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Clinical study of cerebrospinal fluid neuropeptides in patients with primary trigeminal neuralgia

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ABSTRACT

Objectives: To investigate the expression levels of calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide (VIP), and β-endorphin in the cerebrospinal fluid (CSF) and peripheral blood of patients with primary trigeminal neuralgia (TN).
Patients and methods: We included 20 patients with primary TN who underwent percutaneous radiofrequency thermocoagulation and collected four types of samples from all of them: sample A: CSF samples; sample B: peripheral blood samples; sample C: peripheral blood samples collected one day before the operation; sample D: peripheral blood samples withdrawn one day after the operation. Another 20 CSF samples of patients with nervous system disease or gynecological disease were collected as a control (sample E). Samples A and B were obtained at the same time. We also evaluated the expression of CGRP, SP, β-endorphin, and VIP by visual analog scale (VAS) scores one day before and one day after the operation. In addition, heart rate (HR) at baseline and at the time of sample collection, mean arterial pressure (MAP), and all side effects of the procedure were recorded.
Results: Significance were found concerning about CGRP, SP, β-endorphin, and VIP in TN patients and the controls ($P < 0.001$). The expression of CGRP, SP, and VIP in sample A was higher than that in sample E. However, the β-endorphin level in sample A was lower than that in sample E. There was a positive correlation between sample A and B regarding the expression of CGRP, SP, β-endorphin, and VIP ($P < 0.01$). There was no relationship between the time of disease onset and the expression of CGRP, SP, β-endorphin, and VIP in sample A and sample B ($P > 0.05$). No difference was detected between the neuropeptides levels in samples B and C ($P > 0.05$). Notably, VAS in sample D was significantly lower than that in sample C ($P < 0.01$). Finally, there was no difference between the intraoperative HR and MAP values in the studied samples.
Conclusion: In primary TN patients, the blood levels of CGRP, SP, β-endorphin, and VIP were associated with those in CSF samples. There was a significant difference between the levels of the four neuropeptides in CSF and control samples. Our results also indicated that the levels of neuropeptides in blood samples can be tested for those in CSF. The disease onset and duration exerted insignificant effects on the production and release of CGRP, SP, β-endorphin, and VIP.

1. Introduction

Trigeminal neuralgia (TN) is a pain syndrome characterized by intermittent, intense pain in the face along the distribution of one or more branches of the fifth cranial nerve. The condition can impair activities of daily living and lead to depression. However, its exact pathogenesis remains unclear. Some studies suggest that reverberating circuits, ephaptic connections, and a disturbance of central synaptic activity may be involved. Moreover, recent neurochemical experiments indicated a local inflammation of the trigeminovascular system in which the release of excitatory neuropeptides, including substance P, may play an important role. Also, it has been postulated that microcirculation dysfunction and nerve demyelination may be involved in the pathogenesis of this disorder, and can result in increasing the expression of peptides, including calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal polypeptide (VIP), and β-endorphin, and subsequently, it induces

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neurogenic pain. Although animal experiments suggested that the afferent stimulation of trigeminal nerve leads to the increased expression of CGRP, SP, β-endorphin, and VIP, clinical evidence is still absent due to the lack of cerebral spinal fluid (CSF) samples. The purpose of this study was to investigate the expression levels of CGRP, SP, β-endorphin, and VIP in the cerebrospinal fluid (CSF) and peripheral blood of patients with primary trigeminal neuralgia. We also collected CSF samples from normal healthy people as a control.

2. Patients and methods

2.1. Patients

This study has been approved by Ethics Committee of our hospital, and the patients and their family members signed written consent forms.

We collected CSF samples from 20 patients with percutaneous radiofrequency thermocoagulation (mean age 47.75 years, 8 males and 12 females). Their age range was from 26 to 70 years. Two patients had their first branch involved, whereas the second branch was affected in six other, and the third branch was involved in seven cases. Additionally, both the second and the third branches were affected by the disorder in four patients, and one patient had all branches involved. These patients had symptoms for one to ten years, expressed by visual analog scale [1] (VAS) scores from 7 to 10. All patients responded poorly to the conservative treatments. We collected four types of collective samples from them: sample A: CSF samples; sample B: peripheral blood; sample C: peripheral blood withdrawn one day prior to the operation; sample D: peripheral blood collected one day after the operation.

