Cognitive impairment with interferon treatment in patients with chronic hepatitis C

Hiroto Tanaka and Hideyuki Sasaki
Department of Internal Medicine, Wakayama Medical University Kihoku Hospital, Wakayama, Japan
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ABSTRACT
Interferon (IFN) has various side effects, including psychiatric symptoms. Event-related potentials are used as an electrophysiologic index of cognitive disorders. Auditory event-related potentials (P300) are often used in conditions in which cognitive ability is affected. In this study, we evaluated the association between P300, used to assess cognitive impairment, and neuropsychological side effects of IFN treatment in patients with chronic hepatitis C. Subjects were 20 patients with chronic hepatitis C; 13 patients were treated with peg IFN-α2b and ribavirin (riba group), and 7 patients were treated with peg IFN-α2a (alone group). P300 was performed on all patients before treatment and after 1 week, 4 weeks, 2 months, and 3 months of treatment. In addition, 10 patients of them completed the self-rating depression scale (SDS). P300 latency was significantly prolonged at all points of measurement during IFN treatment. No correlation between the change of SDS score and the change rate of P300 latency was shown. Six patients with neuropsychological symptom had a significantly increased change rate of P300 latency compared with patients without neuropsychological symptoms (P < 0.05). Based on P300 findings, this study suggests that patients with chronic hepatitis C treated with IFN may experience significant cognitive impairment.

Interferon (IFN) therapy is an established treatment for patients with chronic hepatitis C (CHC). In particular, the combination of pegylated interferon (peg IFN) and ribavirin, which is an anti-viral medication, has been considered standard therapy for these patients (2). However, this combination therapy is associated with various side effects and some patients cannot tolerate treatment (1, 11). Serious side effects include neuropsychiatric complications such as depression. The use of peg IFN and ribavirin for CHC has also been reported to be associated with high rates of mood disorders and self-reported syndromes of difficulty thinking and concentrating, fatigue, and depression (4–6). In addition, we demonstrated a decrease in regional cerebral blood flow (rCBF) with IFN treatment, suggesting that the neuropsychological side effects induced by IFN treatment may be associated with a decrease in rCBF (13).

Event-related potentials have been used as an index of the electrophysiology of cognitive disorders. For auditory event-related potentials, P300 is often used in conditions in which cognitive ability is affected, such as in patients with dementia. In this study, we evaluated cognitive impairment using P300 findings and the association with neuropsychological side effects in patients with CHC treated with peg IFN.

Subjects included 20 patients with CHC treated with IFN; 13 patients were treated with peg IFNα2b and ribavirin (riba group), and 7 patients were treated with peg IFNα2a (alone group). Patients were excluded if they had any psychological disease or received other cytotoxic drugs such as steroids. Before participating in this study, the purpose, method and possible side effects were explained, and informed consent was obtained from each patient.
Six patients have the neuropsychological symptoms such as depression, dizziness, loss of memory. The change rate of P300 latency in these 6 patients significantly increased compared with that in patients without them (Fig. 3). Based on P300 findings, this study suggests that patients with chronic hepatitis C treated with IFN may experience significant cognitive impairment. Other studies have also shown that patients receiving treatment with IFN experience cognitive impair-

Table 1  
Baseline characteristics of patients treated by IFN

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>alone group</th>
<th>riba group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.4 ± 10.1</td>
<td>57.9 ± 10.9</td>
<td>58.1 ± 9.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/5</td>
<td>6/1</td>
<td>9/4</td>
</tr>
<tr>
<td>Serotype (1/2)</td>
<td>12/8</td>
<td>2/5</td>
<td>10/3</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>54.0 ± 24.5</td>
<td>51.1 ± 28.0</td>
<td>49.8 ± 18.3</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>62.7 ± 26.1</td>
<td>66.4 ± 30.9</td>
<td>58.8 ± 25.2</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>14.6 ± 1.1</td>
<td>14.4 ± 1.6</td>
<td>14.8 ± 0.8</td>
</tr>
<tr>
<td>Plt (10^4/μL)</td>
<td>15.4 ± 5.3</td>
<td>15.3 ± 6.8</td>
<td>15.3 ± 4.8</td>
</tr>
<tr>
<td>P300 (msec)</td>
<td>368.4 ± 33.5</td>
<td>370.3 ± 28.0</td>
<td>367.8 ± 39.6</td>
</tr>
</tbody>
</table>

P300 potentials were recorded from central and parietal locations (Cz and Pz, respectively, according to the International 10-20 System), and were referenced to linked earlobes. An “oddball” paradigm was used in which subjects were asked to silently count rare tones that differed from others in pitch (2000 Hz; probability, 0.2) occurring randomly among non-target events (1000 Hz; probability, 0.8). All subjects could hear the tones clearly and distinguish between the two pitches. Thirty potentials were averaged following target and non-target stimuli (bandpass, 0.1 to 1000 Hz; analysis time, −100 to 900 ms). The P300 response to the rare tone was defined as a large positive peak with a latency of 300 ms or more. The P300 was performed on all patients before treatment and after 1 week, 4 weeks, 2 months, and 3 months of treatment. In addition, 10 patients completed the self-rating depression scale (SDS).

