Solving the Puzzle of Chronic Pain, ME/CFS and Depression

Etiologies, Immunology and Mitochondrial Dysfunction

Feb 29, 2020

Gary Kaplan D.O. DABFM, DABPM, FAAMA
Medical Director
The Kaplan Center of Integrative Medicine
Associate Professor-Georgetown University
School of Medicine

Disclosure of Financial Relationships:

None

Off-Label Usage

None

Learning Objectives

1.Discuss various presentations of Autoimmune Encephalopathy of infectious etiology and mitochondrial dysfunction
2. Explore the etiologies and major drivers of neuroinflammation
3.Discuss mechanisms, biomarkers and treatments to address mitochondrial dysfunction, and quietening the immune system

Outline

1. Demographics
2. Innate Immune System
3. Gut Microbiome and Autoimmunity
4. Adaptive Immune System
5. Mitochondrial Dysfunction and Cell Danger Response
6. Testing
7. Treatment

"All models are flawed, but some are useful"

George E.P. BOX

Demographics: Fibromyalgia

- One of the most common chronic pain conditions
- Affects an estimated 10 million people in the U.S. and an estimated 3-6% of the world population
- It is most prevalent in women, 75-90% of the people who have FM are women
- The diagnosis is usually made between the ages of 20 to 50 years, but the incidence rises with age so that by age 80, approximately 8% of adults meet the American College of Rheumatology classification of fibromyalgia.

1,10,11

Demographics: ME/CFS

- Between 836,000 and 2.5 million affected in U.S.
- As many as 25% homebound or bedridden
- Pediatric prevalence estimates vary from 0.1 to 0.5%
- 84-91% of adult patients have not been diagnosed
- In adolescents, 3-4 times as many girls as boys diagnosed

Demographics: POTS

- Prevalence is at least 170/100,000
- 40% of patients with CFS also suffer from POTS
- Genetic as well as non-genetic factors such as trauma, bacterial or viral infection, and pregnancy may predispose to POTS
- Strong female predominance

Demographics: Neuropsychiatric Disorders

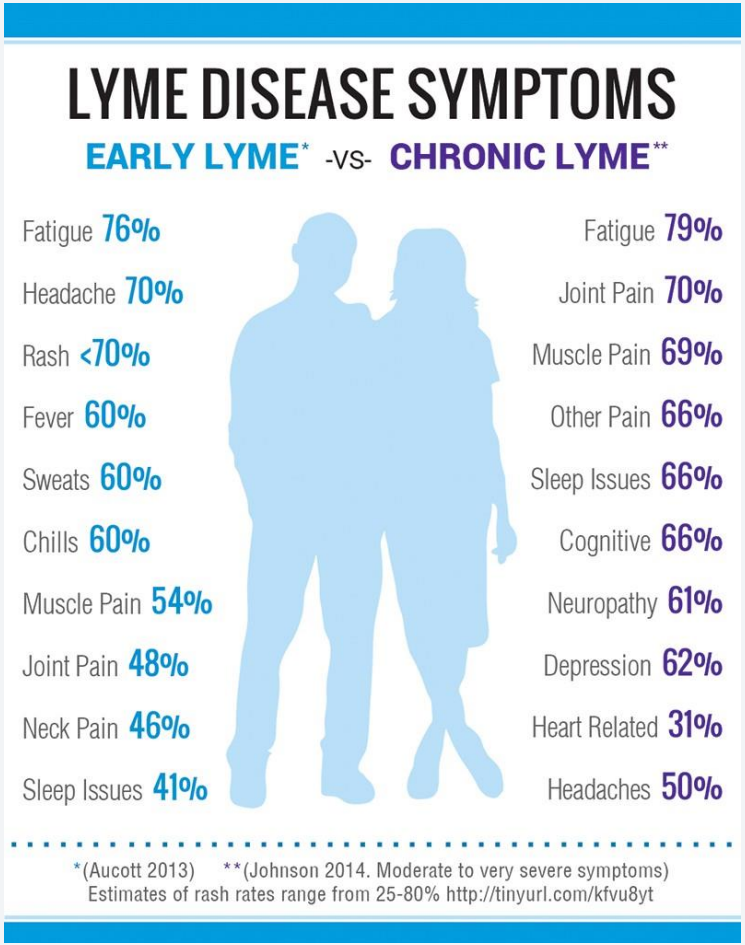
14.8 million	→	Major Depressive Disorder
3.3 million	→	Dysthymia or Chronic Depression
6.8 million	→	Generalized Anxiety Disorder
7.7 million	→	PTSD
6 million	→	Panic Disorder

Total = 38.6 Million People

4,5,6,7,8,9

Demographics: PTLDS

- PTLDS prevalence estimates for 2016 ranged from 69,011 persons to 1,523,869
- Prevalence in 2020 predicted to be as high as 1,944,189 cases



Demographics: PANS/PANDAS

- 1 in 200 children in U.S.
- Approximately 500,000 children are diagnosed with OCD in U.S.
- Approximately 138,000 children are diagnosed with Tourette Syndrome in the U.S.
- 1.5 million+ children were diagnosed with serious anxiety/ phobia/ OCD/ bipolar in a given year (1994-2011)
- "Dr. Swedo estimates that (PANDAS) kids may make up as much as 25 percent of children diagnosed with OCD and tic disorders, such as Tourette syndrome."

THE KAPLAN CENTER
for Integrative Medicine

Comorbidities of Neuroinflammatory Diseases

Depression

- Other Chronic Pain **15%**
- ME/ CFS **60-70%**
- POTS **45.2%**
- Fibromyalgia **65.7%**

ME/CFS

- Depression **45.2%**
- Chemical Hypersensitivity **71.6%**
- POTS **40%**
- Fibromyalgia **57%**
- Sleep Apnea **49%**

POTS

- Depression **Mild-moderate 87%**
- ME/CFS **48%**
- GI symptoms **80%**
- Fibromyalgia **21%**
- Migraines **55%**

Fibromyalgia

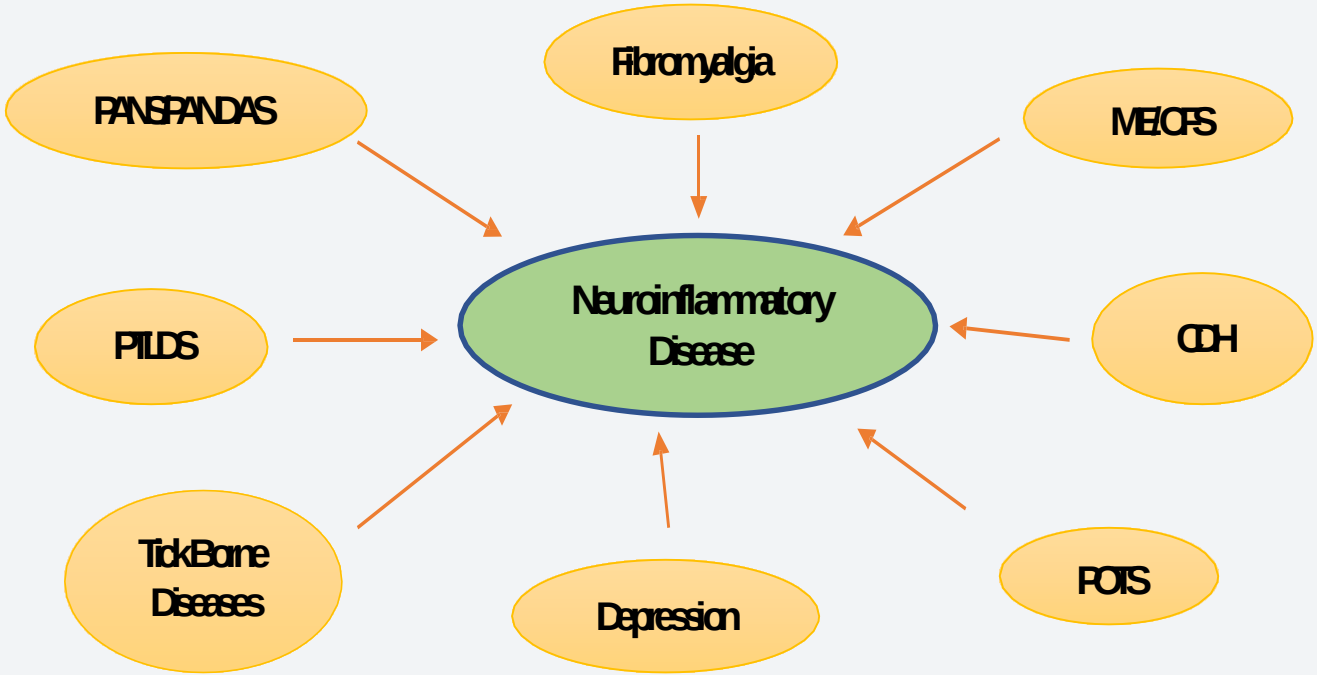
- Depression **67.7%**
- ME/ CFS **37-70%**
- POTS **21%**
- Autoimmune **20-30%**
- Sleep Disorder **90%**

PTLDS

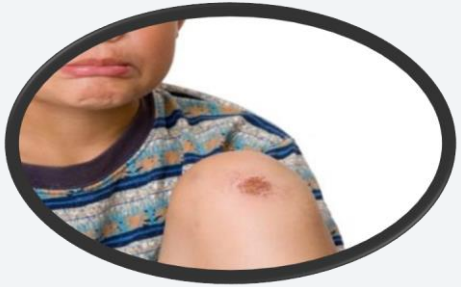
- Depression **45.2%**
- ME/CFS??
- POTS Case series **7 patients**
- Fibromyalgia **8%**
- GAD **25.8%**

[84-106]

Neuroinflammatory Diseases



What is Inflammation?



Neuroinflammation

- Activation of reactive CNS elements in response to altered brain homeostasis caused by infections (PAMPs) and other initiators of cell death such as **trauma**, **ischemia**, **hypoxia and toxins** (DAMPS)
- A coordinated response in the brain involving the innate immune system (microglia, astrocytes, mast cells) and the peripheral immune system, which infiltrate into the CNS following injury
- Alternatively, and perhaps concurrently the activation of the adaptive immune system directed towards neuronal cells (autoimmune Encephalopathy)

15,16

Neuroinflammatory Diseases

- PANDAS/PANS
- Fibromyalgia
- ME/CFS
- POTS
- PTLDS
- Neuropsychiatric Disorders

- Multiple Sclerosis
- Amyotrophic Lateral Sclerosis
- Parkinson's Disease
- Alzheimer's Disease

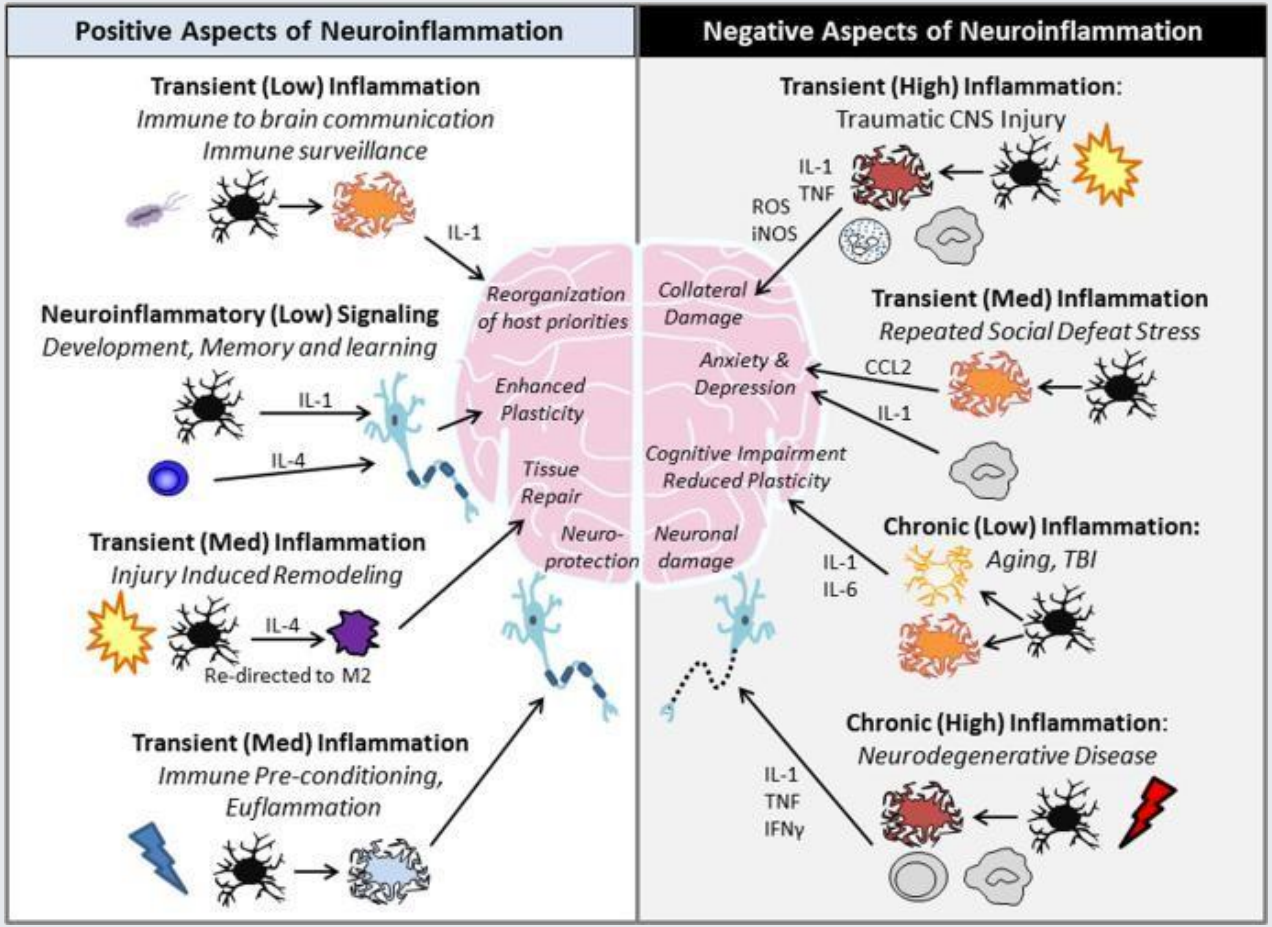
15,16

NEUROINFLAMMATION

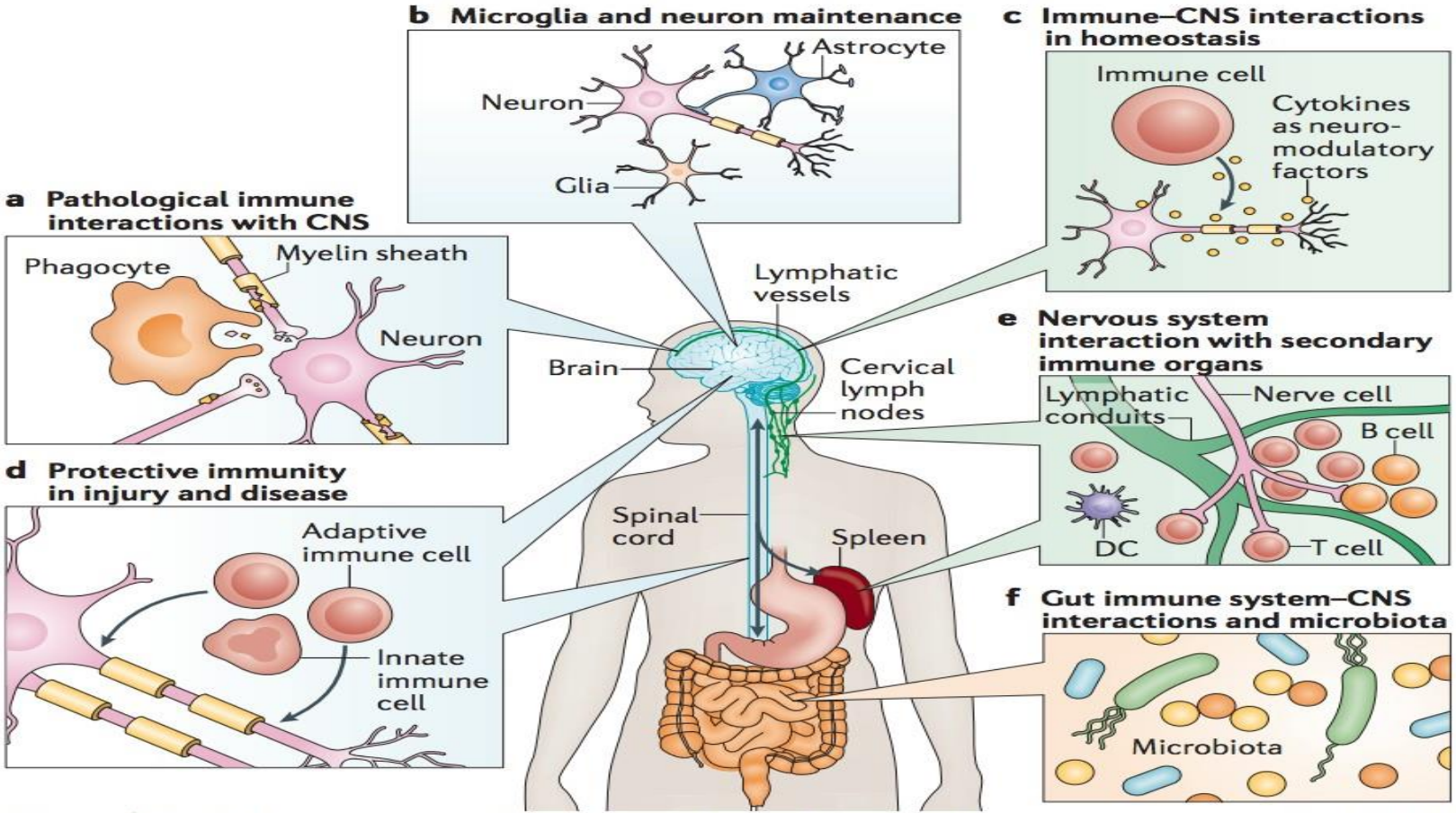
- Neuroinflammation is:
    1. Neurodysregulatory
    2. Neurodegenerative

13, 14

Aspects of Neuroinflammation



Immune Cells in the CNS

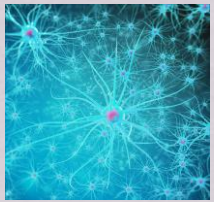



Innate Immune System

Innate Immune Cells in the CNS

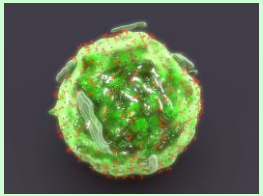
Glial Cells

Astrocytes



Mast Cells

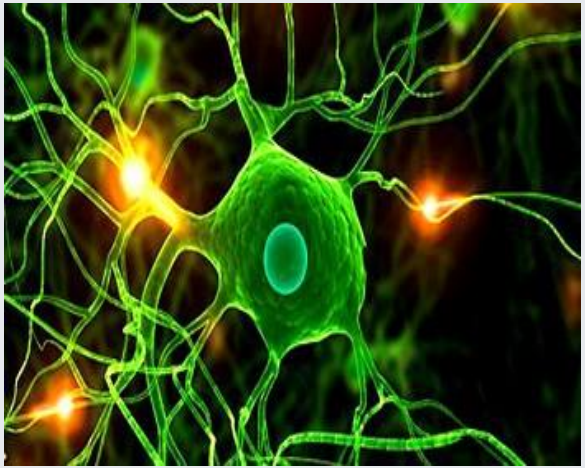
Mast Cells



Innate Immune System Major Players

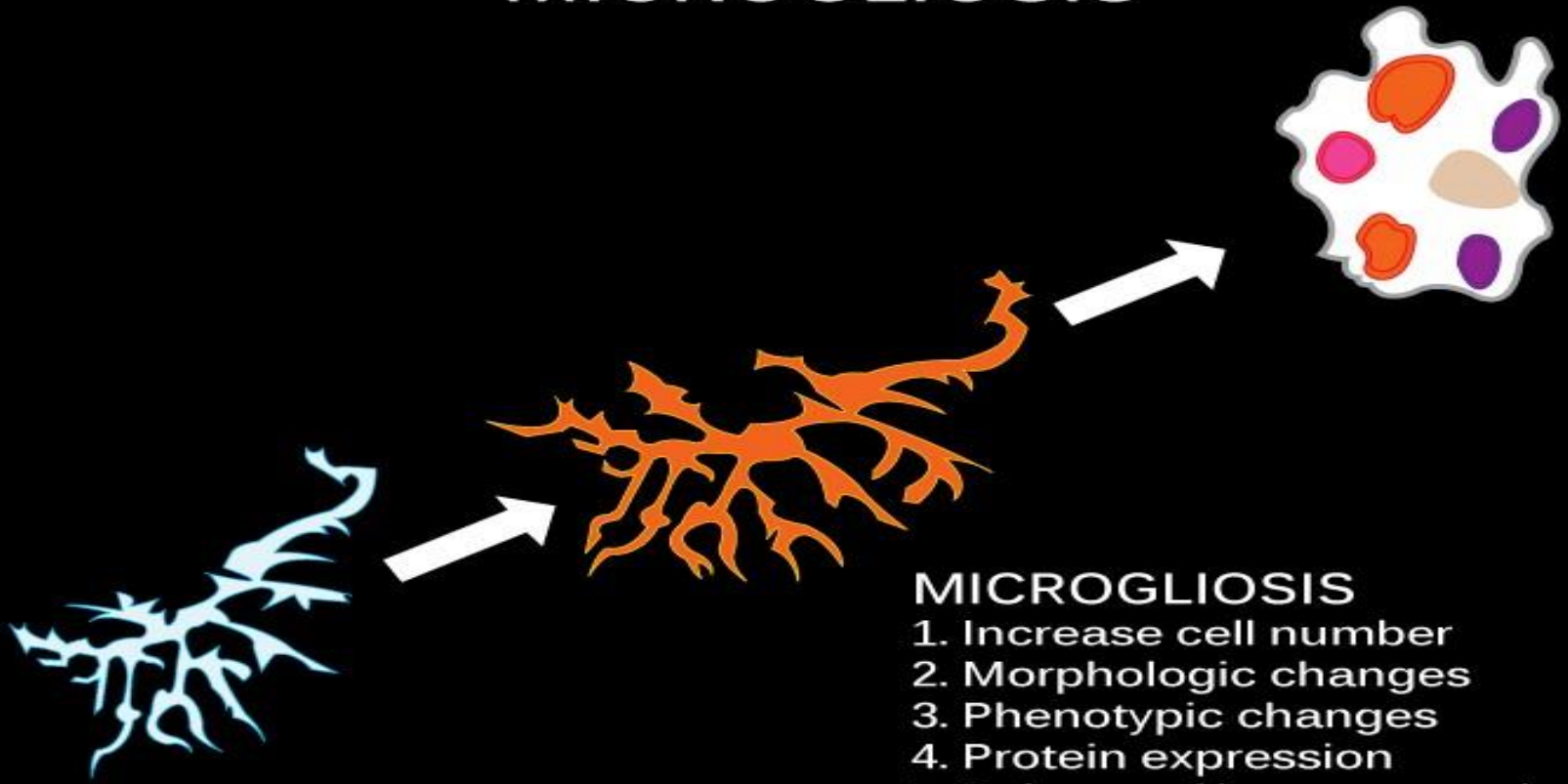
MICROGLIA

- Microglia are resident cells of the brain involved in regulatory processes critical for development, maintenance of the neuronal environment, injury and repair”
- “Electricians” of the Central Nervous System (CNS)
- Innate immune cells of the CNS



