AN INVESTIGATION OF HUMAN PLASMA PROTEIN BIOMARKERS IN BURNING MOUTH SYNDROME

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INTRODUCTION

Burning mouth syndrome (BMS) is a heterogeneous neuropathic pain condition of elusive aetiology, however inflammatory and aberrant neuronal processes may contribute to the pathology. Many BMS patients exhibit psychiatric co-morbidity and such patients are frequently managed with antidepressant drugs. Microtubules are fundamental to neuronal structure and plasticity and alterations in brain α-tubulin post-translational modifications (PTMs), including acetylated tubulin (Acet-Tub), tyrosinated tubulin (Tyr-Tub), detyrosinated tubulin (Glu-Tub) and Δ2-tubulin (Δ2-Tub), have been implicated as biomarkers in animal models of affective disorders [1].

The aims of this study were:

- To assess the plasma microtubule profile in BMS patients and controls;
- To assess the plasma cytokine signature in BMS patients and controls;
- To correlate these signatures with clinical profiles.

METHODS

Patient recruitment: Ethical approval was obtained from University College Cork Teaching Hospitals, the School of Medicine at Trinity College Dublin, and the Tallaght and St. James' Hospitals, Dublin. Age- and sex-matched controls (*n* = 10) and BMS patients (*n* = 10) completed the self-rated 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$) questionnaire and a Visual Analogue Scale (VAS) to quantify oral pain. Clinical histories were obtained from all patients.

Plasma Analysis: Peripheral venous blood samples were obtained by venepuncture and plasma was aspirated following centrifugation. Plasma samples (*n* = 20) were analysed by infrared Western Blot to quantify plasma α-tubulin PTMs. Plasma cytokines were measured using the V-PLEX human pro-inflammatory panel assay. Data were analysed using Student's t-test, one-way ANOVA, and linear regression.

CONCLUSION

- In this study we provide evidence for specific microtubule protein and cytokine signatures in plasma that correlate with depression and antidepressant treatment in patients.
- Previous work describes an overexpression of plasma Acet-Tub and reduced hippocampal microtubule dynamics in endogenous models of depression (Wistar Kyoto rat) [1, 2]. This effect has further been shown to normalise following long-term antidepressant treatment in these preclinical models.
- **The findings of this study support plasma α-tubulin PTMs and Interleukin-8 as indicators of treatment intervention in a cohort of BMS patients with potential relevance to other affective disorders. Future work aims to integrate and validate the observed microtubule and cytokine profiles in clinical samples.**

REFERENCES

1. Bianchi, M et al. 2009. Fluoxetine administration modulates the cytoskeletal microtubular system in the rat hippocampus. Synapse 63: 359–364.
2. Prenderville, J et al. 2015. Ketamine and 3beta-Methoxy-pregnenolone exhibit an antidepressant effect in the endogeneously "depressed" Wistar Kyoto rat: a microtubular mechanism? In CINP Thematic Meeting on Stress, inflammation and focus on novel antidepressant targets.

RESULTS

(1)

