Biomarkers Illuminating Pain After Stroke

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Background

70% of stroke survivors report shoulder pain in the acute post- stroke period, and half will go on to develop chronic shoulder pain (hemiplegic shoulder pain or HSP).[1-7]

Chronic HSP is predictive of lengthened hospitalization, worsened outcomes, decreased quality of life, depression, and physical deconditioning.[4,6-10]

Evidence points to three physiologic sources of HSP either acting separately or in combination:[1,7-8] musculoskeletal lesions; impaired motor control; and altered peripheral and central nervous system activity.[1,6-8,11]

Because the underlying processes are unclear, 30% of HSP sufferers are left with pain and impairment refractory to any currently available treatments.[7]

Electroencephalogram (EEG) spatial patterns are recognized biomarkers in many pain conditions,[14-22] but is not researched in HSP.

Methods

Sample: 11 stroke survivors (Table 1 and 2) with self-reported HSP > 3 months. Those with a pre-stroke pain condition were excluded.

Measures: 19 electrode EEG, self-report pain and interference measures = Brief Pain Inventory (BPI), PROMIS 8a and 29, Pain Vigilance and Awareness Questionnaire (PVAQ). Self-report of the EEG experience was collected using a NRS 0-10 scale and one open text question.

Analysis: EEG regions of interest included the standard pain network. Analysis of brain function was completed individually and compared to a database of asymptomatic brains, matched by age, gender, and handedness. Baseline differences were analyzed in amplitude, power, and relative power for delta, theta, alpha, low beta, high beta, gamma, theta/beta ratio, and alpha/beta ratios between the HSP and normal EEG. A Laplacian montage was used to minimize the effect of medications on the EEG.
Instruments were scored according to instructions and descriptive statistics applied. Qualitative content analysis was used to code the open text responses.

Ethical Considerations

Investigational Review Board approval for this study was given by the Center for the Human Protection of Subjects at University of Texas Health Science Center at Houston and MD Anderson Cancer Center, both in Houston, Texas.

Results

Table 1. Demographics

Age (median [IQR])	**53 [48.5, 61.5]**
BMI (median [IQR])	25 [22.19, 28.87]
Months Since Stroke (median [IQR])	34 [23, 58]
Laterality (%)	Right 50%/ Left 40
Comorbidity (%)	↑Blood Pressure 82 ↑ Cholesterol 55
Smoking (%)	None 64/ Past 27/ Current 9
Race (%)	Black 55/ White 36
Gender (%)	Female 55%
Marital Status (%)	Married 64

Table 2. NIH Stroke Severity Scale Score

NIHSS Score	(n(%))
3	1 (12.5)
4	1 (12.5)
7	2 (25.0)
8	1 (12.5)
10	2 (25.0)
27	1 (12.5)

There was an increase in cortical power in the slower frequencies (< 7 HZ), with a concomitant decrease in beta frequencies (Fig 1).

Yet 33% presented with an increase in beta power and also exhibited the same type of stroke.

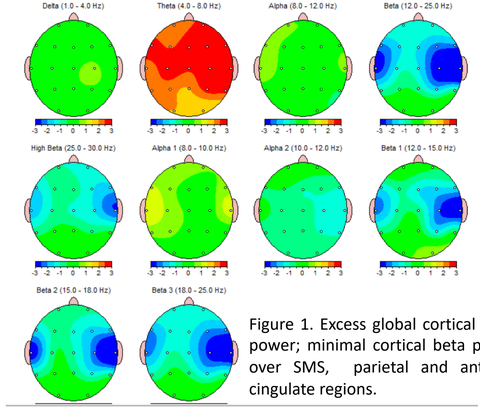

Figure 1. Excess global cortical delta power; minimal cortical beta power over SMS, parietal and anterior cingulate regions.

Connectivity analysis showed disruption within patients (Fig. 2):

- Lack of power in beta (15-25 HZ) was consistent among patients.
- Beta connectivity was most frequently affected with deviances > 3 SD, where alpha was within normal limits in 2 of the patients.
- Two patients who did not show reduced alpha and/or beta connectivity were patients 2 & 5, who both had MCA-type strokes.
- Phase lag is used to estimate connectivity that eliminates volume conduction effects. Phase lag tended to be at least 3 standard deviations slower than a normative database in 88%.
- BPI Severity Scale mean of 5 indicating moderate pain (range 2 – 10), and BPI Intensity scale mean of 4.3 (range 0.28 – 10).

AM-PAC activity scale basic mean 20 and daily mean 21.
PVAQ demonstrated a mean score of 54 (range 33 – 78).
All consented patients completed all instruments and all study requirements.

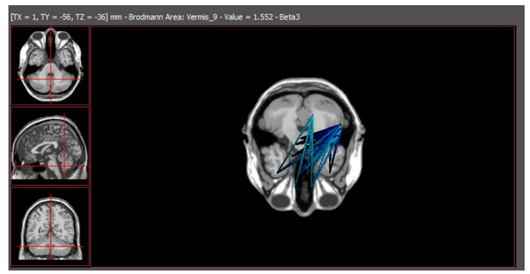

Figure 2. Slow connectivity in the pain network in the beta band.

Conclusions

Our EEG findings may be unique to HSP patients. The cortex showed overall slowing much like in other types of direct insults to the brain (TBI). One potential mechanism for an increase in power in slow EEG frequencies is a compromise to cerebral blood flow, which then may have an impact on metabolism and neuronal function.

EEG as an exploratory biomarker for HSP has the potential to advance translational medicine by determining unique targets for diagnosis, neuromodulatory interventions, and for medications. It is easily adoptable in clinical testing and health care settings.

The subjects in this pilot reported HSP that was not adequately treated. Most of the subjects indicated under or un-treated pain based on their instrument scores, with only one participant reporting more medication prescriptions than the others, lower BPI pain scores, low PVAQ score indicating less pain vigilance, and higher function scores on the AM-PAC instruments.

This study demonstrates that qEEG is a feasible and low-cost pain biomarker option with low treatment burden.

Implications for Patient Care

HSP reduces quality of life. As up to 29% of those prescribed opioids for chronic pain misuse them, a large percentage of stroke survivors could become statistics in the opioid crisis.[23]

Though the AM-PAC activity scale basic and daily had similar means demonstrating a higher level of function in this sample, the PVAQ mean score indicated a moderate level of pain vigilance. Despite limited residual disability, pain reporting and thinking about pain was moderately high.

There is an urgent need to develop non-pharmacological interventions for pain management in stroke survivors.

References