Presentation 7 – Dan Clauw

The Cause(s) and Potential Treatments of Chronic Multisymptom Illnesses Following the First Gulf War

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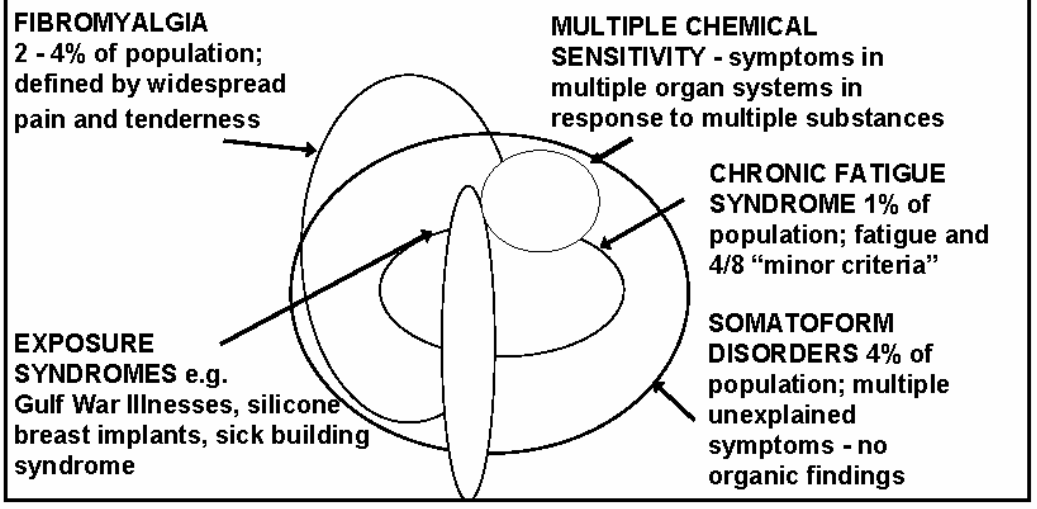
Outline of Talk

- Background of CMI and "old" findings
- Relevant preliminary data
- Treatment of CMI

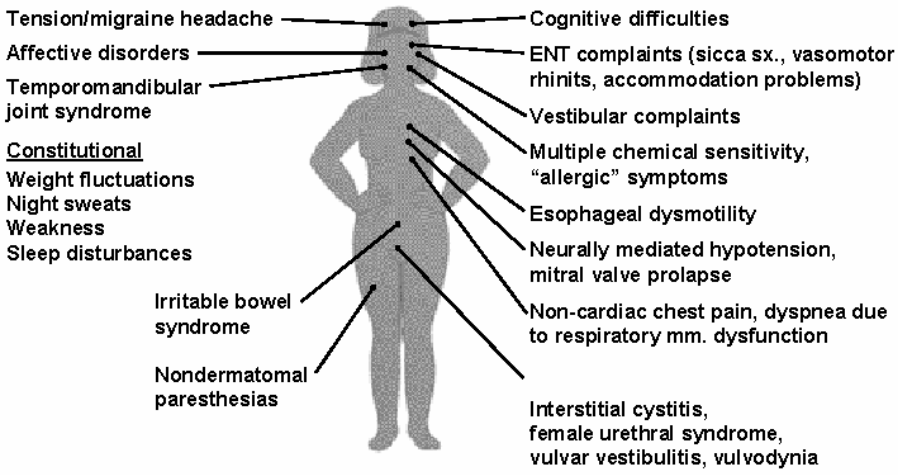
Chronic Multi-symptom Illnesses (CMI)

- Term coined by the CDC in 1999 to describe multiple somatic symptoms in Gulf War veterans (Fukuda et. al. JAMA 1999)
- This study and subsequent studies in the general population using factor analytic techniques (e.g., Doebbling et. al. Am J Med 2000) identified 3 – 4 symptom factors that cluster in the populations
  - Multifocal pain
  - Fatigue
  - Cognitive difficulties
  - Psychological symptoms
- This and subsequent studies demonstrated that approximately 10 – 15% of the population suffers from a syndrome characterized by two or more of these symptoms

"Systemic" Chronic Multisymptom Illnesses



Regional Chronic Multisymptom Illnesses



In Addition to the CMI Seen Commonly in the General Population, is There a Superimposed "Neurological Damage" Disorder?

