PGF2α levels with nerve injury and oxidative stress in patients with traumatic brain injury. Methods: A total of 56 patients who were diagnosed with traumatic brain injury in Pidu District People’s Hospital between May 2014 and February 2017 were selected as the TBI group, and 45 volunteers who received physical examination in the hospital during the same period were selected as control group. Serum samples were collected to determine the contents of Tau, 8-iso-PGF2α, nerve cell apoptosis molecules and anti-oxidation molecules. Results: Serum Tau, 8-iso-PGF2α, Bax, Caspase-3 and Caspase-9 levels in TBI group were significantly higher than those in control group while Bcl-2, GSH, VitE, GSH-Px, SOD and HO-1 levels were significantly lower than those in control group; serum Bax, Caspase-3 and Caspase-9 levels in TBI patients with higher Tau level were significantly higher than those in TBI patients with lower Tau level while Bcl-2 level was significantly lower than that in TBI patients with lower Tau level; serum GSH, VitE, GSH-Px, SOD and HO-1 levels in TBI patients with higher 8-iso-PGF2α level were significantly lower than those in TBI patients with lower 8-iso-PGF2α level. Conclusion: Abnormal elevation of Tau and 8-iso-PGF2α levels in serum of patients with traumatic brain injury is related to the excessive apoptosis of nerve cells and the excessive activation of oxidative stress.

1. Introduction

Traumatic brain injury (TBI) is a common clinical trauma type with high fatality rate and disability rate[1,2]. The occurrence of nerve injury in patients with TBI involves multiple factors and multiple stages, outside violence can directly cause nerve cell damage, intracerebral hematoma formation can cause oppressive brain damage, and increased formation of local metabolites can cause secondary damage to nerve cells[3]. Tau protein (Tau) and 8-iso prostaglandins F2α (8-iso-PGF2α) are newly discovered apoptosis- and oxidative stress-related molecules respectively in recent years, the former affects nerve cell apoptosis through Bax/

Bcl-2 pathway[4], and the latter is the reaction product of arachidonic acid and oxygen free radical in the process of oxidative stress[5]. In order to define the relationship of Tau and 8-iso-PGF2α content change with the illness in patients with traumatic brain injury, we analyzed the correlation of serum Tau and 8-iso-PGF2α levels with nerve injury and oxidative stress in patients with traumatic brain injury in the following study.

2. Clinical information and research methods

2.1 Clinical information of subjects

A total of 56 patients who were diagnosed with traumatic brain injury in Pidu District People’s Hospital between May 2014 and February 2017 were selected as the TBI group of the study, all patients were with traumatic brain injury confirmed by skull
CT, patients combined with heart, lung, abdomen and other important viscera injury were eliminated, and patients with history of cerebrovascular diseases and mental illness were also ruled out. 45 volunteers who received physical examination in Pidu District People’s Hospital during the same period were selected as control group, and all of them were without history of trauma, cerebrovascular disease or mental illness. 45 volunteers who received physical examination in Pidu District People’s Hospital during the same period were selected as control group, and all of them were without history of trauma, cerebrovascular disease or mental illness. There was no significant difference in general data between the two groups (P>0.05).

2.2 Research methods

2.2.1 Sample collection
3-5 mL of cubital venous blood was collected respectively from TBI group on admission and from control group during physical examination, the blood was let stand at room temperature for 20-30 min, then coagulated and centrifuged in centrifuge for 20 min at a speed of 3 000 r/min, and then the upper serum was taken and stored at -80 ℃.

2.2.2 Index detection
Serum samples of the two groups were taken, enzyme-linked immunosorbent assay kit was used to determine the contents of Tau, 8-iso-PGF2 α, Bax, Bcl-2, Caspase-3 and Caspase-9, and radioimmunoassay kit was used to detect the contents of GSH, VitE, GSH-Px, SOD and HO-1.

2.3 Statistical methods
SPSS 19.0 software was used to input data, the median of serum Tau and 8-iso-PGF2 α levels in TBI group were calculated and used to divide the TBI patients into those with high Tau and 8-iso-PGF2 α levels and those with low Tau and 8-iso-PGF2 α levels. Differences in data between two groups were by t test and P<0.05 was the standard of statistical difference in test results.

3. Results

3.1 Serum Tau and 8-iso-PGF2 α levels
Serum Tau and 8-iso-PGF2 α levels in TBI group were (6.72±0.92) ng/mL and (562.41±74.84) pg/mL respectively; serum Tau and 8-iso-PGF2 α levels in control group were (1.48±0.20) ng/mL and (98.36±10.37) pg/mL respectively. After t test analysis, serum Tau and 8-iso-PGF2 α levels in TBI group were significantly higher than those in control group. Differences in serum Tau and 8-iso-PGF2 α levels were statistically significant between two groups of subjects (P<0.05).