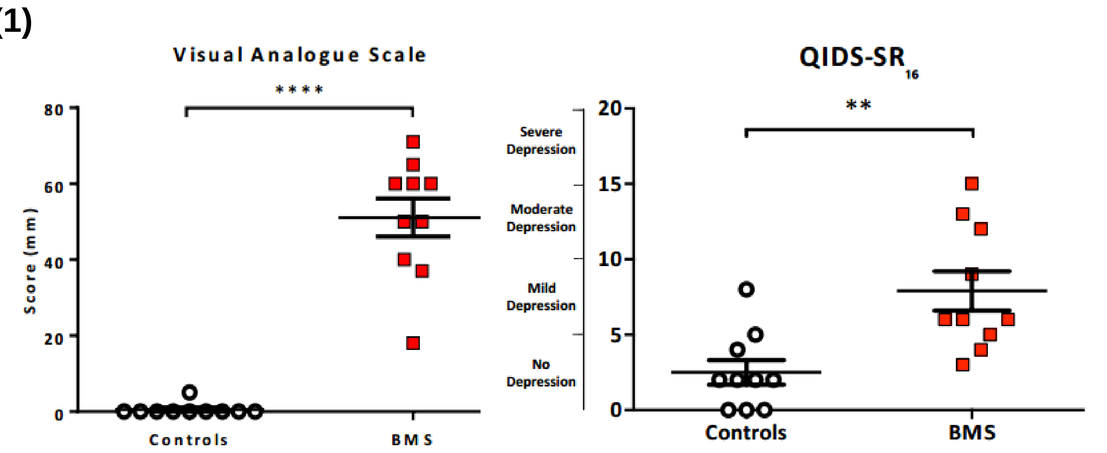
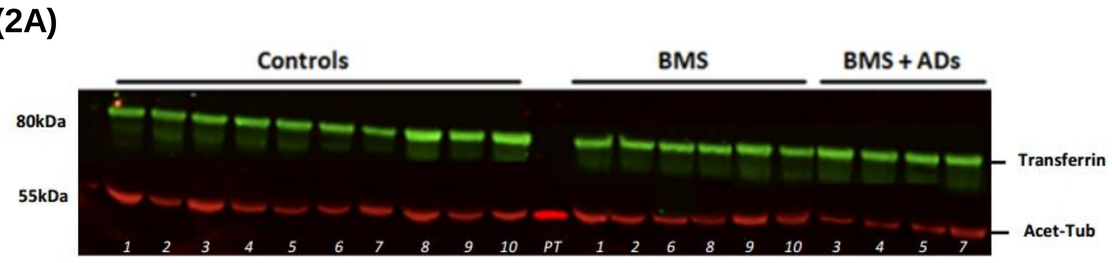


Figure 1. Oral pain and depression scores are enhanced in BMS patients
****p<0.0001, by Student's t-test. **p = 0.0024, by Student's t-test. *n* = 10 per group.

(2A)



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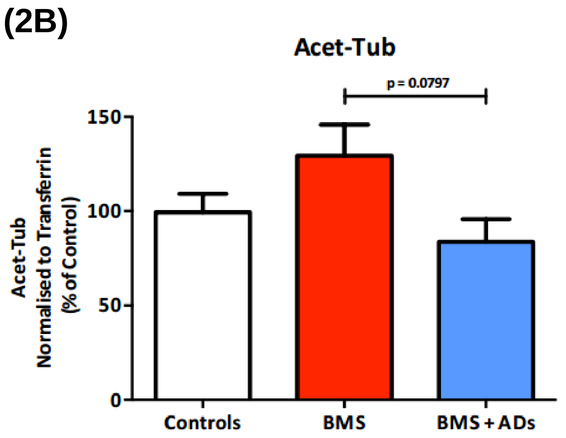

(2C)

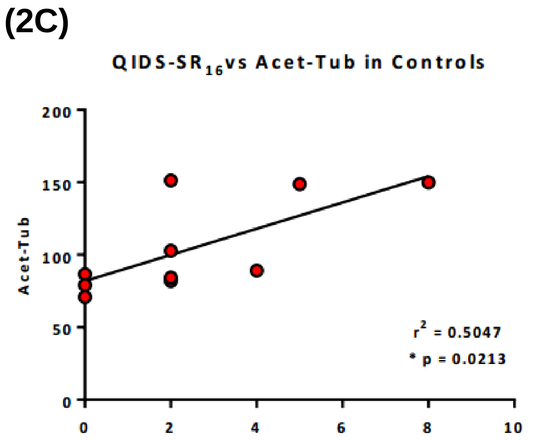

Figure 2. A reduction in plasma Acet-Tub is associated with antidepressant treatment in BMS patients
2A. Representative Western Blot of Acet-Tub infrared detection in plasma: Control (*n* = 10), BMS (*n* = 6), and BMS + Antidepressants (*n* = 4) groups. PT; Pure Tubulin (positive control).
2B. Antidepressant treatment is associated with a non-significant reduction in plasma Acet-Tub. p = 0.0797, by one-way ANOVA. Data is expressed as mean ± SEM. ADs, antidepressants.
2C. Increased Acet-Tub is significantly correlated to increased depression severity in controls. *p <0.05, by linear regression.