18, 19, 20, 21

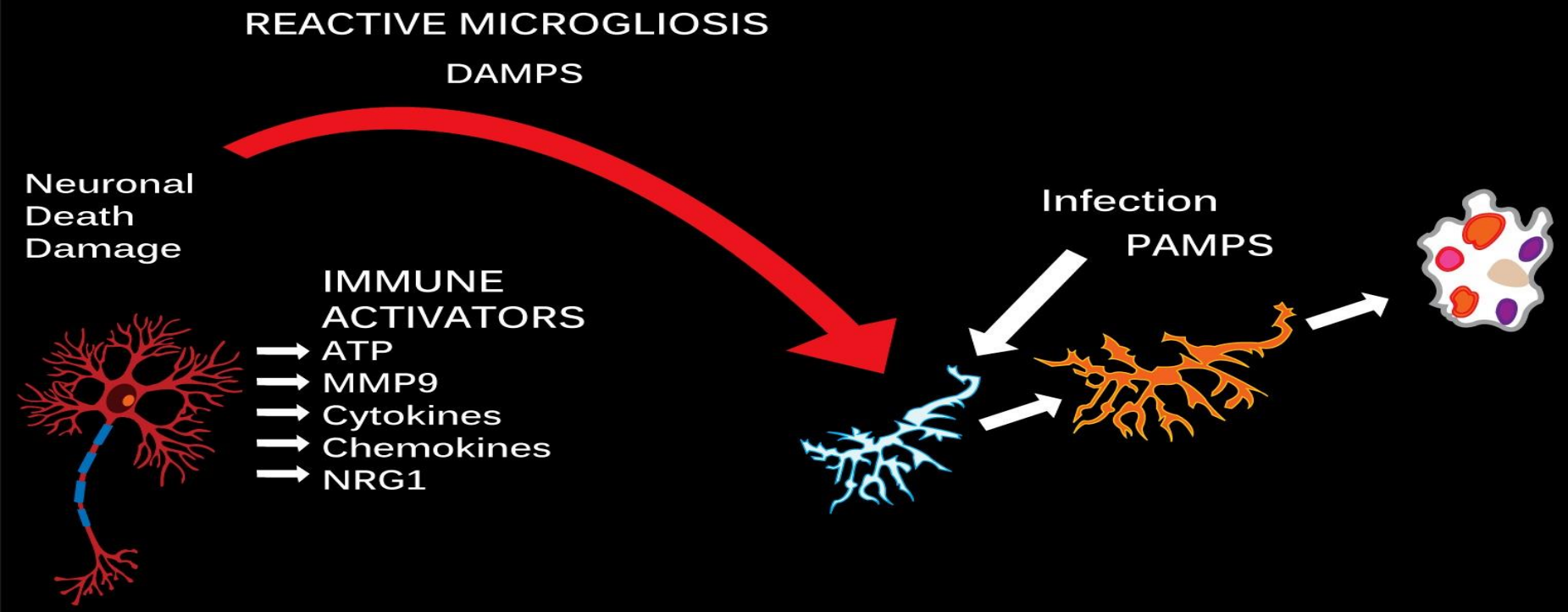
MICROGLIOSIS



MICROGLIOSIS

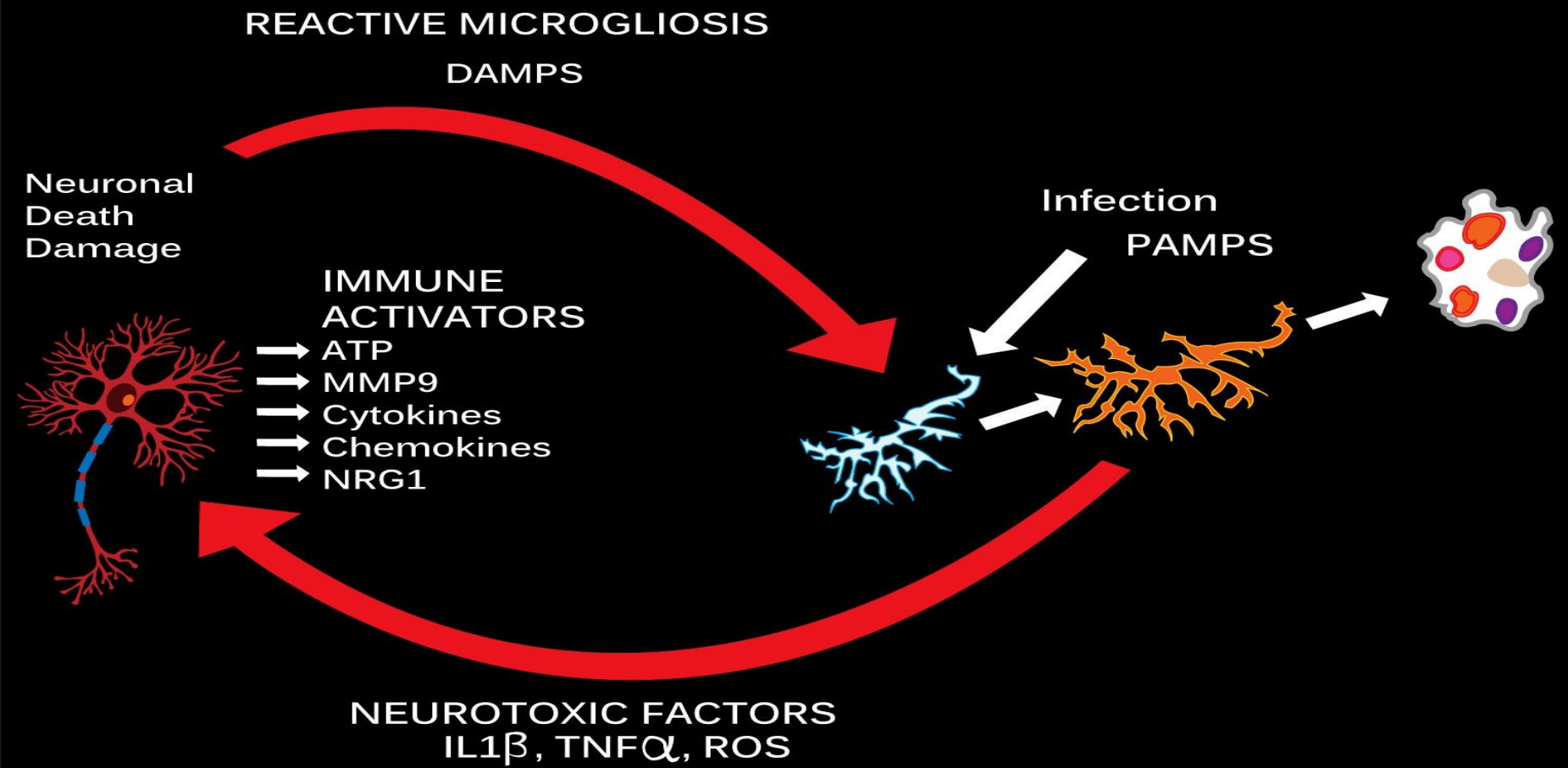
1. Increase cell number
2. Morphologic changes
3. Phenotypic changes
4. Protein expression
5. Release of immunoregulatory products

NEUROIMMUNE INTERFACE



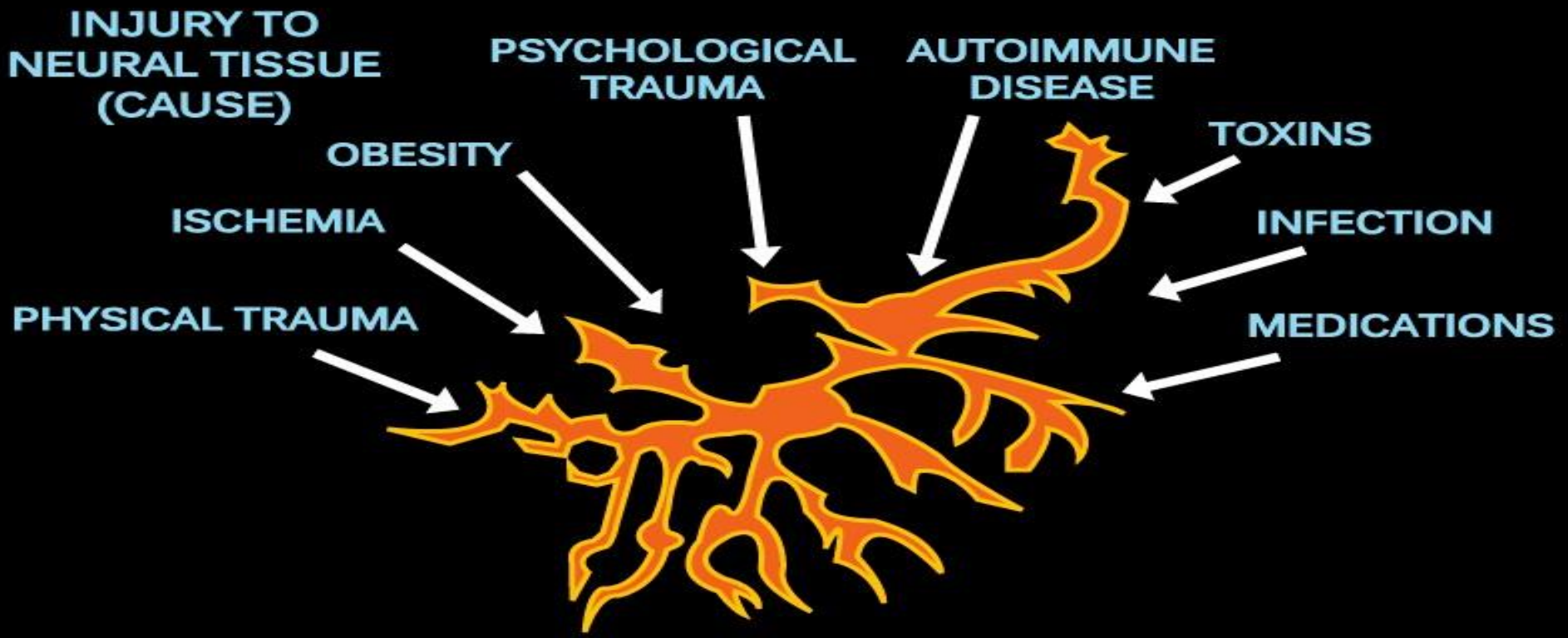
22, 23, 24

NEUROIMMUNE INTERFACE



22, 23, 24

NEUROIMMUNE INTERFACE



18,27,28,29,30

NEUROIMMUNE INTERFACE

INFLAMMATORY RESPONSE (EFFECT)

CYTOKINES

IL1β

ROS

CHEMOKINES

SYMPTOMS REPORTED

- Depression
- Anxiety
- Fatigue/Malaise
- Sleep Disturbances
- Endocrine Dysfunction

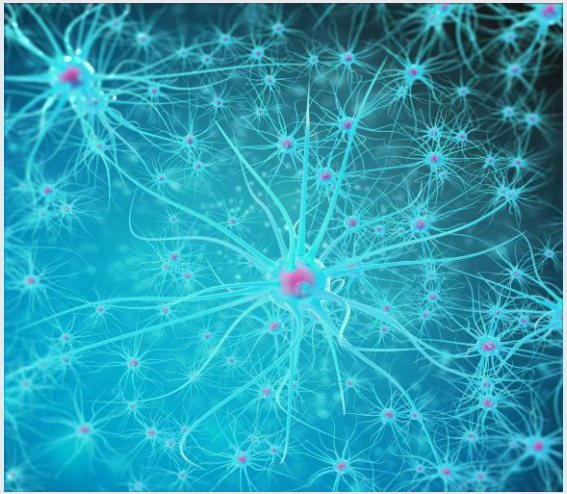
- Pain
- GI Dysfunction
- Fever
- POTS

23,24

Innate Immune System Major Players

Astrocytes

- Support the blood brain barrier and modulate blood flow in the brain
- Structural support
- Modulate synaptic transmission
- Modulate microglial activity
- Role in spinal and central sensitization
- Role in nervous system repair “glial scar”
- Metabolic support contain glycogen and are capable of gluconeogenesis. Provided nutrients to the neurons

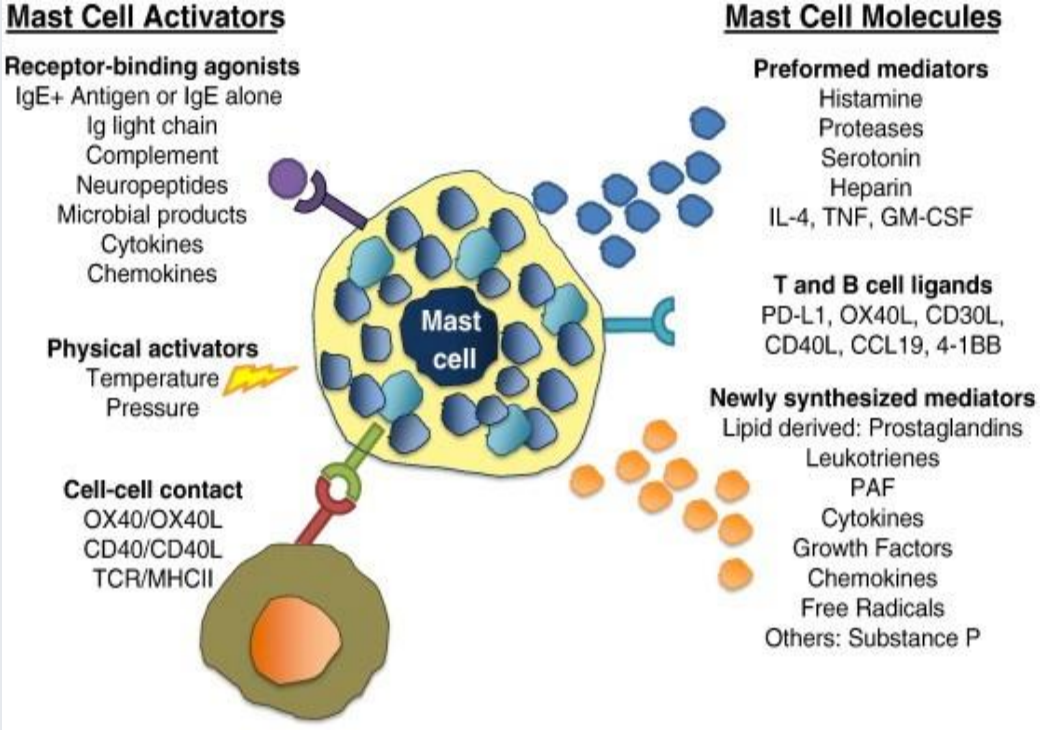


31,32,33

Innate Immune System Major Players

MAST CELLS

Mast cells release immune-modulators, chemo-attractants, vasoactive compounds, neuropeptides and growth factors in response to allergens, pathogens, emotional stress and tissue damage constituting a first line of host defense



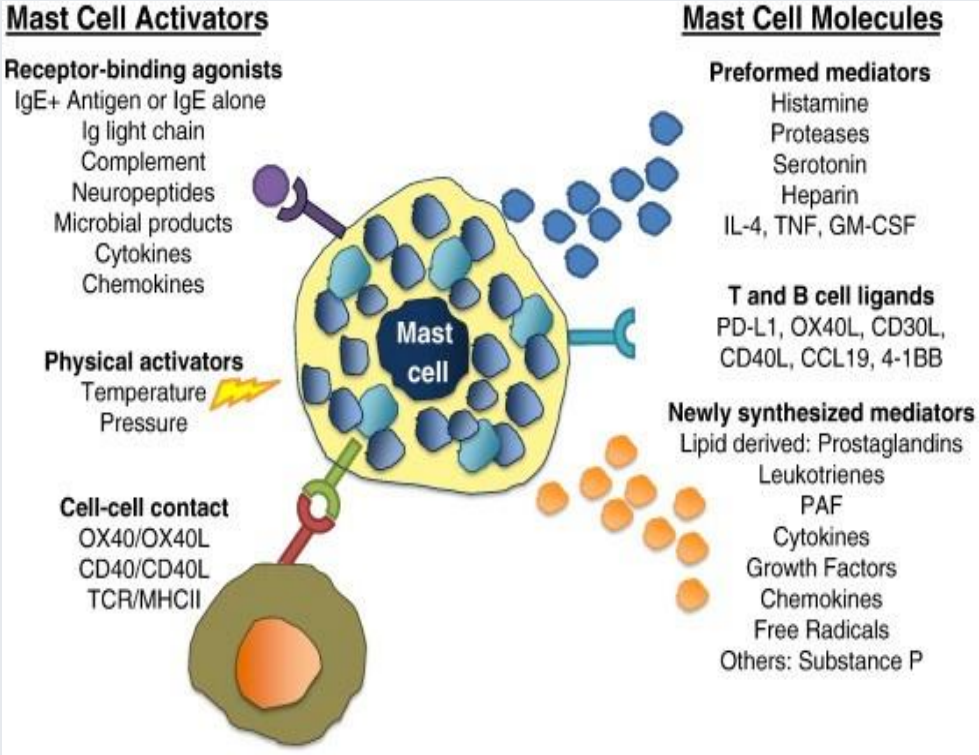
35,36,37,38,39, 107

Innate Immune System Major Players

MAST CELLS

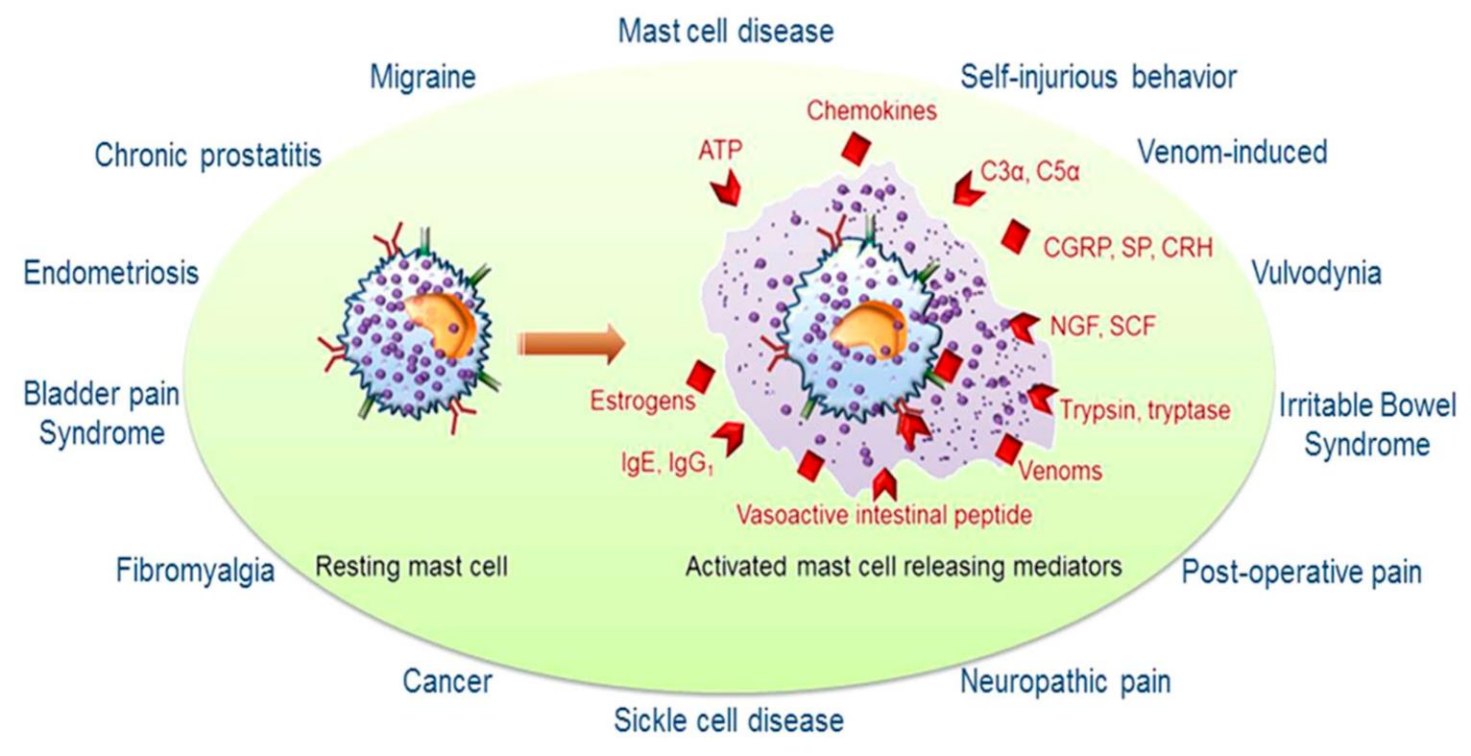
Mast cells are capable of **selective** degranulation, of pre-formed mediators and newly synthesized mediators

"Not an all or none response"



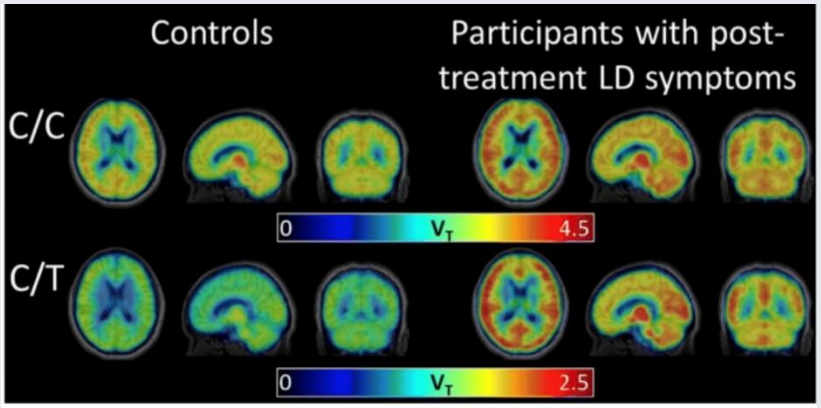
Innate Immune System Major Players

MAST CELLS



PAMPs Activate Innate Immune Cells in the Brain

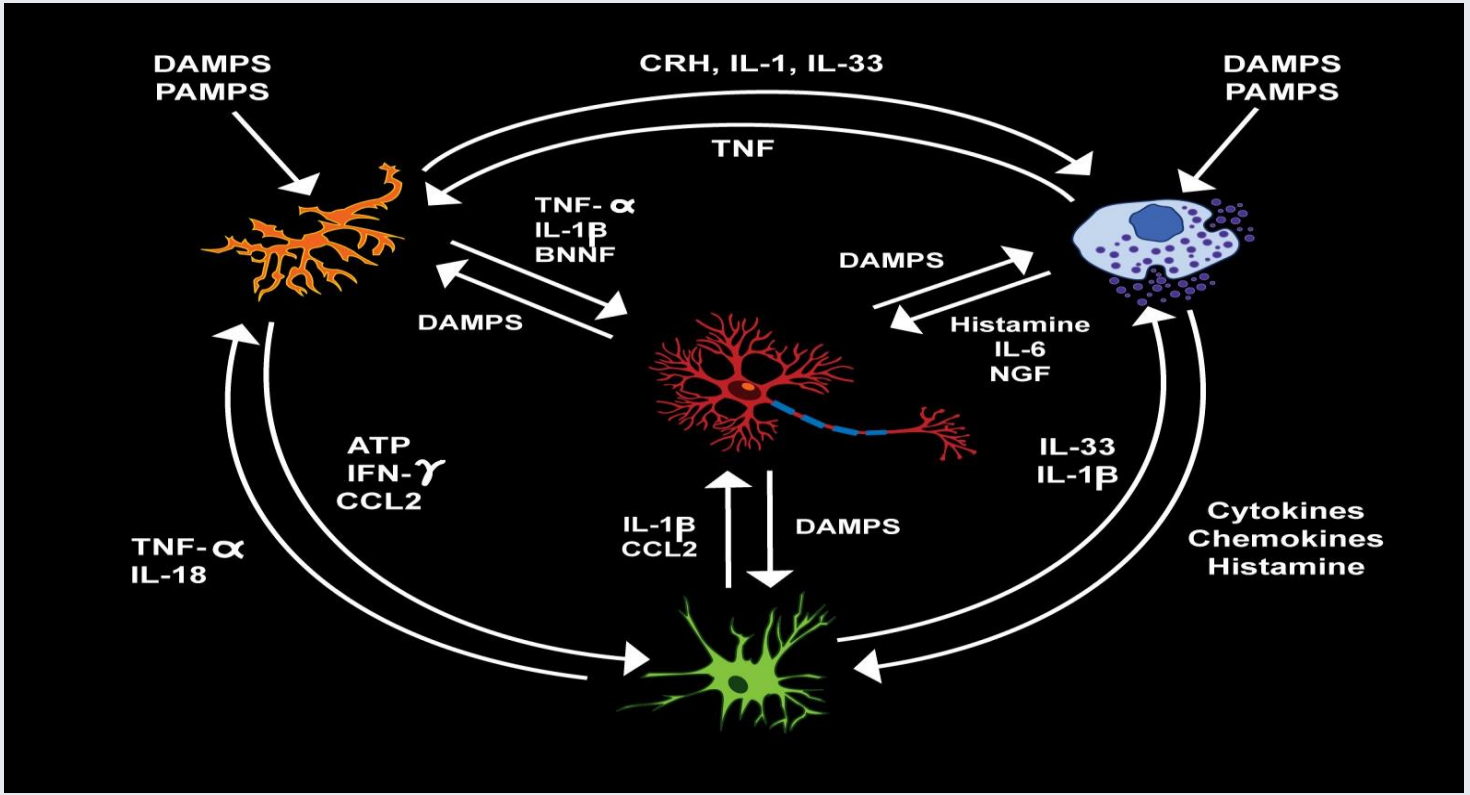
- TSPO, a mitochondrial protein highly increased by activated microglia and reactive astrocytes
- PET scan data showed higher levels of TSPO within **8 brain regions** in patients with persistent symptoms following treated Lyme Disease compared to healthy controls