	Yes	No
Population-based	1/200 Nonspecific (Haley 1999; Kang 2002) 2-3x ALS (Horner 2003)	Several others Increased in all veterans (Weisskopf 2005)
Case-control Neurological study	Nonspecific (Haley 1997)	(Sharief 2002; Lee 2005)
Abnormal functional imaging	Abnormal MRS (Haley 2000)	Abnormal fMRI Abnormal imaging in CMI
Abnl autonomic fxn	(Haley 2004)	(Stein 2004)

What Causes CMI?

- Genetics
- "Triggers"
- Mechanisms
  - Relationship between physiologic and psychologic factors
  - Disordered sensory processing
  - Autonomic/neuroendocrine dysfunction

Genetics of Fibromyalgia

- Clearly is a strong familial predisposition
  - Most recent work by Arnold et al suggest >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with affective disorders[1]
- Genes that may be involved
  - 5-HT_{2A} receptor polymorphism T/T phenotype[2]
  - Serotonin transporter[3]
  - Dopamine D4 receptor exon III repeat polymorphism[4]
  - COMT (catecholamine o-methyl transferase)
    - Shown to be involved in pain transmission[5]
    - Slightly different in FM[6]
    - Predictive of development of TMD[7]

1. Arnold et al. *Arthritis Rheum.* 2004;50:944-952; 2. Bondy et al. *Neurobiol Dis.* 1999;6:433-439; 3. Offenbaecher et al. *Arthritis Rheum.* 1999;42:2482-2488; 4. Buskila et al. *Mol Psychiatry.* 2004;9:73; 5. Zubieta et al. *Science.* 2003;2999:1240-1243; 6. Gursoy et al. *Rheumatol Int.* 2003;23:104-107; 7. Diatchenko et al. *Hum Mol Genet.* 2005;14:135-143.

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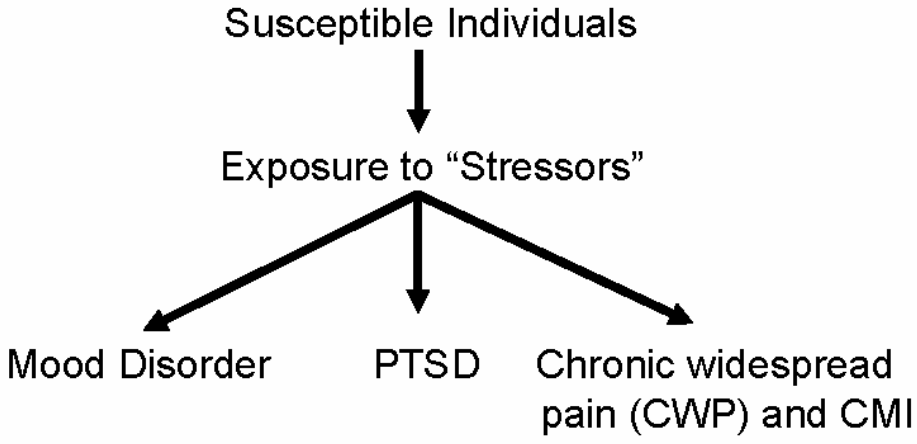
"Stressors" capable of triggering these illnesses – supported by case-control studies

- Infections (e.g., parvovirus, EBV, Lyme, Q fever; not common URI)
- Physical trauma (automobile accidents)
- ? Psychological stress / distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Certain catastrophic events ***(war, but not natural disasters)*** *(Clauw, Engel, Aronowitz, Jones, Kipen, Kroenke, Ratzan, Sharpe, Wessely. J Occup Environ Med, 2003)*

