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Several studies have suggested that there are clinical similarities between individuals who developed unexplained illnesses associated with Gulf War deployment or Persian Gulf Syndrome (PGS), and persons who are diagnosed with conditions such as fibromyalgia (FMS) and chronic fatigue syndrome (CFS). In the present study in progress, we sought to confirm that these physiologic abnormalities could be identified in larger groups of persons with FMS/CFS, and that these same types of physiologic abnormalities could be identified in persons with PGS.

A total of 79 subjects have been studied to date including 38 patients with FMS, CFS (or both), 27 age-and gender-matched healthy normal controls, and 14 persons who developed three or more unexplained symptoms within one year of being deployed to the Persian Gulf. Our findings in FMS/CFS patients duplicated our pilot data and demonstrated that the FMS/CFS group displayed increased peripheral and visceral pain sensitivity, a higher prevalence of esophageal (smooth muscle) dysmotility, and diminished sympathetic and (a trend towards) lower parasympathetic tone as measured by 24 hour heart rate variability (HRV). In general, the PGS patients demonstrated the same qualitative differences as patients with FMS/CFS, although these were less pronounced, including intermediate levels of pain sensitivity, smooth muscle tone, and autonomic tone assessed by HRV. These data, though very preliminary, support the notion that the same underlying pathophysiologic processes that may be operative in illnesses such as FMS and CFS are present in persons with PGS.

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INTRODUCTION

In 1990 and 1991, the U.S. deployed approximately 700,000 troops to the Persian Gulf to liberate Kuwait from Iraqi occupation. Fortunately, there were relatively few combat and non-combat related injuries and diseases during this conflict in comparison with previous military campaigns, and most veterans of this conflict who did develop illness had diagnosable and treatable conditions [1,2]. However, the symptoms of approximately 20% of those with symptoms have not been explained, and this constellation of symptoms occurring in this setting has been termed the Persian Gulf Syndrome (PGS).

We contend that the only unique aspect of the PGS is the location and timing of troop deployment. Similar illnesses have been noted after nearly every major conflict, although these syndromes have had different names and attributions. *More importantly, similar syndromes occur at a high rate in the general population, with the currently preferred terms being fibromyalgia (FMS), chronic fatigue syndrome (CFS), somatoform disorder, and multiple chemical sensitivity (MCS).*

We have been extensively involved in the study of these latter illnesses, and there are substantial data suggesting that these syndromes are not discrete entities, but rather fall within a continuum. All of these illnesses are typically both initiated and perpetuated by a variety of physical and emotional stressors, as may have occurred in deployment to the Gulf War and upon return home. The study of these illness has shown that there are a number of objective abnormalities in the human "stress response" which can be identified that are likely responsible for the symptoms seen in these entities.

The purpose of this proposal is to demonstrate that these same objective neurohormonal abnormalities are present in individuals with PGS, and are at least partly responsible for the symptoms noted in these individuals. There are several axes of the stress response that can independently or concurrently function aberrantly in these conditions, including the autonomic nervous system, the hypothalamic-pituitary axes, and descending anti-nociceptive pathways. Specific symptomology results when each of these systems function improperly. In this study we propose to demonstrate that: 1) individuals with PGS display centrally mediated disturbances in autonomic tone, and this leads to vasomotor instability and smooth muscle dysmotility, and symptoms such as irritable bowel syndrome, and migraine headaches, 2) individuals with PGS display diffuse disturbances in nociception (pain threshold) that are partly responsible for many of the pain-related symptoms seen in this condition (e.g., myalgia, arthralgia, sore throat), and 3) the same neuroendocrine changes seen in FMS, and CFS, characterized by blunting of the hypothalamic-pituitary axes, are seen in PGS, and contribute substantially to the fatigue seen in this condition.

