The Post-Pandemic Hangover: Dealing with The Physical and Mental Consequences

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OAND Fall 2023

The Final Wave : Stats

- Original studies released Jan 2020 showed that 1 in 10 people infected become long haulers.

Nature Medicine 2020:26;1803

- Studies released March 2021 showed numbers are now 1 in 4 people.
- 33% of patients did not need to be hospitalized to develop LHS.

MedRxiv, Mar 2021https://doi.org/10.1101/2021.03.03.21252086

The Final Wave : Stats

- As of the start of 2023, 45% of COVID survivors, regardless of hospitalization status have gone on to experience at least one unresolved symptoms for 4 months or longer post infection.

Lancet Jan 2023, vol 55, 101762

- “Reinfected people are twice as likely to die and 3 times as likely to be hospitalized with COVID than those infected only once, regardless of their vaccination status.”

Scientific American Feb 2023

People at a loss!

- The majority of Long Haulers test negative for the virus 3 weeks after the onset of the viral infection.
- According to the CDC there is nothing specific to test for lasting post viral symptoms.
- There doesn’t appear to be a difference in those who have different variants of the virus.

UC Davis Health

Post Viral Syndrome

- Symptoms that occur for weeks, months or years after the resolution of the infection

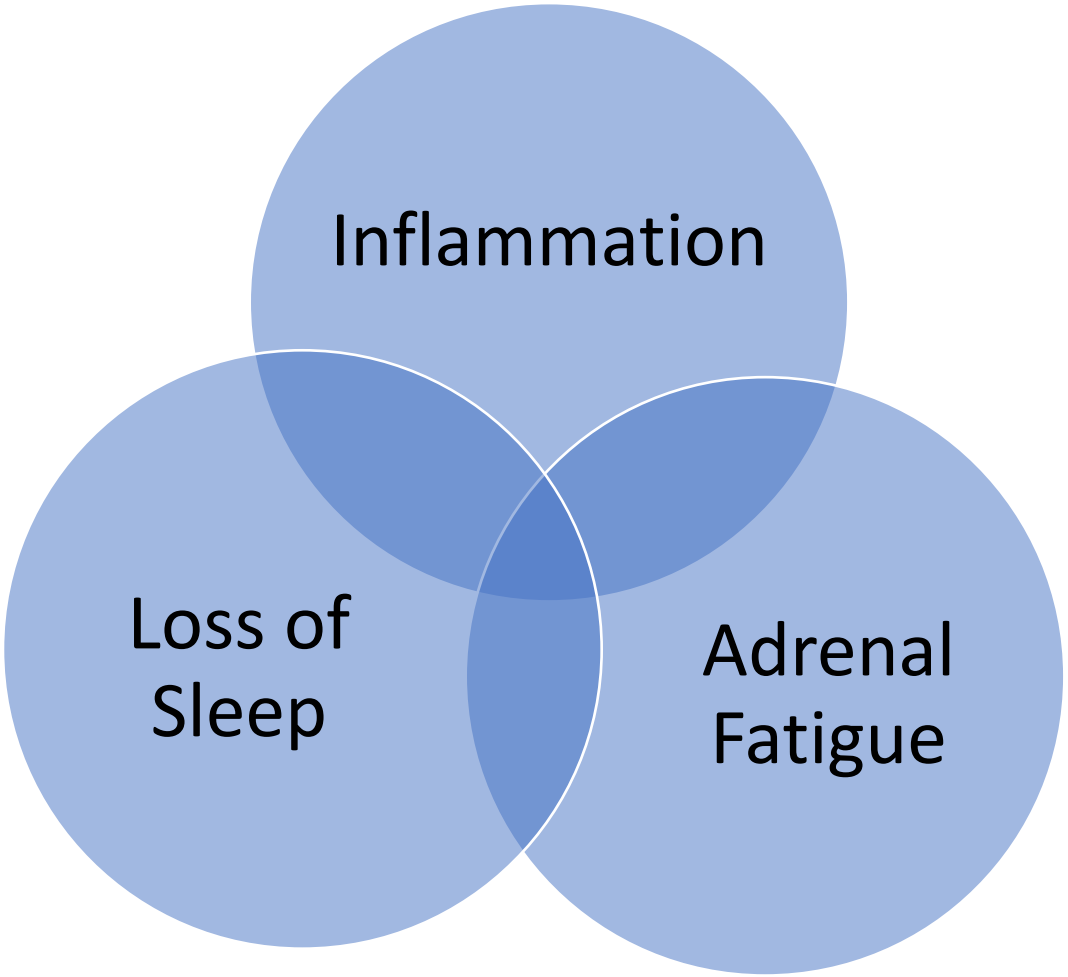
- Etiological Theories:
  - Inability of the immune system to fully clear the virus
  - Decreased immune response
  - Prolonged inflammatory response
  - Stress - physical and mental
  - Sleep

