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Title of Research Project:

Plasma calcitonin gene-related peptide (CGRP) levels in trigeminal neuralgia and healthy controls

Background

Trigeminal neuralgia (TN) is a neuropathic pain disorder considered one of the most painful conditions involving the orofacial region. Classical trigeminal neuralgia represents 80-90% of TN cases and has unremarkable clinical and imaging findings. The term symptomatic (or secondary) accounts for the minority of patients and the symptomatology is secondary to another neurological disease involving the trigeminal system. TN is considered a rare condition, with an incidence of 27 per 100,000/year, more common in individuals older than 60 years and more frequently affecting women.

There is no objective laboratory test to confirm the diagnosis of TN, which is mostly based on specific characteristics, involving the trigeminal nerve distribution. Typically the maxillary nerve (V2) or mandibular nerve (V3) distribution are the most affected with brief, sudden, stabbing, electric shock-like, and severe pain attacks, usually lasting for seconds to 2 minutes. In addition, there are often tactile trigger areas for attacks of pain and periods of spontaneous remission.

Despite decades of studies, TN pathophysiology is still unclear and remains a challenge for clinicians. Several theories have been suggested in attempt to explain the causes of TN. The most widely reported in the literature include vascular compression of the trigeminal nerve and axonal demyelination due to nerve compression. In addition, the ignition hypothesis has been postulated as a possible mechanism, which is described as specific abnormalities or injuries of the trigeminal afferent neurons resulting in hyperexcitable primary sensory neurons. None of these hypotheses can explain all of the clinical phenomena of this condition.

Moreover, excitatory neuropeptides, including substance P, β -endorphin and CGRP may also play a role in the trigeminal neuralgia. Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide released from activated trigeminal sensory afferents. Prior studies demonstrated elevated levels of CGRP ictally in episodic migraine and interictally in chronic migraine. Its role in migraine is best-validated, but has also been found to be elevated in chronic paroxysmal hemicrania and cluster headache. CGRP-targeted therapies currently in clinical studies include anti-CGRP and anti-CGRP receptor monoclonal antibodies (mAbs) and CGRP receptor antagonists. They have been studied in phase II and III studies for migraine with promising results.

With regards to CGRP level in patients with trigeminal neuralgia, there is only one study reported in the literature. Its results demonstrated higher levels of CGRP in the cerebrospinal fluid of patients with trigeminal neuralgia compared with patients without the disease. However, these findings have not been validated to our knowledge and involve several methodological limitations. Those include assessment of only medically refractory TN patients, which in turn were compared with a control group of patients hospitalized due neurological or gynecological diseases. In addition, peripheral blood levels of CGRP were obtained from TN patients, but not from control group patients. Although there is a potential correlation between CGRP and trigeminal neuralgia, there is lack of studies about this topic. Thus, the present study aims to evaluate CGRP levels utilizing plasma samples. This is a

simple and safe method, with a very low complication risk rate that could improve diagnosis and treatment of patients with TN.

Methods

Thirty subjects with trigeminal neuralgia and thirty healthy control subjects (without history of headaches other than episodic tension-type headaches and primary stabbing headache) will be prospectively enrolled. In this study, we will use techniques described in previous studies for the study of patients with migraine to establish whether CGRP levels are elevated in the plasma of patients with trigeminal neuralgia, compared to healthy control. Plasma samples will be collected when subjects are at their baseline pain level in subjects who have TN.

This will be a single-site study at MGH. This is the ideal setting for such a study, and we could complete subject enrollment in 12 months. Venipuncture will be performed at MGH Clinical Research Center and will be collected in a de-identified manner. After centrifuging process, plasma samples will be stored at MGH until they are sent to Eli Lilly and Co., where the assays will be performed using a highly sensitive Quanterix immunoassay.

Statistical analysis will be performed at MGH. Assuming that CGRP levels are normally distributed or can be transformed to be normally distributed, we will test our hypotheses using *t*-Test. If levels of CGRP are not normal and transformations fail, group comparisons will be made using the Mann-Whitney U-test.

Inclusion Criteria

Males or females

- Ages of 18 and 65 years.
- Able to provide informed consent.
- Meeting prespecified criteria for trigeminal neuralgia and not meeting criteria for any primary headache disorders other than episodic tension-type headache (as per ICHD-3 beta criteria).

Exclusion Criteria:

- Females who know that they are pregnant.
- Patients with headache disorders outside of trigeminal neuralgia and episodic tension-type headache (as per ICHD-3 beta criteria).
- Recent prior treatment with onabotulinum toxin-A or other botulinum toxin within 12 weeks prior to enrollment.
- Recent prior treatment with trigeminal nerve blocks within 4 weeks prior to enrollment.
- Recent prior use of a triptan, ergot derivative, butalbital-containing compound, or opioid, within 24 hours prior to plasma collection.