All statistical procedures were performed using commercially available software (Statview ver 5.0 for Macintosh). Results were expressed as means ± SD. Nonparametric methods (Mann-Whitney U test) were used for comparisons between treatment groups. All reported P-values were two-sided, and P < 0.05 was considered significant.

There were no significant differences in patient characteristics between the riba group and the alone group (Table 1). Mean P300 latency was significantly prolonged at all points of measurement during IFN treatment in total 20 patients of both groups (Fig. 1a). In addition, the change rate of P300 latency was more than 10% at all points of measurements during IFN treatment in both groups (Fig. 1b). The comparison of the change rate of P300 latency between the riba and the alone group showed no significant differences (Fig. 2). No correlation between the change of SDS score and the change rate of P300 latency was shown among subjects who completed the SDS. In addition, no correlation between age and the change rate of P300 latency was shown (data not shown). Six patients have the neuropsychological symptoms such as depression, dizziness, loss of memory. The change rate of P300 latency in these 6 patients significantly increased compared with that in patients without them (Fig. 3).

Based on P300 findings, this study suggests that patients with chronic hepatitis C treated with IFN may experience significant cognitive impairment. Other studies have also shown that patients receiving treatment with IFN experience cognitive impair-

![Fig. 1](image-url)  
\( \text{a: Mean P300 latency was significantly prolonged at 1 week, 1 month, 2 months, and 3 months during IFN treatment. b: The change rate of P300 latency was more than 10% at 1 week, 1 month, 2 months, and 3 months during IFN treatment.} \)
Cognitive impairment with interferon (9, 10, 12). In addition, it has been suggested that physiological alterations occurring among patients receiving IFN-α treatment are associated with cognitive impairment (8). However, in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis Trial (HALT-C) study, Fontana et al. showed that the frequency of cognitive impairment for patients with CHC did not increase at week 24 compared with baseline, suggesting that the cognitive function of patients with CHC did not worsen with peg IFN and ribavirin retreatment (3). Therefore, whether significant cognitive impairment occurs among patient with CHC treated with IFN, especially peg IFN and ribavirin, is controversial. This discrepancy may be due to differences in study design or methodology. In this report, the main findings of our study are that when using P300 to measure electrophysiologic changes as an index of cognitive impairment in patients with CHC receiving IFN treatment, IFN was shown to cause significant cognitive impairment. This cognitive impairment was not correlated with depressive mood changes among those in whom depressive mood was assessed.

Other studies have reported that electrophysiologic changes, as shown on quantitative electroencephalograms, were associated with cognitive impairment during IFN treatment (7, 8, 14). Thus electrophysiologic assessments may be sensitive to changes in cognitive impairment. In addition, we reported a decrease in rCBF with IFN treatment, as shown on single photon emission computed tomography (SPECT), suggesting that neuropsychological side effects of IFN treatment may be associated with a decrease in rCBF (13). However, methods such as SPECT are expensive and time-consuming. Thus, event-related potentials are commonly used as an electrophysiologic index of cognitive disorders. P300 auditory event-related potentials are often examined in patients with dementia and other cognitive disorders and offer a simple, inexpensive, and useful method of evaluating cognitive dysfunction.

Lieb et al. indicated that even low-doses of IFN-α induced cognitive impairment independent from depressive symptoms, which might be related to functional disturbances in the prefrontal cortex and the hippocampus (10). In addition, it was reported that IFN-α treatment increased the activity of indoleamine-2,3-dioxygenase, which is followed by an increase in the conversion of tryptophan to kynurenine. Kynurenine metabolites have toxic effects on brain function via the over-stimulation of NMDA-receptors, which may lead to excitotoxic cell death and hippocampal atrophy (15). Those reports may account for our findings that treatment with peg IFN induces cognitive impairment independent from depression. However, the limitation of our study is small number study, and is that this study have not other methodology of assessment of cognitive function.
In conclusion, based on findings of P300 used as an electrophysiologic index of cognitive impairment, this study suggests that IFN treatment in patients with CHC may be associated cognitive impairment.

REFERENCES