[연수강좌]

MMUS 환자의 기능의학적 진단과 치료

정 승 필

영남의대

Multiple Medically Unexplained Symptoms (MMUS)

-의학적으로 설명할 수 없는 증상들-

- *Medically unexplained symptoms(MUS), whitch include fatigue, low back pain, abdominal upset, headache, dizziness, or feelings of weakness, account for a sustantial proportion of all consultations in primary care*

Kroenk K. Am J Med 1989;86:262-6.

Multiple Medically Unexplained Symptoms (MMUS)

Table 1
Medically unexplained syndromes by specialty

Specialty	Syndrome
Allergy	MCS, SBS
Cardiology	Atypical chest pain
Dentistry	Temporomandibular joint dysfunction
Ear, nose, and throat	Globus syndrome
Gastroenterology	Irritable bowel syndrome
Gynecology	Chronic pelvic pain, premenstrual syndrome
Infectious diseases	CFS
Neurology	Tension headache
Rheumatology	Fibromyalgia

MCS: Multiple chemical sensitivity
SBS: Sick building syndrome
CFS: Chronic fatigue syndrome

Multiple Medically Unexplained Symptoms (MMUS)

- *Musculoskeletal pain : 30.3 %*
- *Abdominal pain & other GI symptoms :17.7%*
- *ENT symptoms : 7.8%*
- *Fatigue : 3.9%*
- *Dizziness : 3.5%*

(n=231)