3.2 Serum nerve cell apoptosis molecule levels and their correlation with Tau
Analysis of serum nerve cell apoptosis molecules Bax (ng/mL), Bcl-2 (pg/mL), Caspase-3 (ng/mL) and Caspase-9 (pg/mL) levels between two groups of subjects was as follows: serum Bax, Caspase-3 and Caspase-9 levels in TBI group were significantly higher than those in control group while Bcl-2 level was significantly lower than that in control group. Differences in serum Bax, Bcl-2, Caspase-3 and Caspase-9 levels were statistically significant between two groups of subjects (P<0.05).
Analysis of the correlation of serum Tau level with nerve cell apoptosis molecules Bax, Bcl-2, Caspase-3 and Caspase-9 levels in TBI group was as follows: serum Bax, Caspase-3 and Caspase-9 levels in TBI patients with higher Tau level were significantly higher than those in TBI patients with lower Tau level while Bcl-2 level was significantly lower than that in control group. Differences in serum Bax, Bcl-2, Caspase-3 and Caspase-9 levels were statistically significant between TBI patients with different Tau levels (P<0.05).

3.3 Serum anti-oxidation molecule levels and their correlation with 8-iso-PGF2 α
Analysis of serum anti-oxidation molecules GSH (U/mL), VitE (ng/mL), GSH-Px (U/mL), SOD (U/mL) and HO-1 (ng/mL) levels between two groups of subjects was as follows: serum GSH, VitE, GSH-Px, SOD and HO-1 levels in TBI group were significantly lower than those in control group. Differences in serum GSH, VitE, GSH-Px, SOD and HO-1 levels were statistically significant between two groups of subjects (P<0.05).
Analysis of the correlation of serum 8-iso-PGF2 α level with anti-oxidation molecules GSH, VitE, GSH-Px, SOD and HO-1 levels in
Table 3.
Serum anti-oxidation molecule levels in TBI group and control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>GSH</th>
<th>VitE</th>
<th>GSH-Px</th>
<th>SOD</th>
<th>HO-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI group</td>
<td>56</td>
<td>0.26±0.05</td>
<td>7.68±0.94</td>
<td>113.52±14.56</td>
<td>78.65±9.35</td>
<td>11.48±1.84</td>
</tr>
<tr>
<td>Control group</td>
<td>45</td>
<td>0.65±0.09</td>
<td>12.56±1.85</td>
<td>225.47±31.48</td>
<td>132.57±19.84</td>
<td>23.52±3.85</td>
</tr>
<tr>
<td>α</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 4.
Serum anti-oxidation molecule levels in TBI patients with different 8-iso-PGF2α levels.

<table>
<thead>
<tr>
<th>8-iso-PGF2α level</th>
<th>n</th>
<th>GSH</th>
<th>VitE</th>
<th>GSH-Px</th>
<th>SOD</th>
<th>HO-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low level</td>
<td>28</td>
<td>0.38±0.07</td>
<td>9.56±1.25</td>
<td>178.52±20.39</td>
<td>109.34±13.27</td>
<td>17.26±2.35</td>
</tr>
<tr>
<td>High level</td>
<td>28</td>
<td>0.12±0.02</td>
<td>5.12±0.78</td>
<td>52.85±7.69</td>
<td>47.37±5.62</td>
<td>5.72±0.71</td>
</tr>
<tr>
<td>α</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

TBI group was as follows: serum GSH, VitE, GSH-Px, SOD and HO-1 levels in TBI patients with higher 8-iso-PGF2α level were significantly lower than those in TBI patients with lower 8-iso-PGF2α level. Differences in serum GSH, VitE, GSH-Px, SOD and HO-1 levels were statistically significant between TBI patients with different 8-iso-PGF2α levels (P<0.05).

4. Discussion

Neurologic damage process in TBI patients involves multiple factors and multiple stages, the direct trauma of outside violence to the brain is the most important factor that causes nerve function damage, and in the process of disease progression, apoptosis and oxidative stress reaction activation can also cause secondary damage to nerve function[6,7]. Tau is an important protein involved in cellular microtubule structure and axon cytoskeleton structure formation in brain tissue. The outside violence damage to the brain tissue can cause the massive release of Tau into the extracellular space, which will enter into the blood circulation through the cerebrospinal fluid and the damaged blood brain barrier[8]. Tau, moreover, will be abnormally highly expressed in the process of cell damage and accumulate in the local tissue, which causes microtubule structure collapse and axon dysfunction, and can also cause excessive apoptosis of cells[9,10]. In order to make clear the relation between Tau content change and traumatic brain injury, serum Tau contents in patients with traumatic brain injury and healthy volunteers were analyzed in the study, and the results showed that serum Tau content in TBI group was significantly higher than that in control group. This indicates that the increase of Tau content is closely related to the occurrence of traumatic brain injury, and it is speculated that the destruction of nerve cells caused by traumatic brain injury will lead to the increase of Tau release; Tau expression also increases in the process of nerve cell damage, and the destruction of nerve cells on the basis will cause more Tau to be released into the blood circulation.