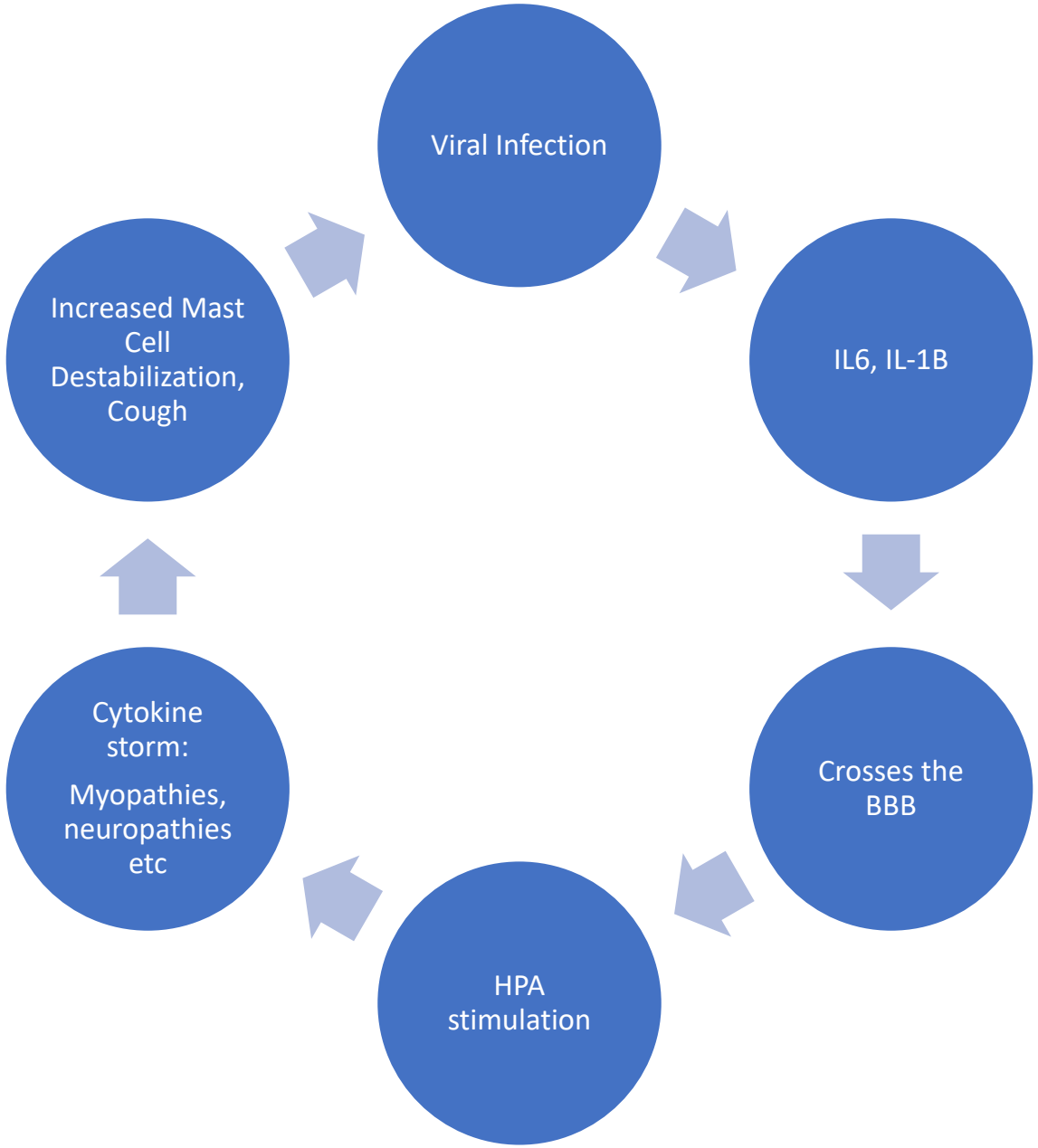
Post Viral Symptoms

- Physical
  - Fatigue…CFS
  - Shortness of breath
  - Dizziness and brain fog
  - Chronic cough
  - Allergic symptoms – rash, sinus congestion
  - Joint, chest muscle pain
  - Numbness and tingling
  - Chronic headaches
  - Loss of smell
  - Symptoms worse after mental or physical activities.

Cluster of Symptom Etiology:

Med Hypotheses, 2020; 1444:110055
Ann Intern 2020; Med 173:262-267




Viral Infection
IL6, IL-1B
Crosses the BBB
HPA stimulation
Cytokine storm:
Myopathies, neuropathies etc
Increased Mast Cell Destabilization, Cough

Post Viral Cough

- Chronic Cough
  - Cough is one of the most common presenting symptoms
  - Those with higher fevers had longer lasting coughs
  - Antitussive therapies offer little relief.
  - Anti-inflammatories have a much better resolution.
  - Disruption of sleep led to prolonged cough
  - Poor Recovery.
    - Etiology – Inflammation, decreased sleep.

Lancet Respir Med. 2022;9(5):533-544

Post Viral Cough

- “Inflammatory invasion” of the vagal sensory neurons = cough reflex.
- Neuroinflammatory response leads to peripheral and central hypersensitivity of cough pathways.
- Post viral syndrome neuroinflammatory response directly stimulates the HPA axis and heightens Substance P
- Gabapentin or opioids provide minimal response unless combines with anti-inflammatories.
- Most effective combo: anti-inflammatory + neuromodulator (benzo)

Lancet Respir Med. 2022;9(5):533-544

Post Viral Cough

- Elevated ESR
- *Elevated CRP.
- Elevated D-dimer
- Elevated ALT, AST and serum albumin
- Elevated cortisol
- Level of elevation is indicative of severity and length of persistence of cough.
- **Post COVID persistent CRP strongly associated with future pneumon*ia

Annnals of Clin Microbio and Antimicrob. 2020, 19(18)
Egyptian Liver Journal, 2021, 11:74

Post Viral Loss of Smell

- Loss of smell
  - COVID attacks the ACE2 receptor on the surface of cells.
  - Older theory : Substentacular cells have many ACE2 receptors, leaving the olfactory sensory neurons “vulnerable and deprived of nutrients.”
  - Newer postmortem research shows it is due to high IL6 in the olfactory bulbs and the mast cells.
  - 2% never recover.
    - Etiology - Inflammation.

Nature 2021: 589, 342-242

Post Viral Congestion/Allergies?

- Congestion and sneezing
  - Hyper inflammation from a virus degranulates mast cells.
  - When comparing post viral patients to highly allergic MCA patients, the severity and prevalence of symptoms is identical.
  - Cortisol, IL6 and Mast Cells have a cyclical symptomatic response.
  - Elevated ESR, CRP, IL6, IgG's and histamine.
    - Etiology – Inflammation and cortisol

Int J Infect Dis. 2021; 112:217-226

Int J of Inf Dis. 2020;100:327-332

Int J Infect Dis. 2021; 112:217-226

Treatment for Cough, Smell and Allergies

- Reduction in IL6, TNFa, IL-1B. Stabilize Mast Cells

- **Liposomal Glutathione** – 250 mg BID with food for 8 weeks then reduce to once/day.
- **N-Acetyl Cysteine** – 900 mg BID empty stomach for 8 weeks then reduce to 1 per day
- **Quercetin 200 mg +Nettles 200 mg –** BID empty stomach. Must stay on this well past resolution of symptoms.

BioMol Concepts 2021;12:16-26
Int J of Mol Sci 2020;21:1393
Adv Integr Med 2020:7(4);232-239

Post Viral Myopathies/Arthralgia

- Joint and Muscle Pain
  - Arthritis / Arthralgia, myofascial pain, fibromyalgia.

- Elevation in creatine kinase seen in 35% of post viral myalgic/myositis patients.
- Muscle biopsy shows viral induced type 1 interferonopathy.
- Increased Substance P in muscles from altered HPA response.

Applied Sci 2022;12:2, 557

Frontiers in Immunology 2022;12

- Etiology - Inflammation and altered adrenal response.

John Hopkins Medicine

Treatment for MSK Conditions

- Reduction in IL6, TNFa, IL-1B, IFN, MMP3's, rebuild collagen.

- **Liposomal Glutathione** – 250 mg BID with food for 8 weeks then reduce to once/day.
- **N-Acetyl Cysteine** – 900 mg BID empty stomach for 8 weeks then reduce to 1 per day
- **Boswellia 100mg, Ginger 100 mg, tumeric 100 mg, quercetin 38 mg combo** – 1 BID empty stomach for 8 weeks and reduce to 1 per day
- **Hydrolyzed Collagen** – 10 grams once or twice a day with food.

BioMol Concepts 2021;12:16-26
Int J of Mol Sci 2020;21:1393
Adv Integr Med 2020:7(4);232-239

Post Viral Brain Fog, Dizziness and Headaches

- Hospitalized patients were more likely to experience symptoms.
- Odds ratio ranges from 1.8 to 3.0:
  - Impairment in attention, executive function, vertigo and headaches.
- Inflammation in the vestibular nerves.
- Reduction in blood flow due to rise in clotting factors and inflammation (vestibular neuritis/labyrinthitis)
- Adrenal Fatigue – orthostatic BP…sleep.

Int J Immunopathol Pharmacol 2021 :35:2058
Brain Behav Immun. 2020;87:18-2

- Etiology – Inflammation, altered adrenal response, insomnia.

JAMA Network Open- Neurology October 2021

Treatment for Dizziness and Headaches

- Reduction in IL6, TNFa, IL-1B. Increase mitochondrial output, support adrenals.