Additionally, we also collected CSF samples from 20 control patients. Specifically, these patients were hospitalized because of neurological diseases (mainly neuromuscular disorders) or gynecological diseases (mainly cervical polyp). Patients with other disorders were excluded by clinical examination, laboratory analyses, and medical history inspection.

Samples A and B were obtained at the same time. We also determined the concentrations of CGRP, SP, β-endorphin, and VIP, and obtained VAS score values one day before and after the operation. In addition, baseline heart rate (HR) and mean arterial pressure (MAP) and their values at the time of sample collection were measured, and all side effects of the procedure conducted were recorded.

3. Methods

3.1. Sample collection from TN patients

1. On day 1, prior to the operation, we obtained 3 mL peripheral blood samples of sample C.
2. On the day of percutaneous radiofrequency thermocoagulation, we collected 0.3 mL CSF of sample A. Meanwhile, 3 mL of peripheral blood was obtained of sample B. Further, percutaneous radiofrequency thermocoagulation was performed in these patients. Specifically, the patients underwent surgery in the form of radiofrequency thermocoagulation (RFT) of the affected division or divisions of the trigeminal nerve under intravenous short-acting anesthesia using C-arm radiological guidance. The straight temperature monitoring electrode was used to perform an initial lesion at 60–70 °C for 120 s, and the patient was awakened for sensory testing. The lesion was repeated at the same temperature and duration if sensory deficit was not evident.
3. On day 1 after the operation, we obtained 3 mL peripheral blood samples of sample D.

All samples were centrifuged at 1800 r/min for 5 min and stored at −80 °C in a refrigerator. The blood samples of sample B, C, and D were all withdrawn from the external jugular vein.

3.2. Collection of samples from the control patients

1. On the day prior to the procedure, we explained the procedure of the lumbar puncture to the patients or their representatives and obtained a signed informed consent. After the patient relaxed completely, we measured the mean arterial pressure and heart rate three times and obtained the respective average value.
2. On the day of the operation, initially the patient received an injection with 500 mL of sodium lactate ringer's, and we monitored their indices of HR, MAP, and SpO2. Then, we performed the standard protocol of lumbar puncture and withdrew 0.3 mL of CSF according to the textbook of ADAMS AND VICTOR'S MANUAL OF NEUROLOGY.
3. All samples were centrifuged at 1800 r/min for 5 min. Then, we collected the supernatants and stored these samples in a refrigerator at −80 °C. All samples were analyzed within one month.
4. We recorded the values of all vital signs, including HR and MAP. One week after the procedure, we also recorded the heart rates and observed carefully for the appearance of any side effects, including low heart rate, hypertension, hypotension, dizziness, and headaches. To prevent spontaneous intracranial hypotension induced by CSF leakage, all patients were requested to remain in a lying position for 48 h after the procedure.

3.3. Measurements of neuropeptide concentrations

We applied ELISA kits (Abnova Company) to determine the concentrations of CGRP, SP, β-endorphin, and VIP of all studied samples.

In addition, we obtained VAS scores (within the range 0–100) one day prior to and one day after the operation, HR and MAP values at baseline and at the time of sample collection. All side effects, including a slow heart rate, hypertension, hypotension, dizziness, and headache, were recorded after the procedure.

To prevent headache caused by intracranial low pressure, all patients were requested to remain in a lying position on their beds for 48 h after the lumbar puncture.

3.4. Statistical processing

All values are shown as mean ± standard deviation. We used SAS9.2 software for analysis. To determine statistical significance, *t*-test, ANOVA, and the Student–Newman–Keuls test were utilized. To correlate neurochemical and clinical parameters, we employed the Spearman's rank correlation coefficient. To correct for the number of statistical tests performed, we applied the Bonferroni inequality index. Values of $P < 0.05$ or $P < 0.01$ were considered statistically significant.

4. Results

Table 1 shows the characteristics of the studied patients and controls, including age, gender, and pain location and duration.

As indicated in Table 2, the concentrations of CGRP, SP, and VIP were significantly higher in TN patients as compared to those in the controls, whereas the concentration of β-endorphin was significantly lower ($P < 0.001$).

As seen in Table 3, there was a significant difference between the levels of neuropeptides in the different groups.

Fig. 1 presents the correlation between the levels of neuropeptides in CSF and venous blood of TN patients. Specifically, our results