(132) Use of a depression biomarker panel to diagnose depression in chronic pain patients

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Chronic pain and depressive illness are debilitating disease states that to share common pathophysiology. We used a blood test and algorithm which provides a score based upon the serum levels of biomarkers in the neuroinflammatory and metabolic pathways. Patients with depression ≥5 have a 90% probability of major depressive disorder (MDD). In this study we determined MDDScores and investigated the depression related alterations in biomarker expression in a series of CIP patients. The CIP group consisted of 35 patients with documented centralized intractable pain. Median age was 51±9.2 years. Twenty-three (67%) were female and twelve (33%) were male. Each had a blood sample drawn for serum immunoassay levels of 9 biomarkers: (alpha-1 antitrypsin, Apolipoprotein CIII, Brain Derived Neurotrophic Factor (BDNF), Cortisol, Epidermal Growth Factor [EGF], Myeloperoxidase [MPO], Prolactin [PRL], Resistin [RETN], and soluble TNF receptor II [TNFR2]). The CIP patients were distributed into two groups based upon their depression score. Seventeen patients had depression <5 while 18 had scores ≥5. Analysis of serum cortisol levels indicated that patients with scores <5 had a mean cortisol level of 17.8 ± 13.2 μg/dL while those with a score ≥5 had mean levels of 9.5 ± 4.9 μg/dL ($p = 0.017$). The HPA axis biomarker EGF was also significantly different in the two groups. Patients with scores <5 had a mean EGF level of 272.8 ± 176 pg/mL while those with a score ≥5 had mean levels of 427.3 ± 206.9 pg/mL ($p = 0.024$). Our results indicate that a depression score was able to segregate CIP patients into 2 groups. Patients with a depression score ≥5 indicative of MDD had lower cortisol levels (perhaps due to prolonged opioid use) and elevated serum EGF, a stimulator of adrenocorticotropin.

(133) Adrenocorticotropin hormone as a biomarker of uncontrolled severe, chronic pain

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Adrenocorticotropin (ACTH) is the major pituitary stress hormone that stimulates adrenal hormones to be secreted into the serum in an effort to eliminate or heal injured tissue that may cause pain. When pain occurs, signals are transmitted to the thalamus which stimulates the corticotropin releasing hormone in the hypothalamus to cause the pituitary to hyper-secrete ACTH into the serum. Given this physiologic mechanism, ACTH should be elevated in uncontrolled pain, and, if pain is uncontrolled for an extensive time period, pituitary reserve and production of ACTH may not be able to meet the stress demand of pain, and it, therefore, will drop in the serum. This study was done to test this premise and determine if serum ACTH concentration can serve as a biomarker of uncontrolled pain. Sixty-one (61) consecutive chronic pain patients who had failed standard pain treatments including low to moderate opioid dosages were referred for evaluation and management. Prior to any change in any patient's treatment regimen, an early morning ACTH serum concentration was determined. Five (9.1%) had elevated and 10 (16.4%) patients had low ACTH serum concentrations. Over a 90 day period patients were treated by progressively raising their daily opioid dosage until their pain was controlled to the point that they could physiologically function and carry out activities of daily living. During the opioid titration period any known deficient adrenal or gonadal hormone was replaced. All but two patients normalized their ACTH serum concentrations. The two who did not normalize were believed to have pituitary insufficiency due to traumatic brain injury and/or an autoimmune disorder. This study indicates that ACTH serum abnormalities may occur in uncontrolled pain and will normalize with adequate pain control unless the pituitary is affected by an organic disease.

(134) Pituitary-adrenal failure in severe, chronic pain patients

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Hormone testing is a new entry into pain management. Recent technological and logistical advances now make it possible to obtain immediate access to hormone profile testing so that complete hormone information is available to outpatient pain care. As a result, profound hormone abnormalities are now being identified in pain patients. Reported here are 61 chronic pain patients who were referred for evaluation and treatment after failing standard pain therapies. All described their pain as constant, uncontrolled, and with flares that were "excruciating and unbearable." Patients were weak, fatigued, and bed or house-bound. Hormone testing revealed pituitary-adrenal failure in 7 (11.5%) as defined by a deficiency of adrenocorticotropin (ACTH), and two or more hormone deficiencies of these hormones: cortisol, pregnenolone, dehydroepiandrosterone, progesterone, or testosterone. Hormone levels were dangerously low in some patients. Three (3; 4.9%) patients showed serum cortisol levels under 1.0 ug/dl, 1 (1; 1.6%) had a trace level of pregnenolone, and 3 (3; 4.9%) had testosterone levels under 3.0 ng/dl. All patients were immediately treated with replacement of all deficient adrenal-gonadal hormones as well as enhanced pain control with opioids. Hormone administration and opioids were titrated upward until serum hormone levels were in normal range and the patient had enough pain control to function, leave home unassisted, and carry out activities of daily living. It is unknown as to how many severe, chronic pain patients may have, in the past, unknowingly died of pain-induced, pituitary-adrenal failure. The perilously low hormone levels found in the patients reported here represent pituitary-adrenal failure, and if these patients' hormonal status had worsened, death would likely have occurred. Severe, chronic pain patients who report symptoms of severe weakness, fatigue, depression, and reclusivity, and do not respond to standard pain treatments should be screened for pituitary-adrenal failure.

(135) Cytochrome P450 defects in pain treatment failures

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A long-time question in pain treatment is why patients with similar, painful injuries or conditions may require great differences in dosages of opioids and other drugs. Cytochrome P450 enzymes are principally found in the liver and intestine and they metabolize almost 75% of pharmaceuticals used in pain treatment. Cytochrome P450 (CYP450) enzyme testing capability is now widely accessible to pain practitioners. Reported here is a series of 101 severe, chronic pain patients who had failed standard pain treatments including a minimal daily dosage of 100 mg equivalence of morphine. Patients were in active medical treatment between January 2012 and October 2014. They were tested by buccal swab for these CYP450 enzymes; (1) CYP 2D6; (2) CYP 2C9; (3) CYP 2C19. A normal CYP450 enzyme was graded extensive. Abnormal or defective enzymes were graded poor, rapid, or intermediate. Ninety-one (91) of 101 patients (90.1%) had one or more CYP450 defects. Twenty-eight (28; 27.7%) patients had two and 8 (7.9%) had defects in all 3 CYP450 enzymes. A total of 132 defects were found in the 101 patients. The number of single CYP450 enzymatic defects were: 2D6 (43, 42.6%); 2C19 (52, 51.4%); and 2C9 (37, 36.6%). The percentage (90.1%) of defective CYP450 enzymes in this group of patients appears considerably higher than the general population. Epidemiologic data collected to date suggests that no more than 50% of the general population has a CYP450 defect. This study indicates that chronic pain patients who fail standard treatments, including a relatively high opioid dosage, may have CYP450 enzymatic defects that are at least partially responsible for failure of standard treatments. Patients who fail standard pharmacologic treatments including opioids should be tested for CYP450 enzymatic defects to determine if there may be a genetic basis for non-standard therapy.