Laurence J Kirmayer et al. Can J Psychiatry.2004;49:663-672

Chronic fatigue syndrome

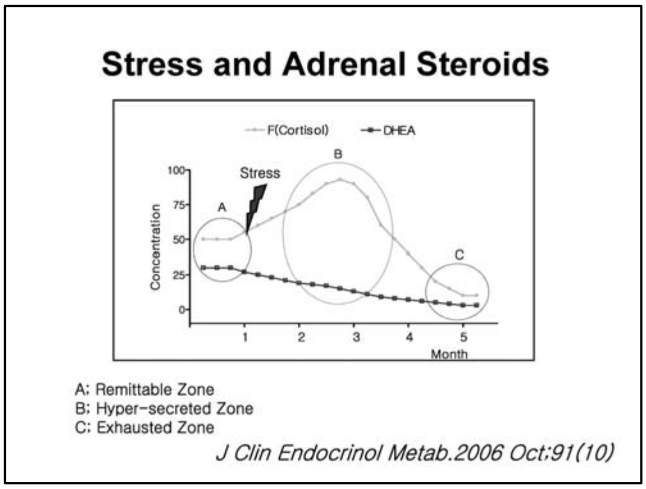
- 1차 증상

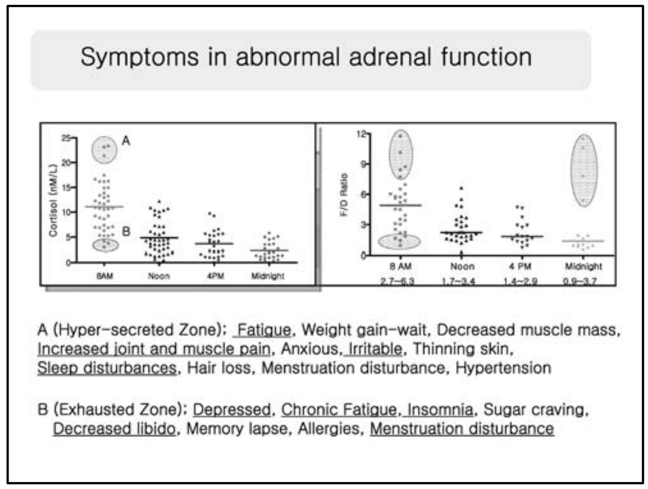
명백한 원인 없이 적어도 6개월 이상 피로감

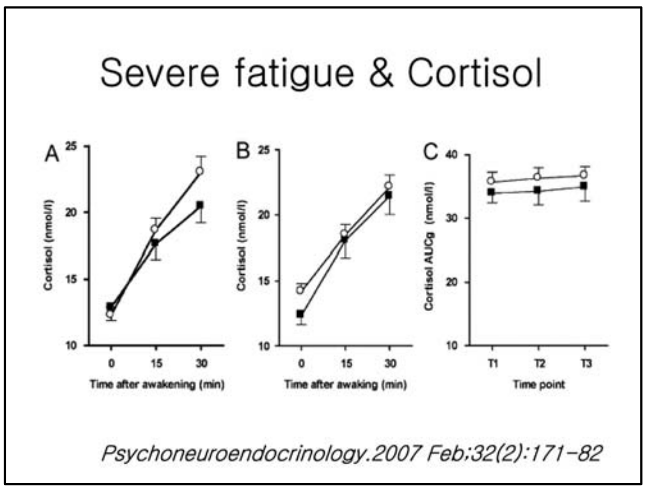
- 추가 증상

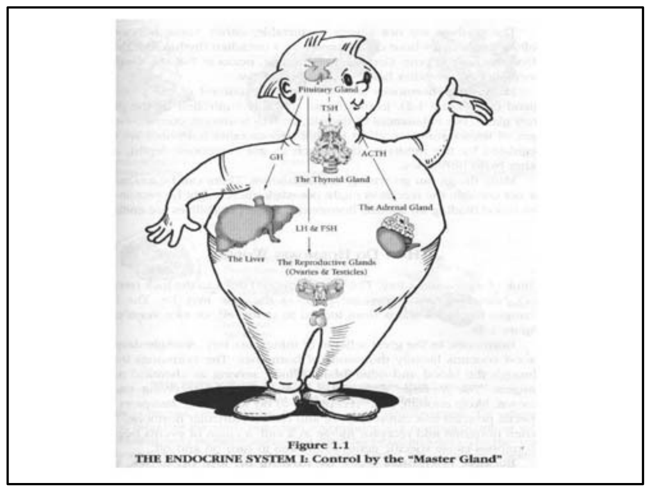
- 단기 기억 및 집중력 장애
- 인후통
- 림프절 통증
- 근육통
- 다발성 관절통
- 두통(새로운 형태나 심한 정도를 가진)
- 수면장애 및 개운하지 않는 수면
- 활동 후 피로 (24시간 이상 지속)

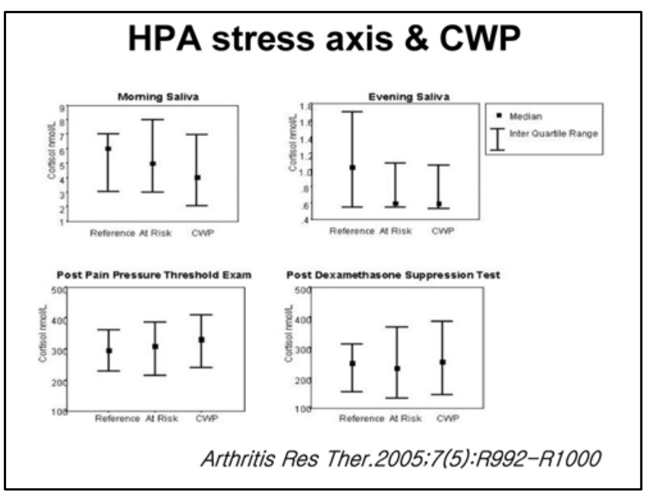
CDC criteria, Ann Intern Med 1994;121:953-9

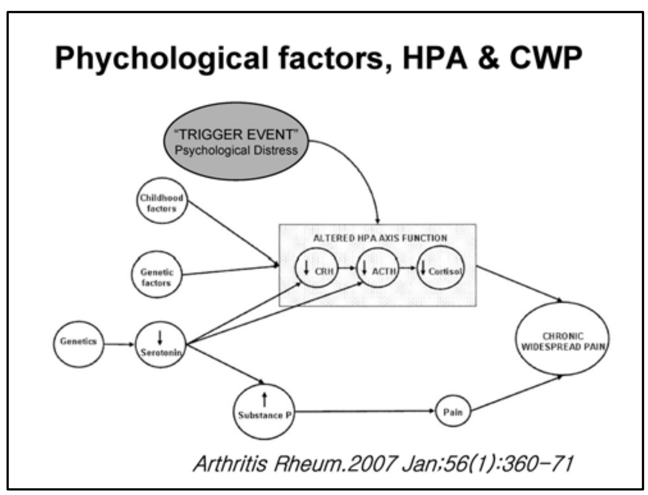

Stress and Adrenal Steroids
F(Cortisol)
DHEA
Stress
A
B
C
Concentration
Month
A; Remittable Zone
B; Hyper-secreted Zone
C; Exhausted Zone
J Clin Endocrinol Metab.2006 Oct;91(10)