- **Liposomal Glutathione** – 250 mg BID with food for 8 weeks then reduce to once/day.
- **N-Acetyl Cysteine** – 900 mg BID empty stomach for 8 weeks then reduce to 1 per day.
- **Valerian 200mg, Chamomile, 100 mg, Lemon Balm 100mg, Passion Flower 100mg, Melatonin 1.5mg combo** - 2 caps at 8:30 or 9 prn.
- **CoQ 10** – 200mg cap BID with food for 4 weeks and then 1 per day
- **Magnesium L-Threonate 145mg** – 2 caps BID with food
- **Lactium 175mg, L-theanine 50mg**– 2 caps BID empty stomach for 4-8 weeks and then reduce in half.

Post Viral Neuropathy

- Result of inflammation to the nerves located outside the brain and spinal cord.
- ¼ of dorsal root ganglia neurons (connect the peripheral NS and the spinal cord) express mRNA that viral spike proteins can attach to.
- Elevation in creatine kinase and CRP with complete resolution of immune modulators.
- Most frequently seen is mixed sensorimotor neuropathy.
  - Numbness, pain, burning and stabbing sensations and weakness- tz with antivirals unsuccessful.

Cureus 2020; 12(11) e11452
American Acad of Neuro. 2022;9(3)

Treatment for Neuropathies

- Reduction in IL6, TNFa, IL-1B, IFN, rebuild myelin sheath.

- **Liposomal Glutathione** – 250 mg BID with food for 8 weeks then reduce to once/day.
- **N-Acetyl Cysteine** – 900 mg BID empty stomach for 8 weeks then reduce to 1 per day.
- **Omega 3 fats** – 1200 mg BID with food until 4 weeks post neuralgia then reduce in half.

Clin J Pain 2010 26(2):168-72
J of Ind Acad of Oral Med and Rad, 2018 , 30:2;137-141
Adv Integr Med 2020:7(4);232-239

Treatment for Physical Symptoms

- Reduce the inflammatory response.
  - Inflammation arises from adrenals, lack of stage 4 sleep, immune, genetics- you must treat all stimuli simultaneously.
  - Must use supplementation that targets the genes, not just the cytokines.
  - Use supplementation at higher dose for 4 weeks past no symptoms then reduce the dose in half.
  - Reduce sugar intake.
  - Don’t over exercise.

Post Viral Symptoms- Emotional

- Mental/Emotional
  - Rates of clinical anxiety and depression have risen 24.6% in the past 2 years.
  - Presently 59% suffer from clinical anxiety, depression or PTSD.
  - 1 in 5 people who experienced a viral infection are projected to experience *chronic or relapsing* anxiety, depression or insomnia for years to come.

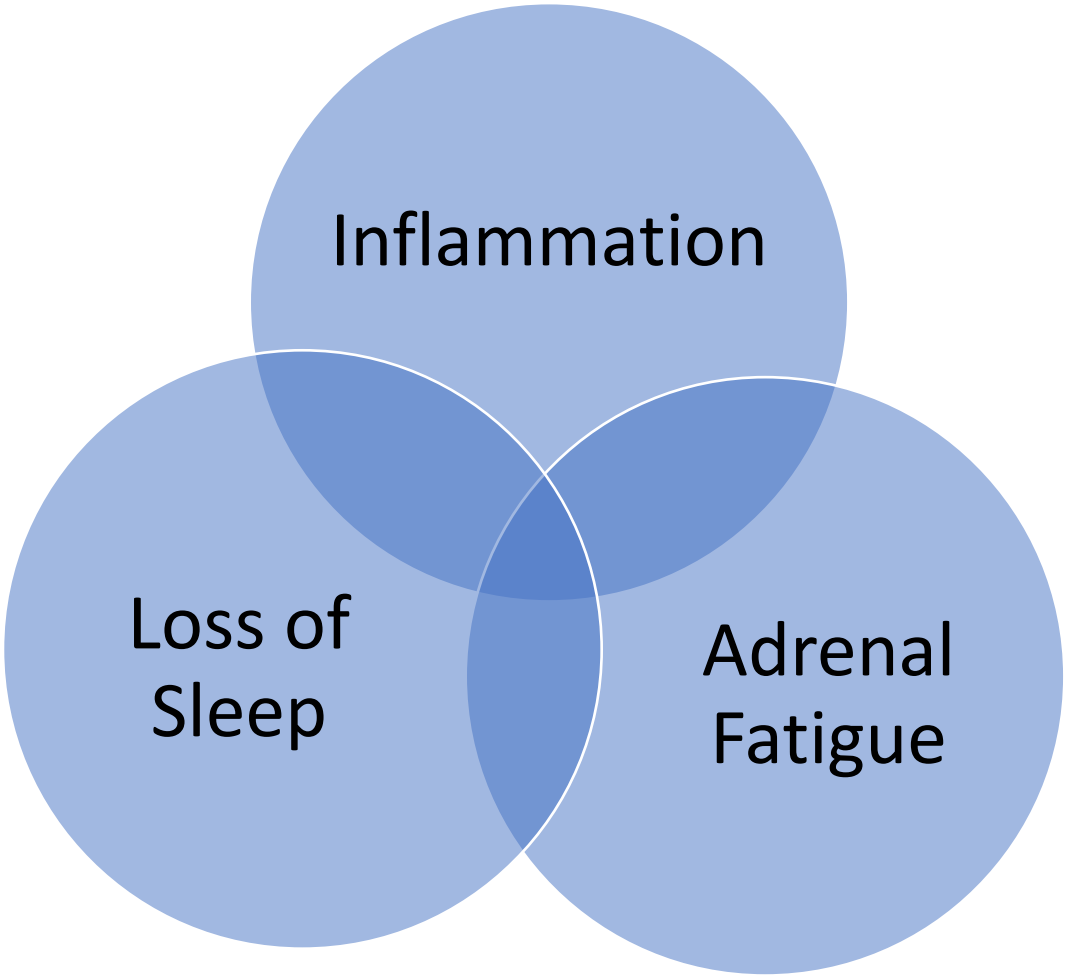
Etiology – Increased HPA output.