The relationship between Tau and apoptosis has received increasing attention in recent years, and the excessive accumulation of Tau in local tissues can break the balance of Bcl-2/Bax and affect cell apoptosis. Increase of Tau content can cause the Bcl-2 hyperphosphorylation and weaken the Bcl-2 ability to be combined with Bax, and the Bax molecules can form homodimer after the Bcl-2 and Bax heterodimer structure is separated, which will form the channel in mitochondrial membrane for cytochrome C to enter into the cytoplasm via the mitochondrial membrane[11]. After entering the cytoplasm, Cytochrome C can start caspase cascade amplification reaction, which causes the activation of aspase-9 at first, then eventually activates Caspase-3 and directly mediates apoptosis process through the cascade activation reaction of a variety of molecules[12]. In the study, analysis of the differences in serum contents of apoptosis molecules between patients with traumatic brain injury and healthy volunteers showed that serum Bax, Caspase-3 and Caspase-9 levels in TBI group were significantly higher than those in control group while Bcl-2 level was significantly lower than that in control group. This indicates that Bax/Bcl-2 imbalance and mitochondrial pathway apoptosis activation are related to the occurrence of brain injury. Further analysis the correlation between Tau and mitochondrial pathway apoptosis showed that serum Bax, Caspase-3 and Caspase-9 levels in TBI patients with higher Tau level were significantly higher than those in TBI patients with lower Tau level while Bcl-2 level was significantly lower than that in TBI patients with lower Tau level. This indicates that the abnormally elevated Tau in the serum of patients with brain injury is closely related to the mitochondrial pathway apoptosis of nerve cells.

The damage of nerve function in patients with brain injury is not only related to the direct injury of external violence, but also associated with the activation of oxidative stress response in local tissues after hematoma formation. Intracerebral hematoma formation after brain injury can cause compression of brain tissue, continuous oppression will cause hypoxia and increase the production of oxygen free radicals, and it can cause oxidative stress injury when oxygen free radical generation is beyond the scavenging activity of antioxidants[13]. Neurons, glial cells and endothelial cells in the brain tissue are the attack targets of oxygen free radicals, and the reaction between a variety of compositions in cells and oxygen free radicals can cause cellular structure damage[14,15]. 8-iso-PGF2α is the reaction product of the arachidonic acid in cell membrane, mitochondrial membrane and other structures with oxygen free radicals, the differences in serum 8-iso-PGF2α contents in patients with traumatic brain injury and healthy volunteers were analyzed in the study in order to define the relationship between 8-iso-PGF2α and 8-iso-PGF2α levels.
content change and traumatic brain injury, and the results showed that serum 8-iso-PGF2α content in TBI group was significantly higher than that in control group. This means that the increase of 8-iso-PGF2α content is closely related to the occurrence of traumatic brain injuries, and it is speculated that increasingly generated oxygen free radicals in the local tissue after traumatic brain injury will react with arachidonic acid in the cell membrane and generate 8-iso-PGF2α, and the constantly generated 8-iso-PGF2α will enter into the cerebrospinal fluid and enter into the blood circulation through the damaged blood brain barrier.

The oxidative stress response after brain injury is the process of dynamic change, there are many enzymatic antioxidants and non-enzymatic antioxidants in the local brain tissue, and they have scavenging effect on oxygen free radicals; when the oxygen free radicals are continuously generated and exceed the scavenging capacity of the antioxidant molecules, the oxygen free radicals will accumulate constantly and the antioxidant molecules will be constantly consumed[16]. GSH and VitE are important non-enzymatic antioxidant molecules that can directly combine and remove oxygen free radicals[17]. GSH-Px, SOD and HO-1 are important enzymatic antioxidant molecules that can scavenge oxygen free radicals by catalytic reduction[18]. In the study, analysis of the differences in serum antioxidant molecule contents between patients with traumatic brain injury and healthy volunteers showed that serum GSH, VitE, GSH-Px, SOD and HO-1 levels in TBI group were significantly lower than those in control group. This indicates that the excessive activation of oxidative stress response and the significant consumption of antioxidant molecules are related to the occurrence of brain injury. Further analysis of the correlation between 8-iso-PGF2α and oxidative stress response as well as antioxidant enzymes showed that serum GSH, VitE, GSH-Px, SOD and HO-1 levels in TBI patients with higher 8-iso-PGF2α level were significantly lower than those in TBI patients with lower 8-iso-PGF2α level. This indicates that the abnormal elevation of 8-iso-PGF2α in the serum of patients with brain injury is closely related to the overactivation of oxidative stress and the large consumption of antioxidant molecules.

To sum up, it can be preliminarily concluded that serum Tau and 8-iso-PGF2α levels are unusually high in patients with traumatic brain injury; the rise of Tau is related to the excessive apoptosis of nerve cells, while the increase of 8-iso-PGF2α is related to overactivation of oxidative stress response.

References