Symptoms in abnormal adrenal function
Cortisol (nM/L)
F/D Ratio
8AM
Noon
4PM
Midnight
2.7~6.3
1.7~3.4
1.4~2.9
0.9~3.7
A (Hyper-secreted Zone); Fatigue, Weight gain-wait, Decreased muscle mass, Increased joint and muscle pain, Anxious, Irritable, Thinning skin, Sleep disturbances, Hair loss, Menstruation disturbance, Hypertension
B (Exhausted Zone); Depressed, Chronic Fatigue, Insomnia, Sugar craving, Decreased libido, Memory lapse, Allergies, Menstruation disturbance

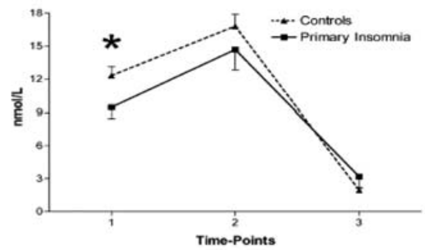

Severe fatigue & Cortisol
A
B
C
Cortisol (nmol/l)
Cortisol AUCg (nmol/l)
Time after awakening (min)
Time after awaking (min)
Time point
Psychoneuroendocrinology.2007 Feb;32(2):171-82


Pituitary Gland
TSH
GH
ACTH
The Thyroid Gland
The Adrenal Gland
LH & FSH
The Liver
The Reproductive Glands
(Ovaries & Testicles)
Figure 1.1
THE ENDOCRINE SYSTEM I: Control by the "Master Gland"


HPA stress axis & CWP
Morning Saliva
Evening Saliva
Median
Inter Quartile Range
Post Pain Pressure Threshold Exam
Post Dexamethasone Suppression Test
Reference
At Risk
CWP
Arthritis Res Ther.2005;7(5):R992-R1000

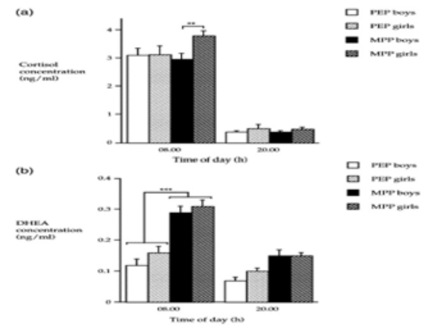

Phychological factors, HPA & CWP
"TRIGGER EVENT"
Psychological Distress
Childhood factors
Genetic factors
ALTERED HPA AXIS FUNCTION
CRH
ACTH
Cortisol
Genetics
Serotonin
Substance P
Pain
CHRONIC WIDESPREAD PAIN
Arthritis Rheum.2007 Jan;56(1):360-71

Cortisol and primary insomnia



Psychoneuroendocrinology.2004 Oct;29(9):1184-91

Cortisol/DHEA ratio



Psychoneuroendocrinology.2004 Feb;29(2):125-40

The cortisol assessment in saliva is a sensitive and reliable method to discriminate normocortisolemic from hypercortisolemic patients.

Exp Clin Endocrinol Diabetes.2005 Apr;113(4)

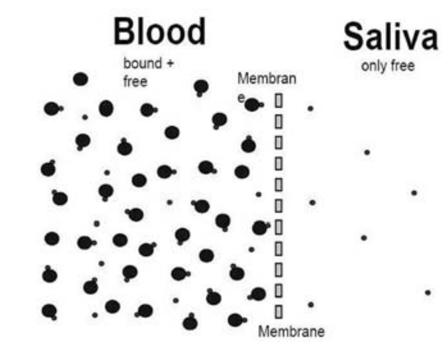
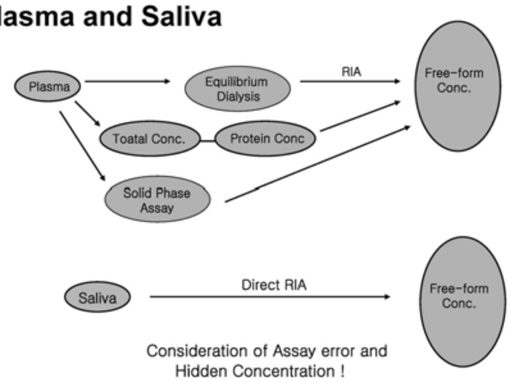
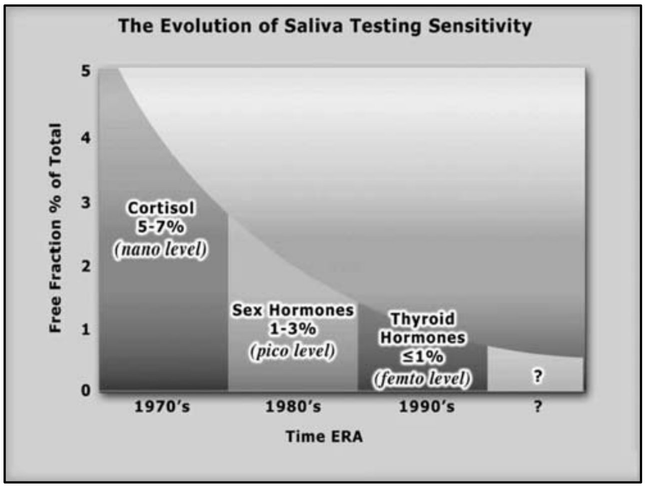