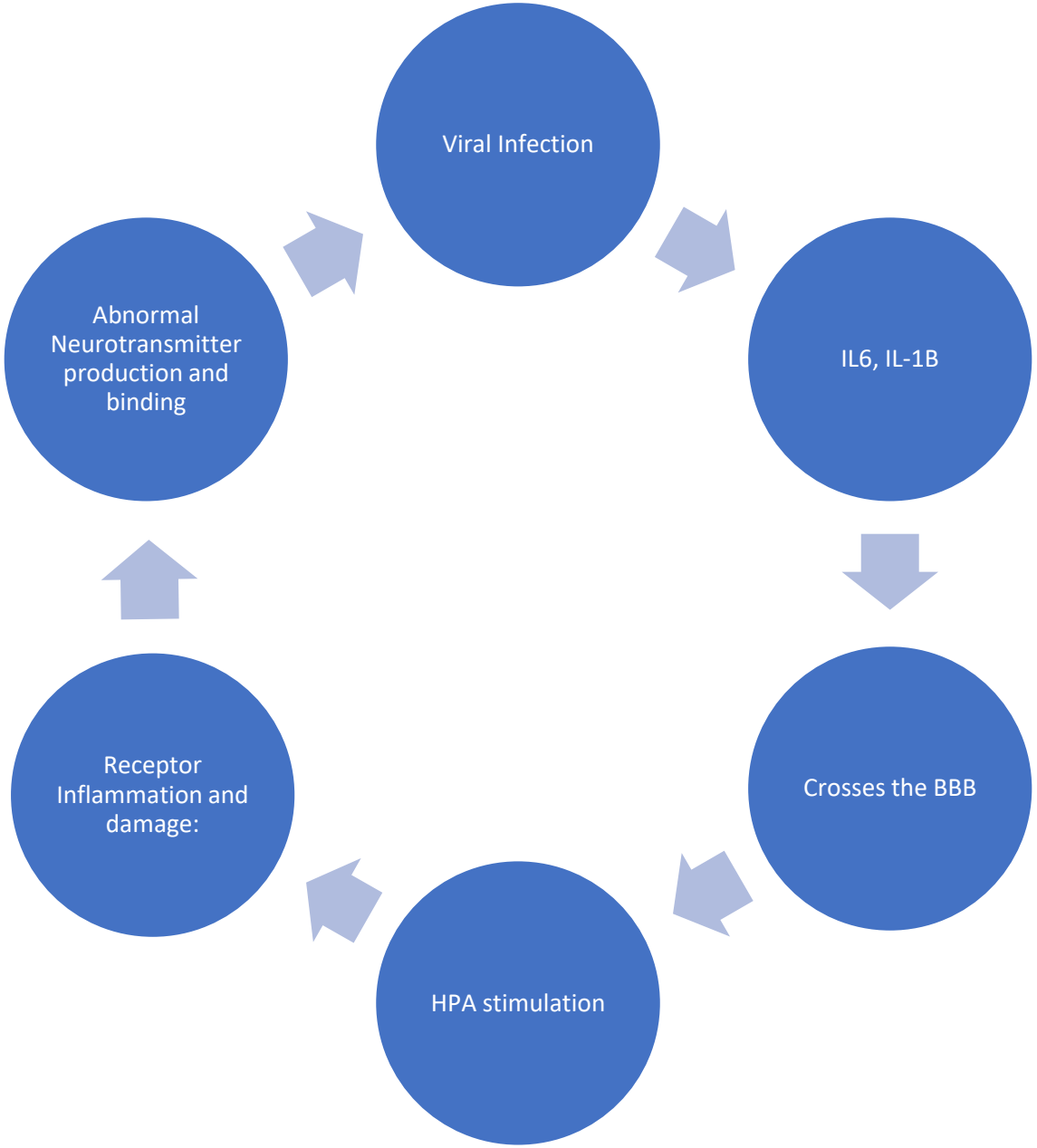
CDC National Center for Health Stats 2021

Lancet Psychiatry 2021;8(2):130-140

Cluster of Symptom Etiology:

Med Hypotheses, 2020; 1444:110055
Ann Intern 2020; Med 173:262-267

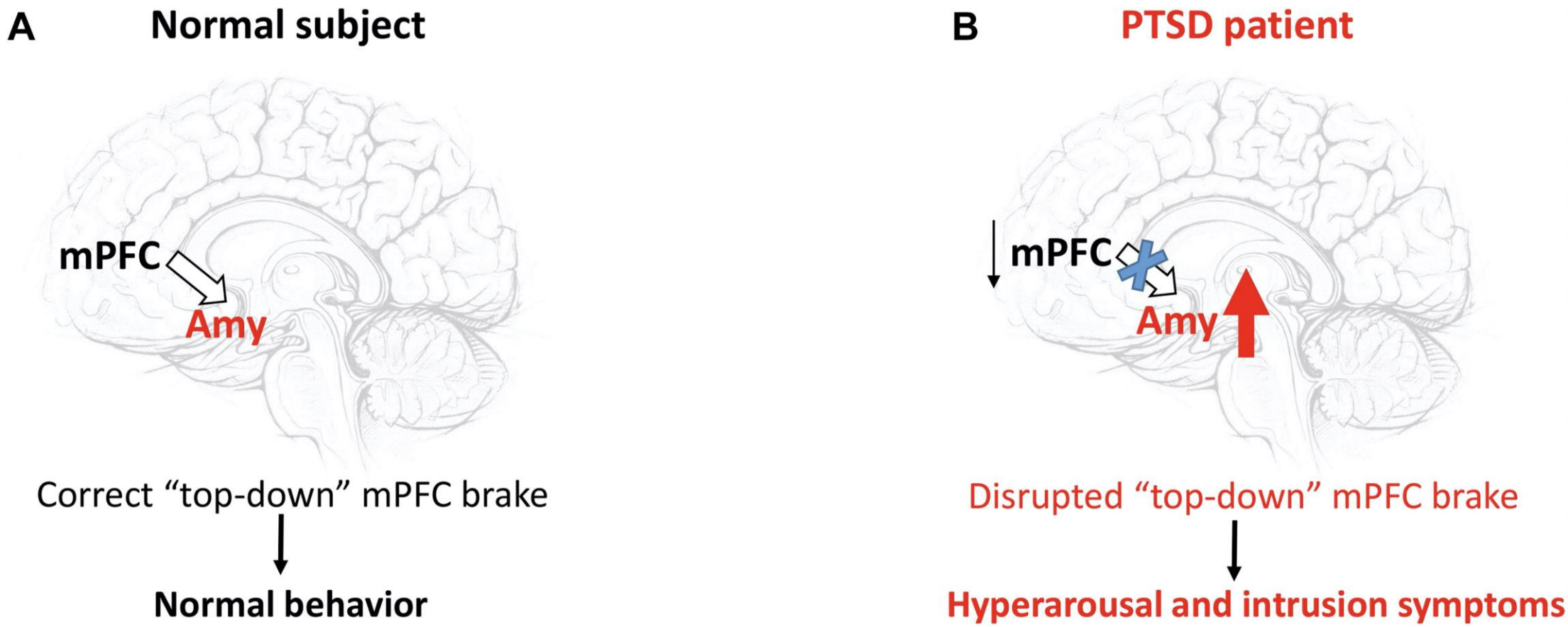



Viral Infection
IL6, IL-1B
Crosses the BBB
HPA stimulation
Receptor Inflammation and damage:
Abnormal Neurotransmitter production and binding

Post Viral Syndrome- Addictions

- Addictions
- 13% of Americans reported starting or increasing opioid substance use as a way of coping with stress over the past 2 years. *CDC*
- 18% increase in overdoses – *AMA*
- 41% increase in alcohol intake – *Harvard Health*
- 63% increase in clinical eating disorders – *Sick Kids hospital*.
  - Etiology - Altered dopamine activity

HPA and Dopamine: *Nat. Rev. Neuorsci. 2018: 19; 535-551*



Treatment for Addictions, Focus and Memory

- Regulate the HPA axis- keep dopamine in PFC
  - **Lactium 175mg, L-theanine 50mg**– 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Increase dopamine
  - **L-Tyrosine** -1000 mg BID empty stomach. Take with lactium combo .
- Support Ghrelin
  - **Dolichos biflores 60 mg, Piper betle 90mg, ALCAR, 150 mg –** 2 caps BID 30 mins to 2 hours before lunch and dinner.
- Reduce Inflammation
  - **Liposomal glutathione and NAC** – dosing as for inflammation
- Re-establish microbiome.
  - **Multi strain Probiotics –50 B**– 2 caps per day with food.

