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Research article

Changes in neurotrophic and inflammatory factors in the cerebrospinal fluid of patients with postherpetic neuralgia

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HIGHLIGHTS

- To examine the changes in neurotrophic and inflammatory factors.
- To study correlation between inflammatory and neurotrophic factors and degree of pain.
- CSF levels of neurotrophic factors positively correlated with inflammatory factors.
- Inflammatory and neurotrophic factors were not correlated with the degree of pain.

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ABSTRACT

Inflammatory and neurotrophic factors are involved in postherpetic neuralgia (PHN), but the association of these factors in the cerebrospinal fluid (CSF) with the level of pain is poorly known. The present study aimed to examine the changes in neurotrophic and inflammatory factors in the CSF of patients with PHN and to study the correlation between these factors and the degree of pain. Fifty patients with PHN and 28 patients with hemifacial spasm (as controls) were recruited between May 2015 and March 2016. CSF levels of inflammatory and neurotrophic factors were measured by ELISA. Compared with controls, patients with PHN had lower CSF levels of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin (NT)-3, NT-5, and P substance (all $P<0.05$), and higher CSF levels of interleukin (IL)-1β ($P=0.050$). Among patients with PHN, CSF BDNF levels were positively correlated to IL-8 ($r_s=0.229$, $P=0.04$); glial cell line-derived neurotrophic factor (GDNF) levels to IL-8 ($r_s=0.326$, $P=0.004$) levels; NGF levels to tumor necrosis factor (TNF)-α levels ($r_s=0.229$, $P=0.044$); NT-3 levels to IL-1β ($r_s=0.228$, $P=0.045$); and NT-5 levels to IL-8 ($r_s=0.388$, $P<0.001$), and TNF-α ($r_s=0.445$, $P<0.001$) levels. Inflammatory and neurotrophic factors were not correlated with the visual analog scale score and von Frey. Multivariable linear regression showed PHN was associated with NGF ($P=0.038$) and BDNF ($P=0.029$), independently from age and major medical history. In conclusion, patients with PHN showed low levels of BDNF, NGF, NT-3, and NT-5. Among patients with PHN, CSF levels of neurotrophic factors positively correlated with inflammatory factors.

1. Introduction

Postherpetic neuralgia (PHN) is a chronic and debilitating pain with dermatomal distribution that persists after healing of herpes zoster rash [1,2]. The traditional definition of PHN is the persistence of neuralgia for ≥1 month after the disappearance of the rash [1], but other definitions also include postherpetic neuralgia for 1–6 months after rash disappearance, persistence of pain >3 months after rash onset, and pain preceding or accompanying the rash and persisting up to 30 days after onset [1,3]. The incidence of PHN in patients with herpes zoster is 9–34% and the incidence increases with age (68% of the cases are ≥50 years old) [1–5]. Risk factors for PHN include older age, greater rash and pain during the herpes zoster episode, ophthalmic location of the acute zoster rash, and severe prodromal pain [1–3,6]. PHN is caused by nervous system damage resulting from reactivation of latent varicella-zoster virus infection [1,2], but the mechanisms leading to PHN are unclear.

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The neurotrophic factors represent a family of small peptides that support the growth, survival, and differentiation of developing and mature neurons, mostly through the receptor tyrosine kinase [7,8]. In the mature nervous system, neurotrophic factors promote neuron survival, induce synaptic plasticity, and modulate the creation of long-term memories [7]. The neurotrophic factors family include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), NT-5, and glial cell line-derived neurotrophic factor (GDNF), among others. Increases in endogenous peripheral NGF by an inflammatory response may lead to the release of a large amount of P substance and CGRP by the nociceptive sensory neurons, leading to sensitization of the central nervous and hyperalgesia [9,10].

Herpes zoster involves local inflammation in the path of the nerve being affected [11]. It has been shown that the induction of a local inflammatory response in rats using prostaglandin E2 and dopamine injection led to a persistent mechanical nociceptor hypersensitivity state that is mediated by interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF)-α [12]. It has been shown that TNF-α plays a pivotal role in nociceptive responses after the resolution of the initial injury [13]. High levels of IL-8 are found in the cerebrospinal fluid (CSF) of patients with PHN [14].

Peripheral nerve injury and subsequent Wallerian degeneration, as can be observed in herpes zoster, will lead to the upregulation of NGF in macrophages, fibroblasts, and Schwann cells at the site of injury [15]. In the same way, BDNF, NT3, and GDNF are upregulated in injured neurons in response to the immune/inflammatory response [9], indicating associations between the inflammatory response and neurotrophic factors. Nevertheless, there are few observations of the levels of inflammatory and neurotrophic factors in the CSF of patients with PHN.

Therefore, the aim of the present study was to examine the changes in neurotrophic and inflammatory factors in the CSF of patients with PHN, and to study the correlation between these factors and the degree of pain.