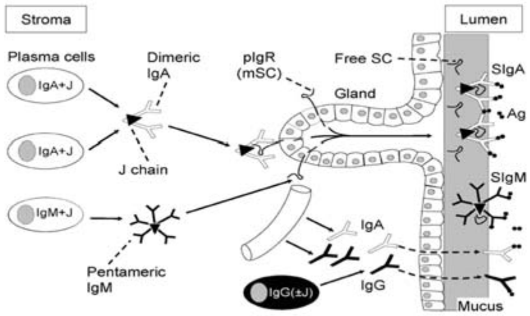
Fig. 1 Free and protein bound steroid hormones in blood and free hormones in saliva
The concentration of free hormones is the same on both sides of the membrane.

Measuring the Free-form levels in Plasma and Saliva





Secretary IgA



Effect of different stressor on salivary SIgA levels

Definition of stressors	Salivary SIgA
Chronic academic stress	Reduced
Acute academic stress	Increased
Acute naturalistic stress	Increased
Laboratory stressors	
Acute coping of challenges	Increased
Passive coping	Reduced

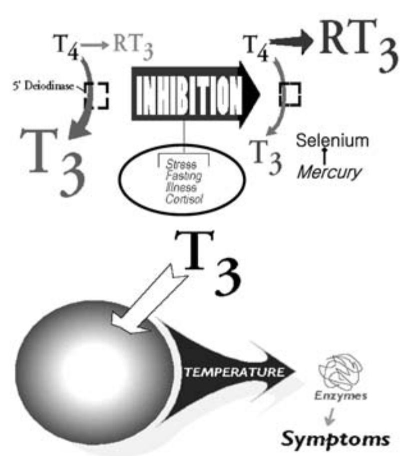
Ann N Y Acad Sci.2007 Mar;1098:288-311

Salivary T3, T4 and sIgA

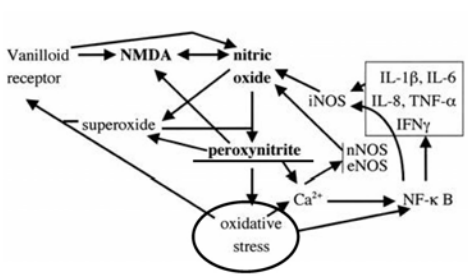
1 sample collected on any day
Any day (Wake up collection)

Thyroid Function and Immune status

Exp Clin Endocrinol. 1985 Apr;85(2):199-203
Biol Psychiatry. 2000 May 15;47(10):891-901
J Behav Med. 2004 Dec;27(6):623-35
J Dent Educ. 2003 Oct;67(10):1091-4



Vicious (NO/ONOO-) cycle diagram (CFS,fibromyalgia)



Pall ML. Nitric oxide and the etiology of chronic fatigue syndrome: Giving credit where credit is due. Med Hypotheses. 2005 Jun 2.

Pall ML. NMDA sensitization and stimulation by peroxynitrite, nitric oxide and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J 16:1407-1417. 2002.

Relation between ONOO- and ascorbic acid, Co-Q10

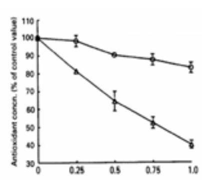


Figure 1 Effect of peroxynitrite on plasma ascorbate (△) and urate (○)

Plasma (5 ml) was incubated for 5 min at 37 °C after addition of peroxynitrite at various concentrations, and subsequently plasma levels of ascorbate and urate were quantified as described in the Materials and methods section. Data (means ± S.E.M. from 3–4 experiments using different plasma samples) are expressed as percentage of values measured in control incubations. Initial plasma concentrations were: 34.0–100.4 μM ascorbate and 154–283 μM urate.