Dopamine Life Hacks.

- Do something new!
- Aged cheddar cheese, walnuts.
- Regular Exercise.
- Nonfood treats!!!
- 8 hours of sleep, every night.

Post Viral Symptoms- Sleep

- Sleep
  - People with sleep disorders are more likely to develop long term viral symptoms.
  - 31% of them are at higher risk of being hospitalized or dying.
  - Those with longer lasting symptoms are twice as likely to develop sleep disorders.
    - Etiology - Inflammation and increased HPA activity.

JAMA Network Open 2021;4(11):e2134241

Treatment for Sleep

- Regulate the HPA axis- push to Parasympathetic side.
  - **Lactium 175mg, L-theanine 50mg** 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Increase Stage 4 sleep, relax and sedate.
  - **Valerian 200mg, Chamomile, 100 mg, Lemon Balm 100mg, Passion Flower 100mg, Melatonin 1.5mg combo -**2 caps at 8:30 or 9 pm and 1 before bed.
  - **Magnesium Glycinate 150 mg**– 1 -2 caps in the evening or before bed
- Reduce Inflammation
  - **Liposomal glutathione and NAC** – dosing as for inflammation
- Re-establish microbiome.
  - **Probiotic**– as above

Post Viral Anxiety/ Depression: Inflammatory Cycle

- All those diagnosed with depression and anxiety have **significantly** higher levels of IL6, TNFa and CRP.
- Conversely depressive/anxious symptoms are more frequent in those with inflammatory conditions.

Psychos3 Med 2009 71:171-186

Stress and Inflammation

- Cytokines act upon GC receptors and upregulate the synthesis of CRH, ACTH and cortisol.
- Cytokines activate indoleamine-2, 3-dioxygenase (IDO), stealing tryptophan and lowering serotonin.
- Cytokines alters the vagal response which in turn increases cortisol and further increases cytokine production.

Biol Psychol 2010 84:290-295
Am J Psychiatry 2013 160:1554-156

Stress and Inflammation

- Glucocorticoids increase the production of the inflammasome NLRP3 which increases IL-1B and IL-18 as well as PGE2 series.
- A loss of negative feedback in the HPA axis stimulates the inflammatory genes (IL6 and TNF-a) and inhibits anti-inflammatory genes (GSH genes).
- Cytokines inflame and reversibly mutate neural receptors.

Brain Behav. Immune. 2007; 21:901-912
Biol. Psychiatry. 2009; 65:732-741

Neurobiol of Stress, 2016; 4:22-33

- The polysaccharide coating of the GI bacteria protect them from degradation.
- The coating also serves to identify the numerous and diverse bacteria to the host.
- Catecholamines increases the breakdown of the coating and alters epithelial pattern recognition receptors (PRRs).
- Recruit cytokines >>>>further degradation of microbial coating

Treatment for Anxiety

- Regulate the HPA axis- push to Parasympathetic side of NS
  - **Lactium 175mg, L-theanine 50mg**– 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Calm and mildly sedate
  - **Ashwagandha 100mg, phosphatidyl serine 50mg, passionflower 100 mg combo** – 2 BID empty stomach PRN.
- Reduce inflammation
  - **Liposomal glutathione and NAC** – dosing as for inflammation.
- Re-establish microbiome.
  - **Probiotic**– as above.

Medina, J. H., Peña, Mol. Neurobiol. 6, 377–386 1992.
Papadopoulos, V. Endocr. Rev. 14, 222–240 1993
Laurent Miclo Emmanuel Perrin. The FASEB Journal June 2001*

Cortisol Life Hacks

- 8 hours of sleep, every night!!
- Hemi-Synch, Binaural beats.
- Meditation, deep breathing and yoga.
  - 20 volunteers -8 weeks of mediation and yoga. Novice meditators showed a change in **1561** genes (upreg 874 for health and down reg 687 for stress) and lowered BP, heart rate. Experienced meditators expressed 2209 new genes, most improving health and body's response to psychological stress.

J A Dusek et al, "Genomic Counter-Stress Changes Induced by Relaxation Response". PLOS ONE vol 3, no. 7:[e2576 (2008)

Treatment for Depression

- Regulate the HPA axis- increase serotonin production and binding and prevent melatonin leaching.
  - **Lactium 175mg, L-theanine 50mg**– 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Increase Serotonin
  - **5-HTP 100 mg** – 1-2 BID empty stomach or with small amount of pure carb.
- Reduce inflammation
  - **Liposomal glutathione and NAC** – dosing as for inflammation.
- Re-establish microbiome.
  - **Probiotic**– as above.

Serotonin Life Hacks

- Boost foods high in tryptophan – turkey, cottage cheese, lean red meat, chicken, EFA's, soy or tofu, nuts and seeds.
- Check your carbohydrate genes, some do better with a higher complex carb diet.
- Exercise regularly.
- 8 hours of sleep every night.
- Spend time in the sun!!!!

Treatment for Emotional Symptoms

- Reset the HPA axis and reduce the inflammatory response.
  - You must reset the HPA axis not just reduce the strength of the sympathetic side or reduce GC output.
  - Inflammation arises from adrenals, lack of stage 4 sleep, immune, genetics- you must treat all stimuli simultaneously.
  - Must use supplementation that targets the genes.
  - Use supplementation at higher dose for 4 weeks past no symptoms then reduce the dose in half.
  - Reduce sugar intake.
  - Don’t over exercise.

Susceptibility and Predictability

- SLC6A20 rs34326463– encodes for an amino acid transporter that interacts with the ACE2 receptor – the main receptor that SARS-Co-V-2 uses to enter into a human cell.

- ACE rs4343– those who are variant have less ACE receptors, and thus less available ”spaces” for the virus to enter.

- Those who are variant for SLC6A20 and normal for ACE have a 1.77 times higher probability of being hospitalized for respiratory failure with SARS-Co-V-2.

- *Journal of virology* ***DOI:*** *10.1128/JVI.00510-20*

Susceptibility and Predictability

- IRF5 rs472814 – speed of reactivity to virus and autoimmune response.
  - Colostrum – 1000 mg – 1 BID empty stomach for 8 weeks then reduce to 1 per day.

- HLADQB1 rs7775228 – major histocompatibility complex gene that makes proteins on the surface of specific immune cells such as mast cells.
  - **Quercetin 200 mg +Nettles 200 mg** 2 BID empty stomach – don't stop his for min of 6 months, then reduce in half.

BDNF rs6252

- *Master Molecule of the brain*.
- Neurotrophic involved in the growth of new neurons and the proliferation and expansion of existing neurons and the maintenance of synapses.
- Increases firing of neuronal pathways to consolidate memory, plays key role in the prevention of age-related memory loss and cognitive function.
- Increases repair of mildly damaged areas of the brain and apoptosis and cellular death of significantly damaged areas.