Clauw, Chrousos; Neuroimmunomodulation, 1997

"Stress" Related Syndromes



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The Physiological / Psychobehavioral Continuum

Population — Primary Care — Tertiary Care

Neurobiological
- Abnormal sensory processing
- Autonomic dysfunction
- HPA dysfunction

Psychosocial factors
- Decreased activity / isolation
- General "distress"
- Cognitive factors
- Maladaptive illness behavior
- Secondary gain issues

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Summary (Scientific)

- Recent research is giving significant insights into the underlying mechanisms of Chronic Multisymptom Illnesses such as Fibromyalgia, Irritable Bowel Syndrome, TMD syndrome
  - CNS disorder
  - Triggered by a variety of "stressors"
  - Abnormalities in brain function, especially in
    - Sensory processing
    - Autonomic nervous system
    - Hypothalamic pituitary adrenal axes
- Very few mechanistic studies have compared GWI to those with CMI that are in general population, but this is an essential "control" group to interpret findings of physiological studies in GWV

Summary (Personal)

- The notion that the Gulf War and other post-deployment syndromes are *either*
  - "Psychological" *or* "physiological"
  - Due to "stress" *or* "toxins"

  is both inaccurate and counter-productive
- Psychological = Physiological
- The evidence that purely psychological stressors are responsible for triggering or worsening CMI is weak
- Stress is a toxin, and toxins are stressors

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New Information

- **The fact that established CMI syndromes do not nearly entirely explain the increased symptoms in Gulf War veterans is largely an artifact of how we define these illnesses**
- Nearly any functional neuroimaging study identifies robust differences between CMI patients and controls
- A revision of the "stress" theory is necessary
  - Original theory was that abnormalities in function of autonomic and HPA systems *caused* illness
  - Present and emerging evidence suggests that baseline differences in the function of these systems act as a *diasthesis* to put individuals at higher risk for developing these illnesses

Distribution of chronic pain among non-deployed and deployed veterans (from CSP #458)

Chronic Pain Characteristic	% Deployed (n)	% Non-Deployed (n)
No Pain	41.27% (393)	54.05% (569)
1-2 Pain Areas	26.33% (275)	25.48% (293)
3+ Pain Areas, Not Widespread	11.29% (126)	9.04% (107)
Widespread Pain	21.11% (255)	11.43% (151)
Any Pain	59.07% (661)	46.20% (555)

21 missing observations. Frequencies are actual, and percents are weighted.

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A Revision of the "Stress" Theory

- In a DoD funded study published in 2004, we hypothesized that a subset of healthy individuals deprived of routine exercise would develop pain, fatigue, and other somatic symptoms (true – about half did), and that autonomic and neuroendocrine responses would change as individuals developed symptoms (they didn't) (Glass, Psychosomatic Research, 2004)
- However, baseline differences in HPA and autonomic function predicted who developed symptoms when they were deprived of exercise
- Subsequently, a large, population-based study showed that baseline HPA function predicted the subsequent development of chronic widespread pain (McBeth Arthritis Res Ther 2005)
- Two ongoing models of post-stress symptoms of relevance to CMI

The Predictors of Pain and Other Somatic Symptoms, and Psychological Sequelae, and Decrements in Performance Following Sleep or Exercise Deprivation

- This ongoing DoD-funded study has recruited 36/128 total subjects, and is a 2 x 2 x 2 design to examine the independent and synergistic effects of exercise and sleep deprivation, as well as the neurobiological measures that predict symptom development.
- The ongoing study has four treatment conditions: control (regular exercise and no sleep restriction), exercise deprivation alone, sleep restriction alone and both exercise deprivation and sleep restriction. We have tested 36 subjects to date (11 control, 6 exercise deprivation, 9 sleep restriction, 10 both exercise deprivation and sleep restriction).

