Correlation of serum inflammatory cytokine and immunoglobulin content with post-herpetic neuralgia in patients with acute herpes zoster

Hai-Jun Shi, Zhi-Qiang Cui
Pain Department, the First People's Hospital of Akesu Prefecture Xinjiang, Akesu 843000, China

ARTICLE INFO

Objective: To study the correlation of serum inflammatory cytokine and immunoglobulin content with post-herpetic neuralgia in patients with acute herpes zoster. Methods: Patients diagnosed with herpes zoster in our hospital between May 2012 and October 2015 were selected and divided into herpes zoster-post-herpetic neuralgia group (VZV-PHN group) and herpes zoster-control group (VZV-Con group) according to the incidence of post-herpetic neuralgia (PHN); healthy volunteers receiving physical examination in our hospital during the same period were selected as normal control group (Con group). Results: Serum β-EP, NT, IFN-γ and IL-2 levels of VZV-PHN group and VZV-Con group were significantly lower than those of Con group (P<0.05), while SP, VGF, CGRP, IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10, TGF-β1, IgG, IgM and IgA levels were significantly higher than those of Con group (P<0.05); serum β-EP, NT, IFN-γ, IL-2, IgG, IgM and IgA levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05) while SP, VGF, CGRP, IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels were significantly higher than those of VZV-Con group (P<0.05); β-EP and NT were positively correlated with IFN-γ, IL-2, IgG, IgM and IgA, and negatively correlated with IL-4, IL-6, IL-17, TNF-α, IL-10 and TGF-β1; SP, VGF and CGRP were negatively correlated with IFN-γ, IL-2, IgG, IgM and IgA, and positively correlated with IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10 and TGF-β1. Conclusions: Abnormal secretion of inflammatory cytokines and immunoglobulin caused by humoral immune and cellular immune response disorder is associated with the occurrence of post-herpetic neuralgia in patients with acute herpes zoster.

1. Introduction

Herpes zoster is a herpetic skin disease caused by varicella-zoster virus (VZV) infection, and as VZV is with neurotropic property, patients with herpes zoster are mostly combined with neuritis and neuralgia[1,2]. Post-herpetic neuralgia (PHN) is the complication left behind after herpes zoster skin lesion healing, it is with high incidence and difficult to treat[3], it is characterized by chronic neuropathic pain, and the specific pathogenesis is not yet clear. Studies on neuropathic pain in recent years have shown that the abnormal immunoglobulin secretion caused by humoral immune response disorder and the abnormal cytokine secretion caused by cellular immune disorder after VZV infection are closely associated with the occurrence of neuropathic pain[4,5], but the changes of cellular immunity and humoral immunity in patients with herpes zoster are not clear. In the following study, the correlation of serum inflammatory cytokine and immunoglobulin content with post-herpetic neuralgia in patients with acute herpes zoster was analyzed.

2. Materials and methods

2.1. Research subjects

104 patients diagnosed with herpes zoster in our hospital between May 2012 and October 2015 were selected, the incidence of post-herpetic neuralgia was followed up within 3 months after the healing of herpes zoster, 48 patients with post-herpetic neuralgia...
were included in herpes zoster-post-herpetic neuralgia group (VZV-PHN group) of the study, and 56 patients without post-herpetic neuralgia were included in herpes zoster-control group (VZV-Con group) of the study. 60 healthy volunteers receiving physical examination in our hospital during the same period were selected as normal control group (Con group). VZV-PHN group included 28 male cases and 20 female cases that were 26–81 years old; VZV-Con group included 32 male cases and 24 female cases that were 20–80 years old; Con group included 33 male cases and 27 female cases that were 26–81 years old. The three groups of subjects were not significantly different in general information (P>0.05).

2.2. Serum sample collection methods

5 mL of peripheral venous blood was collected from VZV-PHN group and VZV-Con group of patients in the acute phase after admission, 5 mL of peripheral venous blood was collected from the control group of volunteers during physical examination, the blood was let stand at room temperature for 30 min, then placed in centrifugal and centrifuged for 20 min at 12 000 r/min, and the upper serum was collected, transferred to the new EP tubes and stored at -80 °C.