BDNF rs6265

- Normal Allele is C Variant Allele is G
- Decreased BDNF production
- Decreased neuronal and synaptic repair
- Decreased dendritic growth
- Prolonged neural inflammation
- Increased anxiety and depression
- Increased brain fog and decreased cognitive function
- Increased ADD/ADHD

Support for BDNF rs6265 T Allele

- Astaxanthin- 4 mg BID empty stomach *Nutr Neurosci 2020;23(6):422-431*
- Resveratrol 200 mg- 1 cap BID empty stomach *Neurochem Res. 2011 36(5):761-5*
- Curcumin 400 mg – 1 BID empty stomach
  - (if CYP1A2 is normal)- *Prog Neuropsychopharmacol Biol Psychiatry 2010 1;34(1):147-53*
- 5-HTP 100 mg– 1 BID with food.– (if serotonin genes are hetero or variant)- *Science Daily News, Feb 2010*
- Exercise – especially HIIT if genetics allow for it- *Front Neurosci. 2018*

FKBP5 rs3800373

- Normal Allele is C Variant Allele is A
- FK binding protein – member of the immunophilin protein family.
- Regulates glucocorticoid binding and sensitivity.
- Binding of FKBP5 into the GC receptor reduces cortisol-binding capacity leading to impaired negative feedback regulation.

Wilker S Translational Psychiatry. 2014;4:403Binder

E, Psychoneuroendocrinology. 2009 Dec; 34(1): 186-195

FKBP5 rs3800373

- Characteristics of A allele:
  - Increased FKBP5 expression blocking receptors.
  - Increased loss of negative feedback in the HPA axis.
  - Increased anxiety, depression.
  - Increased addictions of all forms.
  - Prolonged short-term stress response, easier to get “stuck” in a stress loop.
  - Increased PTSD - especially from childhood memories.
  - Increased inflammation. (76%)
  - Reduced Immune response (55%)

NR3C2 rs5522

- Normal Allele is T (A) Variant Allele is C (G)
- Nuclear receptor subfamily C-member is a mineralocorticoid receptor (MR).
- Cortisol binds into the MR initiating negative feedback in the HPA axis.
- The greater the number of MRs, the greater the feedback and thus ability to return to the parasympathetic NS.

Psychoneuroendocrinology 2015 Feb;52:92-110

J of clin Endocrinology and Metaboism, 2006 Dec;91(12): 5083-5089

NR3C2 rs5522

- Characteristics of the C Allele:
  - Fewer mineralocorticoid receptors.
  - Decreased negative feedback in the HPA axis.
  - Increased plasma ACTH.
  - Increased addictions of all forms.
  - Increased anxiety, depression and hyperactivity.
  - Increased ADD/ADHD.
  - Increased inflammation.
  - Decreased immune response.

COMT rs4680

- Normal Allele is G Variant Allele is A
- Catechol-O-methyltransferase is the enzyme produced by the COMT gene.
- It degrades or metabolizes several catecholamines including dopamine, *adrenaline and noradrenaline* along with estrogens and certain drugs.
- COMT is very active in the prefrontal cortex.

Hamidovic et al, 2010

COMT rs4680

- Characteristics of the A allele:
  - Decreased COMT production and activity.
  - Increased catecholamine levels that impairs memory.
  - Increased anxiety (Worrier).
  - Increased fear response associated with PTSD
  - Increased dopamine levels to support memory.
  - Increased rates of aging.

Support for Stress Genes

- Regulate the HPA axis- push to Parasympathetic side of NS
  - **Lactium 175mg, L-theanine 50mg** BID empty stomach for 8 weeks and then reduce to 1 BID
- Calm and mildly sedate
  - **Ashwagandha 100mg, phosphatidyl serine 50mg, passionflower 100 mg combo** 2 BID empty stomach PRN.
- Reduce inflammation
  - **Liposomal glutathione and NAC** – dosing for inflammation.
- Re-establish microbiome.
  - **Probiotic** – as above.
- Why not Rhodiola???

TPH2 rs4570625

- Normal Allele is G Variant Allele is T
- Tryptophan hydroxylase is the enzyme made by the TPH2 gene that converts tryptophan into 5-HTP, the precursor to serotonin.
- TPH2 is most active in the brain.
- Serotonin is converted into melatonin, affecting sleep.

TPH2 rs4570625

- Characteristics of the Variant Allele:
  - Low TPH production.
  - Increased depression.
  - Increased addictions, especially alcohol and food.
  - Increased anxiety.
  - Difficulties sleeping, especially waking at 5 am.
  - Increased muscle myalgia and fatigue.

5-HTTLPR rs11867581

- Normal Allele is A Variant Allele is G
- 5-HTTLPR is a serotonin transporter gene that is responsible for the re-uptake of serotonin.
- The normal A allele is called the "long version" or "L" and is associated with normal transportation and production of serotonin from the bowel.
- The variant G allele, the "short version" or "S", is associated with far less serotonin production and transportation from the bowel.

5-HTTLPR rs11867581

- Characteristics of the G Allele:
  - Decreased serotonin production and transportation out of the intestines.
  - Decreased serotonin uptake.
  - Increased depression.
  - Difficulty letting go of past events, PTSD.
  - Increase alcohol intake, craving and binging.
  - Increased sugar cravings, especially chocolate.
  - Increased myalgia.

Biol Psychiatry 2009: 66(2): 102-9

MAOA rs77905

- Normal Allele is G Variant Allele is A
- MAOA gene produces the enzyme monoamine oxidase A.
- Monoamine oxidase A is involved in the breakdown of the neurotransmitters serotonin, epinephrine, norepinephrine, and dopamine.

MAOA rs77905

- Characteristics of the ”G” Allele:
  - Note, the normal allele is the one that carries the risk.
  - Increased MAOA production.
  - Increased clearance of serotonin.
  - Increased binge eating and drinking.
  - Increased addictions.
  - Increased depression and decreased motivation.
  - Decreased anxiety.

Treatment for Serotonin Genes

- Regulate the HPA axis- increase serotonin production and binding and prevent melatonin leaching.
  - **Lactium 175mg, L-theanine 50mg** 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Increase Serotonin
  - **5 HTP 100 mg** – 1-2 BID empty stomach.

DRD2 rs6277

- Normal Allele is A Variant Allele is G
- Dopamine receptor D2 is a crucial dopamine receptor that stimulates dopaminergic pathways involved in reward, addiction, learning, motivation and pleasure.
- Several dopamine receptors on the kidneys, and abnormal coding for this gene alters the Renin Angiotensin System (RAS), increasing bloating, edema and blood pressure.

DRD2 rs6277

- Characteristics of the G Allele:
  - Reduced DRD2 receptors.
  - Less pleasure derived from everyday events.
  - Frequent excitement seeking behavior.
  - Increased addictions.
  - Increased interaction with FTO and MC4R.
  - Increased food cravings for chips, cheese, nuts and wine.
  - Increased ADD and ADHD.

DRD2/ANKK1 rs1800497

- Normal Allele is G Variant Allele is A
- Second most important dopamine receptor that stimulates dopaminergic pathways.
- This gene, along with DRD2 is involved in demyelination

DRD2/ANKK1 rs1800497

- Characteristics of the A Allele:
  - Reduced DRD2/ANKK1 receptors.
  - Less pleasure derived from everyday events.
  - Frequent excitement seeking behavior.
  - Increased addictions.
  - Increased interaction with FTO and MC4R.
  - Increased food cravings for chips, cheese, nuts and wine.
  - Increased ADD and ADHD.