Data suggest that if spirochete antigens remain in the CNS after antibiotic treatment, they may facilitate a persistent neuroimmune response linked to neuropsychiatric symptoms of PTLDS

Innate Immune System

CNS Mediators of Neuroinflammation



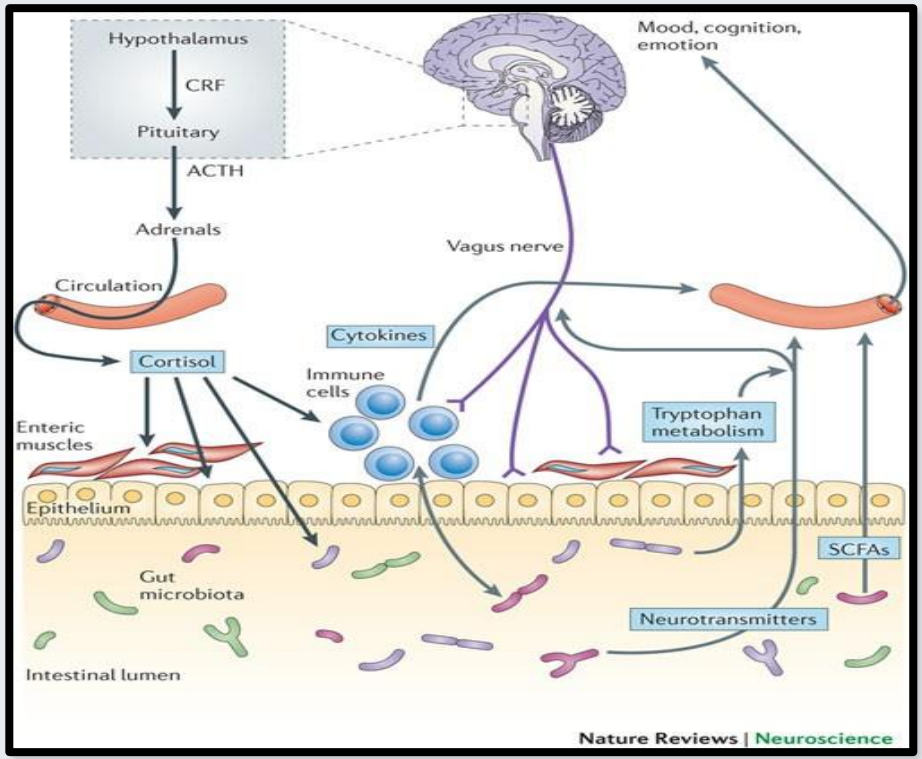
40, 41, 42,43,44,45

THE KAPLAN CENTER
for Integrative Medicine


Innate Immunity
Gut Microbiome

Microbiome-Gut-Brain Axis

Bidirectional communications between the gut and the brain occur via:



- Central Nervous System
- Autonomic Nervous System
- Enteric Nervous System
- Endocrine-Hypothalamic-Pituitary-Adrenal
- Immune
- Humoral

Microbiome-Gut-Brain Axis

- Controls the maturation and development of the Enteric Nervous System (ENS) and Central Nervous System (CNS)
- Resilience- influences stress activity

47, 48, 49

Microbiome-Gut-Brain Axis

- Memory via regulation of BDNF
- Cognitive functioning
- Blood brain barrier

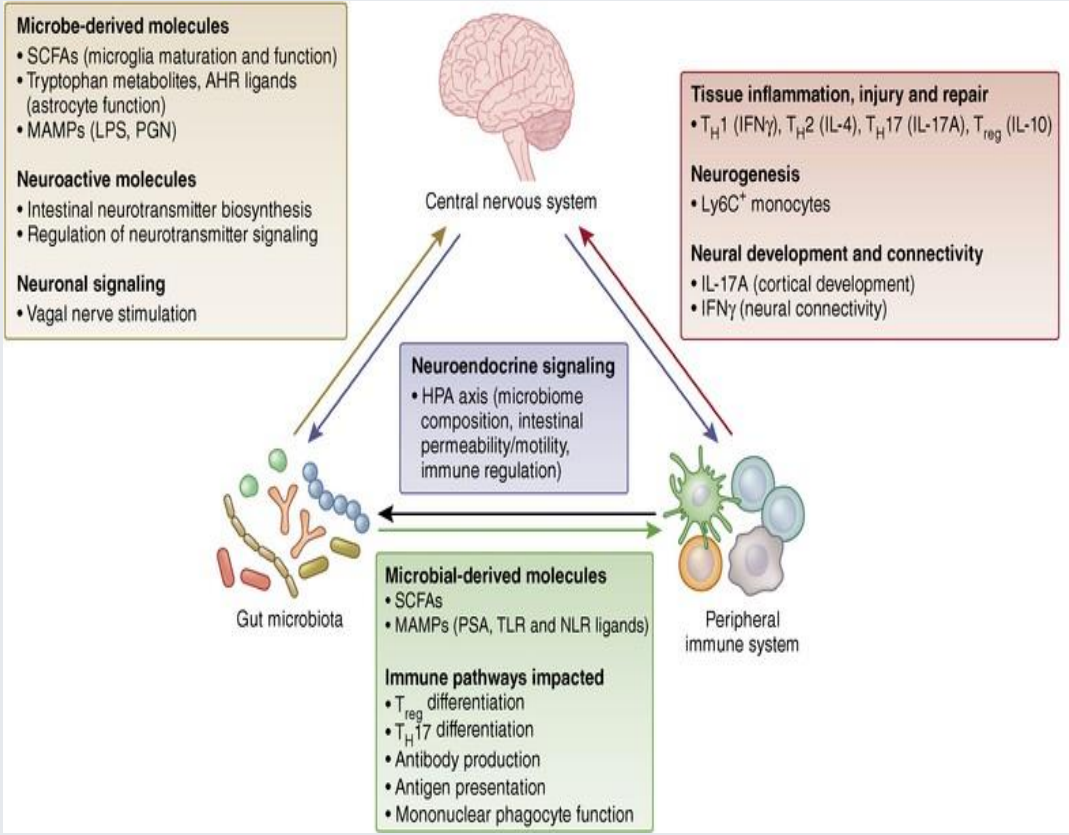
Leaky gut= leaky brain

Leaky brain = leaky gut

50,51,52,53

Gut Microbiome and Innate Immune System in the CNS

- Structural bacterial components such as LPSprovide low-grade tonic stimulation of the innate immune system.
- Excessive stimulation due to bacterial dysbiosis, small intestinal bacterial overgrowth, or increased intestinal permeability may produce systemic and/or central nervous system inflammation



108, 109

Gut Dysbiosis and Autoimmunity

- 70% of the immune system is located in the GI tract

- Interaction between the gut microbiome and the gut wall determines the health and development of the adaptive immune system

- Evasion of microbial species through the permeable gut wall into systemic circulation can initiate autoimmunity, in hosts with a genetic predisposition

Unhealthy Gut = Unhealthy Immune System = UNHEALTHY US

Neuroinflammatory Disease Associated with Disruption of the Gut Microbiome

- Anxiety/Depression
- Autism Spectrum Disorders
- Parkinson's Disease
- Multiple Sclerosis
- Alzheimer's Disease
- Chronic Fatigue Syndrome

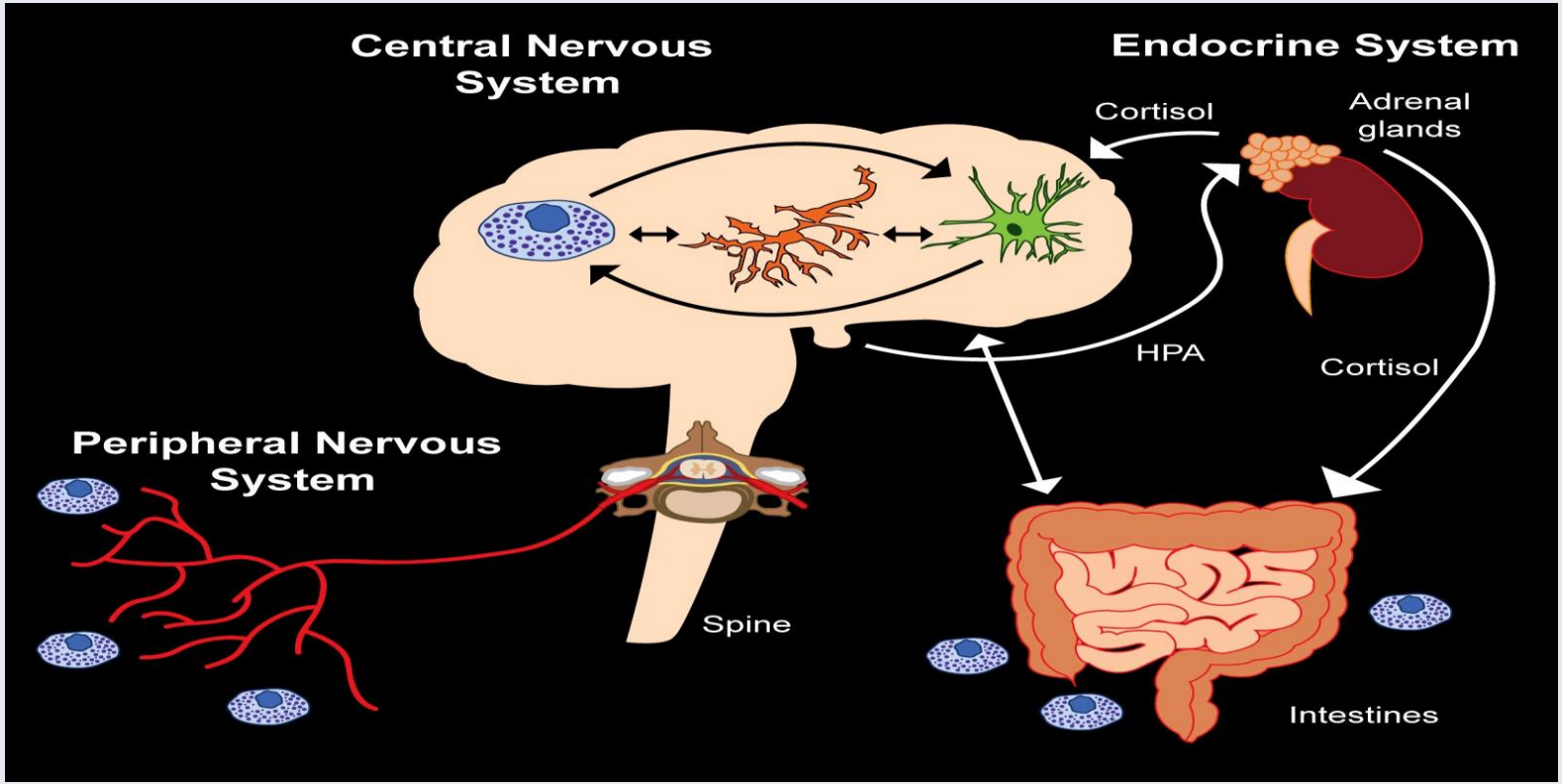
55,56,57,58,59,60,61

Chronic Pain Conditions Associated with Alteration Of Gut Microbiota

- Chronic Prostatitis
- Chronic Pelvic Pain
- Visceral Pain
- Migraine
- Fibromyalgia
- Arthritis

62,63,64

A New Map of Neuroinflammation



40, 41, 42,43,44,45


Innate Immunity
Gut Microbiome
Adaptive Immunity

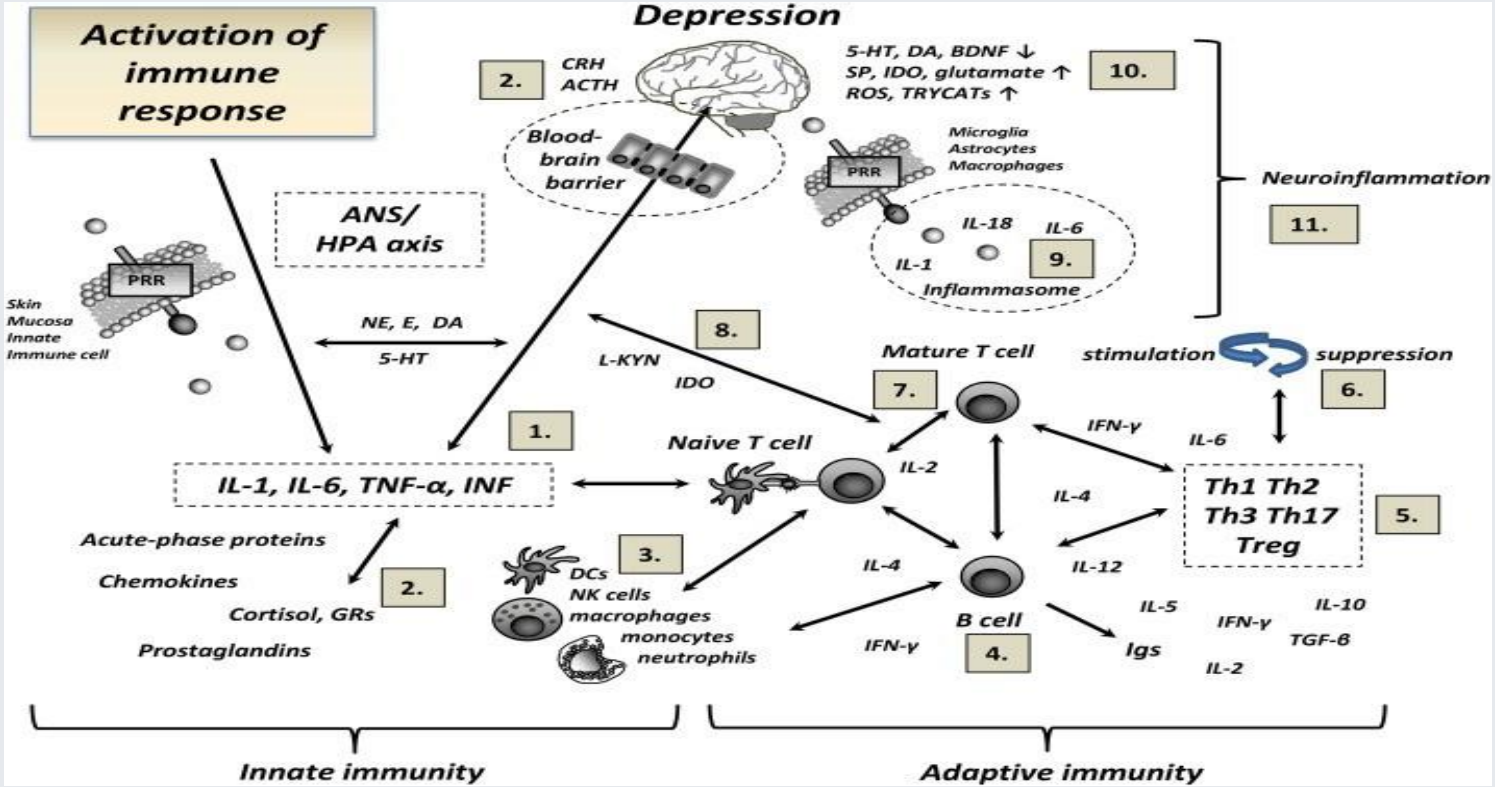
Adaptive Immune System

When Things Go Wrong

- Autoimmunity is a condition where the adaptive immune system is attacking its own healthy cells and tissues
- Autoimmune Disease is the result of the aberrant immune response
- About 5% of the population suffers from an autoimmune disease
- Examples of Autoimmune Disease:
  - Multiple Sclerosis
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
  - Sjörgren's
  - Hashimoto's Thyroiditis

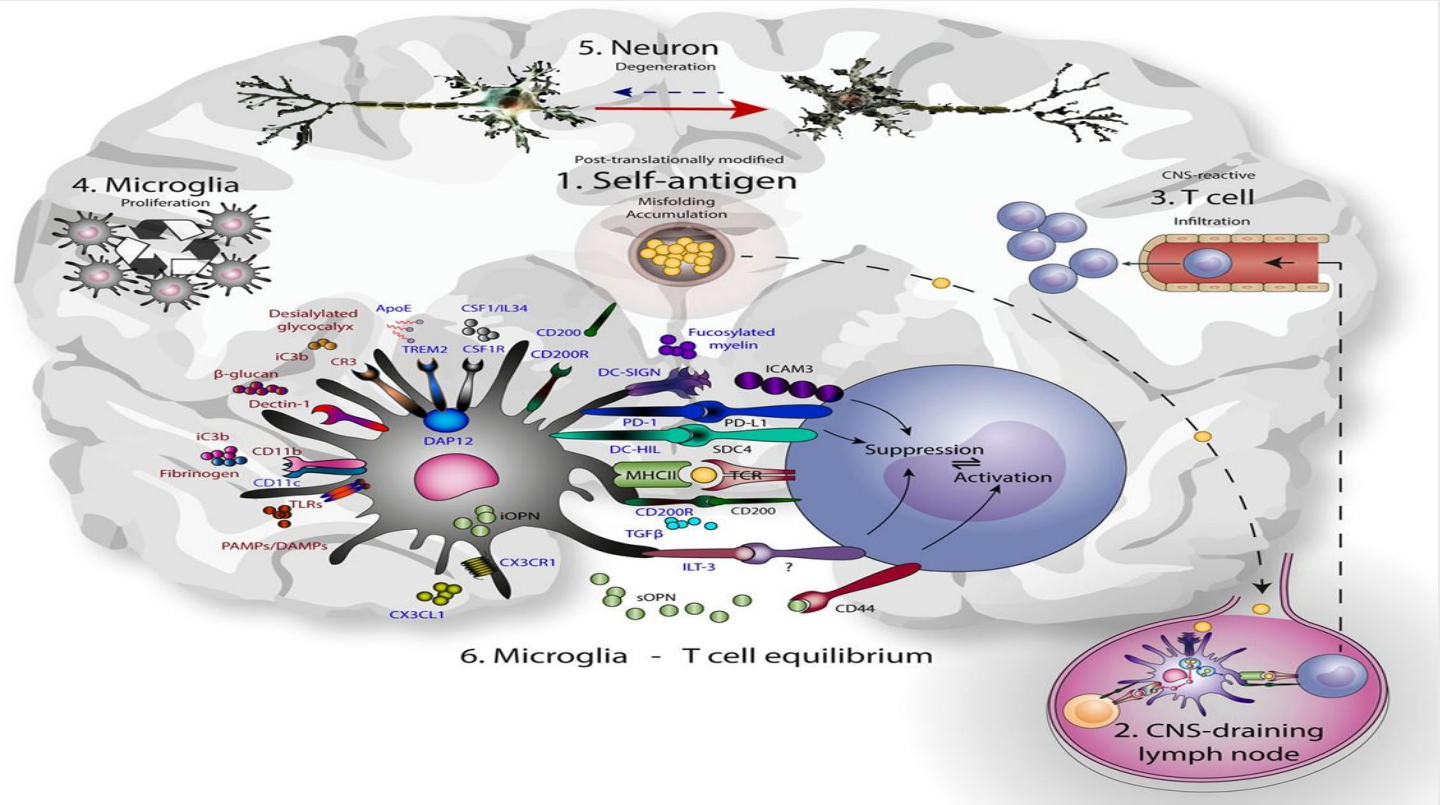
Adaptive Immune System

Depression Model



Innate-Adaptive Systems Communication

Microglia- T Cell Equilibrium



Autoimmune Encephalopathy

Extends beyond the recognized clinical and radiological spectrum of "limbic Encephalitis"... Includes a subacute or insidious onset of:

- Confusional state
- Psychosis
- Delirium
- Memory loss
- Hallucinations
- Movement disorder
- Sensory or motor complaints
- Seizures
- Dyssomnia
- Ataxia
- Eye movement problems
- Nausea
- Vomiting
- Inappropriate antidiuresis
- Coma
- Dysautonomia or hypoventilation

Autoimmune Encephalopathy of Infectious Etiology

What Is Autoimmune Encephalopathy of Infectious Etiology?

Clinical Presentations

- Neuropsychiatric symptoms
- Chronic headaches
- Sensory or motor complaints
- Seizures
- Dyssomnia
- Chronic Fatigue
- Fibromyalgia
- Dysautonomia

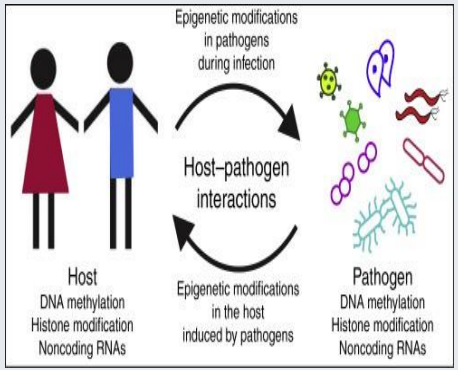
Infectious Etiologies

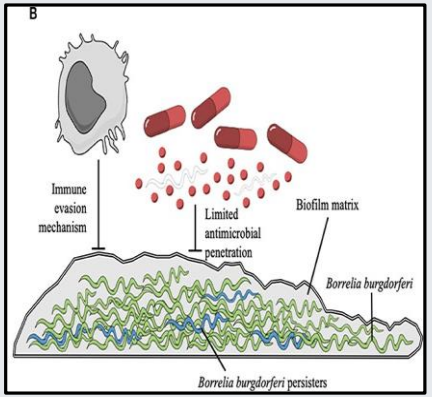
- Streptococcus
- Mycoplasma Pneumoniae
- Bartonella
- Toxoplasmosis
- Influenza
- Babesia
- Borrelia
- Epstein Barr Virus