Association Between Baseline Autonomic and HPA Function and Subsequent Development of Symptoms

	McG Sens	McG VAS	MFI-gen	PVT lapses	CESD	Anxiety
AM cortisol	-0.238	-0.263	-0.457	-0.466	-0.306	-0.599
ULF	-0.539	-0.706	0.317	-0.512	-0.091	-0.173
VLF	-0.547	-0.671	0.186	-0.526	-0.198	-0.317
TP	-0.548	-0.697	0.312	-0.534	-0.120	-0.224

The Predictors of Pain and Other Somatic Symptoms, and Psychological Sequelae, Following a Motor Vehicle Collision

- Patients being evaluated in the Emergency Department (ED) after MVC were recruited into an ongoing multicenter study which includes ED baseline assessment and 1-month outcome evaluation.
- ED assessment includes salivary cortisol collection and 20 minute Holter monitor recording. Outcome evaluation includes assessment of persistent MVC-related neck or back pain, significant PTSD symptoms (IES-R score ≥ 33), and significant depressive symptoms (CES-D ≥ 27).
- Cortisol samples were assayed using the Diagnostic Products Corporation Coat-a-Count cortisol kits. HF HRV was assessed using HF power spectral analysis (0.15 to 0.4-Hz).
- To date, follow-up data has been obtained in 48 of 49 enrolled patients who have reached the 1 month follow-up time point (98%, 28 female, 20 male, age 18-84, mean 36.4 years).

Association between mean ED HRV and presence of early and persistent pain and psychological sequelae

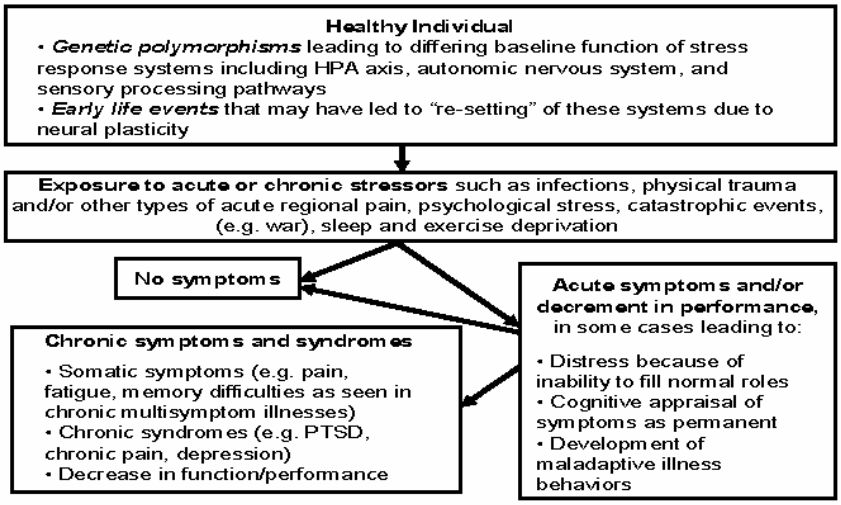
Mean ED HF HRV[1] by Group	Pain 3-7 days after MVC	Moderate or severe neck and/or back pain at 1 Month	PTSD at 1 Month
Present	146±118	185±119	614±661
Not present	566±534	539±583	278±225
t	3.494	2.618	-2.038
p value	.002	.015	.028

[1]High frequency heart rate variability, [2]Defined by Neck pain and back pain summed NRS scores ≥ 10, [3]Defined by IES-R score ≥ 33

Association between mean ED cortisol level and persistent pain and psychological sequelae 1 month after MVC

1 Month Outcome (n)	ED Cortisol (ug/mL)
No Symptoms (26)	.33 ± .46
Pain Only (10)	.27 ± .29
PTSD ± Pain (5)	.18 ± .10
Depression ± Pain (2)	1.48 ± 2.0
Depression & PTSD ± Pain (5)	.52 ± .50
ANOVA F statistic (p value)	2.777 (.039)

The Etiology of Post-"Stress" Syndromes



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