2.3. Serum index detection methods

Enzyme-linked immunosorbent assay kits were used to determine serum β-EP, NT, CGRP, SP, VGF, immunoglobulin G (IgG), IgM, IgA, interferon γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), IL-4, IL-6, IL-10, IL-17, IL-21 and TGF-β1 levels. All the steps were conducted according to the instruction manual.

2.4. Statistical analysis

SPSS20.0 software was used to input and statistically process data, measurement data analysis among three groups was by t test, pairwise comparison was by LSD-t test, correlation analysis was by Pearson test and P<0.05 meant statistical significance in the obtained results.

3. Results

3.1. Serum pain-related medium levels

Analysis of serum pain media β-EP, NT, SP, VGF and CGRP among three groups of subjects is shown in Table 1: serum β-EP and NT levels of VZV-PHN group and VZV-Con group were significantly lower than those of Con group (P<0.05), while SP, VGF and CGRP levels were significantly higher than those of Con group (P<0.05); serum β-EP and NT levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05), while SP, VGF and CGRP levels were significantly higher than those of VZV-Con group (P<0.05).

3.2. Serum CD4+ T lymphocyte subset–related cytokine levels

Analysis of serum Th1 cytokines IFN-γ and IL-2 as well as Th2 cytokines IL-4 and IL-6 among three groups of subjects is shown in Table 2: serum IFN-γ and IL-2 levels of VZV-PHN group and VZV-Con group were significantly lower than those of Con group (P<0.05), while IL-4 and IL-6 levels were significantly higher than those of Con group (P<0.05); serum IFN-γ and IL-2 levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05), while IL-4 and IL-6 levels were significantly higher than those of VZV-Con group (P<0.05). Pearson correlation analysis showed that serum IFN-γ and IL-2 levels were positively correlated with β-EP and NT, and negatively correlated with SP, VGF and CGRP; IL-4 and IL-6 levels were negatively correlated with β-EP and NT, and positively correlated with SP, VGF and CGRP.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>β-ET</th>
<th>NT</th>
<th>SP</th>
<th>VGF</th>
<th>CGRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZV-PHN group</td>
<td>48</td>
<td>5.92±0.77*</td>
<td>3.25±0.42*</td>
<td>6.53±0.78*</td>
<td>13.59±1.68*</td>
<td>7.76±0.79*</td>
</tr>
<tr>
<td>VZV-Con group</td>
<td>56</td>
<td>8.31±0.94*</td>
<td>5.63±0.71*</td>
<td>4.13±0.55*</td>
<td>7.86±0.93*</td>
<td>4.59±0.67*</td>
</tr>
<tr>
<td>Con group</td>
<td>60</td>
<td>17.54±1.93</td>
<td>10.39±1.78</td>
<td>2.31±0.31</td>
<td>4.03±0.52</td>
<td>3.06±0.41</td>
</tr>
</tbody>
</table>

*: compared with Con group, P<0.05; †*: compared with VZV-Con group, P<0.05.

Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IFN-γ (pg/mL, x±s)</th>
<th>IL-2 (pg/mL, x±s)</th>
<th>IL-4 (pg/mL, x±s)</th>
<th>IL-6 (pg/mL, x±s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZV-PHN group</td>
<td>48</td>
<td>15.84±2.31*</td>
<td>11.03±1.28*</td>
<td>36.86±5.51*</td>
<td>15.68±1.75*</td>
</tr>
<tr>
<td>VZV-Con group</td>
<td>56</td>
<td>27.49±3.16</td>
<td>17.86±2.26</td>
<td>22.15±3.28</td>
<td>9.25±1.04</td>
</tr>
<tr>
<td>Con group</td>
<td>60</td>
<td>42.15±5.68</td>
<td>32.42±4.47</td>
<td>14.25±1.67</td>
<td>5.69±0.67</td>
</tr>
</tbody>
</table>