Autoimmune Mechanisms

Molecular Mimicry

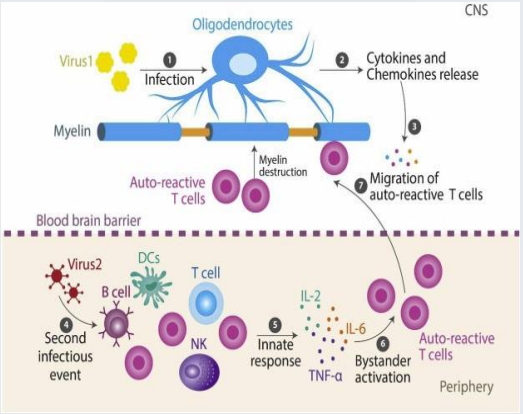
Epigenetics

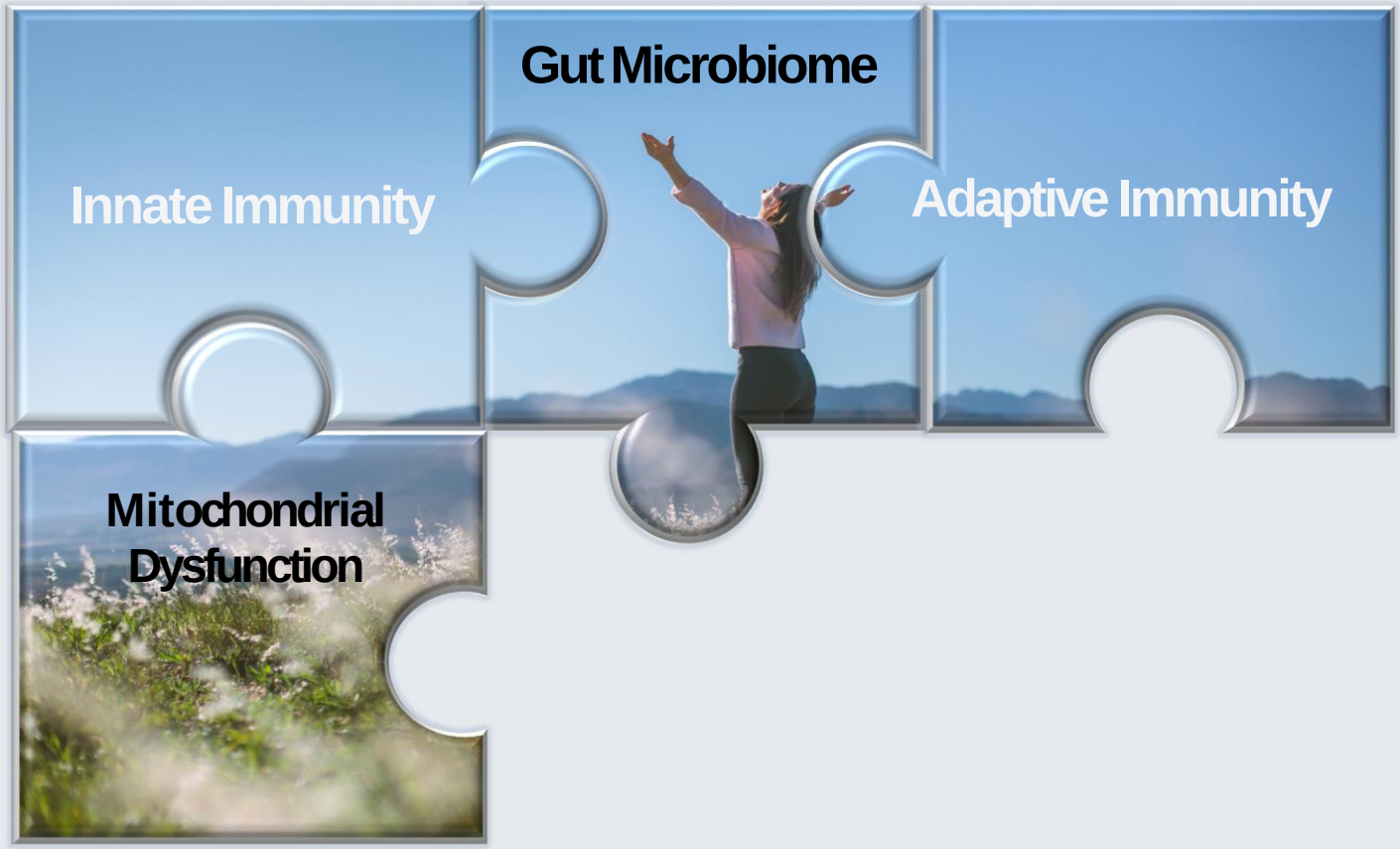




Microbial Persistence

Bystander Activation



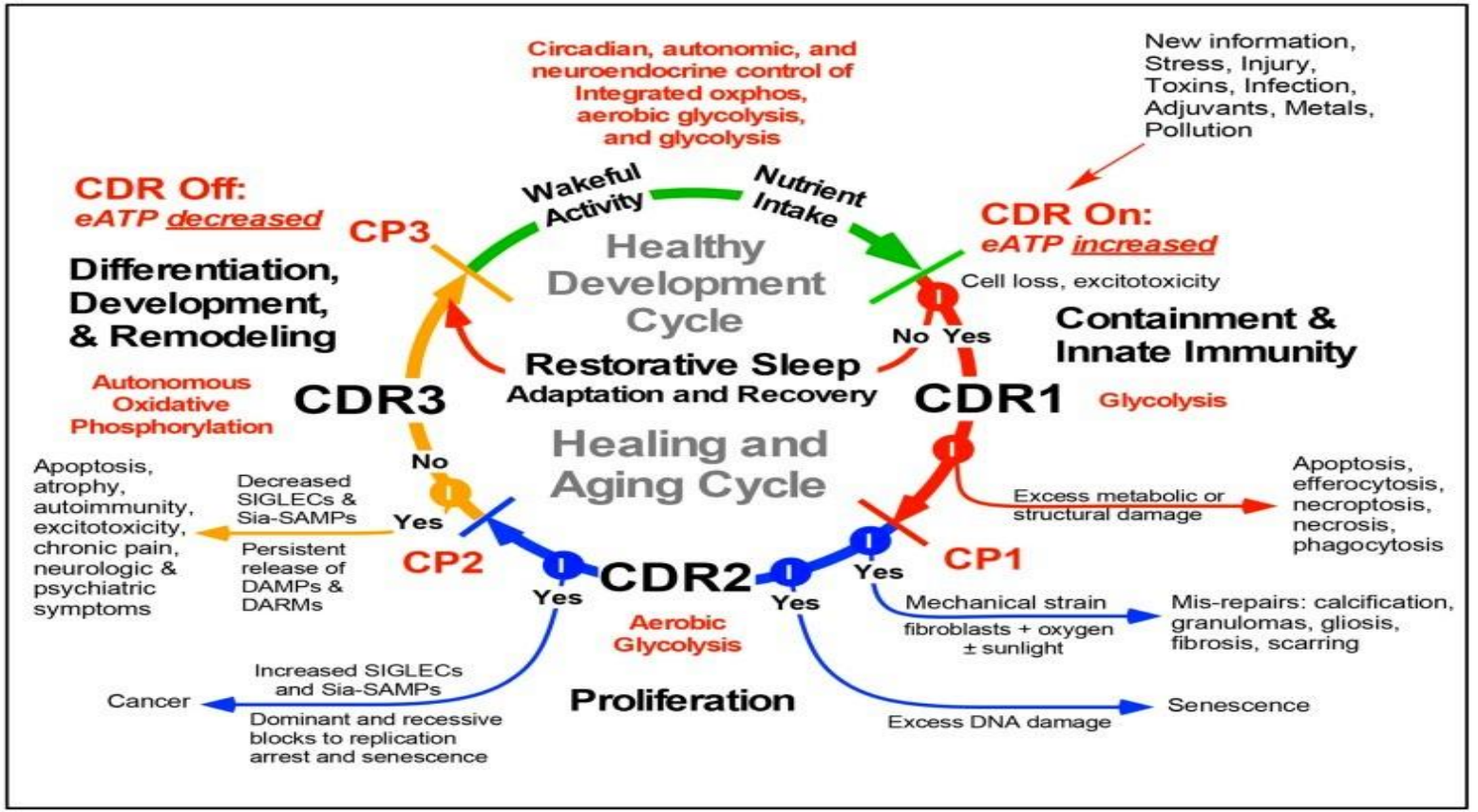

Innate Immunity
Gut Microbiome
Adaptive Immunity
Mitochondrial Dysfunction

Cell Danger Response: Mitochondrial Dysfunction

- Mitochondria are evolved to sense all of the chemical, physical and microbial threats according to the induced changes in electron flow available for normal metabolism
- Mitochondria are located at the hub of the wheel of metabolism
- Mitochondrial proteome is regulated according to tissue- specific needs, responds to injury, food quality, exercise, environmental pollution, and coordinates CDR
- Contains 1300 proteins tailored to meet the needs of each different cell type, and catalyze over 500 chemical reactions in metabolism
- Mitochondria represents the front lines in cellular defense and innate immunity

79,80,81

Cell Danger Response: Mitochondrial Dysfunction



Mitochondrial Dysfunction and Gut Microbiome

- Chronic activation of CDR alters both the physical habitat of the distal Bowel and the availability of resources in the form of dietary nutrients
- The increase in oxidizing conditions associated with the CDR in the gut lining lead to changes in the uptake, intracellular processing of different metabolites leading to:
  1. An increase in gluten sensitivity
  2. Alteration in permeability and species composition
  3. Dysbiosis with alternated diarrhea and constipation
  4. Changes in behavior resulting from communication abnormalities between the ENS and CNS

Mitochondrial Dysfunction and ME/CFS

- Abnormal mitochondrial morphology in muscle biopsy tissue and defects in aerobic metabolism not characteristic of muscle disuse was seen in patient diagnosed with ME/CFS
- Evidence of Lowered ATP production, impaired oxidative phosphorylation and mitochondrial damage
- Increased levels of pro-inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-α, and elastase, and increased O&NS may inhibit mitochondrial respiration, decrease the activities of the electron transport chain and mitochondrial membrane potential, increase mitochondrial membrane permeability, interfere with ATP production and cause mitochondrial shutdown

Mitochondrial Dysfunction and Fibromyalgia

Int J Mol Sci. 2019 Feb; 20(3): 765.
Published online 2019 Feb 11. doi: 10.3390/ijms20030765
PMCID: PMC6386947
PMID: 30754674

Mitochondrial Dysfunction in Skeletal Muscle of a Fibromyalgia Model: The Potential Benefits of Melatonin

Gaia Favero,[1,†] Francesca Bonomini,[1,2,†] Caterina Franco,[1] and Rita Rezzani[1,2,*]

r information ▸ Article notes ▸ Copyright and License information Disclaimer

act

Go to:

yalgia syndrome (FMS) is considered a musculoskeletal disorder associated to other symptoms
ng chronic pain. Since the hypothesis of FMS etiogenesis is consistent with mitochondrial
ction and oxidative stress, we evaluated the pathophysiological correlation among these factors
g some proteins involved in the mitochondrial homeostasis. We focused our attention on the roles of
ome proliferator activated receptor gamma coactivator-1alpha (PGC-1α), mitofusin2 (Mfn2), and
me Q10 (CoQ10) in reserpine-induced myalgic (RIM) rats that manifest fibromyalgia-like chronic
g the pathophysiology of
FMS. In fact, their
tochondrial homeostasis.
toms of this disease and

Home / Current Molecular Medicine, Volume 16, Number 2

Fibromyalgia and Bipolar Disorder: Emerging Epidemiological Associations and Shared Pathophysiology

Authors: Bortolato, B.; Berk, M.; Maes, M.; R.S. McIntyre, R.S. McIntyre; Carvalho, A.F.
Source: Current Molecular Medicine, Volume 16, Number 2, 2016, pp. 119-136(18)
Publisher: Bentham Science Publishers

< previous article view tab

Abstract References Cit

Fibromyalgia (FM) is a prevale
fatigue, sleep disturbances ar
frequently co-occur in individu
remarkable phenomenologica
was carried out in the Pubme
pertaining to the epidemiolog

J Biol Regul Homeost Agents. 2017 Jan-Mar;31(1):17-20.

Fibromyalgia and bipolar disorder: extent of comorbidity and therapeutic implications.

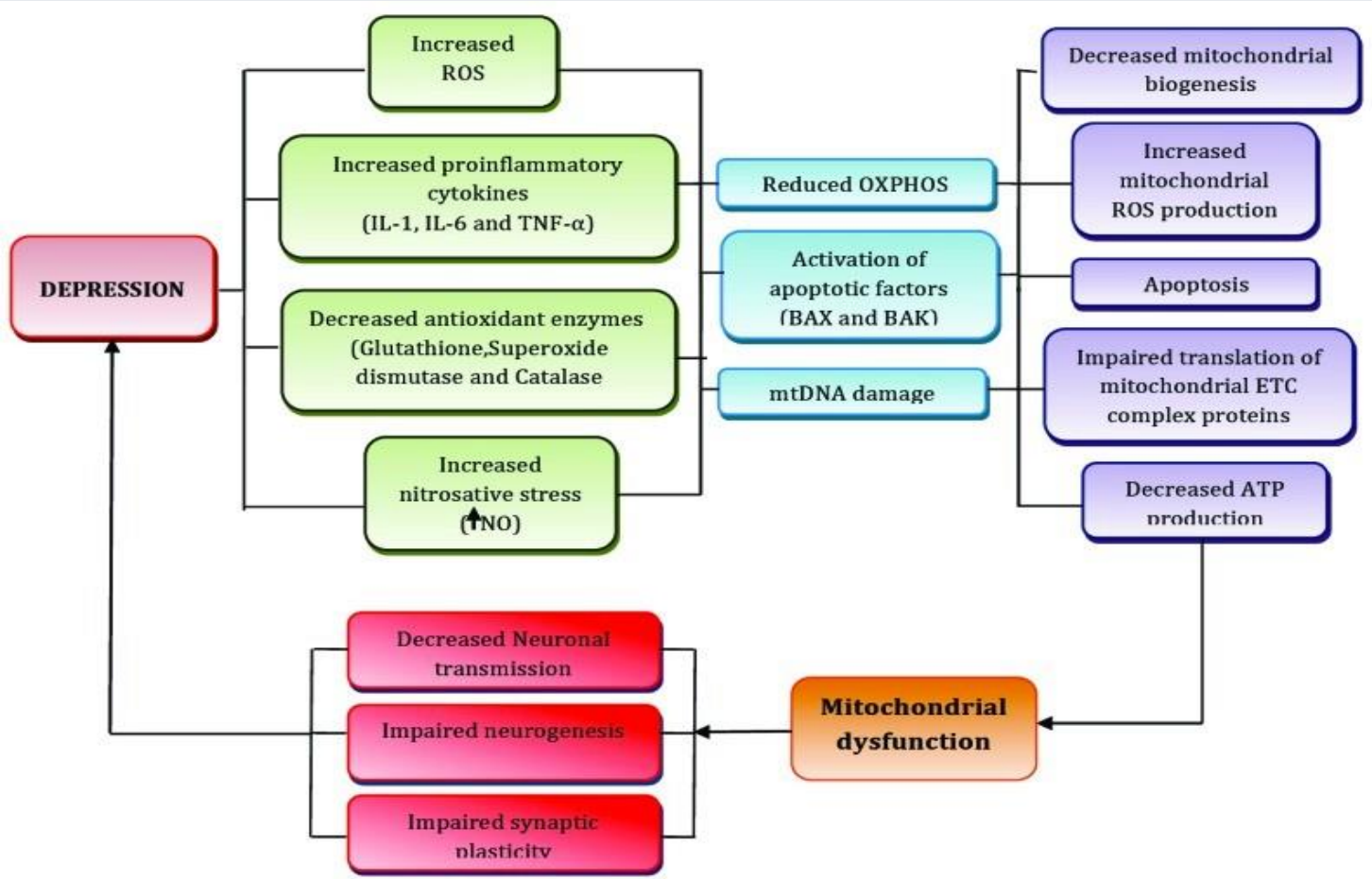
Di Tommaso Morrison MC[1], Carinci F[2], Lessiani G[3], Spinas E[4], Kritas SK[5], Ronconi G[6], Caraffa AI[7], Conti P[8].

Author information

Abstract

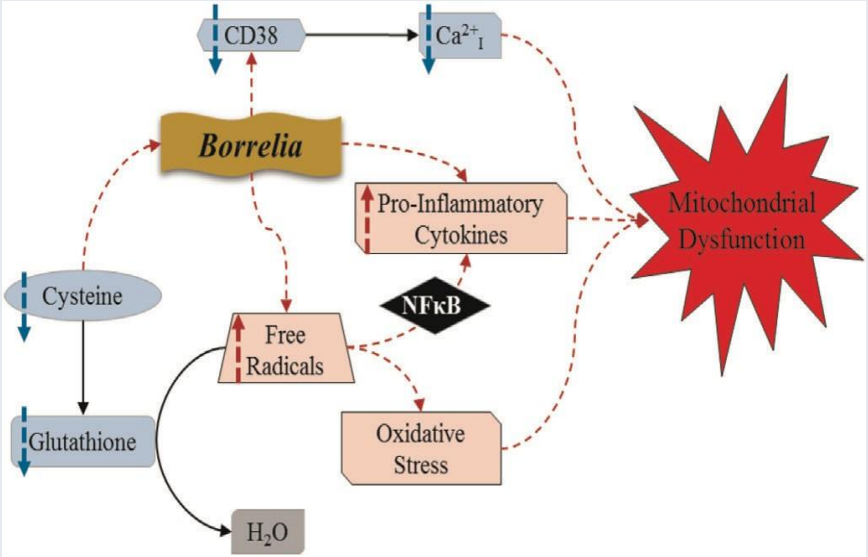
Fibromyalgia (FM) is a syndrome that affects muscles and soft tissues. Presenting symptoms include chronic muscle pain, fatigue, sleep problems and psychological symptoms, including depression and anxiety. There exists strong evidence of a comorbidity between FM and Bipolar Disorder (BD). In this study, papers from 2006 to February 2016 that examined the comorbidity and etiological similarities of FM and BD were reviewed, as well as the therapeutic implications of these findings. The reviewed articles showed that an adequate psychiatric screening for BD is recommended in FM patients with depressive symptoms, in order to decrease administration of antidepressants for BD, due to the lack of proven efficacy, and to limit antidepressant-induced mania. Alternative therapies, such as agomelatine, memantine and psychotherapic treatment should be considered.

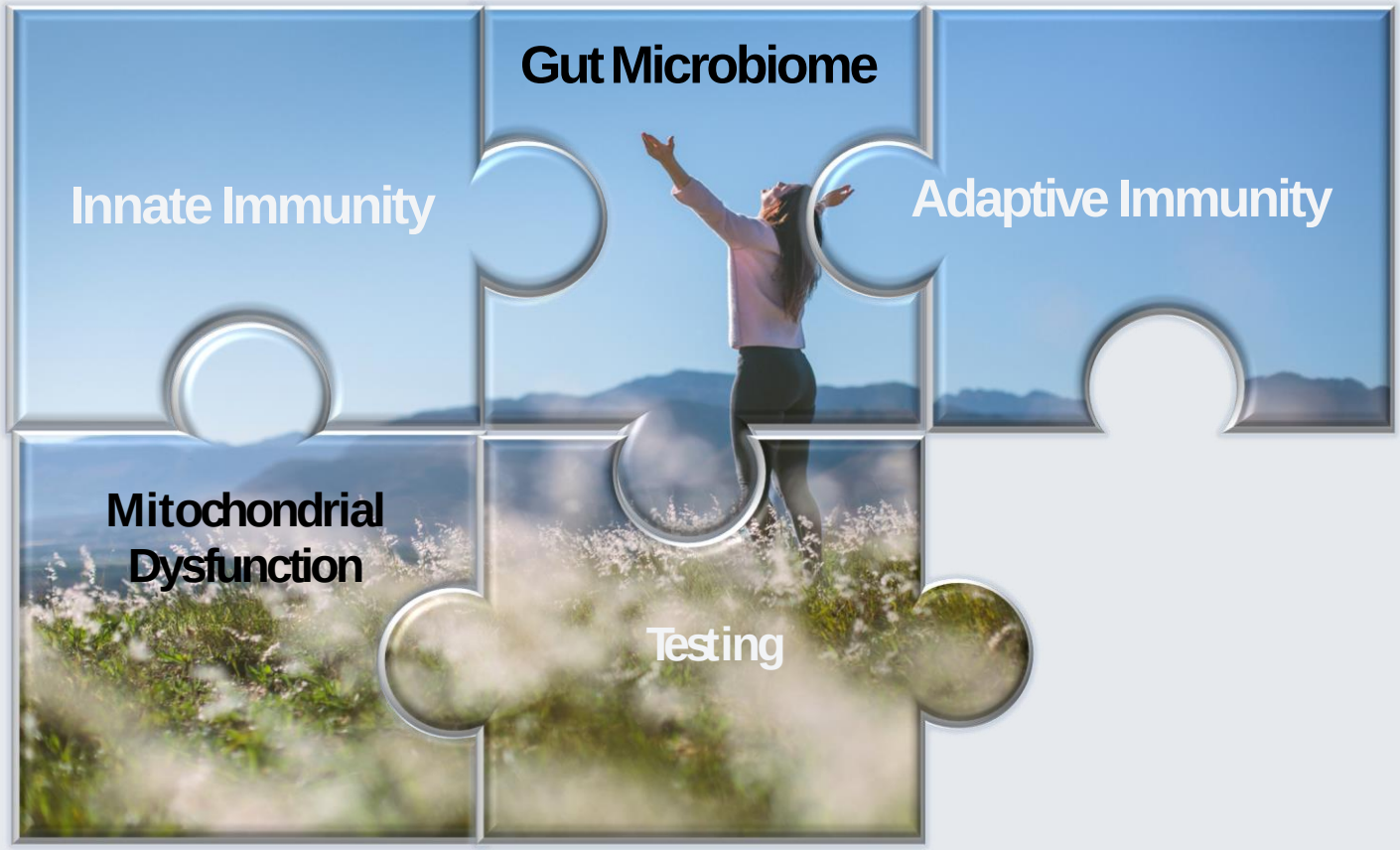
Mitochondrial Dysfunction and Depression



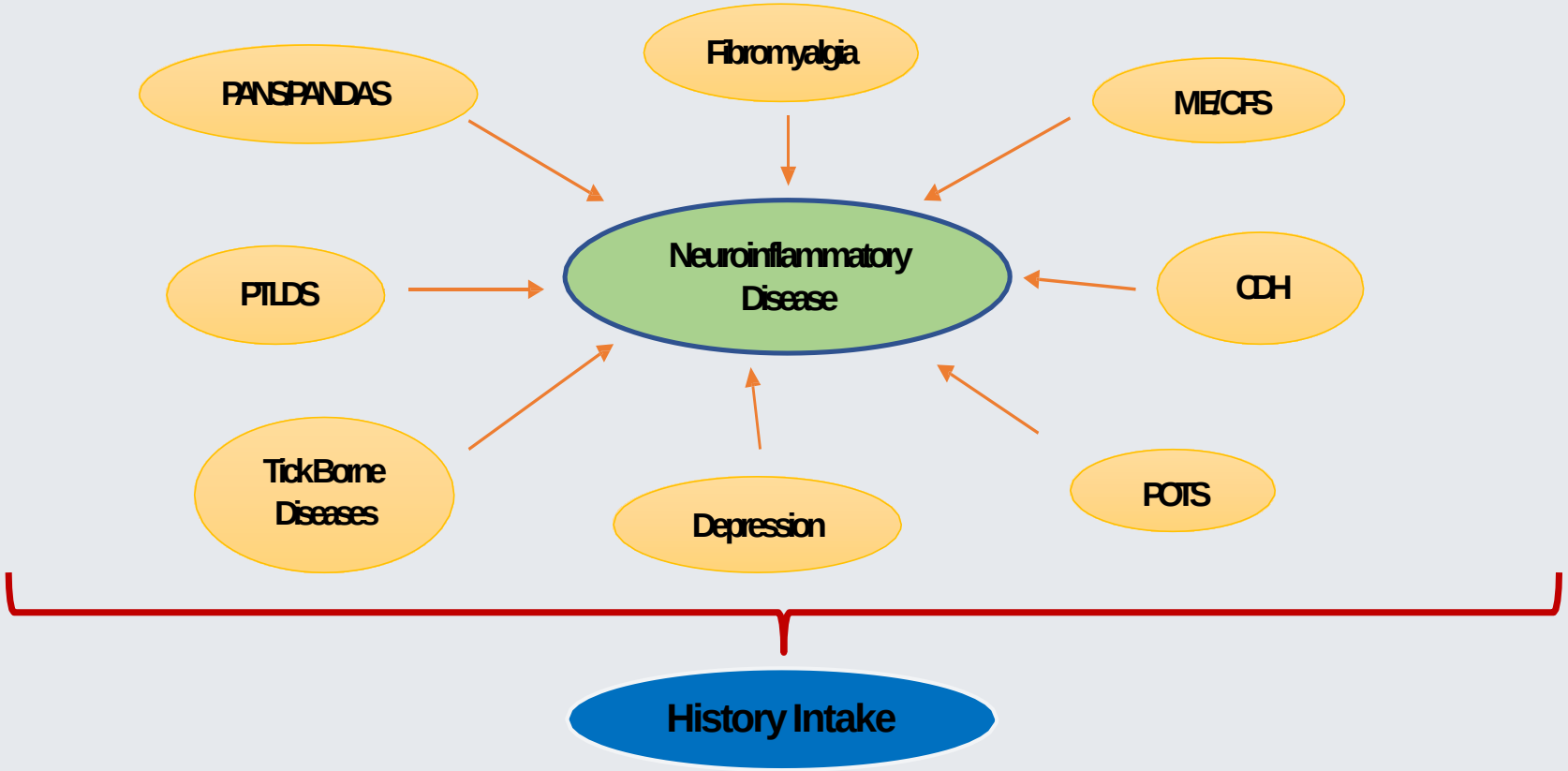
Mitochondrial Dysfunction and Lyme Disease

- Results have shown a significant rise in mitochondrial superoxide, indicative of a state of oxidative stress in Lyme borreliosis patients.
- Evidence of a significant decrease in levels of cytosolic ionized calcium in PBMCs.
- These imbalances could cause oxidative stress, depolarization of the mitochondrial membrane, disruption of intracellular communication, and a release of pro-inflammatory cytokines