Treatment for Dopamine

- Regulate the HPA axis- keep dopamine in PFC
  - **Lactium 175mg, L-theanine 50mg**– 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Increase dopamine
  - **L-Tyrosine** 1000 mg BID empty stomach. Take with lactium combo.
- Support Ghrelin
  - **Dolichos biflores 60 mg, Piper betle 90mg, ALCAR, 150 mg–** 2 caps BID 30 mins to 2 hours before lunch and dinner.

IL6 rs1800795

- Inflammatory cytokine that is stimulated during infections, fevers, injury, exercise, stress, obesity and toxicity.
- Recruits' neutrophils and thus B cells to increase inflammation to attack a pathogen.
- Increases inflammation in blood vessels and stimulates TNFa and CRP.
- Crosses BBB to increase PGs to increase body temperature and inflames receptors increasing depression and altering BDNF.

IL6 rs1800795

- Normal Allele is C
- Variant Allele is G
- Increased IL6.
- Increased inflammation and reduced glutathione.
- Crosses the BBB inflaming neural receptors.
- Increased insomnia, sleep disturbances, anxiety and depression.

Bashati M, et al, Cytokine 2017 Nov;99:132-138

TNFa rs1800629

- Cell-signaling cytokine expressed in T and B cells, NK cells, macrophages, fibroblasts and dendritic cells.
- Modulates cellular differentiation, remodeling, tissue adhesion and the acute phase of immune reactions.
- Induces apoptosis, and stimulates inflammation via increasing production of IL6, IL-1B and MMP3's.

Greco L, et al, Am J Hum Gen 1998 62, 669-675

Saif K, et al, Sci Rep 2016;6:32677

TNFa rs1800629

- Normal Allele is G
- Variant Allele is A
- Increased TNFa production.
- Increased inflammation.
- Crosses the BBB inflaming neural tissues.
- Increased risk of CV disease, IBS, allergies, asthma, psoriasis, arthritis and autoimmune disorders.
- Increased HPA activity and sleep disturbances.

MMP3 rs679620

- Produces matrix metalloproteinases.
- Breaks down extracellular matrix proteins
- Degrades collagen types 1, 2, 4 and 10
- Breaks down proteoglycans, fibronectin, laminin and elastin.
- Very active in bones, joints, tendons, GI tract and skin.

MMP3 rs679620

- Normal Allele is T Variant Allele is C
- Increased MMP3 production.
- Increased activation of other MMP3's.
- Increased inflammation.
- Increased tendonopathies, arthritides and myalgia

COL1A1 rs1800012

- Produces collagen type 1
- Collagen type 1 is the main component of fibrils, the building blocks of collagen and cartilage.
- Collagen type 1 accounts for 85%

COL1A1 rs1800012

- Normal Allele is A Variant Allele is C
- The variant allele is the advantageous allele.
- Increased collagen type 1 production.
- Decreased tendinopathies.
- Decreased arthritis.
- Decreased inflammation.

Support for Inflammatory/Musculo-Skeletal

- **Liposomal Glutathione** – 250 mg BID with food for 8 weeks then reduce to once/day.
- **N-Acetyl Cysteine** – 900 mg BID empty stomach for 8 weeks then reduce to 1 per day
- **Boswellia 100mg, Ginger 100 mg, tumeric 100 mg, quercetin 38 mg combo** – 1 BID empty stomach for 8 weeks and reduce to 1 per day
- **Hydrolyzed Collagen** – 10 grams once or twice a day with food.
- **Resveratrol** – 200 mg BID empty stomach for 8 weeks and reduce to once per day,

BioMol Concepts 2021;12:16-26

Int J of Mol Sci 2020;21:1393

Adv Integr Med 2020:7(4);232-239

Glutathione Genes

- GSTP1 – rs1695 (AG)
- SOD2 – rs4880 (AG, CT)
- NQO1 – rs1800566 (GA, CT)
- Variants have up to 75% less GSH production.
- Lower GSH increases IL6 and TNFa.
- IL6 and TNFa decrease intracellular GSH.
- Treatment – Liposomal Glutathione, NAC, Astaxanthin – higher or prolonged doses.

Case Study 1 - Jason

- Jason is a 53 yr. old male who has been active and healthy his whole life.
- Only pre-existing condition - mild asthma and slower recovery from workouts when he “over-trained”.
- After a vaccine he had mild symptoms of fever, myalgia that impeded his regular workouts, headaches which he had never experienced before and heavy chest for 5 days.
- 7 months later he was still more tired than normal, “wandering” joint pain with the occasional numbness in the toes which he assumed as decreased circulation from less exercise.

Jason’s Genotyping

- IL6: GG- increased inflammation
- TNFa: - GA – increased inflammation
- MMP3: TC – increased collagenous breakdown
- HLADQB1: TT – normal mast cell function
- IRF5: GG – normal immune response
- GSTP1 : AG – slowed phase 2 detoxification, increased inflammation
- SOD2: AG – slow phase 2, lower mitochondrial output, increased inflammation.

Jason’s Interpretation

- Jason had kept his inflammation low through a clean diet, lifestyle and sleep patterns.
- When he overtrained and increased the wear and tear and stress on his body, he would “feel it for longer” by mildly stimulating his MMP3, IL6 and TNFa.
- The vaccine stimulated his IL6 and TNFa genes into full gear. His slower phase 2 detoxification genes meant he could not clear the inflammatory bi-products well, further increasing his inflammation.
- This triggered his mast cells, despite normal function, and ramped up his MMP3 production both in his lungs and blood vessels in the brain.

Jason’s Program

- Liposomal Glutathione – 250 mg BID with food for 8 weeks, then reduce once per day – always.
- NAC – 900 mg BID empty stomach for 8 weeks, ten reduce to once per day - always
- Quercetin 200 mg- Nettle 200 mg– 2 caps BID for 6 weeks, then reduce to 2 per day for 6 weeks and then off.
- Hydrolyzed collagen – 10 grams BID in water empty stomach for 2 tubs, then reduce to once per day -always.

Jason’s Outcome

- By day 10 Jason’s myalgic pain was about 50% better with only 2 episodes of numbness and only 1 headache.
- Within 2 weeks the heaviness in Jason’s chest dramatically reduced.
- By the end of the 4th week his breathing was normal, had only had one more very mild numbness episode, and his joint pain and myalgia was ”almost normal”.
- He over trained one day which brought on fatigue and myalgia for the following 2 days as well as a headache.
- For 3 days he increased fluids and took a 3rd dose of GSH and NAC.
- 6 months later, he is on his maintenance doses of supplements and essentially symptom free, even if he over trains for a day.

Case Study 2 -Michael

- Michael had suffered from allergies and asthma most of his life.
- He got an upper respiratory tract infection that greatly aggravated his allergenic and asthmatic symptoms. He had difficulty breathing, hives on his chest, headaches daily and difficulty sleeping.
- He increased the use of his puffers which moderately helped, but the rashes and headaches did not abate.
- 3 weeks later his sleep worsened, and joint pain and stiffness began.
- This went on for over 6 months.

Michael’s Genotyping

- IL6: CC- normal inflammation
- TNFa: - GA – increased inflammation
- MMP3: TT – normal collagenous breakdown
- COL1A1: AA – decreased repair of collagen
- HLADQB1: CC – increased mast cell degranulation
- IRF5: GA – heightened immune response.
- GSTP1 : AA – normal phase 2 and inflammation
- SOD2: AA – normal phase 2, normal mitochondrial output and inflammation.