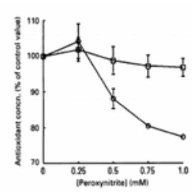


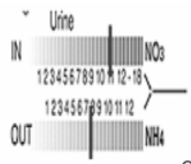
Figure 2 Effect of peroxynitrite on the lipid-soluble plasma antioxidants α-tocopherol (□) and ubiquinol-10 (○)

Plasma (5 ml) was incubated with various concentrations of peroxynitrite for 5 min at 37 °C, and subsequently α-tocopherol and ubiquinol-10 were measured as described in the Materials and methods section. Data (means ± S.E.M. from 3–4 experiments using different plasma samples) are expressed as percentage of values measured in control incubations.

A Van der Vliet Interactions of peroxynitrite with human plasma and its constituents: oxidative damage and antioxidant depletion. Biochem J. 1994 October 1; 303(Pt 1): 295-301.

Urine NO3 & NH4 test

NO/ONOO- system 저하
ETS 문제 가능성
Highly reduced state
Low AA (BCAA) 공급



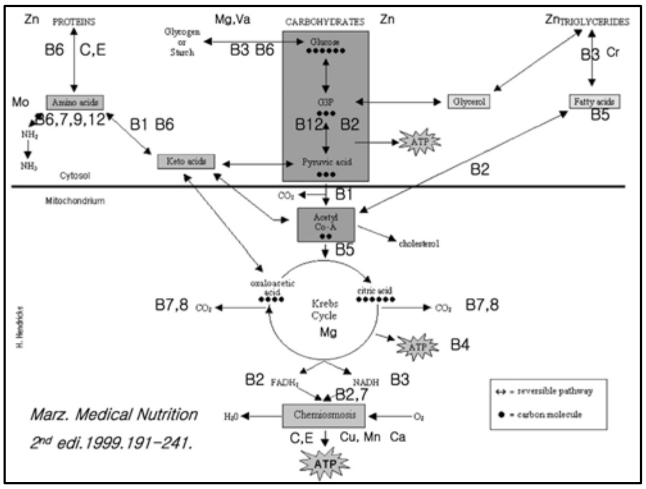
NO/ONOO- system 항진
Peroxynitrite 생산 증가
Oxidative stress 항진

Low protein diet
Low AA (BCAA) 공급
K-bicarbonate 공급
Anabolism (dominant)

Glutamine loss (buffer)
Nitrogen toxicity (neural)**
High protein, catabolic
Dysbiosis

Journal of Clinical Endocrinology and Metabolism Vol. 82, No. 1, The Endocrine Society, 1997

J Clin Invest. 1972 July; 51(7): 1852-1860.



Marz. Medical Nutrition
2nd edi. 1999. 191-241.

Commonly Used Supplements for Mitochondrial Dysfunction

Supplement	Dose range
Coenzyme Q_{10}	4.3-15 mg/kg/d, 200 mg tid maximum
levo-carnitine	100 mg/kg/d, 1000 mg tid maximum
Thiamine (B_1)	50-200 mg/d
Riboflavin (B_2)	50-600 mg/d
Vitamin K_3	5-80 mg/d
Folate	1-10 mg/d
Lipoic acid	12.5mg/kg/d, 400 mg tid maximum
Vitamin E	200-1200 IU/d in divided doses
Vitamin C	100-2000 mg in divided doses
Selenium	25-50 mcg/d

Treatment of Mitochondrial Cytopathies
Deborah R. Gold, M.D. and Bruce H. Cohen, M.D.
Semin Neurol 21(3):309-325, 2001.

ECS : Electro Chemical Screening

- 체액 (body fluid) 검사법
- Electrical & nutritional balancing

- *Indicator :*
- pH : Hydrogen ion (cation) 농도
- ORP : Oxidation - Reduction potential
- rH_2 : Oxidative stress
- r : Electrical resistivity (ohm)
- Zeta potential : Colloidal characteristic
- Anabolic / Catabolic status : cellular permeability
- Brix : Energy production (Sugar level)
- Protein utilization : Liver function
- ANS range : Sympathetic & Parasympathetic

Biologic ionization as applied to human nutrition, 2002

SIBO (small intestinal bacterial overgrowth)

- Irritable bowel syndrome(11-14%)과 관련
- 식후 가스팽만, 장 움직임 이상, 장 과민
- 자율신경장애, 면역자극, 뇌-장 연결 이상
- 영양소 흡수 장애의 요인
- IBS환자의 84% : lactulose breath test 이상
- SIBO 치료 후 75% : IBS 증상 호전

JAMA. 2004;292:852-858

Malabsorption

TABLE 111-1. CAUSES OF MALABSORPTION IN THE ELDERLY

Cause	Risk Factors/ Predisposing Conditions	Presentation	Diagnosis	Specific Treatment