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The temporal relationship between daily stress and delayed modulation of chronic headache pain

Chelsea Clark

Introduction

Headache pain affects a large portion of the population and can be very disabling for those who experience it. About 4% of general practitioner visits in the medical field are made up of headache consultations, and one of the most common reasons for referral to a neurologist is headache pain [1]. It is estimated that greater than 10% of the entire global population suffers from migraine, about 40% suffer from tension-type headache (TTH), and 5% suffer from chronic daily headache, although these estimates vary widely between studies [2-5]. Primary headache refers to headache disorders with no exogenous cause [5]. Secondary headaches, which are caused by some other condition, often produce very extreme, even life-threatening acute pain. However, the pain from primary headaches should not be overlooked; primary headaches very often greatly reduce quality of life and result in significant long-term disability.

Although there are many types of primary headache, the most prevalent are migraine and tension-type headache [6]. Migraines are characterized by a headache with associated features, which can include throbbing pain, sensitivity to sensory stimuli such as light or sound, or sensitivity to head movement itself. TTH does not present with these associated features [5]. For migraine sufferers, head pain stems from an inherited tendency to have headaches. Environmental factors, or ‘triggers’, are very influential on headache patterns of migraine patients. It seems that the brain of a migraine sufferer is very sensitive to environmental stimuli and less tolerant to changes in the environment [5]. In general, most headache patients experience fluctuations in headache pain intensity, duration, and frequency. There are many known factors that influence this variability. For example, many foods can serve as triggers, and also alcohol, weather, exercise, stress, and menstruation can have an effect [5, 7].

Primary headaches can often become long-term problems. There is much debate over what should be considered a chronic headache disorder. Because headaches are generally presented in the form of “attacks”, it is hard to categorize when these attacks become a chronic condition. Chronic headaches are generally defined as a patient having a headache 15 days of the month for at least three months [8]. For the purposes of this study, we aim to address those patients who have symptoms of headaches on a minimum of 10 days a month, on average.

This study will focus on the role of stress in the fluctuations in headache pain. Stress is known to be a contributing factor in many headache disorders [5, 7, 9-13]. The body responds to various environmental conditions with a stress response, which activates the hypothalamic-pituitary axis, to protect the body. When this stress response is activated in a chronic way, the body can be worn down, which eventually results in disease [9]. Stress can affect headaches in many ways. In some cases, it may serve as a trigger that leads to fluctuations in pain, or it may be a predisposing factor to having headaches. Frequent headaches can also play a role in creating more stress for a patient, potentially resulting in negative feedback loops. In particular, stress can be one of the components leading to the progression of chronic headache forms from infrequent, episodic headaches [14]. It is poorly understood how exactly stress affects

headache pain, but it probably directly influences the processes that produce and modulate pain [9]. Although the mechanisms may not yet be clearly understood, it is clear that stress is an important factor in the mediation of headache pain.

In light of this knowledge, it may be important to further study the correlation between stressful events in a headache patient's life and the onset of a headache. Previous studies have found a 10 day delay in the onset of perceived pain flares following a stressful event in patients with fibromyalgia syndrome (FS) and complex regional pain syndrome (CRPS) [15-21]. Using serial lag correlations, these studies found low correlations between stressful events and same day pain. Instead, the largest relationship found was between levels of stress and perceived pain intensity occurring 10 days later. This relationship was shown to correlate with the release of the thyroid hormone thyroxine [21]. This study aims to investigate the relationship between headache pain and stress to see if the results describing the 10 day delay in pain onset for other chronic pain disorders (FS and CRPS) also apply to chronic headache pain.

Materials and Methods

This study was approved by the Institutional Review Board at the University of Puget Sound (Protocol #PT1112-003) on April 13, 2012 and informed consent was obtained from all participants.

Subjects were recruited from local physical therapy clinics and were identified as having frequent headaches with the following inclusion criteria: 1) diagnosis of primary headache pain (including but not limited to migraine, tension-type headache, or cluster headache), 2) experiencing headaches on average 10 days per month, with a history of these headaches for at least one year, 3) over the age of 18, 4) willing and able to complete daily paper and pencil inventories, 5) no diagnoses for any other conditions that may be the cause of the headaches. Two subjects completed the study. Subject 1 was a 53 year-old female. She had been experiencing headache pain, diagnosed as cluster migraine, for 18 years. Subject 2 was a 21 year-old female, with a five year history of frequent headache, diagnosed as migraine headaches.

The subjects were given a daily paper and pencil inventory for a period of 10 weeks, to be completed in the evening before going to sleep. This was used to assess the average level of perceived stress throughout the day and perceived pain at its worst during the day. The sensory (MPQSF-S) and affective (MPQSF-A) dimensions of daily perceived pain were assessed using the McGill Pain Questionnaire Short Form (MPQSF). The range of possible scores for MPQSF-S was 0-33 and for MPQSF-A was 0-12. Daily pain intensity levels were assessed using the visual analog pain scale (VAPS). Participants were asked to mark their level of pain at its worst in the last 24 hours on a 10 cm line, with No Pain to the left and Most Pain Imaginable on the right. The visual analog stress scale (VASS) was used to assess daily levels of perceived stress. Participants were asked to mark their average level of stress on a 10 cm line, with No Stress to the left and Most Stress Imaginable to the right. Serial lag correlations were determined using a linear regression model. Serial lag correlations using the Pearson Product-Moment correlation coefficients were done from 0-14 days.