After patients are seen at the Washington, D.C. VAMC for a Comprehensive Clinical Evaluation (CCE), they are asked if they would like to be involved in this research, which is performed at Georgetown University Medical Center. To date, 14 patients have been studied, as well as 38 FMS/CFS patients, and 27 healthy normal controls (these latter groups are for comparison). There have been no untoward or unexpected adverse events as a result of this testing. We will continue to recruit individuals for this study, with the goal to study 40 PGS patients, 20 controls, and 20 FMS/CFS patients.

We feel that the study we have designed will lead to important insights into the symptoms experienced by some Persian Gulf veterans. The demonstration of common underlying

pathophysiologic mechanisms in FMS, CFS, and the Persian Gulf veterans will be tremendously beneficial, in that this should lead both to more effective treatment of these individuals, and perhaps to effective strategies regarding avoidance of this problem in future conflicts.

EXPERIMENTAL METHODS

Overview. The current study is being conducted on individuals who have been admitted to the Washington, D.C. VAMC, one of the three Persian Gulf Referral Centers created in August of 1992. This project is a multidisciplinary collaborative effort, involving individuals from Georgetown University Medical Center and the VAMC, as well as consultants from the National Institutes of Health who are recognized as international experts on the effects of stress on the neuroendocrine and autonomic systems. The participants in this study are admitted to the Clinical Research Center (CRC) at Georgetown for two days. Over the course of two days, participants undergo a series of studies that permit the concurrent evaluation of a number of physiologic and biochemical parameters.

The physiologic studies performed measure both the qualitative and quantitative aspects of a number of symptoms, and include specialized testing of peripheral and visceral nociception, and smooth muscle motility. We also evaluate multiple indices of autonomic function, including neurohormone levels at baseline and after standardized stressors, and cerebral spinal fluid (CSF) levels of nociceptive neurotransmitters.

We are employing several control groups: 1) "healthy normals", 2) Persian Gulf War (PGW) patients without a symptom or feature being studied, and 3) individuals with CFS and FMS. The purpose of the healthy normal control group is to show that the PGS patients differ from age and gender matched controls; this is the most common type of control group employed for this type of study. However, merely identifying that the group mean of a variable in PGS patients differs from that in a control group will tell us very little about PGS. For this reason, for each hypothesis we study two other control groups. The first is a cohort of PGW patients without the symptoms or feature being studied. We know from experience that there is tremendous heterogeneity in the clinical and pathophysiologic expression of disorders such as PGS, such that within the group of PGS patients, some patients will and others will not exhibit a certain feature (e.g. smooth muscle dysmotility). In this instance, for example, we would predict from our pilot data that approximately half of the 40 PGS patients we study will display objective evidence of smooth muscle dysmotility on manometric study. The hypothesis being tested with this variable is that the smooth muscle dysmotility is due to centrally mediated autonomic dysfunction. Thus, we will divide the entire group of patients with PGS into those with and without smooth muscle dysmotility, and demonstrate that that the group with dysmotility exhibits autonomic dysfunction, and those without dysmotility do not display autonomic dysfunction. The group of PGS patients without dysmotility should only differ from those with dysmotility with regards to that single variable, and should thus be better matched thanalternative control groups.

Finally, we will compare the results of the pathophysiologic studies with the same tests performed concurrently in FMS and CFS, to demonstrate that there are no differences between the PGS patients and the FM/CFS groups.

Subject recruitment. We will evaluate 40 consecutive PGW veterans who are referred to the Washington VAMC for a CCE, and 20 age- and gender-matched healthy controls, and 20 persons who have FM/CFS. Because PGW veterans without certain symptoms will also be serving as controls (see above), we chose to study a larger number of patients than controls.