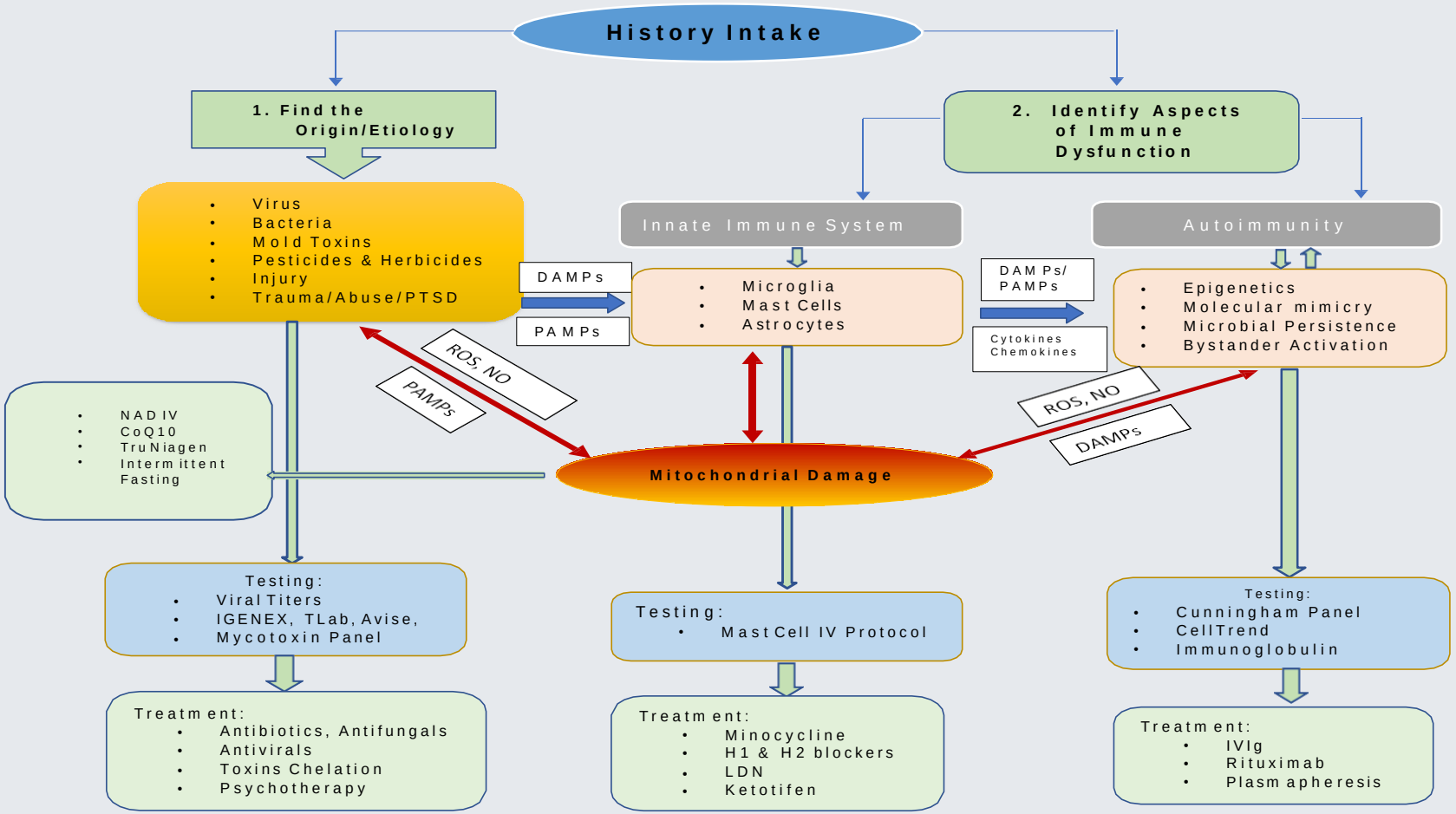



Gut Microbiome
Innate Immunity
Adaptive Immunity
Mitochondrial Dysfunction
Testing

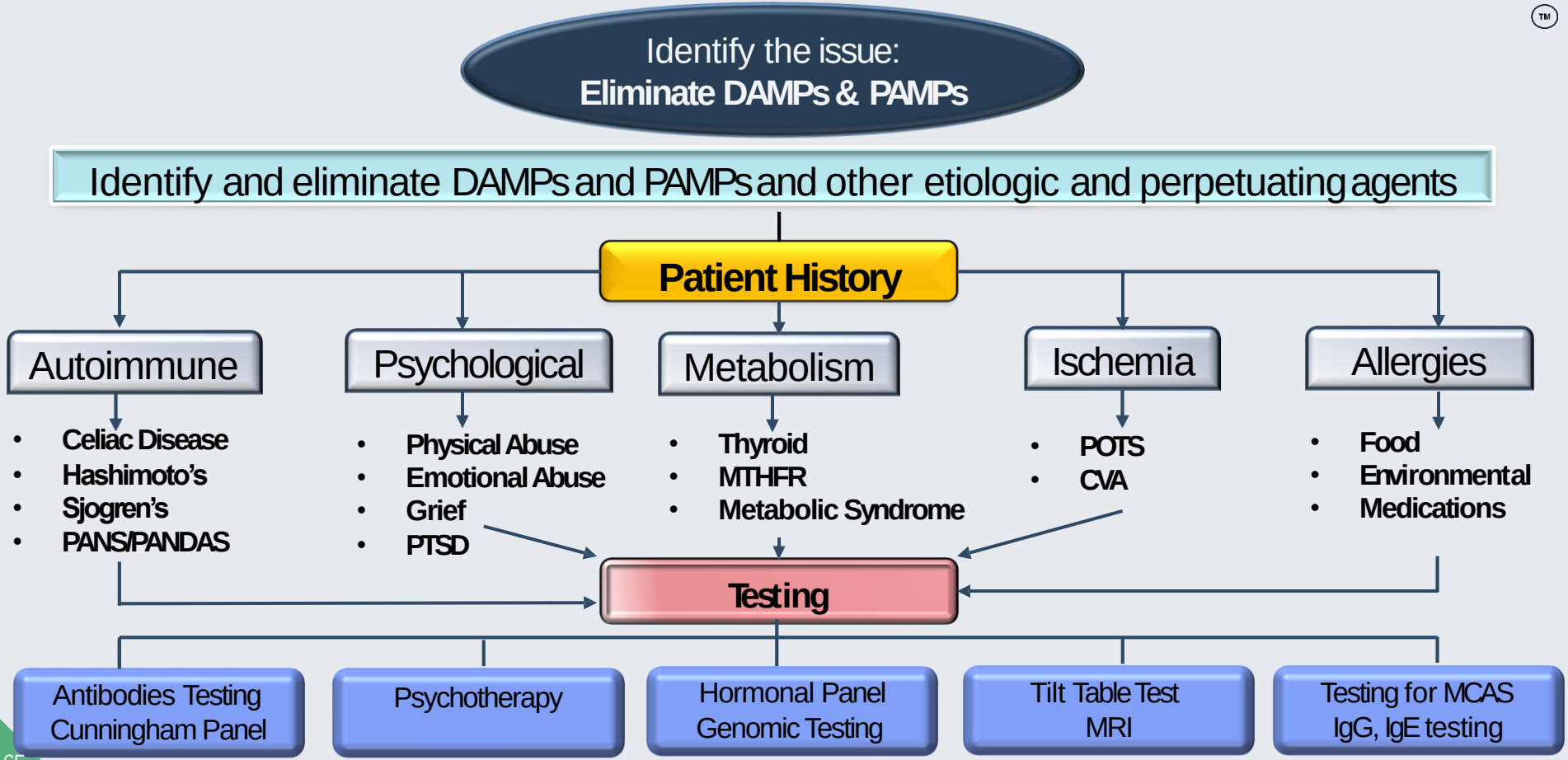
Our Model


PANS/PANDAS
Fibromyalgia
ME/CFS
PTLDS
Neuroinflammatory Disease
CCH
Tick Borne Diseases
Depression
POTS
History Intake

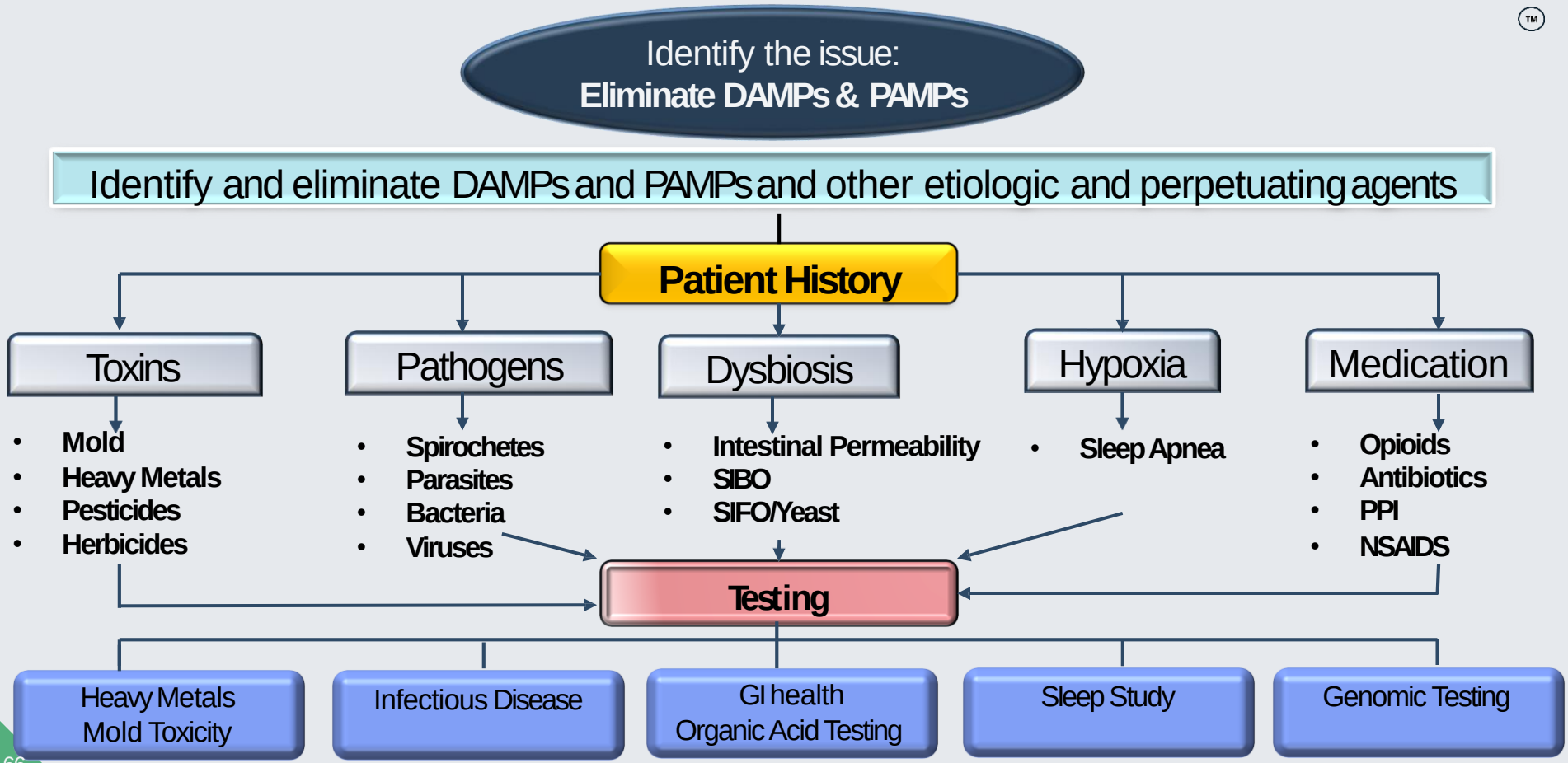
Our Model


History Intake
1. Find the Origin/Etiology
2. Identify Aspects of Immune Dysfunction
Virus
Bacteria
Mold Toxins
Pesticides & Herbicides
Injury
Trauma/Abuse/PTSD
DAMPs
PAMPs
Innate Immune System
Microglia
Mast Cells
Astrocytes
DAMPs/ PAMPs
Cytokines Chemokines
Autoimmunity
Epigenetics
Molecular mimicry
Microbial Persistence
Bystander Activation
ROS, NO
PAMPs
ROS, NO
DAMPs
NAD IV
CoQ10
TruNiagen
Intermittent Fasting
Mitochondrial Damage
Testing:
Viral Titers
IGENEX, TLab, Avise,
Mycotoxin Panel
Testing:
Mast Cell IV Protocol
Testing:
Cunningham Panel
CellTrend
Immunoglobulin
Treatment:
Antibiotics, Antifungals
Antivirals
Toxins Chelation
Psychotherapy
Treatment:
Minocycline
H1 & H2 blockers
LDN
Ketotifen
Treatment:
IVIg
Rituximab
Plasmapheresis

Our Model


Identify the issue:
Eliminate DAMPs & PAMPs
Identify and eliminate DAMPs and PAMPs and other etiologic and perpetuating agents
Patient History
Autoimmune
Psychological
Metabolism
Ischemia
Allergies
Celiac Disease
Hashimoto's
Sjogren's
PANS/PANDAS
Physical Abuse
Emotional Abuse
Grief
PTSD
Thyroid
MTHFR
Metabolic Syndrome
POTS
CVA
Food
Environmental
Medications
Testing
Antibodies Testing
Cunningham Panel
Psychotherapy
Hormonal Panel
Genomic Testing
Tilt Table Test
MRI
Testing for MCAS
IgG, IgE testing

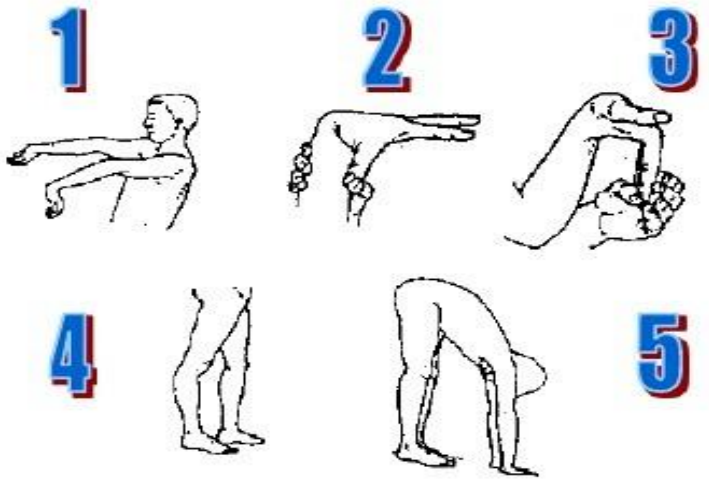
Our Model


Identify the issue:
Eliminate DAMPs & PAMPs
Identify and eliminate DAMPs and PAMPs and other etiologic and perpetuating agents
Patient History
Toxins
Pathogens
Dysbiosis
Hypoxia
Medication
• Mold
• Heavy Metals
• Pesticides
• Herbicides
• Spirochetes
• Parasites
• Bacteria
• Viruses
• Intestinal Permeability
• SIBO
• SIFO/Yeast
• Sleep Apnea
• Opioids
• Antibiotics
• PPI
• NSAIDS
Testing
Heavy Metals
Mold Toxicity
Infectious Disease
GI health
Organic Acid Testing
Sleep Study
Genomic Testing

Beighton Score Ehlers Danlos Syndrome

The Beighton Score

- A popular screening technique for hypermobility.
- Requires the performance of 9 maneuvers.
- A point is gained for each movement that the subject can positively perform.
- A **minimum** of 3 points to be considered mildly hypermobile.
- A **maximum** of 9 points would indicate extreme hypermobility.
- Is easy and quick to perform, even in large populations.
- Movements 1-4 are performed on both the right and left sides of the body.

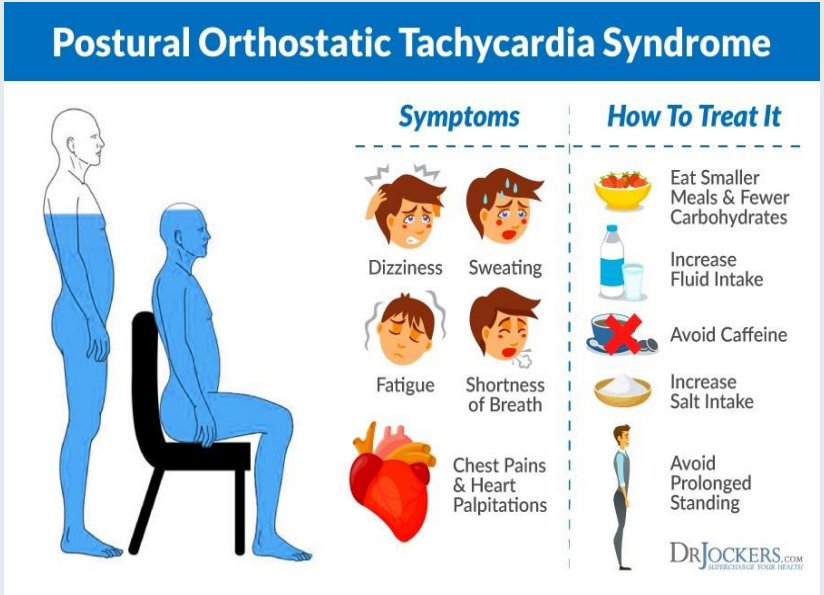


Total = 9 possible points

"Hypermobility Syndrome", Rosemary Keer & Rodney Grahame, (2003)

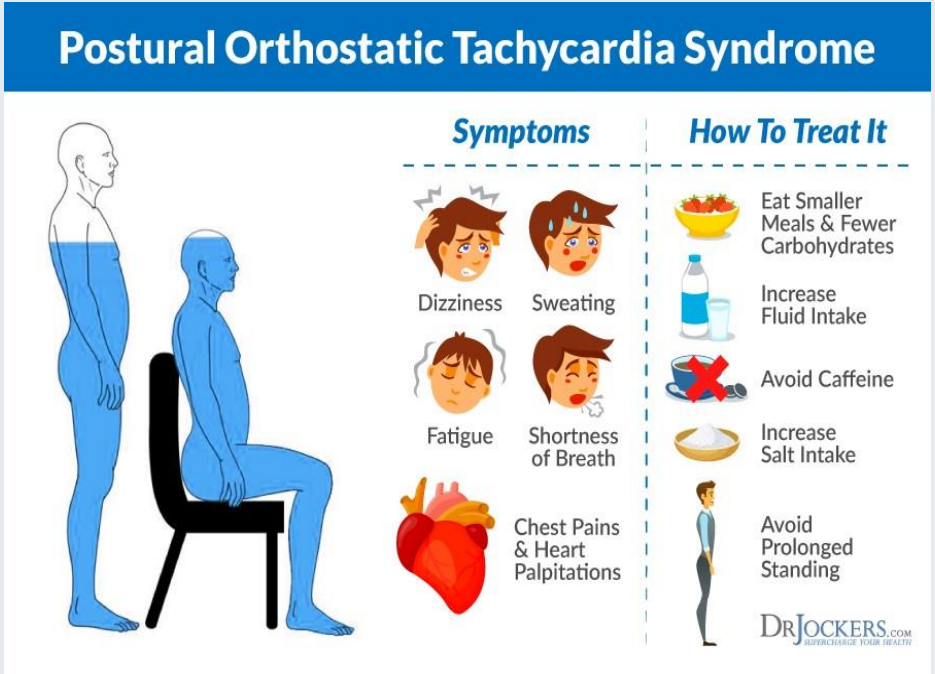
Testing: POTS

- Formal testing for POTS is done under the supervision of a physician with a tilt table test.
- Testing can also be done in the office or at home:
- After lying for 5 minutes, the patient's blood pressure and heart rate will be measured. This will be repeated upon standing, and at 3, 5, and 10 minutes.
- The test is positive for POTS when there is an increase in heart rate of 30 BPM in adults and 40 BPM in children and adolescents.



Treatment for POTS

- Water intake
- Salt pills
- Compression clothing
- Exercise
- Beta blockers
- Fludrocortisone
- Midodrine
- Quinton water



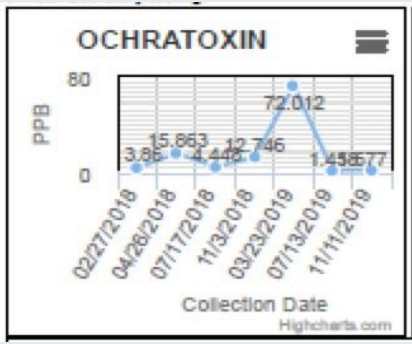
Testing: Heavy Metals Panel

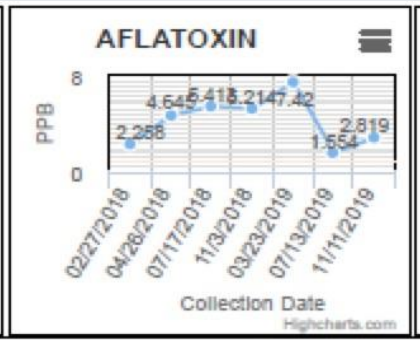
TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	17	< 35	
Antimony	(Sb)	< dl	< 0.2	
Arsenic	(As)	10	< 80	
Barium	(Ba)	2.1	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	0.3	< 4	
Cadmium	(Cd)	0.4	< 1	
Cesium	(Cs)	6.8	< 10	
Gadolinium	(Gd)	< dl	< 0.8	
Lead	(Pb)	12	< 2	
Mercury	(Hg)	9.2	< 4	
Nickel	(Ni)	2.5	< 10	
Palladium	(Pd)	< dl	< 0.15	
Platinum	(Pt)	< dl	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.2	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	1.6	< 5	
Tungsten	(W)	0.2	< 0.4	
Uranium	(U)	< dl	< 0.04	

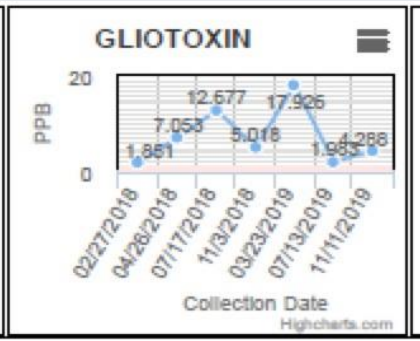
URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	20.5	30- 225	

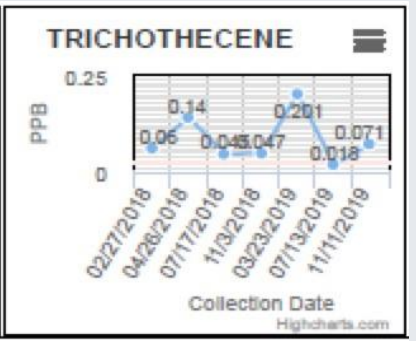
Testing: Mycotoxin Panel

Code	Test	Specimen	Value	Result	Not Present If less than	Equivocal If between	Present If greater or equal
E8501	Ochratoxin A	Urine	1.67700 ppb	Not Present	1.8 ppb	1.8-2.0 ppb	2.0 ppb
E8502	Aflatoxin Group (B1,B2,G1.G2)	Urine	2.81900 ppb	Present	0.8 ppb	0.8-1.0 ppb	1.0 ppb
E8503	Trichothecene Group (Macrocyclic): Roridin A, Roridin E, Roridin H, Roridin L-2, Verrucarin A, Verrucarin J, Satratoxin G, Satratoxin H, Isosatratoxin F	Urine	0.07100 ppb	Present	0.02 ppb	0.02-0.03 ppb	0.03 ppb
E8510	Gliotoxin Derivative	Urine	4.28800 ppb	Present	0.5 ppb	0.5-1.0 ppb	1.0 ppb









Mycotoxins

Mycotoxin	Transmission	Health Impact
Aflatoxins: B1, B2, G1, G2, M1, M2	• Peanuts and peanut products, corn, wheat, rice, cottonseed, nuts, eggs, dairy products, figs • Water-damaged buildings	Hepatotoxicity, bile duct hyperplasia, hemorrhage of intestinal tract and kidneys, carcinogenesis (liver tumors), **immunotoxin**, mutagenic, **neurotoxic**.
Ochratoxins A	• Cereal grains (wheat, barley, oats, corn), dry beans, moldy peanuts, cheese, coffee, raisins, grapes, dried fruits, wine • Water-damaged buildings	Nephrotoxic, liver damage, teratogenesis, kidney tumors, **neurotoxic**, **immunotoxin**, class 2B possible human carcinogen
Trichothecenes (T-2, Deoxynivalenol, diacetoxyscirpenol (DON),Satratoxin)	• Corn, wheat • Water-damaged buildings • Biologic warfare	**Neurotoxins**, **Immunotoxin**, Digestive disorders, oral lesions, hemorrhage of stomach, heart, intestines, lungs, bladder, kidney, edema
Gliotoxin	• Water-damaged buildings • GI Tract infections	**Immunotoxin,** cytotoxic, genotoxic, apoptotic cell death inducer
Patulin	Apples, apple juice, wheat, moldy feed	Brain and lung edema, lung hemorrhage, paralysis of motor nerves, convulsions, carcinogenesis
Zearalenone	Corn, hay	Estrogenic effects (edema of vulva, uterine enlargement), testicular atrophy, enlargement o mammary glands, abortion

112, 113, 114, 115

Treatment of Mycotoxicity

Remediation

- The most important component of treatment is **complete avoidance** of further exposure to the water-damaged environment
- In addition to **all items contaminated by these environments**

Treatment of Mycotoxicity

- Shoemaker Protocol
- Sequestering Agents:
  - Ø Cholestyramine
  - Ø Clay
    - ➢ Chlorella
    - ➢ Charcoal
- Glutathione, antioxidants
- Amphotericin B Nasal spray: 5mg capsule in 24cc distilled water with LoxaSperse & EDTA 1%. Irrigate nostrils BID
- Probiotics
- Hypoallergenic Diet
- Saunas and Exercise

Testing: Lyme Disease

Lyme ImmunoBlot IgM Serum
IGX Criteria: **Positive**
CDC/NYS Criteria: **Positive**
***
[REVISED REPORT: EFFECTIVE APRIL 10, 2019]

Lyme ImmunoBlot IgM detects antibodies to B. burgdorferi strains and species

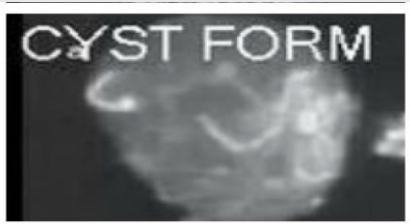
Band (kDa)	23*	31*	34*	39*	41*	93
Intensity	+	-	-	-	++	-

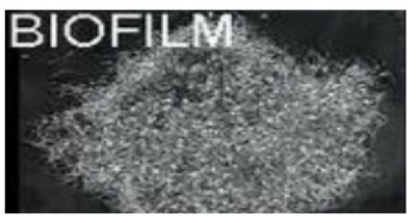
Band Intensity: Positive: + to ++++, Indeterminate: Ind, Negative: (-)

INTERPRETATION	IGX CRITERIA	CDC/NYS CRITERIA
Positive	2 or more of the starred bands are present (+): 23*, 31*, 34*, 39*, 41* kDa	2 or more of the following bands are present (+): 23*, 39*, 41* kDa
Negative	Does not meet IGX criteria for a positive.	Does not meet CDC/NYS criteria for a positive.