*: compared with Con group, P<0.05; †*: compared with VZV-Con group, P<0.05.
Analysis of serum Th17 cytokines IL-17, IL-21 and TNF-α as well as Treg cytokines IL-10 and TGF-β1 among three groups of subjects is shown in Table 3: serum IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels of VZV-PHN group and VZV-Con group were significantly higher than those of Con group (P<0.05); serum IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels of VZV-PHN group were significantly higher than those of VZV-Con group (P<0.05). Pearson correlation analysis showed that serum IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels were negatively correlated with β-EP and NT, and positively correlated with SP, VGF and CGRP.

3.3. Serum immunoglobulin levels

Analysis of serum immunoglobulin IgG, IgM and IgA among three groups of subjects is shown in Table 4: serum IgG, IgM and IgA levels of VZV-PHN group and VZV-Con group were significantly higher than those of Con group (P<0.05); serum IgG, IgM and IgA levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05). Pearson correlation analysis showed that serum IgG, IgM and IgA levels were positively correlated with β-EP and NT, and negatively correlated with SP, VGF and CGRP.

4. Discussion

VZV has neurotropic property, and the herpes skin caused by its infection will still left over PHN after healing[6]. PHN belongs to neuropathic pain and is clinically common, but the exact pathogenesis is not clear. In recent years, study on neuropathic pain has confirmed that the changes in the levels of β-EP, NT, SP, VGF, CGRP and other pain media are closely related to the process of neuropathic pain. β-EP and NT are the neurotransmitters with analgesic effect, and they can be combined with corresponding receptors and then increase the pain threshold and relieve the degree of pain[7]; SP and VGF are the neuromedins that can cause pain, increase the excitability of neurons and mediate neuropathic pain process[8]; CGRP can dilate blood vessels and increase the microcirculation permeability function, and it can also inhibit substance P degradation and increase the secretion of inflammatory mediators, which further increase the degree of pain[9]. In the study, analysis of the content of serum pain-related media in patients with acute herpes zoster showed that serum β-EP and NT levels of VZV-PHN group and VZV-Con group were significantly lower than those of Con group (P<0.05) while SP, VGF and CGRP levels were significantly higher than those of Con group (P<0.05). This means that serum pain-related medium levels are abnormal in patients with herpes zoster. Further analysis of the relationship between these pain-related media and PHN showed that serum β-EP and NT levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05) while SP, VGF and CGRP levels were significantly higher than those of VZV-Con group (P<0.05). This confirms that the changes of serum pain-related medium levels in patients with acute herpes zoster are related to the incidence of PHN after herpes skin healing.

The humoral immune and cellular immune disorder caused by VZV infection can cause the abnormal secretion and release of a variety of immunoglobulins and cytokines. Abnormal secretion of immunoglobulins is closely associated with the low antiviral immune response in the body, which causes the VZV re-replication in trigeminal ganglia, dorsal root ganglion and other parts, and leads to the occurrence of PHN[10,11]. In the study, analysis of serum levels of immunoglobulins showed that serum IgG, IgM and IgA levels of VZV-PHN group and VZV-Con group were significantly higher than those of Con group (P<0.05). This means that VZV infection will activate humoral immune response, induce plasma cell maturation and differentiation and synthesize various immunoglobulins, and the immunoglobulins secreted into the blood circulation can kill and eliminate the virus. Further analysis of the relationship between these immunoglobulins and PHN showed that serum IgG, IgM and IgA levels of VZV-PHN group were significantly lower than