Studying individuals who are being admitted to the VAMC for a CCE has several advantages over the use of alternative sources of PGS patients: 1) individuals in our study will be

well screened for alternative causes of symptoms, and will be precluded from participation, and 2) these individuals will have extensive baseline testing performed as part of the CCE which will be available for analysis.

a) *Definition of PGS.* Because there is no widely-accepted definition of PGS, this is a difficult issue. We sought to develop a definition of PGS that would truly select individuals who served in the Gulf War who have a significant unexplained illness. Thus, the definition we have employed for purposes of this study is that: 1) unexplained symptoms developed within 6 months of participation in the Gulf War, and continue to be active, and 2) those symptoms include 3 or more of the following: myalgia, arthralgia, headache, fatigue severe enough to limit activities, cognitive dysfunction, sensitivity to multiple environmental substances, pulmonary symptoms, and GI symptoms. We recognize that not all will agree with this definition, and if a consensus definition is developed before we begin this study, that definition will be used instead. However, we feel that this definition encompasses most of the symptoms which have been reported by Persian Gulf participants with unexplained symptoms, yet the definition is not too restrictive to identify only individuals who would meet the established criteria for FMS, CFS, MCS, etc.

b) *Inclusion and exclusion criteria.* Entry and exclusion criteria, other than meeting the above noted PGS criteria, include: *1)* ages 18 to 60, and *2)* subjects must not consume any antidepressant, tricyclic compound, benzodiazepine, anti-inflammatory, or antipsychotic medication for two weeks prior to study (these drugs interfere with testing being performed).

Control recruitment. Twenty healthy normal individuals, and twenty patients with FM and/or CFS, who are matched for age and gender to represent the study population will be randomly selected. These individuals will be compensated for participation, and the primary source of controls will be employees and patients at Georgetown University Medical Center.

Methods. Eligible patients and controls will give informed consent and be scheduled for admission to the Georgetown University Medical Center CRC. The testing throughout the day will occur in the CRC, except for the gastroenterology portion. The schedule of testing is listed below, and the sequence will be identical for subjects and controls. This testing sequence is similar to that utilized in our pilot studies, so we are comfortable that patients will be able to tolerate testing without difficulty, and tests that are sensitive to fatigue (e.g. cognitive testing) are scheduled in the morning. Methods for each test, and justification where appropriate, are described in detail below.

	Day One	Day Two
MORNING	Serum and blood collection (8AM) [Begin 24-hour urine collection and Holter monitoring] Tender point examination Tilt table testing COGSCREEN	Serum and blood collection (8AM) [Remove Holter monitor and complete 24 hour urine collection] Dolorimeter exam Gastroenterology evaluation
AFTERNOON	Structured Clinical Interview (SCID) Serum collection (4PM)	
EVENING	Complete self-report questionnaires	

Serum collection. Serum and plasma are collected utilizing standard venipuncture techniques. As noted, blood is drawn at standardized times throughout the study to eliminate discrepancies due to diurnal variation. Samples are placed on ice immediately and kept dark until they can be centrifuged. Sera will be distributed into several aliquots and stored at -70°C at two different locations.

Dolorimeter examination. A dolorimeter is a simple mechanical pressure gauge designed to quantify pain threshold and tolerance. For this examination, the pressure (in kg) necessary to produce discomfort (pain threshold) and unbearable pain (pain tolerance) at 18 designated tender points and 4 control points is recorded. This testing will produce five variables for each subject: tender point threshold and tolerance, control point threshold and tolerance, and tender point count.

Since there is such a high correlation between the first four values ($r>.85$ in our pilot studies), we will utilize the tender point threshold as the measure of peripheral pain for primary data analysis. This test had the least variance and best ability to separate FM patients from controls in our pilot data.

Autonomic function. *Overview.* The assessment of autonomic function in humans is complex. There are no tests of either sympathetic or parasympathetic function that are all-encompassing. In ordinary situations, there are a number factors controlling of visceral motor function, including central autonomic input (which we are measuring), nonadrenergic noncholinergic (NANC) nerves, local reflex loops, and local neurochemical effects. Because symptoms suggestive of smooth muscle dysmotility occur in several organs in CFS, we hypothesize that *aberrant centrally mediated autonomic input* is the predominant stimulus for the abnormal motility. Although the tests we have chosen will assess total autonomic tone, we will focus on those tests which measure the central component of autonomic tone.