Results

Subject 1

During the 10 week observation period, Subject 1 experienced five episodes of peak stress and six peaks in pain (Fig. 1). Using serial lag correlations, the strongest relationship between reported stress and pain was for pain experienced 10 days after a stressful event ($r = 0.63$, $p < 0.005$), as shown in Fig. 2. Four of the peaks in stress reported were followed 10 days later by a peak in pain intensity (Fig. 1).

Figure 1. Visual analog stress score (VASS) with visual analog pain scores (VAPS) 10 days later across the 10 week observation period for Subject 1.

Figure 2. Serial lag correlations between daily visual analog stress scales scores and lagged visual analog pain scale scores up to 14 day lag for Subject 1.

Subject 2

Over the 10 week observation period, Subject 2 experienced a period of high stress levels from day 12-29. The greatest number of headache-free days occurred during the period between days 22-38 (Fig. 3). Serial lag correlations revealed the strongest relationship between stress and pain levels for pain experienced 10 and 11 days following a stressor ($r = -0.37$ and $r = -0.46$, respectively, $p < 0.05$), as shown in Fig. 4. It is important to note that the correlation coefficients were negative for Subject 2, as compared to the positive values for Subject 1. VASS scores with VAPS scores 10 days later (VAPS Lag 10) can be visualized in Fig. 3.

Figure 3. Visual analog stress score (VASS) with visual analog pain scores (VAPS) 10 days later across the 10 week observation period for subject 2.

Figure 4. Serial lag correlations between daily visual analog stress scales scores and lagged visual analog pain scale scores up to 14 day lag for Subject 2.

Discussion

Our results varied widely between the two subjects studied. For Subject 1, the results are consistent with previous work on FS and CRPS showing a 10 day delay in pain following a stressful event. This subject showed high correlations between stress and headache pain levels 10 days later ($r = 0.63$, $p < 0.005$; Fig. 1 and 2). This suggests that stress may impact chronic headache pain in a similar way that it does other chronic pain syndromes, such as FS and CRPS.

When an individual experiences stress, the hypothalamic-pituitary-thyroid (HPT) axis is activated [9]. Emotional arousal activates the paraventricular nucleus of the hypothalamus, which stimulates the thyroid gland to release thyroxine (T4) and triiodothyronine (T3). When released by the thyroid, thyroxine is immediately bound by thyroxine-binding globulins (TBGs). The TBGs make thyroxine inactive for the time that it is bound. Research has shown that the release of free thyroxine from the TBGs produces a peak 10 days after initial release by the thyroid [18, 22]. This means that when the HPT is activated by stress, thyroxine is released, but does not become active in the body for 10 days. Increased thyroxine levels can lead to increased anxiety as well as increased nerve excitability, which can both contribute to an increase in perceived pain levels [23]. This mechanism is strongly supported by a study finding that every peak in stress in a patient with CRPS was followed 10 days later by a peak in pain and an elevation of free thyroxine levels [21].

Figure 5. A plausible mechanism for thyroxine release related to delayed increase in pain perception.

There is some debate over whether stress leads to an increase or decrease in thyroid hormone release. For example, in a review of the HPT axis response to stress, Selye concludes that thyroid hormone release can either increase or decrease, depending on the species and type of stressor [22].

The data from Subject 2 did not follow the same trend as did those from Subject 1. A strong correlation was found between stress and decreased pain 10 days later ($r = -0.37$, $p < 0.05$) as well as 11 days later ($r = -0.46$, $p < 0.05$) (Fig. 3 and 4). This suggests a different mechanism for pain modulation in response to stress for Subject 1 compared to Subject 2. As we still see a strong correlation for a 10 day lag, it is possible that for this patient, increased stress leads to a decrease in HPT activity, leading to less thyroxine production. A decrease in free thyroxine levels 10 days later would ultimately lead to decreased pain perception. When the thyroid gland is signaled to turn down production of thyroxine, it may take a bit longer for this effect to take place, which may explain the strong correlation of day 11 in addition to day 10.

The findings of this study have many implications for headache patients and their therapists, as well as for other healthcare providers. For patients, it is often frustrating to manage seemingly random fluctuations in headache pain. The present data suggest that highly stressful events may lead to elevated pain perception 10 days later, or decreased pain perception 10 days later, depending on the individual and type of stressor. Healthcare providers may be able to help patients determine if their pain fluctuations follow this trend and, if so, can manage treatment accordingly.

Conclusion

Based on the findings of this investigation, it appears reported stress is associated with changes in perceived pain intensity occurring 10 days later. However, the two subjects in this investigation manifested that relationship in diametrically opposed ways wherein headache pain seemed to increase as a function of stress in one yet decrease in the other. This investigation lends some support to the notion that the stress-related release of thyroxine may be a delayed mediator of chronic pain states.

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