2. Materials and methods

2.1. Patients

Patients with PHN and hemifacial spasm were recruited at the Aviation General Hospital of China Medical University between May 2015 and March 2016. The patients with hemifacial spasm were used as controls. PHN was defined as pain persisting for ≥90 days following the diagnosis of herpes zoster [16]. Patients with PHN taking antidepressants (pregabalin; half-life of 6.3 h) and painkillers (oxycodone; half-life of 4.5 h) discontinued these drugs for five half-lives before study participation. Hemifacial spasm was diagnosed in the presence of clonic movements of the orbicularis oculi, corrugator, frontalis, orbicularis oris, platysma, and/or zugomatus muscles, diagnosed either clinically and/or by electromyography [17]. Controls had to be without antidepressants and antiepileptics for at least 2 months. For all subjects, exclusion criteria were: 1) multiple sclerosis; 2) history of meningitis; 3) Parkinson's disease; 4) history of head trauma; 5) recent treatment (<2 months) with immunosuppressive drugs or hormones; or 6) any other acute infectious diseases such as upper respiratory tract infection or acute appendicitis. Ultimately, 50 patients with PHN and 28 controls were included.

The study was approved by the ethical committee of the Aviation General Hospital of China Medical University. A written informed consent was obtained from each participant.

2.2. Samples and data collection

CSF was sampled during the course of the disease. Pain threshold was tested using Von Frey filaments [18,19] and tactile examination (allodynia, hyperalgesia or hypoesthesia) [20]. Age, disease location, time of onset, and self-reported degree of pain (using a visual analog scale (VAS) [21]) were also recorded.

3. ELISA

CSF samples were centrifuged at 3000 rpm and 4 °C for 15 min. The supernatants were kept at −80 °C until analysis. NGF, BDNF, GDNF, NT-3, NT-5, IL-1β, IL-8, calcitonin gene-related peptide (CGRP), P substance, and TNF-α levels were determined by ELISA, according to the manufacturers' instructions. Absorbance was determined at 450 nm on a DENLEY DRAGON Wellscan MK 3 microplate reader (Thermo Fisher Scientific, Waltham, MA, USA). The following kits were used: human NGF ELISA kit (MBS2509465; MyBioSource, San Diego, CA, USA; detection threshold: 15 pg/ml; intra- and inter-assay coefficient of variation of <10%); human BDNF ELISA kit (ab99978; Abcam, Cambridge, MA, USA; detection threshold of 15 pg/ml; intra- and inter-assay coefficient of variation of <10%); human GDNF ELISA kit (MBS355310; MyBioSource, San Diego, CA, USA; detection threshold: 15 pg/ml; intra- and inter-assay coefficient of variation of <8.9%); human NT3 ELISA kit (ab100615;Abcam, Cambridge, MA, USA; detection threshold of 15 pg/ml; intra- and inter-assay coefficient of variation of <10%); human 5-NT ELISA kit (MBS9302155; MyBioSource, San Diego, CA, USA; detection threshold of 16 pg/ml; intra- and inter-assay coefficient of variation of <10%); human P substance ELISA kit (ab133029;Abcam, Cambridge, MA, USA; detection threshold of 15 pg/ml; intra- and inter-assay coefficient of variation of <10%); human CGRP ELISA kit (MBS2500141; MyBioSource, San Diego, CA, USA; detection threshold of 1.5 pg/ml; intra- and inter-assay coefficient of variation of <10.2%); human IL-1β ELISA kit (ab100562;Abcam, Cambridge, MA, USA; detection threshold of 1.5 pg/ml; intra- and inter-assay coefficient of variation of <11%); human IL-8 ELISA kit (ab46032; Abcam, Cambridge, MA, USA; detection threshold of 3 pg/ml; intra- and inter-assay coefficient of variation of <10%); and human TNF-α ELISA kit (ab46087; Abcam, Cambridge, MA, USA; detection threshold of 15 pg/ml; intra- and inter-assay coefficient of variation of <10.3%).

3.1. Statistical analysis

Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared using the independent samples *t*-test. Non-normally distributed continuous data were expressed as median (range) and compared using the Mann-Whitney *U* test for independent samples. Categorical variables were expressed as proportions and compared using the Chi-square or Fisher's exact test, as appropriate. The Spearman correlation test was used to determine the correlation coefficient (r_s) and *P* values. A multivariable linear regression was performed using age, group (PHN *vs.* control), and major past history as the independent variables, and the levels of neurotrophic and inflammatory factors in cerebrospinal fluid as the dependent variables. Statistical analysis was performed using SPSS 17.0 (IBM, Armonk, NY, USA). Two-sided *P*-values <0.05 were considered to be statistically significant.

4. Results

4.1. Characteristics of the patients

Table 1 presents the characteristics of the patients. Patients with PHN were older and had a higher frequency of major past history than controls. There were no differences between the two groups for gender ($P > 0.05$).