Treatment of Lyme Disease

INTRACELLULAR	EXTRACELLULAR	L-FORM/ CYSTIC	PERSISTERS
• Doxycycline • Macrolides • Fluoroquinolones	• Cephalosporin • Penicillin	• Flagyl • Tindamax	• Disulfiram • Dapsone





New Treatments of Lyme Disease

DAPSONE

- Effective treatment against slow growing, intracellular persister bacteria like leprosy
- Anti-parasitic properties (Babesia)
- Patients report significant improvements in Lyme and Babesia related symptoms
- Has anti-inflammatory effects in autoimmune conditions

DISULFIRAM

- Novel potential treatment for chronic Lyme Borreliosis
- Has anti-mycobacterial properties
- Anti-parasitic properties (Babesia)
- Has been recognized to have anti-cancer agents, and reduces plaque-burden in a mouse model of Alzheimer's disease

Treatment of Lyme Disease

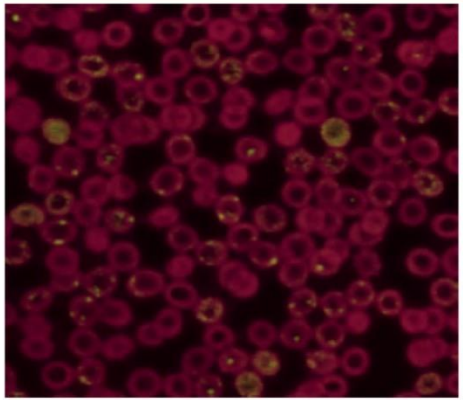
Detoxification

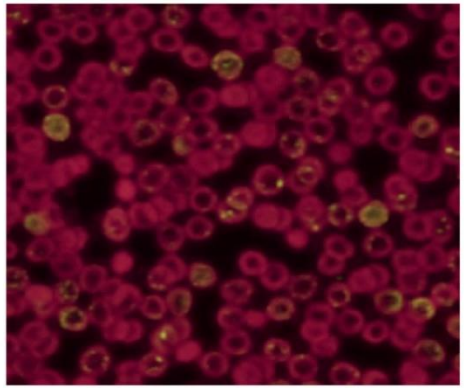
- Glutathione
- N-acetylcysteine
- Methylated B complex (MTHFR)
- IV Vitamins
- Epsom Salt Baths
- Infrared Sauna
- Dry Brushing
- Gentle Exercise
- Acupuncture
- Magnesium citrate/taurate/glycinate
- Activated Charcoal
- Ultra Binder/ GI Detox
- Hypoallergenic Diet/Detox food plan
- Lymphatic Drainage

Testing: Bartonellosis

TEST RESULT		
Target	**Method**	**Result**
B. henselae 23s rRNA	*in situ* hybridization and Confocal Laser Microscopy	Your result is: **Positive** (Research Use Only) (Reference value is "negative")

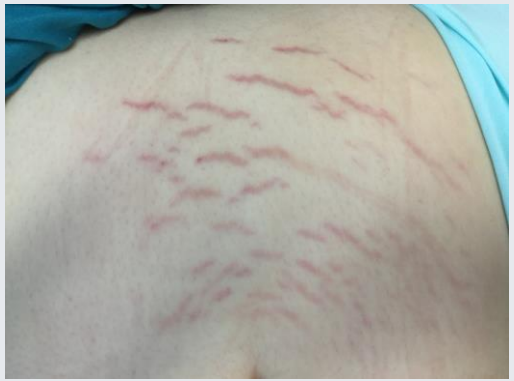
REPRESENTATIVE IMAGES

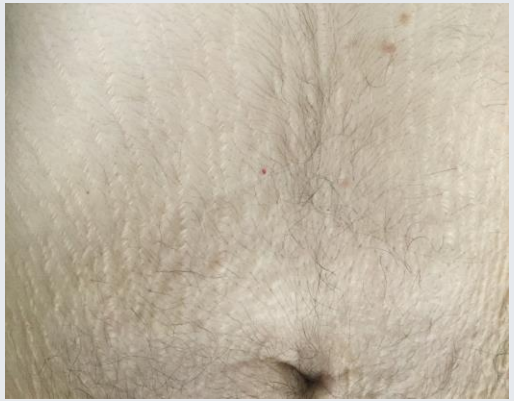




Images obtained using a Confocal Laser Microscope.

Comments: strongly positive for intra- and extra-cellular location





Treatment of Bartonella Infection

Active Phase

- Rifampin
- Doxycycline
- Clarithromycin
- Azithromycin

Stationary Phase (Persisters)

- Methylene Blue
- Clotrimazole
- Gentamycin
- Daptomycin

Testing: Babesiosis

BABESIOSIS

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
B. microti IFA - IgM	Serum	**2560**	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
B. microti IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
Babesia FISH	W blood	**Pos**		
B. duncani IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
B. duncani IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer

B. microti IFA - IgG	Serum	**640**	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
Babesia FISH	W blood	Neg		
B. duncani IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
B. duncani IFA - IgG	Serum	**160**	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer

Babesia FISH	W blood	**Pos**		
B. duncani IFA - IgM	Serum	**80**	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
B. duncani IFA - IgG	Serum	**320**	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer

Babesia FISH	W blood	**Pos**		
B. duncani IFA - IgM	Serum	**40**	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer

Treatment of Babesia Infection

- Atovaquone **PLUS** Azithromycin; OR
- Clindamycin **PLUS** Quinine (this combination is the standard of care for severely ill patients)

Managing Herxheimer Reactions

"temporary worsening of the symptoms of Lyme disease that occurs when the Lyme spirochete is being killed off by antibiotics, creating inflammation…These Herx reactions produce cytokines, which then create ***inflammatory*** *symptoms, including increased* ***fever***, ***muscle and joint pain***, ***headaches***, ***cognitive impairment***, *and a general worsening of the underlying symptomology."*

Dr. Richard Horowitz

Managing Herx Reactions

- N-acetylcysteine
- IV vitamins W/ Glutathione
- Resveratrol
- Curcumin
- Alka-seltzer Gold
- Alpha Lipoic Acid
- Lemon Juice
- Epsom salt baths
- Infrared Sauna
- Acupuncture
- Magnesium
- Burbur/Pinella

Testing: Epstein Barr Virus (EBV)

Test results most likely indicate the following:				
VCA-IgM	**VCA-IgG**	**EA-D, IgG**	**EBNA, IgG**	**Possible Interpretation**
Negative	Negative	Negative	Negative	No infection, symptoms due to another cause, susceptible to EBV infection
Positive	Positive	Negative	Negative	Early, primary infection
Negative or positive	Positive	Positive	Negative	Active infection, though EA-D IgG may persist for life in about 20% of people
Negative	Positive	Negative	Positive	Past infection
Negative	Positive	Positive	Positive	May indicate reactivation of virus

https://labtestsonline.org/tests/epstein-barr-virus-ebv-antibody-tests

Treatment of Epstein Barr Virus (EBV)

- Antiviral Agents
- Cimetidine
- Vitamin C
- Vitamin D
- Resveratrol
- Astragalus

Personal Experience:

- Monolaurin
- Transfer Factors Multi-immune
- Transfer Factors Plasmyc

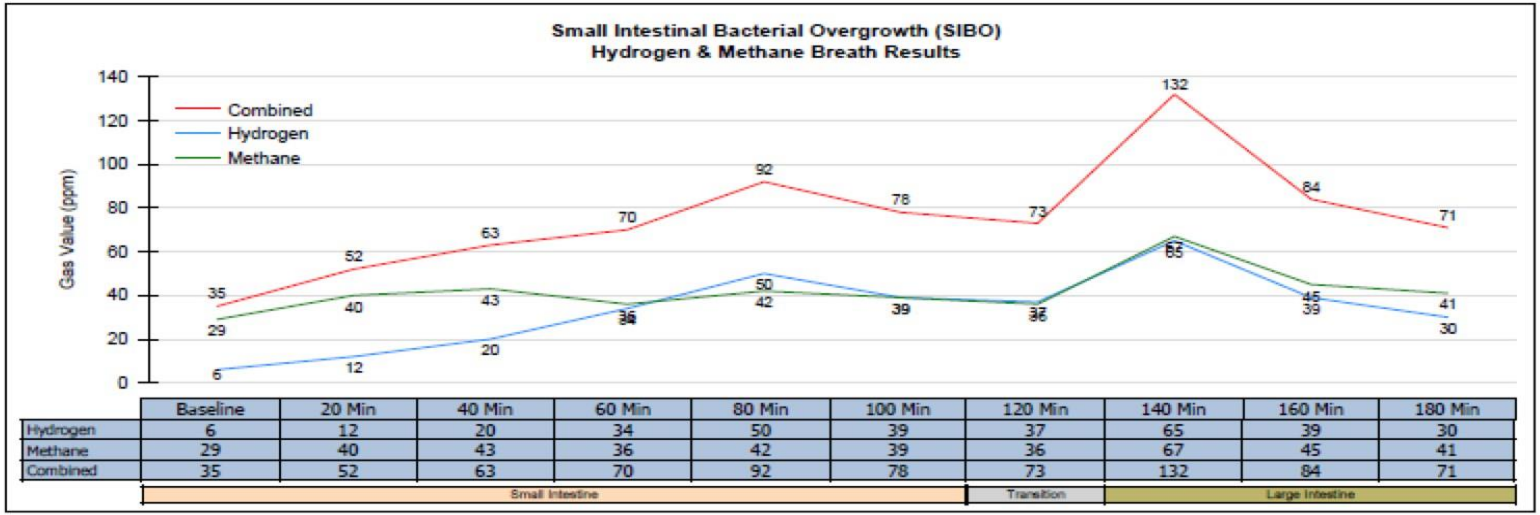
Testing: SIBO

Summary Report of Hydrogen & Methane Breath Analysis with Carbon Dioxide Correction

Gasses Analyzed	Patient Result	Expected
Increase in Hydrogen (H_2)	44 ppm (high)	< 20 ppm
Increase in Methane (CH_4)	14 ppm (high)	< 12 ppm (< 3 ppm[2])
Increase in combined H_2 & CH_4	58 ppm (high)	< 15 ppm[3]

Analysis of the data suggests	Bacterial overgrowth is suspected[2,3,4]

Number	Expected Location	Collection Interval	ppm H2	ppm CH4	Combined	Sample Normalization[1] ppm CO2	fCO2
1	Small Intestine	Baseline	6	29	35	4.4	1.25
2		20 Min.	12	40	52	3.3	1.66
3		40 Min.	20	43	63	4.1	1.34
4		60 Min.	34	36	70	4.0	1.37
5		80 Min.	50	42	92	3.5	1.57
6		100 Min.	39	39	78	3.5	1.57
7	Transition	120 Min.	37	36	73	3.7	1.48
8	Large Intestine	140 Min.	65	67	132	3.7	1.48
9		160 Min.	39	45	84	3.9	1.41
10		180 Min.	30	41	71	3.5	1.57

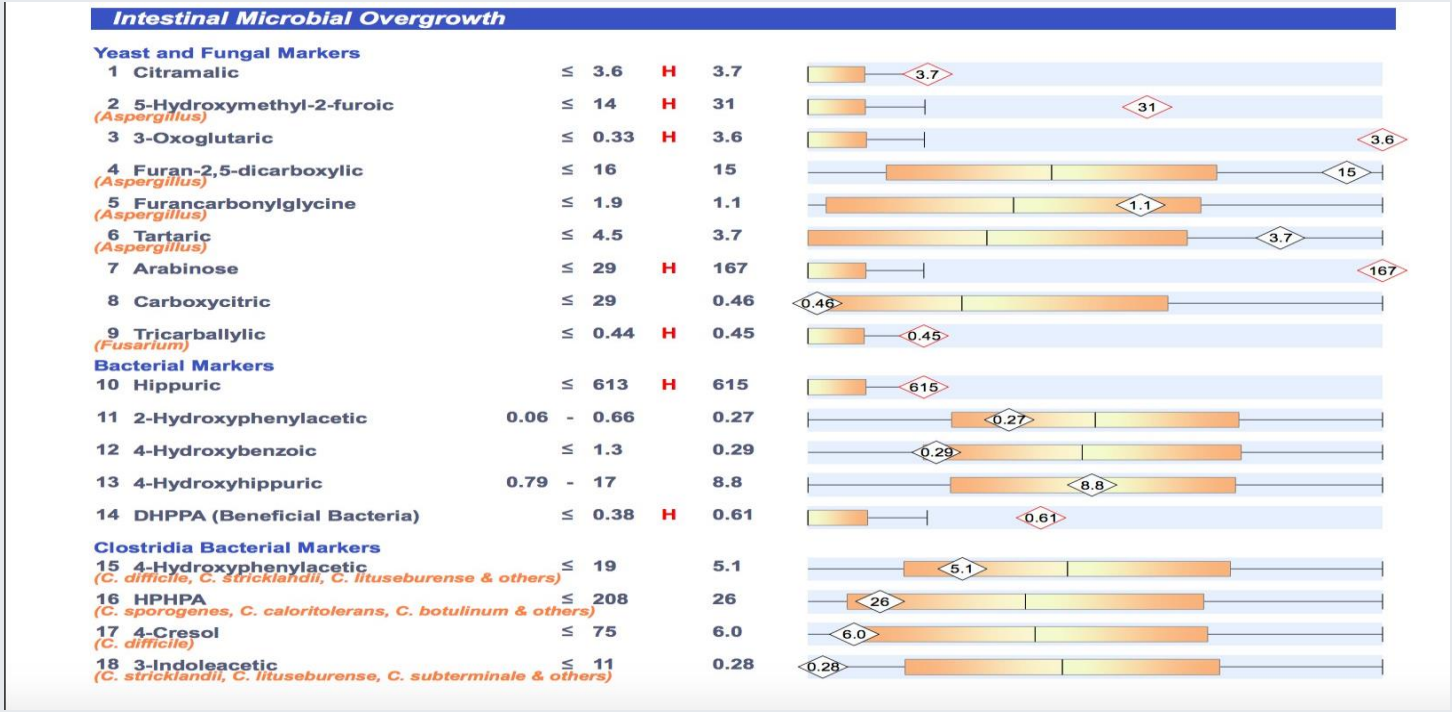


	Baseline	20 Min	40 Min	60 Min	80 Min	100 Min	120 Min	140 Min	160 Min	180 Min
Hydrogen	6	12	20	34	50	39	37	65	39	30
Methane	29	40	43	36	42	39	36	67	45	41
Combined	35	52	63	70	92	78	73	132	84	71
	Small Intestine						Transition	Large Intestine		

Treatment of SIBO

- Antibiotics: Rifaximin, Neomycin
- Herbal Protocols:
  - Candibactin AR, BR
  - Biocidin
  - SIBOtic
  - Rotation Protocol for recurrent SIBO: Allimax, Berberine, ADP, Neem
- Low FODMAP Diet for 6-8 weeks
- Probiotics
- Biofilm Disruptors: Buluoke, Biofilm Phase 2 Advanced, Bismuth
- Digestive Enzymes

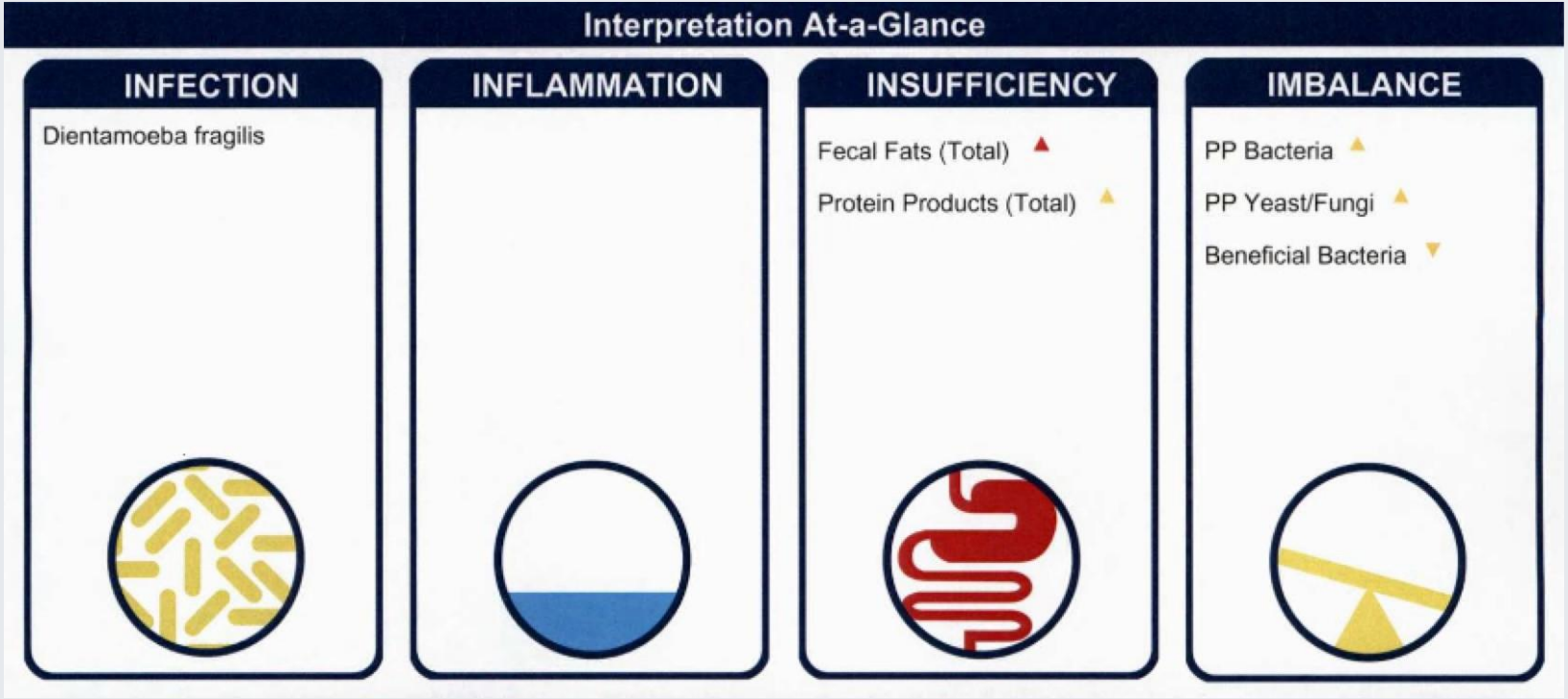
Testing: Organic Acid Testing



Intestinal Microbial Overgrowth

Yeast and Fungal Markers						
1	Citramalic		≤ 3.6	H	3.7	3.7
2	5-Hydroxymethyl-2-furoic (*Aspergillus*)		≤ 14	H	31	31
3	3-Oxoglutaric		≤ 0.33	H	3.6	3.6
4	Furan-2,5-dicarboxylic (*Aspergillus*)		≤ 16		15	15
5	Furancarbonylglycine (*Aspergillus*)		≤ 1.9		1.1	1.1
6	Tartaric (*Aspergillus*)		≤ 4.5		3.7	3.7
7	Arabinose		≤ 29	H	167	167
8	Carboxycitric		≤ 29		0.46	0.46
9	Tricarballylic (*Fusarium*)		≤ 0.44	H	0.45	0.45
Bacterial Markers						
10	Hippuric		≤ 613	H	615	615
11	2-Hydroxyphenylacetic	0.06 -	0.66		0.27	0.27
12	4-Hydroxybenzoic		≤ 1.3		0.29	0.29
13	4-Hydroxyhippuric	0.79 -	17		8.8	8.8
14	DHPPA (Beneficial Bacteria)		≤ 0.38	H	0.61	0.61
Clostridia Bacterial Markers						
15	4-Hydroxyphenylacetic (*C. difficile, C. stricklandii, C. lituseburense & others*)		≤ 19		5.1	5.1
16	HPHPA (*C. sporogenes, C. caloritolerans, C. botulinum & others*)		≤ 208		26	26
17	4-Cresol (*C. difficile*)		≤ 75		6.0	6.0
18	3-Indoleacetic (*C. stricklandii, C. lituseburense, C. subterminale & others*)		≤ 11		0.28	0.28

Testing: GI Effects



Fixing the Gut Dysbiosis

MICROBIOME BALANCE	FUNGAL INFECTIONS	INTESTINAL PERMEABILITY	NUTRITIONAL DEFICIENCIES
• PROBIOTICS • PREBIOTICS • YEAST-TYPE PROBIOTICS • SPORE-FORMING PROBIOTICS	• DIFLUCAN/NYSTATIN • OIL OF OREGANO • CAPRYLIC ACID • CAT'S CLAW • BLACK WALNUT • BERBERINE • UVA URSI • NEEM • SWEET WORMWOOD	• DE-GLYCYRRHIZED LICORICE • SLIPPERY ELM • ALOE VERA • MARSHMALLOW ROOT • PEPPERMINT • GINGER TEA	• GLUTAMINE • ZINC • CoQ10 • B VITAMINS

Low Histamine Diet

Foods to avoid:

- Ripened and fermented foods
- Canned foods and ready meals
- Alcohol
- Matured cheese
- Beans: chickpeas, soybeans, peanuts
- Nuts: walnuts, cashew nuts
- Chocolates
- Strawberries, tomatoes, papaya
- Artificial coloring, artificial sweeteners and preservatives

Anti-inflammatory Diet

Foods to avoid:

- Artificial coloring, artificial sweeteners and preservatives
- Saturated fats
- Refined Carbohydrates
- Processed Meats
- Too much Alcohol
- Matured cheese
- Fried food
- Sugar

- ❖ **Freshly cooked meat and fish**
- ❖ **Organic Foods**
- ❖ **Good quality protein and good quality fat**
- ❖ **Fresh fruits and vegetables in the allowed list**
- ❖ **Hydration**
- ❖ **Avoid wheat when possible**

Specific Carbohydrate Diet (SCD)

Foods to avoid:

- Processed meats
- Milk
- Wheat
- Fermented foods and drinks
- All artificial sweeteners
- Beans
- Starchy vegetables (polysaccharides)

Low FODMAP Diet

Foods to avoid:

Fermentable

- Oligosaccharides
- Disaccharides
- Monosaccharides
- and
- Polyols

Testing: Epworth Sleepiness Scale

Epworth Sleepiness Scale	Never would doze off	Slight chance of dozing	Moderate chance of dozing	High chance of dozing
1. Do you get sleepy, or doze off, while sitting and reading?	0	1	2	3
2. Do you get sleepy, or doze off, while watching TV?	0	1	2	3
3. While sitting or inactive in a public place (meeting, theater)?	0	1	2	3
4. As a passenger in a car for an hour without a break?	0	1	2	3
5. Lying down to rest in the afternoon?	0	1	2	3
6. Sitting and talking to someone?	0	1	2	3
7. Sitting quietly after lunch without alcohol?	0	1	2	3
8. In a car, while stopped for a few minutes at a traffic light?	0	1	2	3
TOTAL SCORE (Sum of all numbers circled above) Score ε 10 suggest patient is at high risk for Obstructive Sleep Apnea				