In addition to testing basal central autonomic tone, the proposed studies will test the response of the autonomic nervous system to standardized physiologic stressors (pain from dolorimeter exam, mental concentration during cognitive testing, tilt table testing). We are testing

neuroendocrine function and smooth muscle motility in the same manner. We feel that this is a significant strength of the study we have proposed, because all clinical and laboratory evidence in FMS/CFS suggests to an inability to respond normally to physiologic stressors. We propose that PGS patients will exhibit similar aberrant stress responses. The stressors we have chosen are likely to accentuate the anomalies in the stress response, especially when compared to some techniques such as response to valsalva or deep breathing (autonomic testing), or response to CRH (neuroendocrine testing).

Holter monitoring. Heart rate variability monitoring has been demonstrated to be a very accurate means of assessing both the sympathetic and parasympathetic components of autonomic tone [3]. This can be performed by temporal or spectral analysis over an entire 24 hour period, or over short intervals of time, to determine how the autonomic nervous system functions in response to specific stimuli. Individuals with low efferent parasympathetic tone will display an elevated resting heart rate, and heart rate variation with breathing. Sympathetic tone can likewise be assessed with this technique, with tilt table testing as a useful adjunct in this regard. An especially useful feature of Holter monitoring to assess autonomic tone is that it affords a functional assessment of autonomic function over an extended period of time that includes provocative maneuvers and stressful events (tilt table testing as well as visceral and peripheral nociceptive testing). This is especially important since in the chronic phase of these disorders, we hypothesize that individuals may be particularly impaired in their ability to respond to these stressors.

Patients wear a standard ambulatory ECG recorder for the initial 24-hour period of the study. Data will be analyzed using a dedicated Marquette series 8000 analyzer with specialized software for Heart Rate Variability. A diary will be kept so that we can later analyze how the subjects respond to each of these stimuli. In addition, this Holter monitor allows the "marking" of "events" (e.g. the onset of tilt table testing, cognitive testing, lumbar puncture) on the tape, so that the autonomic responses to these specific stressors can be analyzed.

Tilt table testing. Tilt table testing allows a standardized method of assessing primarily the sympathetic component to central autonomic tone. With tilting in normals, the systolic blood pressure may fall as much as 15 mm Hg, whereas the diastolic may drop up to 5 mmHg. Any fall of blood pressure greater than this is considered abnormal. There are few good tests to differentiate afferent from efferent sympathetic dysfunction; perhaps the best is vasopressin release in response to tilt table testing, which is abnormal in aberrant afferent function, and will be utilized in this study [4].

Individuals are supine on a tilt table with foot support and secured in position. The subject rests in this position for at least 10 minutes. Blood pressure and heart rate are recorded using an automatic blood pressure recorder. After 10 minutes, a baseline sample for plasma vasopressin is drawn via the previously placed antecubital catheter into a EDTA tube, and the patient is tilted to a 70 degree head-up position. Blood pressure and heart rate will be recorded every minute, and blood samples are drawn every five minutes through minute-15. As with earlier samples, the blood will be kept on ice and in the dark until centrifugation. All samples are frozen at -70°C for later batch analysis. Vasopressin and Neuropeptide Y will be determined using commercially available I^{125} kits. Utilizing this protocol, normals will display an approximately threefold increase in vasopressin with tilting. Those individuals with afferent sympathetic dysfunction display no change in their vasopressin with tilt, whereas those with sympathetic dysfunction with an intact afferent axis (thus efferent dysfunction) display a 30-fold increase in

vasopressin levels [4].

Gastrointestinal evaluation. For evaluation of esophageal smooth muscle tone, and esophageal nociception, we follow the standard protocols for motility studies and Bernstein tests . The results obtained include baseline manometric data (normal or abnormal, based on defined criteria), as well as the results of three provocative tests (chest pain with edrophonium, dysmotility with edrophonium, and modified Bernstein test). Also, the diameter of an esophageal balloon required to elicit pain is recorded.