Table 3
Comparison of serum Th17 and Treg cytokine levels among three groups of subjects (ng/mL, x±s).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IL-17</th>
<th>IL-21</th>
<th>TNF-α</th>
<th>IL-10</th>
<th>TGF-β1</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZV-PHN group</td>
<td>48</td>
<td>47.69±6.52</td>
<td>22.14±3.28</td>
<td>68.98±9.11</td>
<td>12.35±1.46</td>
<td>29.42±3.52</td>
</tr>
<tr>
<td>VZV-Con group</td>
<td>56</td>
<td>26.23±3.41</td>
<td>13.22±1.88</td>
<td>45.47±5.62</td>
<td>7.59±0.92</td>
<td>18.75±2.15</td>
</tr>
<tr>
<td>Con group</td>
<td>60</td>
<td>15.58±2.03</td>
<td>7.40±0.92</td>
<td>23.15±3.92</td>
<td>4.46±0.56</td>
<td>11.32±1.57</td>
</tr>
</tbody>
</table>

a: compared with Con group, P<0.05; b: compared with VZV-Con group, P<0.05.

Table 4
Comparison of serum immunoglobulin levels among three groups of subjects (mg/mL, x±s).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZV-PHN group</td>
<td>48</td>
<td>10.25±1.25</td>
<td>1.52±0.18</td>
<td>0.36±0.4</td>
</tr>
<tr>
<td>VZV-Con group</td>
<td>56</td>
<td>13.28±1.85</td>
<td>1.92±0.22</td>
<td>0.58±0.07</td>
</tr>
<tr>
<td>Con group</td>
<td>60</td>
<td>8.93±1.02</td>
<td>1.24±0.16</td>
<td>0.22±0.03</td>
</tr>
</tbody>
</table>

a: compared with Con group, P<0.05; b: compared with VZV-Con group, P<0.05.
those of VZV-Con group. This confirms that after VZV infection, the humoral immune response activation is insufficient, and the increased immunoglobulins are not enough to eradicate the virus, the virus remaining in the body will replicate again, lead to the occurrence of PHN and aggravate the degree of pain. In the study, the correlation analysis between immunoglobulins and pain media also further confirmed that inadequate secretion of immunoglobulins could aggravate the pain: serum IgG, IgM and IgA levels were positively correlated with β-EP and NT, and negatively correlated with SP, VGF and CGRP.

The occurrence and development of neuropathic pain not only involve the humoral immune response, but are also associated with the T lymphocyte-mediated cellular immune response disorder. Different T lymphocyte subsets can synthesize and secrete different types of cytokines, act on the peripheral tissue through paracrine and endocrine, and cause pain reactions[12,13]. Th1 and Th2 were the first known T cell subsets, the IFN-γ and IL-2 secreted by Th1 subsets mainly mediate cellular immune response, the IL-4 and IL-6 secreted by Th2 subsets mainly mediate humoral immune response, and the excessive shift of Th1/Th2 balance to Th2 may affect the antiviral immune response[14]; Treg and Th17 are the new T cell subsets discovered in recent years, the former secretes IL-10, TGF-β1 and other inhibitory cytokines, and can inhibit the antiviral immune response; the latter secretes IL-17, IL-21 and TNF-α, and can cause tissue damage and pain[15]. Analysis of the T lymphocyte-related cytokines in the study showed that serum IFN-γ and IL-2 levels of VZV-PHN group and VZV-Con group were significantly lower than those of Con group (P<0.05) while IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels were significantly higher than those of Con group (P<0.05); serum IFN-γ and IL-2 levels of VZV-PHN group were significantly lower than those of VZV-Con group (P<0.05) while IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels were significantly higher than those of VZV-Con group (P<0.05). This means that the weakening of Th1 cell function and the enhancing of Th2, Th17 and Treg cell function are associated with the occurrence of PHN in patients with herpes zoster. Further analysis of the correlation between these cytokines and pain media indicated that serum IFN-γ and IL-2 levels were positively correlated with β-EP and NT, and negatively correlated with SP, VGF and CGRP; IL-4, IL-6, IL-17, IL-21, TNF-α, IL-10 and TGF-β1 levels were negatively correlated with β-EP and NT, and positively correlated with SP, VGF and CGRP.

To sum up, abnormal secretion of inflammatory cytokines and immunoglobulin caused by humoral immune and cellular immune response disorder is associated with the occurrence of post-herpetic neuralgia in patients with acute herpes zoster.

References