Michael’s Interpretation

- Michael had a weaker immune system that did not “see” a pathogen quickly, allowing it to replicate more readily greatly stimulating his unstable mast cells to pump out inflammatory substrates.
- His overall inflammatory and phase 2 detox pathways were quite strong but once mast cells are stimulated, they will stay “on” until they are turned off and further increase cytokine production.
- This then began to inflame his joints which he had difficulty repairing, again increasing his overall inflammatory load.
- His disrupted sleep further hindered healing.

Michael’s program

- Quercetin 200 mg +Nettle 200 mg- 3 BID for 8 weeks empty stomach and then reduce to 2 BID for 6 months then remain on 2 per day.
- Colostrum – 1 gram BID empty stomach for 8 weeks then reduce to 1 per day.
- Protein Powder – 1 scoop (20 grams) per day
- Hydrolyzed Collagen – 10 grams per day with food.
- Anti-inflammatory diet using www.feedyourgenes.ca

Michael's Outcome

- Michael saw very little change for the first 2 weeks but by day 18 he began to feel a significant ease in his breathing and reduction in the rashes.
- By the start of the 3rd week his headaches reduced by about 60% and his joint pain and stiffness improved by 40%.
- At 5 weeks he no longer had any joint stiffness, and his breathing was better than it had been prior to the infection whereby he could reduce his puffers to PRN.
- When spring arrived, 4 months into the program, for the first time he had no increased asthma or allergenic symptoms and no need to increase his puffers.

designs for health

Differential Treatment Plan

- Jason
  - Normal mast cell response triggered through inflammation.
  - Strong immune response.
  - Increased inflammatory response.
  - Increased collagen breakdown.
  - Control of joint pain, rashes, breathing and headaches – controlling IL6, TNFa and reducing production of MMP3's .

- Michael
  - Heightened mast cells triggered through genetics and immunity.
  - Weakened immune response.
  - Close to normal inflammatory response.
  - Decreased collagen repair
  - Control of joint pain, allergies, breathing and headaches – stabilizing mast cells, regulating immune system and repairing collagen.

designs for health

Case Study 3- Mark

- Mark is a 26-year-old male who describes himself as an “all or nothing” person.
- He is a competitive athlete, always pushes himself to excel in everything he does.
- Unable to get to the gym during lockdown Mark quickly found himself unmotivated to work and when he did, his focus and concentration was poor.
- Soon he had little desire to see friends or family and for the first time had low depressive thoughts. He started drinking and smoking pot every night, something he had never done before.
- These new behaviours and feelings lasted for 7 months.

Mark’s Genotyping

- DRD2: GG- less dopamine production and receptors.
- DRD2/ANKK1 :GA - less dopamine production and receptors.
- COMT: GG- fast clearance of dopamine and stress hormones.
- FKBP5: AA-significant increased loss of negative feedback in HPA axis.
- TPH2: TT- decreased serotonin production.
- 5-HTTLPR: AA – normal transportation of serotonin.

Mark’s Interpretation

- From a young age Mark kept his dopamine high through pushing himself in competitive sports and ”competitive” academics.
- Being unable to workout stimulated his stress genes, which in turn stimulated his dopamine and serotonin genes.
- The stress also directly inhibited the production and binding of serotonin and dopamine.
- The alcohol and pot increased neural tissue inflammation which further blocked the serotonin and dopamine.

Mark’s Program

- L-Tyrosine 200 mg, GABA 125 mg, 5 HTP 25 mg combo – 4 caps BID empty stomach for 4 weeks, and then reduce to 3 caps BID until he could return to the gym.
- Lactium 150, l-theanine 50 mg– 2 BID empty stomach until he could return to the gym.
- Created a mini challenge/goal every week (dopamine genes).
- Started him on at home or outdoor workouts.

Mark’s Outcome

- Within 1 week he felt his body ”relax” even though he did not realize it was tense.
- By the end of the 2nd week, his mood began to lift, and he started engaging with friends online.
- His focus and concentration improved by 50-60% by the 3rd week but was almost ”normal” on days he did a workout.
- His desire for chips and alcohol reduced, but not completely yet his motivation to work was close to normal.
- 3 months later the gyms opened, and he stopped his supplements.
- He was fine until the gyms closed again and he did not restart his supplements.
- 3 weeks later most of his symptoms were back, he restarted the supplements and will remain on them until life returns back to normal.

Case Study 4 - Annie

- Annie is a 53 year od female who has always been “troubled”.
- She started drinking at a very young age, would go into depressive bouts before and after drinking, and slowly shut out the world.
- In past few years this was controlled with 5-HTP 50 mg BID
- 3 months into the pandemic these behaviours returned with a vengeance, but this time her focus and concentration also plummeted to the point where she could not perform her job and was fired.
- Her GP put her on Wellbutrin in attempts to reduce alcohol cravings and improve her mood but it made things worse.
- 6 months later she was staying in bed until 2 pm most days, withdrawn from the world.

Annie’s Genotyping

- DRD2: AG - less dopamine production and receptors.
- DRD2/ANK1–:GG - normal dopamine production and receptors.
- COMT:AA- slow dopamine clearance, slower catecholamine clearance.
- FKBP5: AA-significant increased loss of negative feedback in HPA axis.
- TPH2-:TT - little serotonin production.
- 5HTTLPR: AG - decreased serotonin transportation.

Annie’s Interpretation

- Annie genetically has quite strong dopaminergic pathways.
- Her stress pathways which were triggered in lock down pushed her good dopamine to the anterior striatum away from the prefrontal cortex decreasing her focus and mood. Wellbutrin augmented this.
- She makes very little serotonin and has poor serotonin transportation increasing stronger depressive bouts.
- Her triggered stress pathways further blocked her little serotonin production.

Annie’s Program

- 5HTP 100 mg - 3 BID with food for 12 weeks and then reduced her to 2 BID.
- **Ashwagandha 100mg, phosphatidyl serine 50mg, passionflower 100 mg combo**– 1 cap in the am, 2 before bed.
- Lactium 150 mg, l-theanine 50 mg– 2 BID empty stomach for 8 weeks and then reduce to 1 BID
- Took her off Wellbutrin with her GP.
- Encouraged getting out for walks daily.
- 1 square of dark chocolate each time she craved alcohol.

Annie’s Outcome

- Within 1 week Annie’s mood began to lift and by the end of the second week she was getting out of bed around 9 am.
- Her desire to drink reduced by 70% by the end of the 3rd week and her focus and concentration significantly improved.
- At 6 weeks she began applying for jobs again and getting for a walk daily with a girlfriend.
- 9 months later she was working full time from home. She still has dips in mood following by a desire to drink, but now knows how to control them: by temporarily increasing 5-HTP Supreme and adding in 2 Catecholacalm before bed as needed.

Differential Treatment Plan

- Mark
- Genetically low dopamine and serotonin with a poor stress response.
- Able to control dopamine/serotonin through exercise in past .
- Long term control of mood, focus, addictive behavior is by controlling hormone production via exercise and supplementing as needed .

- Annie
- Genetically close to normal dopamine and very low serotonin with a poor stress response.
- Able to control serotonin when stress was low with low dose 5-THP.
- Long term control of mood, focus, addictive behavior is by supporting serotonin production at a higher level and increasing during times of stress.

Q and A

Thank you