The data which will be utilized in primary data analysis are: 1) the presence or absence of baseline dysmotility, which will be compared to autonomic tone, and 2) the diameter of balloon causing nociception, which measures visceral nociception.

Neuroendocrine studies. Samples are collected in a uniform manner, so that we can retain the ability to secondarily analyze the neurohormonal response in a more uniform manner to give us an assessment of the integrity of this system. At this juncture in our understanding of these disorders, we recognize the perturbations in the neuroendocrine system, but are not certain of the physiologic consequences, or whether these are primary or secondary effects. Therefore, we do not feel that further hormonal provocative testing is required. In fact, although provocative tests with "releasing" hormones tests are commonly utilized because conditions and results can be standardized, they give a somewhat artificial understanding of neuroendocrine functional status. We feel that a more relevant physiologic test of the neuroendocrine system in a disorder such as FMS/CFS is to determine how subjects respond to standardized physical and emotional, rather than hormonal, stressors. Therefore, we have designed this study to look at the level of hormones at given points in time (8AM and 4PM), under standardized testing conditions (including physical [lumbar puncture, gastrointestinal] and emotional [cognitive testing] stressors), to determine both the basal level of these hormones and the capacity to change levels in response to a physiologic stimulus. We will have collected this same data taken under identical conditions on both PGS patients and controls, at both baseline and after stressors, which will allow us to assess further the differences between the neuroendocrine function within the group of patients, as well as between PGS patients and controls.

Structured Clinical Interview (SCID) and psychiatric evaluation. An extensive psychiatric evaluation is being performed as part of this study because psychiatric co-morbidity is high in all of the disorders related to PGS, including FMS/CFS, and MCS. As noted previously, psychiatric variables will be used in the secondary analysis of data to determine if these are important co-factors in symptom expression or in the outcomes of physiologic studies. The primary purpose of this portion of the evaluation is to 1) determine the presence of *present* psychiatric disorders, 2) determine the presence of *pre-existing* psychiatric diagnoses, and the effect on the expression of symptoms, and 3) measure the intensity of psychiatric variables such as depression, anxiety, somatic amplification, and use these measures as co-variates to dependent variables such as nociception, autonomic function, and neuroendocrine function.

The psychiatric evaluation utilizes the following instruments, which have all been extensively validated, and have been utilized in research in FMS/CFS, and allied conditions:

1) A Structured Clinical Interview for DSM-III-R (SCID)[5]. The structured clinical interview is used to generate current and lifetime psychiatric disorders such as mood disorders,

anxiety disorders, and somatoform disorders. A PTSD module is included as well. The SCID is widely used as the "gold standard" for psychiatric diagnosis in the research setting. The interview is conducted by either Dr. Epstein or a subordinate who has been appropriately trained. Particular attention will be paid to the timing of all psychiatric symptoms, including somatization symptoms, as they correspond to service in the Persian Gulf War.

2) Beck Depression Inventory (BDI) [6]. The BDI is a 21-item measure of the severity of current depressive symptoms, including both neurovegetative and cognitive symptoms of depression.

4) The RAND 36 item health survey [7]. This survey is a self-report measure of functional health status that has been widely utilized. Eight domains will be assessed: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, social functioning, energy/fatigue, and general health perception.

5) NEO PI-R [8]. The NEO is a self-report inventory for the assessment of personality traits based on a five factor model of personality.

6) Barsky Amplification Scale [9]. This ten item scale measures somatosensory amplification, the tendency to experience somatic sensations as unusually intense or disturbing.

7) Multidimensional Fatigue Inventory . This is a 20-item self-report scale measuring different aspects of fatigue.