(3)

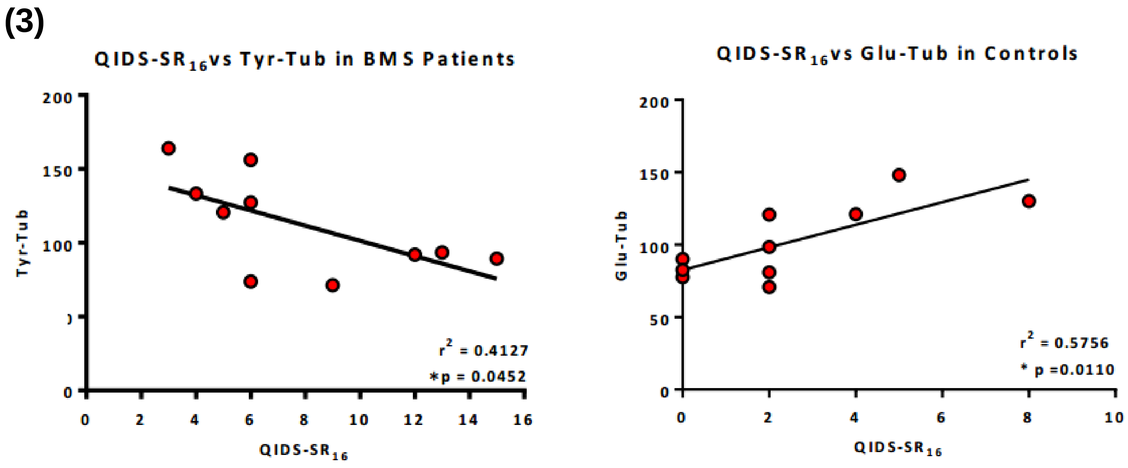

Figure 3. Microtubule PTMs correlate with depression severity
Decreased Tyr-Tub and increased Glu-Tub correlate with increased depression severity in BMS patients and controls, respectively, indicative of reduced microtubule dynamics. *p <0.05, by linear regression.

(4)

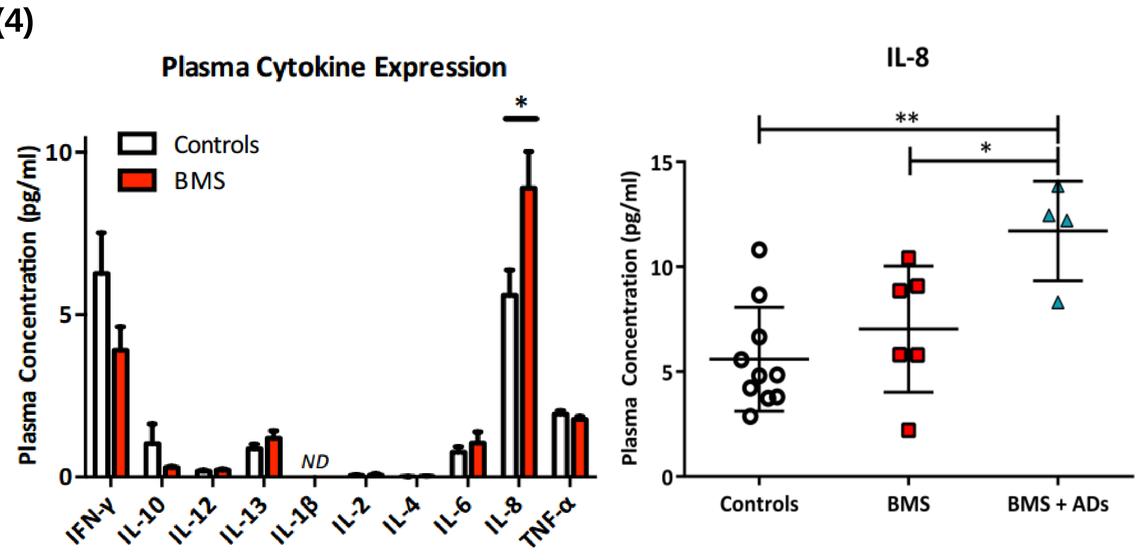

Figure 4. Plasma cytokine profiles in BMS and controls
Interleukin-8 is significantly associated with antidepressant treatment. **p<0.001 *p<0.05, by one-way ANOVA. Data are expressed as mean ± SEM. IL, interleukin; IFN, interferon; TNF, tumour necrosis factor; ND; not detected; AD, antidepressant.