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Relationship Between Delayed Pain Flares, Psychogenic Stress and Free Thyroxine in Patients with Phantom Limb Pain

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IRB Approval

This study was granted approval for participation by human volunteers from the Institutional Review Board of the University of Puget Sound on 2/13/16; IRB protocol #1516-005.

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INTRODUCTION

Phantom limb pain (PLP) involves a variety of painful and debilitating sensations following amputation that are perceived to originate from a limb, or limb segment, that is no longer connected to the body.[1] PLP is a common problem for individuals following an amputation, occurring in 42 to 78% of cases,[1] with severe pain reported in 5 to 10% of cases.[2] Individuals can experience PLP as feelings of stabbing, cramping, burning, clenching, muscle spasms, tingling, and/or paralyzing sensations.[3] While there is no agreement as to the etiology of PLP, current theories involve neuropathic changes, either distally or via central nervous system remodeling.[4] As such, PLP may be considered a form of neuropathic pain and may be potentially modulated by factors that have been established to influence the frequency and/or level of pain experienced in other neuropathic conditions.

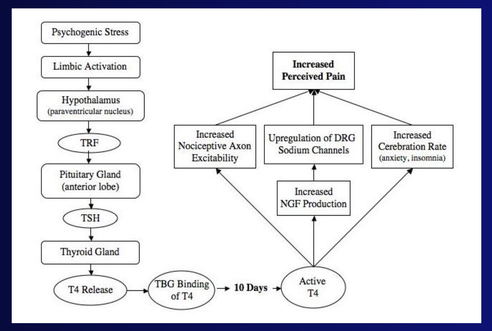

Figure 1. Stress-related release of thyroxine and resulting hormone cascade leading to increased perceived intensity of neuropathic pain 10 days following the stressor. [6]

Previous studies have found a ten-day delay in the onset of perceived pain flares following stressful events in patients with other neuropathic pain syndromes including fibromyalgia syndrome (FS),[5] complex regional pain syndrome (CRPS),[6] and migraine headaches.[7] Using serial lag correlations, these studies found low correlations between stressful events and same day pain. The largest relationship found was between levels for stress and perceived pain intensity occurring ten days later. [8] This is consistent with the established behavior of thyroxine; following secretion it is bound and enters a period of latency for approximately ten days at which point it is released in a metabolically active form that elicits systemic effects.[9] A study involving patients with CRPS provided support for the hypothesis that the stress-related hormone thyroxine may be responsible for the up-regulation of neural pain pathways ten days after its release during stressful events.[6] It is hypothesized that episodes of increased PLP may also be subject to modulation by psychogenic stress and show a similar latent appearance due to the psychogenic release of thyroxine.[8]

If it is established that PLP episodes also appear ten days after salient stressors, this information can be used by people with amputations and their medical caregivers alike to help understand the etiology of painful episodes, predict and plan for their occurrences, and distinguish between stress-related episodes and those brought on by other life activities.

PURPOSE

The purpose of this study was to investigate the temporal relationship between psychogenic stress, stress-related thyroid hormone activity, and the frequency and severity of potentially latent phantom limb pain episodes. Specifically, this study aims to determine whether PLP responds to thyroxine in the same manner as other established neuropathic pain conditions. If the same stress-thyroxine-pain relationship is observed, it would suggest that thyroxine is not acting at the local tissue level and rather acts at the level of the central or peripheral nervous system.

SUBJECTS

This is a case study design with two patient cases, both with long-standing PLP. Participant 1 was a 44-year-old male who had an upper extremity amputation and intact thyroid function. Participant 2 was a 32-year-old male with a history of lower extremity amputation and thyroidectomy which was managed by a stable levothyroxine regimen. Neither reported taking any medication for pain control.

METHODS

Each day, for 10 weeks, participants completed ratings of pain and stress using visual analog scales (VAS), and daily blood samples for FT4 analysis. VAS scores were measured and recorded by two blinded investigators. Serum thyroxine was assessed via a small daily blood draw performed by the participant each evening. Blood samples were collected by the principal investigator daily and refrigerated from the time of collection until mailing, which was conducted on a weekly basis. To ensure the integrity of data, blood samples were mailed to two separate labs which independently analyzed levels of FT4. Thyroxine values from one lab demonstrated internal consistency errors therefore the data from this lab was excluded from analysis.

ANALYSIS

To identify the presence of stress-related delays in both pain flares and FT4 peaks, VAS ratings of stress were compared to FT4 and pain using serial lag correlations of 0-14 days. To determine the relationship between FT4 levels and perceived pain, VAS ratings were analyzed using same-day correlations. All statistical analysis was conducted in Microsoft Excel.