Testing: Sleep Apnea

Testing: Sleep Apnea

Sleep Study Report

Sleep Summary

Start Study Time:	11:04:17 PM
End Study Time:	07:42:50 AM
Total Study Time:	8 hrs, 38 min
Sleep Time	**8 hrs, 2 min**
% REM of Sleep Time:	22.9

Oxygen Saturation Statistics

Mean: 93 Minimum: 81 Maximum: 99

Mean of Desaturations Nadirs (%): 91

Oxygen Desatur. %:	4-9	10-20	>20	Total
Events Number	219	14	0	233
Total	94.0	6.0	0.0	100.0

Oxygen Saturation:	<90	<88	<85	<80	<70
Duration (minutes):	12.9	2.8	0.8	0.0	0.0
Sleep %	2.7	0.6	0.2	0.0	0.0

Respiratory Indices

	REM	NREM	All Night
pRDI:	48.9	56.7	**54.9**
pAHI:	47.8	52.5	**51.4**
ODI:	34.2	27.5	**29.1**

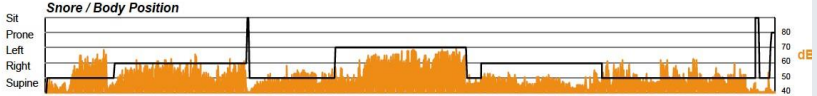
Pulse Rate Statistics during Sleep (BPM)

Mean: 60 Minimum: 43 Maximum: 103

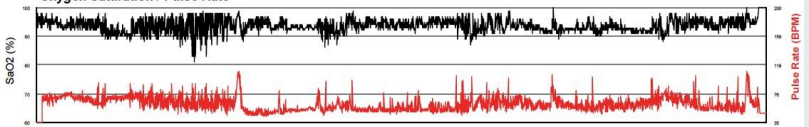
Indices are calculated using valid sleep time of 8 hrs, 1 min.
pRDI/pAHI are calculated using oxi desaturations ≥ 3%

PAT Respiratory Events

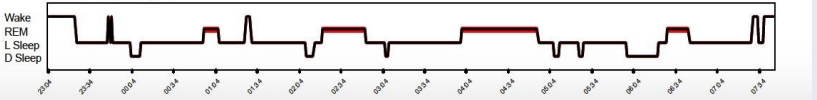
Snore / Body Position



Oxygen Saturation / Pulse Rate



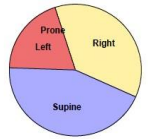
Wake / Sleep stages



Sleep Study Report

Body Position Statistics

Position	Supine	Prone	Right	Left
Sleep (min)	211.3	0.0	177.3	93.5
Sleep %	43.8	0.0	36.8	19.4
pRDI	57.0	N/A	55.2	49.4
pAHI	55.9	N/A	52.5	39.2
ODI	26.5	N/A	38.3	17.3

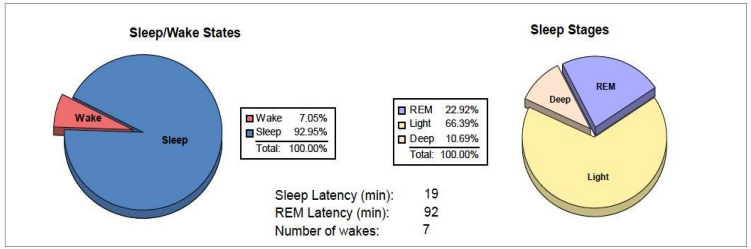


Snoring Statistics

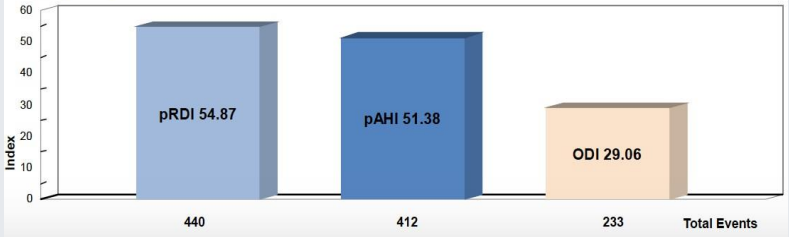
Snoring Level (dB)	>40	>50	>60	>70	>80	>Threshold (45)
Sleep (min)	460.8	151.3	23.8	0.0	0.0	306.8
Sleep %	95.6	31.4	4.9	0.0	0.0	63.6

Mean: 48 dB

Sleep Stages Chart



Respiratory Indices Chart



Treatment of Sleep Apnea

- CPAP machine
- Dental Appliances
- Surgery

Grandriver/Getty Images

Testing: Mast Cell IV Protocol

Mast Cell IV Protocol: 1000 cc 0.9% NS over 2-2.5 hours, as follows:

1. NS for 30 min
2. 30 min after start, administer **Zofran (ondansetren) 4mg** IV push over 60 seconds
3. Restart NS for 30 min
4. 60 min after start, infuse **Diphenhydramine 25 mg diluted in separate 100 ml NS** secondary line, infuse over 15 min (133gtt/min)
5. Continue NS infusion for additional 30 min
6. 105 min after start time, administer **Lorazepam 1 mg** IV SLOW push over 2 minutes
7. Continue NS for additional 30 min
8. 135 min after start time, administer **Ketorolac 30 mg** IV push over 1 min
9. Continue NS infusion until complete

Courtesy of Dr. Tania Dempsey

Testing: Cunningham Panel

Patient Name:
Patient DOB:
Patient ID Number:
Date of Test Report: 01/18/2019

PATIENT REPORT

Submitting Prescriber: Gary Kaplan, DO
Date of Collection: 01/09/2019
Date of Receipt: 01/10/2019

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II[1] (% of baseline)
Patient Result	1:16,000	1:64,000	1:80	1:16,000	156
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	ELEVATED	ELEVATED	NORMAL	ELEVATED	ELEVATED

***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

Testing: Cunningham Panel

Antineuronal Antibodies: the report lists 4 anti-neuronal antibody results which measure circulating levels of autoantibodies directed against specific neuronal antigens, these antigens include:

- Dopamine D_1 receptor (DRD1)
- Dopamine D_{2L} receptor (DRD2L)
- Lysoganglioside-GM1 (LYSO-GM1)
- Tubulin (TUB)

CaM Kinase II: is an enzyme present in neuronal cells and is part of the activation pathway for the production of dopamine

Testing: Immunoglobulin Panel

	Feb 2016	Jan 2017	Apr 2017	Jan 2019	Normal values (mg/dL)
Total IgG (mg/dL)	1001	762	835	920	700-1600
IgG1	466	410	436	430	422-1292
IgG2	349	314	344	347	117-747
IgG3	**21**	**18**	**20**	**18**	**41-129**
IgG4	5	6	5	5	1-291
IgA	175	141		164	90-386
IgM	62	54			20-172
IgE	14	15			0-100 IU/ml

Testing

Sample Date	Parameter	Cut off	Units/ml
11.03.2019	Anti AT1R Antibodies	<10.0 U/ml: negative 10.0-17.0 U/ml: at risk > 17.0 U/ml: positive	13.4 (at risk)
11.03.2019	Anti ETAR Antibodies	<10.0 U/ml: negative 10.0-17.0 U/ml: at risk > 17.0 U/ml: positive	12.8 (at risk)
11.03.2019	*Anti a-1-adrenergic Antibodies*	<7.0 U/ml: negative >7.0 U/ml: positive	16.9 (positive)
11.03.2019	*Anti a-2-adrenergic Antibodies*	<15.0 U/ml: negative >15.0 U/ml: positive	15.9 (positive)
11.03.2019	*Anti ß-1-adrenergic Antibodies*	<15.0 U/ml: negative >15.0 U/ml: positive	22.7 (positive)
11.03.2019	*Anti ß-2-Adrenergic Antibodies*	<8.o U/ml: negative 8.0-14.0 U/ml: at risk >14.0 U/ml: positive	9.5 (at risk)

Addressing the Immune System Manifestations

INNATE

- Low Dose Naltrexone
- Celebrex
- Minocycline
- Palmitoylethanolamide (PEA)
- Acupuncture

MAST CELLS

- IV therapies
- Ketotifen
- H1 Blockers
- H2 Blockers
- Leukotriene
- Cromolyn Sodium
- PEA

ADAPTIVE

- Metformin (mTOR Inhibitor)
- Rapamycin
- IVIg
- Plasmapheresis
- Rituximab
- Exosomes
- Wharton's Jelly
- ?Human Cells and Tissue-based Products (Stem cells)

NUTRITIONAL SUPPLEMENTS

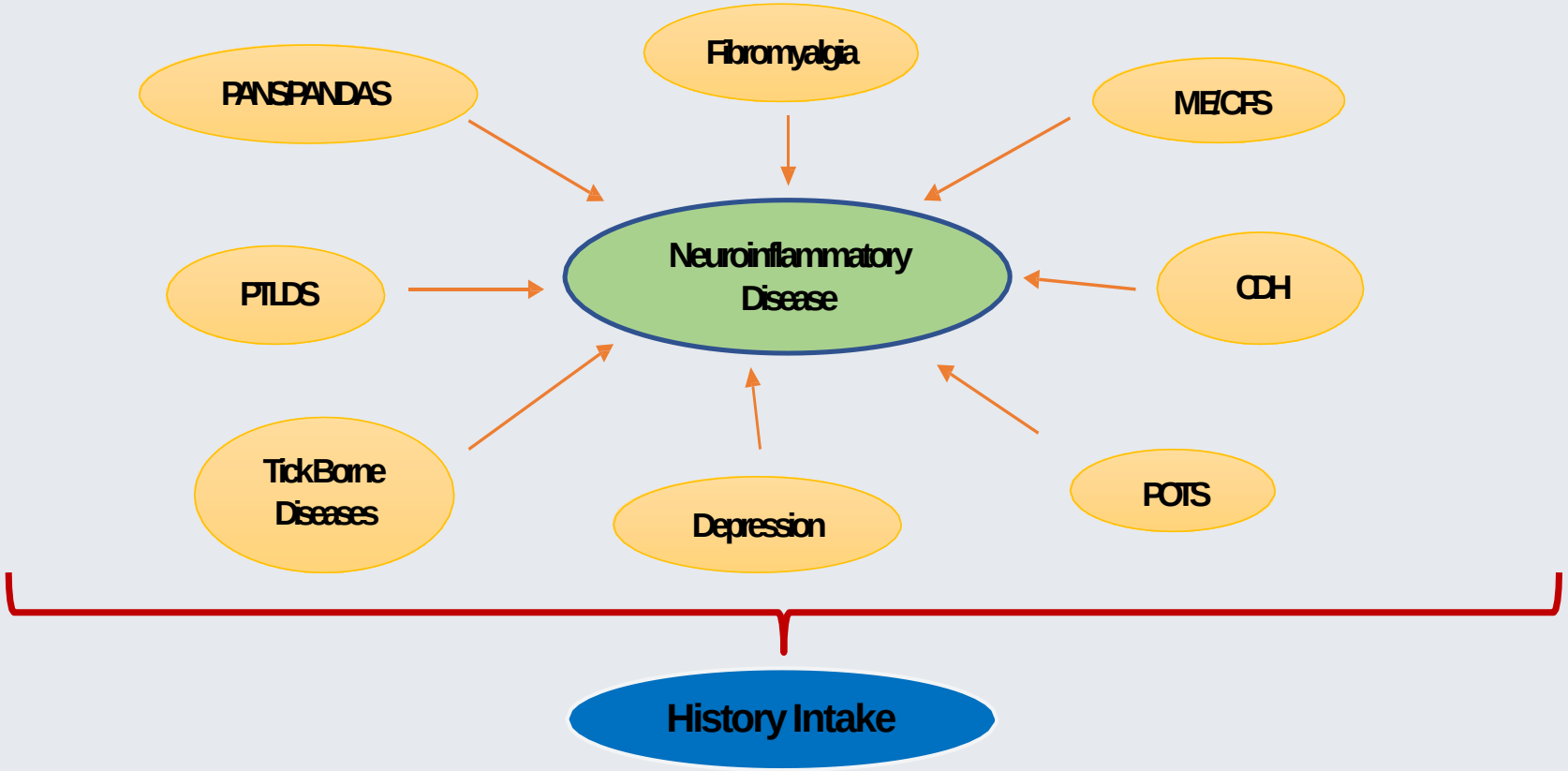
NUTRITIONAL SUPPLEMENTS

- Omega-3 fatty acids: 1.5g – 9g per day
- Vitamin D blood level: 50 – 60 ng/ml
- Liposomal Glutathione: 0.5 -1 tsp twice a day
- NAC: 600 mg TID
- CoQ10: 100 mg – 300 mg TID
- Curcumin: 200 mg QD-BID
- Resveratrol: 500-1,000 mg
- Melatonin: 1 mg – 9 mg a day

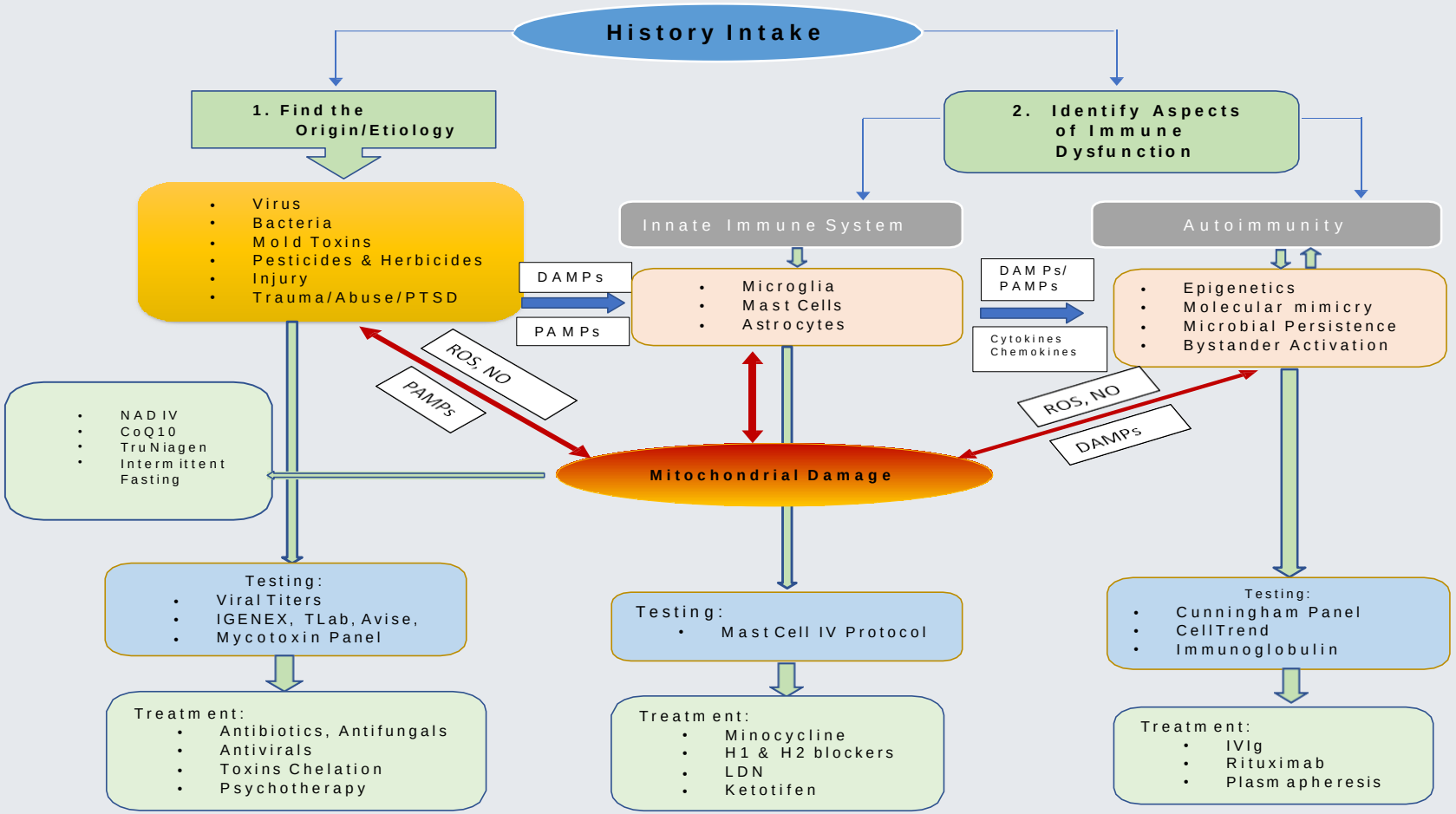
Addressing Mitochondrial Dysfunction

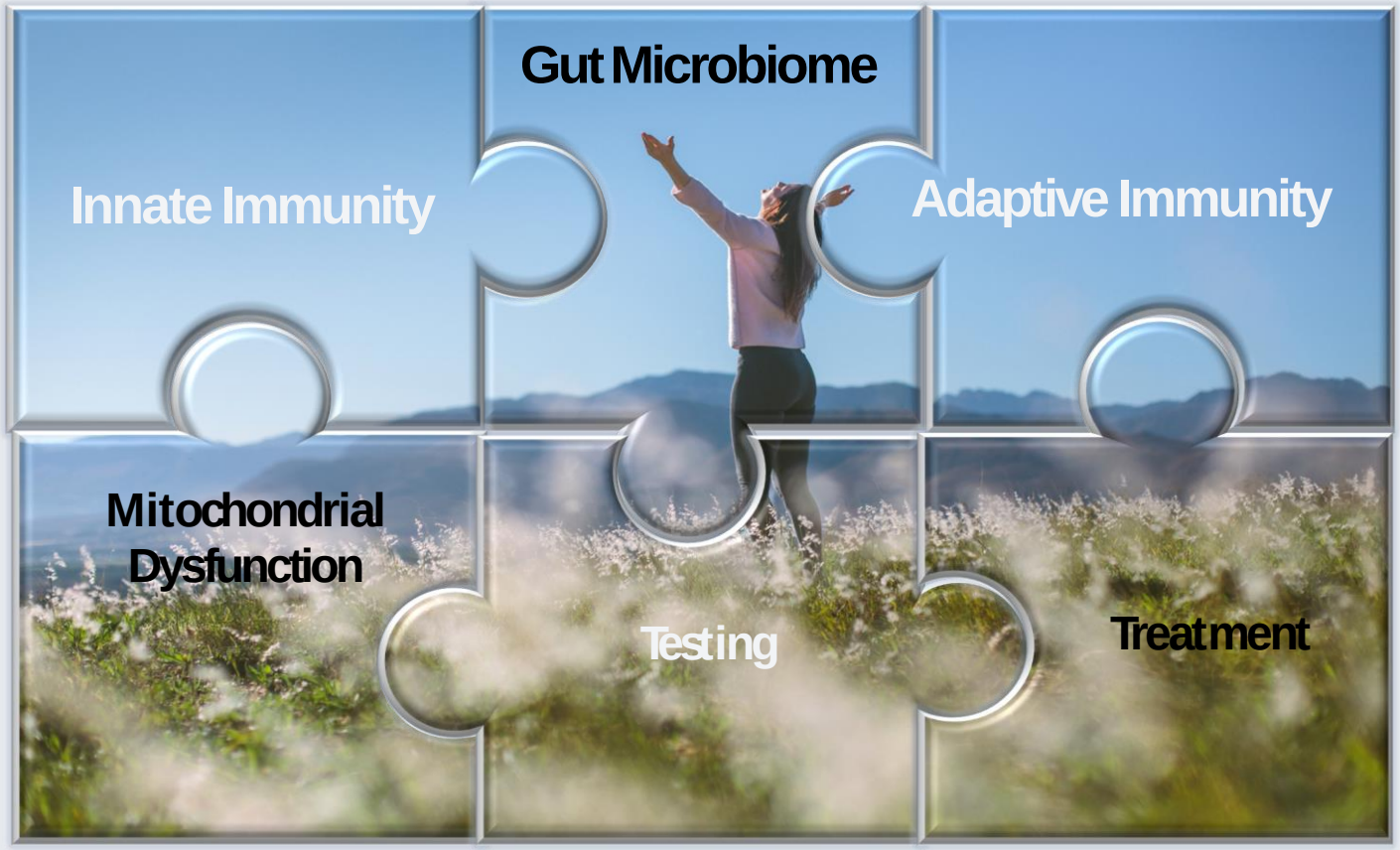
- CoQ10/ UBQH (cannot be taken with Mepron or Malaron): 100-400mg
- D-Ribose
- Acetyl-L-Carnitine: 500- 3000mg
- NAD+ : 300- 1200mg
- Resveratrol 500-1,000 mg
- NMN (Nicotinamide Mononucleotide)
- IV NAD: 6g- ?
- Melatonin 1 mg – 9 mg a day
- Lipid Replacement Therapy (Omega 3)
- Exercise
- Intermittent Fasting

Our Model


PANS/PANDAS
Fibromyalgia
ME/CFS
PTLDS
Neuroinflammatory Disease
CCH
Tick Borne Diseases
Depression
POTS
History Intake

Our Model


History Intake
1. Find the Origin/Etiology
2. Identify Aspects of Immune Dysfunction
Virus
Bacteria
Mold Toxins
Pesticides & Herbicides
Injury
Trauma/Abuse/PTSD
Innate Immune System
Autoimmunity
DAMPs
PAMPs
Microglia
Mast Cells
Astrocytes
DAMPs/ PAMPs
Cytokines Chemokines
Epigenetics
Molecular mimicry
Microbial Persistence
Bystander Activation
ROS, NO
PAMPs
ROS, NO
DAMPs
NAD IV
CoQ10
TruNiagen
Intermittent Fasting
Mitochondrial Damage
Testing:
Viral Titers
IGENEX, TLab, Avise,
Mycotoxin Panel
Testing:
Mast Cell IV Protocol
Testing:
Cunningham Panel
CellTrend
Immunoglobulin
Treatment:
Antibiotics, Antifungals
Antivirals
Toxins Chelation
Psychotherapy
Treatment:
Minocycline
H1 & H2 blockers
LDN
Ketotifen
Treatment:
IVIg
Rituximab
Plasmapheresis


Gut Microbiome
Innate Immunity
Adaptive Immunity
Mitochondrial Dysfunction
Testing
Treatment

"All models are flawed, but some are useful"

George E.P. BOX

I kindly thank you for your attention.