8) Short-form McGill Pain Questionnaire [11]. Consists of 15 descriptors providing information on the sensory, affective, and evaluative dimensions of pain experience and is capable of discriminating among different pain problems.

Self-report questionnaires. Subjects complete a packet of self-report questionnaires designed to evaluate assorted symptoms and perceptions regarding pain and fatigue.

Urine collection. Urine is collected during the initial 24-hour period of the study, for archival storage in potential determination of neurohormonal levels, as noted above.

Computerized Cognitive Testing. This battery takes approximately 50 minutes to administer, and has been validated as a sensitive measure of cognition, especially in the areas of interest (attention and short-term memory) [12]. *In this study, we are using computerized cognitive testing as a psychological stressor, not to test any hypotheses regarding cognition in FMS/CFS. There are considerable animal data suggesting that the physiologic response to physical and emotional stressors may be quite different, so we have incorporated both into our study design.* These data can be secondarily analyzed to determine the factors which predict cognitive impairment, but this is not the primary intent of the study.

Sample Size Calculations. A sample size of 40 FMS/CFS patients and 20 healthy normal controls was chosen for this study, and is more than adequate to test the primary hypotheses. The patient group has been chosen to be larger than the "healthy control" group because to test each of the hypotheses, the patient group will be divided into two groups: one with and the other without the symptom or objective finding (pain, dysmotility, etc.) being studied. For testing differences among means we are seeking to identify a difference of one or more standard deviations between groups as statistically significant ($p=.05$). Differences of less than one standard deviation in this context are unlikely to be biologically meaningful. The standard computation shows 1) that a

sample size of 40 patients and 20 controls gives a power of greater than 90% to detect these differences, even after allowing for moderate adjustments to the p value for multiple hypotheses, and 2) that the projected sample sizes enhanced to include extra cases will produce this same power even when the comparisons are done between two subgroups of the FMS/CFS patients.

Data analysis. All data analysis will be performed with the assistance of Dr. Pezzullo, in his role as the Biostatistical Consultant for this project. Dr. Pezzullo replaces Dr. Chase, who has left the medical center.

Results and Findings: Enrollment for this study will be completed in one year, and thus much of the data (e.g. serum and plasma samples) has yet to be analyzed. A total of 79 subjects have been studied to date including 38 patients with FM, CFS (or both), 27 age-and gender-matched healthy normal controls, and 14 persons who developed three or more unexplained symptoms within one year of being deployed to the Persian Gulf. Preliminary data are available in many of the domains of testing; in other areas all samples will be run at the completion of the study because of concerns re: inter-assay variability. Our findings in FM/CFS patients duplicated our pilot data and demonstrated that the FM/CFS group displayed increased peripheral and visceral pain sensitivity, a higher prevalence of esophageal (smooth muscle) dysmotility, and diminished sympathetic and (a trend towards) lower parasympathetic tone as measured by 24 hour heart rate variability (HRV). In general, the PGS patients demonstrated the same qualitative differences as patients with FM/CFS, although these were less pronounced, including intermediate levels of pain sensitivity, smooth muscle tone, and autonomic tone assessed by HRV.

Conclusions: These data, though very preliminary, support the notion that the same underlying pathophysiologic processes that may be operative in illnesses such as FM and CFS are present in persons with PGS. Also, these data showing diminished magnitude of the same qualitative types of abnormalities as seen in FM/CFS are consistent with clinical studies that have demonstrated that although only a minority of PGS patients meet established criteria for FM or CFS, most have the same qualitative constellations of symptoms. For example, many of these patients display chronic regional (i.e., headache, low back pain) rather than widespread pain, or insufficient tenderness, to meet FM criteria; and/or milder fatigue, or inadequate numbers of "minor symptoms, to meet CFS criteria. If these findings are confirmed this would also be consistent with population-based studies demonstrating that all of these somatic symptoms occur as a continuum in the population, rather than being "present" or "absent", and so it may follow that physiologic correlates will likewise be seen as a continuum.

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