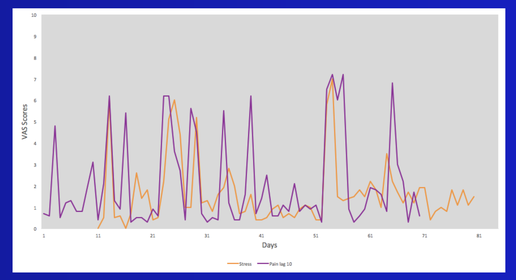

Figure 2. Participant 1 visual analog stress scale (VASS) and visual analog pain scale (VAPS) lagged by 10 days.

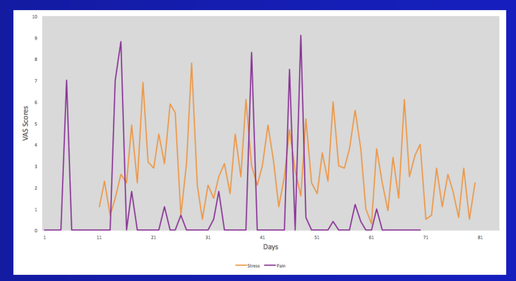

Figure 3. Participant 2 visual analog stress scale (VASS) and visual analog pain scale (VAPS) lagged by 10 days.

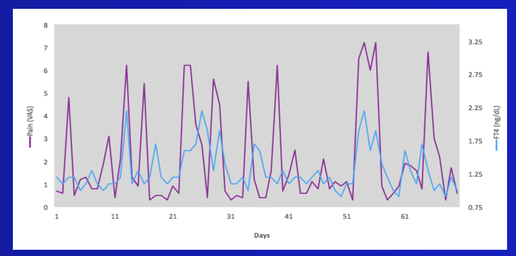

Figure 4. Participant 1, same-day visual analog pain scores (VAPS) and FT4 relationship.

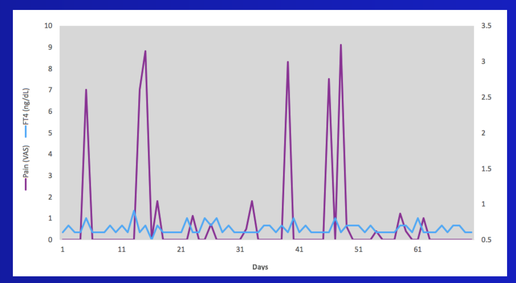

Figure 5. Participant 2, same-day visual analog pain scores (VAPS) and FT4 relationship.

RESULTS

Serial lag correlations between stress and pain, and stress and FT4, demonstrated the strongest relationship on the tenth day following a salient psychogenic stressor. The relationship between participants' ratings of stress and pain ten days later is demonstrated in Figure 2 and Figure 3 for participants 1 and 2, respectively. Correlations between these values were $r = +0.53$ ($p<0.001$) for participant 1, and $r = -0.05$ ($p>0.05$) for participant 2. Correlations between ratings of stress and serum FT4 ten days later were $r = +0.74$ ($p<0.001$) for participant 1 and $r = -0.02$ ($p>0.05$) for participant 2. Figures 4 and 5 demonstrate the relationship between ratings of same-day pain and thyroxine for participants 1 and 2, respectively. Correlations between these values were $r = +0.47$ ($p<0.001$) for participant 1 and $r = -0.02$ ($p>0.05$) for participant 2.

DISCUSSION

This case comparison suggests that there is a relationship between stress, thyroxine and pain flares in patients with PLP who have an intact thyroid. Our findings with participant 1 are consistent with previous literature, which has illustrated a peak in reported levels of pain and FT4 ten days following a stressful event.[6] This relationship was not observed in participant 2, who had a history of thyroidectomy. This difference supports the hypothesis that stress-related FT4 levels are contributing to modulation of pain since participant 2 did not demonstrate stress-related FT4 fluctuations due to his stable regimen of levothyroxine. Because in PLP the local tissue in the area of perceived pain no longer exists this indicates that thyroxine is not modulating pain at the local tissue level and is instead exerting its effects at the peripheral or central nervous system level. Since participants with PLP demonstrated the same stress-thyroxine-pain relationship that has been observed in other neuropathic pain conditions, it could be hypothesized that other neuropathic pain conditions are also being modulated at the central or peripheral level by thyroxine.

CONCLUSIONS

These findings support the hypothesis that FT4 levels related to psychogenic stress are associated with delayed flares in PLP, suggesting that PLP behaves in the same way as other neuropathic pain conditions and that thyroxine acts at the level of the central or peripheral nervous system to upregulate pain pathways.

RELEVANCE

Patients with PLP may benefit from understanding the relationship between stress and pain, as this information can help them predict and plan for painful episodes. This may also prevent them from excessively limiting their activities to avoid increases in pain.