Dr. Gary Kaplan, D.O. DABFM, DABPM, FAAMA
Medical Director, Kaplan Center for Integrative Medicine
Clinical Associate Professor, Georgetown University School of Medicine
Author, Total Recovery: Breaking the Cycle of Chronic Pain and Depression

References

1 Gaskin, D.J., & Richard, P. (2012). The economic costs of pain in the United States. Journal of Pain, 13(8), 715-724. doi:10.1016/j.jpain.2012.03.009
2Grace, P.M., Hutchinson, M.R., Maier, S.F., & Watkins, L.R. (2014). Pathological pain and the neuroimmune interface. Nature Reviews Immunology, 14, 217–231. doi:10.1038/nri3621
3- Dahan, S., Tomljenovic, L., & Shoenfeld, Y. (2016). Postural Orthostatic Tachycardia Syndrome (POTS)– A novel member of the autoimmune family. Lupus, 25(4), 339–342. https://doi.org/10.1177/0961203316629558
4Arnow, B.A., Blasey, C.M., Lee, J., Fireman, B., Hunkeler E.M., Dea, R., …Hayward, C. (2009). Relationships among depression, chronic pain, chronic disabling pain, and medical costs. Psychiatric Services, 60(3), 344-350. doi:10.1176/appi.ps.60.3.344
5Arnow, B.A., Hunkeler E.M., Blasey, C.M., Lee, J., Constantino, M.J., Fireman, B., Hayward, C. (2006). Comorbid depression, chronic pain and disability in primary care. Psychosomatic Medicine, 68, 262-268. doi:10.1097/01.psy.0000204851.15499.fc
6 Bair, M.J., Robinson, R.L., Eckert, G.J., Stang, P.E., Croghan, T.W., & Kroenke, K. (2004). Impact of pain on depression treatment response in primary care. Psychosomatic Medicine, 66(1), 17-22. doi:10.1097/01.psy.0000106883.94059.c5
7 Bair, M.J., Robinson, R.L., Katon, W., & Kroenke, K. (2003) Depression and pain comorbidity: A literature review. Archives of Internal Medicine, 163(20), 433-445. doi:10.1001/archinte.163.20.2433
8Bair, M.J., Wu, J., Damush, T.M., Sutherland, J.M., & Kroenke, K. (2008) Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosomatic Medicine, 70(8), 890-897. doi:10.1097/PSY.0b013e318185c510
9 Centers for Disease Control and Prevention. (2011). 47.5 million U.S. adults report a disability; arthritis remains most common cause. Retrieved from CDC http://www.cdc.gov/features/dsadultdisabilitycauses
10 https://www.cdc.gov/arthritis/basics/fibromyalgia.htm
11 http://www.fmaware.org/about-fibromyalgia/prevalence/
12 http://pandasnetwork.org/statistics/
13Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13(7):533–548. doi:10.1038/nrd4334
14- Hurley LL, Tizabi Y. Neuroinflammation, neurodegeneration, and depression. Neurotox Res. 2013;23(2):131–144. doi:10.1007/s12640-012-9348-1
15Young, T. L., Zychowski, K. E., Denson, J. L., & Campen, M. J. (2019). Blood-brain barrier at the interface of air pollution-associated neurotoxicity and neuroinflammation. Role of Inflammation in Environmental Neurotoxicity, 3, 295
16 DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. J Neurochem. 2016;139 Suppl 2(Suppl 2):136–153. doi:10.1111/jnc.13607
17Kipnis, J., Filiano, A. The central nervous system: privileged by immune connections. *Nat Rev Immunol* **18,** 83–84 (2018). https://doi.org/10.1038/nri.2017.152
18- Graeber, M.B. (2010). Changing face of microglia. Science, 330(6005), 783-788. doi:10.1126/science.1190929
19 Graeber, M.B., & Streit, W.J. (2009). Microglia: Biology and pathology. Acta Neuropathologica, 119(1), 89-105. doi:10.1007/s00401-009-0622-0
20 kraft, a.d., & harry, g.j. (2011). features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. international journal of environmental research & public health, 8(7), 2980-3018. doi:10.3390/ijerph8072980
21robinson, m.e., craggs, j.g., price, d.d., perlstein, w.m., & staud, r. (2011). gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. journal of pain, 12(4), 436-443. doi:10.1016/j.jpain.2010.10.003
22 Grace, P.M., Hutchinson, M.R., Maier, S.F., & Watkins, L.R. (2014). Pathological pain and the neuroimmune interface. Nature Reviews Immunology, 14, 217–231. doi:10.1038/nri3621
23 Walker, A.K., Kavelaars, A., Heijnen, C.J., & Dantzer, R. (2014). Neuroinflammation and comorbidity of pain and depression. Pharmacological Reviews, 66(1), 80-101. doi:10.1124/pr.113.008144
24Walters, E.T. (2014). Neuroinflammatory contributions to pain after SCI: Roles for central glial mechanisms and nociceptor-mediated host defense. Experimental Neurology, 258, 48-61. doi:10.1016/j.expneurol.2014.02.001

References

25 Arne;, Herwald, Heiko; Egesten,. 2016. On PAMPs and DAMPs., Journal of innate immunity, 8(5), 427 - 428. (ISSN: 1662-811X) PMID: 27522675
26Tang, D., Kang, R., Coyne, C. B., Zeh, H. J., & Lotze, M. T. (2012). PAMPs and DAMPs: Signal 0s that Spur Autophagy and Immunity. Immunological Reviews, 249(1), 158–175. http://doi.org/10.1111/j.1600-065X.2012.01146.x
PMCID: PMC3662247
27Hinwood, M., Morandini, J., Day, T.A., & Walker, F.R. (2012). Evidence that microglia mediate the neurobiological effects of chronic psychological stress on the medial prefrontal cortex. Cerebral Cortex, 22(6), 1442-1454. doi:10.1093/cercor/bhr229
28 Jurgens, H.A., & Johnson, R.W. (2012). Dysregulated neuronal-microglial cross-talk during aging, stress and inflammation. Experimental Neurology, 233(1), 40-48. doi:10.1016/j.expneurol.2010.11.014
29püntener, u., booth, s.g., perry, v.h., & teeling, j.l. (2012). long-term impact of systemicbacterial infection on the cerebral vasculature and microglia. journal of neuroinflammation, 9, 146. doi:10.1186/1742-2094-9-146
30rock, r.b., gekker, g., hu, s., sheng, w.s., cheeran, m., lokensgard, j.r., & peterson, p.k. (2004). role of microglia in central nervous system infections. clinical microbiology reviews, 17(4), 942-964. doi:10.1128/cmr.17.4.942-964.2004
31Nathalie;, Vasile, Flora; Dossi, Elena; Rouach,. 2017. Human astrocytes: structure and functions in the healthy brain., Brain structure & function. (ISSN: 1863-2653).
PMID: 28280934
32 Sofroniew, M. V., & Vinters, H. V. (2010). Astrocytes: biology and pathology. Acta Neuropathologica, 119(1), 7–35. http://doi.org.proxy.library.georgetown.edu/10.1007/s00401-009-0619-8
33 Ji, R.-R., Berta, T., & Nedergaard, M. (2013). Glia and pain: Is chronic pain a gliopathy? Pain, 154(0 1), S10–S28. http://doi.org.proxy.library.georgetown.edu/10.1016/j.pain.2013.06.02
34 Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology (K;, Saijo, Kaoru; Glass, Christopher. 2011. Microglial cell origin and phenotypes in health and disease., *Nature reviews. Immunology,* 11(11), 775 - 787. (ISSN: 1474-1733), copyright (2011)
35Skaper, S. D., & Facci, L. (2012). Mast cell–glia axis in neuroinflammation and therapeutic potential of the anandamide congener palmitoylethanolamide. Philosophical Transactions of the Royal Society B: Biological Sciences, 367(1607), 3312–3325. http://doi.org.proxy.library.georgetown.edu/10.1098/rstb.2011.0391
PMCID: PMC3481533
36 Theoharides, T. C., Alysandratos, K.-D., Angelidou, A., Delivanis, D.-A., Sismanopoulos, N., Zhang, B., …Kalogeromitros, D. (2012). Mast cells and inflammation. Biochimica et Biophysica Acta, 1822(1), 21–33. http://doi.org.proxy.library.georgetown.edu/10.1016/j.bbadis.2010.12.014
PMCID: PMC3318920
37 Greeley, C. S., & Karst, W. A. (2013). Mast Cells in the Human Dura: Effects of Age and Dural Bleeding (letter). Child's Nervous System : ChNS : Official Journal of the International Society for Pediatric Neurosurgery, 29(11), 10.1007/s00381–013–2275–5. http://doi.org.proxy.library.georgetown.edu/10.1007/s00381-013-2275-5
38 Skaper, S. D., Facci, L., & Giusti, P. (2014). Mast cells, glia and neuroinflammation: partners in crime? Immunology, 141(3), 314–327. http://doi.org.proxy.library.georgetown.edu/10.1111/imm.12170
PMCID: PMC3930370
39Yoshida, G. J. (2015). Mast Cells, Mastocytosis, and Related Disorders. The New England Journal Of Medicine, 373(19), 1884-1885. doi:10.1056/NEJMc1510021#SA2 PMID: 26154789
40- Aich, A.; Afrin, L.B.; Gupta, K. Mast Cell-Mediated Mechanisms of Nociception. Int. J. Mol. Sci. 2015, 16, 29069-29092. , PMC4691098
41 Laura;, Skaper, Stephen. D.; Giusti, Pietro; Facci,. 2012. Microglia and mast cells: two tracks on the road to neuroinflammation., The FASEB journal, 26(8), 3103 - 3117. (ISSN: 0892-6638).
42 Skaper, S. D., Facci, L., & Giusti, P. (2014). Mast cells, glia and neuroinflammation: partners in crime? Immunology, 141(3), 314–327. http://doi.org.proxy.library.georgetown.edu/10.1111/imm.12170
43Chatterjea, D., & Martinov, T. (2015). Mast cells: versatile gatekeepers of pain. Molecular Immunology, 63(1), 38–44. http://doi.org.proxy.library.georgetown.edu/ 10.1016/j.molimm.2014.03.001
44- Theoharides, Theoharis.. 2017. Neuroendocrinology of mast cells: Challenges and controversies., Experimental dermatology. (ISSN: 0906-6705).
45 Dráber, P.; Lagunowich, LA; Dráberová, E.; Viklický, V.; Damjanov,. 1988. Heterogeneity of tubulin epitopes in mouse fetal tissues., Histochemistry (Berlin), 89(5), 485 - 492. (ISSN: 0301-5564).
46 *Mindaltering microorganisms: the impact of the gut microbiota on brain and behaviour © 2012 Nature Publishing Group. Used with permission from Macmillan Publishers* Ltd: [Nature Reviews Neuroscience], Cryan, J. F., & Dinan, T. G. (2012, October). Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nature Reviews Neuroscience, 13*, 701-712. doi:10.1038/nrn3346, copyright 2012.

References

47Bischoff, S. C., Barbara, G., Buurman, W., Ockhuizen, T., Schulzke, J.-D., Serino, M., …Wells, J. M. (2014). Intestinal permeability – a new target for disease prevention and therapy. BMC Gastroenterology, 14, 189. http://doi.org.proxy.library.georgetown.edu/10.1186/s12876-014-0189-7

48 Erratum. (2016). Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology, 29(2), 240.

49Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology, 28(2), 203–209.

50 97- DeGruttola, A. K., Low, D., Mizoguchi, A., & Mizoguchi, E. (2016). Current understanding of dysbiosis in disease in human and animal models. Inflammatory Bowel Diseases, 22(5), 1137–1150. http://doi.org.proxy.library.georgetown.edu/10.1097/MIB.0000000000000750

51Engen, P. A., Green, S. J., Voigt, R. M., Forsyth, C. B., & Keshavarzian, A. (2015). The Gastrointestinal Microbiome: Alcohol Effects on the Composition of Intestinal Microbiota. Alcohol Research : Current Reviews, 37(2), 223–236.

52Bischoff, S. C., Barbara, G., Buurman, W., Ockhuizen, T., Schulzke, J.-D., Serino, M., …Wells, J. M. (2014). Intestinal permeability – a new target for disease prevention and therapy. BMC Gastroenterology, 14, 189. http://doi.org.proxy.library.georgetown.edu/10.1186/s12876-014-0189-7

53M. Vázquez, D. Vélez, V. Devesa, In vitro evaluation of inorganic mercury and methylmercury effects on the intestinal epithelium permeability, Food and Chemical Toxicology, Volume 74, December 2014, Pages 349-359, ISSN 0278-6915, https://doi.org/10.1016/j.fct.2014.10.022.

54Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans [published correction appears in Science. 2018 May 4;360(6388):]. *Science*. 2018;359(6380):1156–1161. doi:10.1126/science.aar7201

55 Rieder, Ryan; Wisniewski, Paul J; Alderman, Brandon L; Campbell, Sara. 2017. Microbes and mental health: A review., *Brain, behavior, and immunity*. (ISSN: 0889-1591)

56Rea, K., Dinan, T. G., & Cryan, J. F. (2016). The microbiome: A key regulator of stress and neuroinflammation. Neurobiology of Stress, 4, 23–33. http://doi.org.proxy.library.georgetown.edu/10.1016/j.ynstr.2016.03.001

57Ghaisas, S., Maher, J., & Kanthasamy, A. (2016). Gut microbiome in health and disease: linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. Pharmacology & Therapeutics, 158, 52–62. http://doi.org.proxy.library.georgetown.edu/10.1016/j.pharmthera.2015.11.012

58Sokovic, M., Ciric, A., Glamoclija, J., Skaltsa, H.,. Biological Activities of Sesquiterpene Lactones Isolated from the Genus Centaurea L. (Asteraceae),Current Pharmaceutical Design, volume 23, issue , pages 1-20, year 2017, issn 1381-6128/1873-4286, doi 10.2174/1381612823666170215113927

59Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B. and Cryan, J. F. (2016), Stress and the Microbiota–Gut–Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. CNS Neurosci Ther, 22: 102–117. doi:10.1111/cns.12490

60 Petra, A. I., Panagiotidou, S., Hatziagelaki, E., Stewart, J. M., Conti, P., & Theoharides, T. C. (2015). Gut-microbiota-brain axis and effect on neuropsychiatric disorders with suspected immune dysregulation. Clinical Therapeutics, 37(5), 984–995. http://doi.org.proxy.library.georgetown.edu/10.1016/j.clinthera.2015.04.002

61 Rieder, Ryan; Wisniewski, Paul J; Alderman, Brandon L; Campbell, Sara. 2017. Microbes and mental health: A review., Brain, behavior, and immunity. (ISSN: 0889-1591)

62Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B. and Cryan, J. F. (2016), Stress and the Microbiota–Gut–Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. CNS Neurosci Ther, 22: 102–117. doi:10.1111/cns.12490

63 Dai, Y., Wang, H., Wang, X., Kaye, A., Sun, Y.,. Potential Beneficial Effects of Probiotics on Human Migraine Headache: A Literature Review. Pain Physician. 2017 Feb;20(2):E251-E255.

References

64Cámara-Lemarroy, C. R., Rodriguez-Gutierrez, R., Monreal-Robles, R., & Marfil-Rivera, A. (2016). Gastrointestinal disorders associated with migraine: A comprehensive review. World Journal of Gastroenterology, 22(36), 8149–8160. http://doi.org.proxy.library.georgetown.edu/10.3748/wjg.v22.i36.8149
65Autoimmunity and Autoimmune Disease. https://pathology.jhu.edu/autoimmune/definitions
66- Immune System in health and disease, From Bellanti,JA: Immunology IV: (2010)
67Chen, S. J., Wang, Y. L., Fan, H. C., Lo, W. T., Wang, C. C., & Sytwu, H. K. (2012). Current status of the immunomodulation and immunomediated therapeutic strategies for multiple sclerosis. Clin developmental immunology, 2012, 970789. doi:10.1155/2012/970789
68Haapakoski, R., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2016). Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. Progress in neuro-psychopharmacology & biological psychiatry, 66, 63–72. doi:10.1016/j.pnpbp.2015.11.012
69Schetters, S., Gomez-Nicola, D., Garcia-Vallejo, J. J., & Van Kooyk, Y. (2018). Neuroinflammation: Microglia and T Cells Get Ready to Tango. Frontiers in immunology, 8, 1905. doi:10.3389/fimmu.2017.01905
70 Autoimmune Encephalopathy, Caselli, Richard J. et al. Mayo Clinic Proceedings, Volume 85, Issue 10, 878 – 880
71Kayser, M. S., & Dalmau, J. (2011). The emerging link between autoimmune disorders and neuropsychiatric disease. The Journal of neuropsychiatry and clinical neurosciences, 23(1), 90–97. doi:10.1176/appi.neuropsych.23.1.90
72 https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/92116
73Oldstone M. B. (2014). Molecular mimicry: its evolution from concept to mechanism as a cause of autoimmune diseases. Monoclonal antibodies in immunodiagnosis and immunotherapy, 33(158–165. doi:10.1089/mab.2013.0090
74Tempera, Italo, and Paul M. Lieberman. "Epigenetic regulation of EBV persistence and oncogenesis." Seminars in cancer biology. Vol. 26. Academic Press, 2014.
75- Milavetz, Barry I., and Lata Balakrishnan. "Viral epigenetics." Cancer Epigenetics. Humana Press, New York, NY, 2015. 569-596.
76 Fujinami, Robert S., et al. "Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease." Clinical microbiology reviews 19.1 (2006): 80-94.
77Oldstone, M. B. A. "Molecular mimicry, microbial infection, and autoimmune disease: evolution of the concept." Molecular Mimicry: Infection-Inducing Autoimmune Disease. Springer, Berlin, Heidelberg, 2005. 1-17.
78Cunningham MW. Molecular Mimicry, Autoimmunity, and Infection: The Cross-Reactive Antigens of Group A Streptococci and their Sequelae. Microbiol Spectr. 2019;7(4):10.1128/microbiolspec.GPP3-0045-2018. doi:10.1128/microbiolspec.GPP3-0045-2018
79Naviaux RK. Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. Biology (Basel). 2019;8(2):27. Published 2019 May 11. doi:10.3390/biology802002
80- Naviaux, Robert K. "Metabolic features of the cell danger response." Mitochondrion 16 (2014): 7-17.
81 Campbell, Graham, and Don J. Mahad. "Mitochondrial dysfunction and axon degeneration in progressive multiple sclerosis." FEBS letters 592.7 (2018): 1113-1121.
82Weinberg, S.E., Singer, B.D., Steinert, E.M. *et al.* Mitochondrial complex III is essential for suppressive function of regulatory T cells. *Nature* **565,** 495–499 (2019). https://doi.org/10.1038/s41586- 018-0846-z
83Bystander Activation and Autoimmunity. Pacheco Y1, Acosta-Ampudia Y1, Monsalve DM1, Chang C2, Gershwin ME3, Anaya JM4. J Autoimmun. 2019 Sep;103:102301. doi: 10.1016/j.jaut.2019.06.012. Epub 2019 Jul 17

84Aaron LA, Herrell R, Ashton S, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001;16(1):24–31. doi:10.1111/j.1525-1497.2001.03419.x
85Larkin, D., & Martin, C. R. (2017). The interface between chronic fatigue syndrome and depression: A psychobiological and neurophysiological conundrum. Neurophysiologie Clinique/Clinical Neurophysiology, 47(2), 123-129.
86 Raj, V., Opie, M., & Arnold, A. C. (2018). Cognitive and psychological issues in postural tachycardia syndrome. Autonomic Neuroscience, 215, 46-55.
87 Anderson, J. W., Lambert, E. A., Sari, C. I., Dawood, T., Esler, M. D., Vaddadi, G., & Lambert, G. W. (2014). Cognitive function, health-related quality of life, and symptoms of depression and anxiety sensitivity are impaired in patients with the postural orthostatic tachycardia syndrome (POTS). Frontiers in physiology, 5, 230.
88Noyes, A. M., & Kluger, J. (2015). A tale of two syndromes: Lyme disease preceding postural orthostatic tachycardia syndrome. Annals of Noninvasive Electrocardiology, 20(1), 82-86.
89- Hassett, A. L., Radvanski, D. C., Buyske, S., Savage, S. V., Gara, M., Escobar, J. I., & Sigal, L. H. (2008). Role of psychiatric comorbidity in chronic Lyme disease. Arthritis Care & Research, 59(12), 1742-1749.
90 Lichtenstein, A., Tiosano, S., & Amital, H. (2018). The complexities of fibromyalgia and its comorbidities. Current opinion in rheumatology, 30(1), 94-100.
91 Fitzcharles, M. A., Perrot, S., & Häuser, W. (2018). Comorbid fibromyalgia: a qualitative review of prevalence and importance. European Journal of Pain, 22(9), 1565-1576.
92Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity: A Literature Review. Arch Intern Med. 2003;163(20):2433–2445. doi:10.1001/archinte.163.20.2433
93- Anjum, I., Sohail, W., Hatipoglu, B., & Wilson, R. (2018). Postural Orthostatic Tachycardia Syndrome and Its Unusual Presenting Complaints in Women: A Literature Minireview. Cureus, 10(4), e2435. https://doi.org/10.7759/cureus.2435
94 Chemali, K., & Mc Neeley, K. (2014). Co-Morbidities of Neuropathic Postural Orthostatic Tachycardia Syndrome and of the Autonomic Neuropathies (P1. 093).
95Staud, Roland. (2009). Autonomic dysfunction in fibromyalgia syndrome: Postural orthostatic tachycardia. Current rheumatology reports. 10. 463-6. 10.1007/s11926-008-0076-8.
96- Gracely, R. H., Ceko, M., & Bushnell, M. C. (2012). Fibromyalgia and depression. Pain research and treatment, 2012, 486590. https://doi.org/10.1155/2012/486590
97Bernik, M., Sampaio, T. P., & Gandarela, L. (2013). Fibromyalgia comorbid with anxiety disorders and depression: combined medical and psychological treatment. Current pain and headache reports, 17(9), 358
98 Mariman, A., Delesie, L., Tobback, E., Hanoulle, I., Sermijn, E., Vermeir, P., ... & Vogelaers, D. (2013). Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. Journal of psychosomatic research, 75(5), 491-496.
99Hudson, J. I., Goldenberg, D. L., Pope Jr, H. G., Keck Jr, P. E., & Schlesinger, L. (1992). Comorbidity of fibromyalgia with medical and psychiatric disorders. The American journal of medicine, 92(4), 363-367.
100Keskindag, B., & Karaaziz, M. (2017). The association between pain and sleep in fibromyalgia. Saudi medical journal, 38(5), 465–475. https://doi.org/10.15537/smj.2017.5.17864
101- Bucourt, E., Martaillé, V., Goupille, P., Joncker-Vannier, I., Huttenberger, B., Réveillère, C., & Mulleman, D. (2019). A Comparative Study of Fibromyalgia, Rheumatoid Arthritis, Spondyloarthritis, and Sjögren's Syndrome; Impact of the Disease on Quality of Life, Psychological Adjustment, and Use of Coping Strategies. Pain Medicine.
102- Chelimsky, G., Kovacic, K., Nugent, M., Mueller, A., Simpson, P., & Chelimsky, T. C. (2015). Comorbid conditions do not differ in children and young adults with functional disorders with or without postural tachycardia syndrome. The Journal of pediatrics, 167(1), 120-124.
103- Chang, M. H., Hsu, J. W., Huang, K. L., Su, T. P., Bai, Y. M., Li, C. T., ... & Chen, M. H. (2015). Bidirectional association between depression and fibromyalgia syndrome: a nationwide longitudinal study. The Journal of Pain, 16(9), 895-902.

Favero, G., Bonomini, F., Franco, C., & Rezzani, R. (2019). Mitochondrial Dysfunction in Skeletal Muscle of a Fibromyalgia Model: The Potential Benefits of Melatonin. International journal of molecular sciences, 20(3), 765. https://doi.org/10.3390/ijms20030765

104Castro-Marrero, J., Faro, M., Aliste, L., Sáez-Francàs, N., Calvo, N., Martínez-Martínez, A., ... & Alegre, J. (2017). Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: a nationwide population-based cohort study. Psychosomatics, 58(5), 533-543

105 Cook Jr, G. A., & Sandroni, P. (2018). Management of headache and chronic pain in POTS. Autonomic Neuroscience, 215, 37-45.

106Bucourt, E., Martaillé, V., Goupille, P., Joncker-Vannier, I., Huttenberger, B., Réveillère, C., & Mulleman, D. (2019). A Comparative Study of Fibromyalgia, Rheumatoid Arthritis, Spondyloarthritis, and Sjögren's Syndrome; Impact of the Disease on Quality of Life, Psychological Adjustment, and Use of Coping Strategies. Pain Medicine.

107Walker, M. E., Hatfield, J. K., & Brown, M. A. (2012). New insights into the role of mast cells in autoimmunity: evidence for a common mechanism of action?. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1822(1), 57-65.

108 Galland L. (2014). The gut microbiome and the brain. Journal of medicinal food, 17(12), 1261–1272. https://doi.org/10.1089/jmf.2014.7000

109Fung, T. C., Olson, C. A., & Hsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. Nature neuroscience, 20(2), 145–155. https://doi.org/10.1038/nn.4476

110 Bansal, Y., & Kuhad, A. (2016). Mitochondrial Dysfunction in Depression. Current neuropharmacology, 14(6), 610–618. https://doi.org/10.2174/1570159x14666160229114755

111Peacock, B. N., Gherezghiher, T. B., Hilario, J. D., & Kellermann, G. H. (2015). New insights into Lyme disease. Redox biology, 5, 66–70. https://doi.org/10.1016/j.redox.2015.03.002

112- Sobral, M. M. C., Faria, M. A., Cunha, S. C., & Ferreira, I. M. (2018). Toxicological interactions between mycotoxins from ubiquitous fungi: Impact on hepatic and intestinal human epithelial cells. Chemosphere, 202, 538-548.

113- Hope, J. (2013). A review of the mechanism of injury and treatment approaches for illness resulting from exposure to water-damaged buildings, mold, and mycotoxins. The Scientific World Journal, 2013.

114- Ratnaseelan, A. M., Tsilioni, I., & Theoharides, T. C. (2018). Effects of mycotoxins on neuropsychiatric symptoms and immune processes. Clinical therapeutics.

115- Council for Agricultural Science. (2003). Mycotoxins: Risks in plant, animal, and human systems (No. 139). Council for Agricultural.

116 Kerr, J. R. (2019). Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. Journal of clinical pathology, jclinpath-2019.

117Coughlin, J. M., Yang, T., Rebman, A. W., Bechtold, K. T., Du, Y., Mathews, W. B., Lesniak, W. G., Mihm, E. A., Frey, S. M., Marshall, E. S., Rosenthal, H. B., Reekie, T. A., Kassiou, M., Dannals, R. F., Soloski, M. J., Aucott, J. N., & Pomper, M. G. (2018). Imaging glial activation in patients with post-treatment Lyme disease symptoms: a pilot study using [11C]DPA-713 PET. Journal of neuroinflammation, 15(1), 346. https://doi.org/10.1186/s12974-018-1381-4

118 https://www.itamar-medical.com/