

Most of the parts of this theory of me/cfs me/Cfs etiology are not novel, but I think this ultra specific arrangement of them is. So, I will give credit where credit is due, for the individual parts. Jeff Wood (mechanicalbasis.org)... Jen Brea, for discussing connections between mcas and infections and connective tissue damage. @hip on the forum phoenixrising, for coining the term and idea “dual factor theory of ME/CFS outbreaks”

I will also try and make the organization chronological, from embryo to adult.

And I will try and break down pathology from macro to micro levels in a way that makes sense, and include a summary of both the theory and the important gaps left to fill/investigate, at the end. (Editor note, especially harp on the known unknown environmental variable/s that causes inflammation and immune suppression)

In utero:

1. Neural tube defects, either congenital tethered cord or chiari, are likely to be an issue in me/Cfs patients, and can be caused by in utero exposures to organophosphate pesticides like chlorpyrifos. <https://www.sciencedirect.com/science/article/pii/S2090506815001049> , <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6029725/>
 - Often these issues are mildly symptomatic until a major infection or environmental exposure
2. Some sort of hyper mobile phenotype
 - a. Again not necessarily symptomatic, and perhaps not fully meeting criteria for a connective tissue disorder, but some level of hyper mobility, seems somewhat common in this population

Onset/Trigger of ME/CFS

1. Infection
 - a. Certainly the most common reported trigger <https://www.cdc.gov/me-cfs/about/possible-causes.html>
 - b. Probably not sufficient to cause me/cfs *on it's own*, eg we dont know why the [~10 percent of patients with mono](#) or [~25 percent of patients with Lyme disease](#) go on to develop a chronic illness while the rest fully recover
 - c. What those other infections? Less important but list them
2. Environmental exposure
 - a. Most commonly reported is mold exposure. However pesticide exposures and other chemicals are plausible too.
 - b. **Very specific outdoor toxins/bio toxins have been reported to be associated with me/cfs, not just moldy buildings, but these have not been identified and studied, so most of what I say here is theory and speculation. As a side note, I personally think that the indoor and outdoor toxins are the most important triggering and maintaining factor in this illness. We dont know**

exactly what these toxins or combinations of toxins are, but we have guesses and theories, some that are backed up by recent scientific literature (nanoparticle theory)

<https://paradigmchange.me/wp/outdoor-toxins/>

<https://www.pnas.org/content/115/27/7087>

<https://cfsuntied.net/2014/12/04/and-now-for-something-completely-different/>

- c. Heavy metals--either through ingestion or nanoparticle inhalation (car exhaust is a common form of this), or through fog (mercury fog
<https://news.ucsc.edu/2019/11/wilmers-mercury.html>)
- 3. Or, Dual Factor theory
 - a. A combination of immune suppressant and an infection. The immune suppressant can be an environmental exposure , although not limited to
<https://forums.phoenixrising.me/threads/me-is-not-mould-intolerance-mould-intolerance-is-not-me.51792/page-6#post-856637>
 - b. Cite studies on immune suppressing effects of various bio toxins, and also the fungal/viral colonization together making things difficult for immune system
[trichothecenes immune suppression](#) , [zinc nanoparticles increase cyanobacteria toxicity/immune suppression](#)
 - c. Quote Hip from pr
 - d. Discuss how it explains geographic effect/shape of outbreaks in way that purely-'just quote from Hip here or erik
- 4. Physical trauma
 - a. Car accidents, whiplash etc

Central pathologies (post trigger)

- 1. Macro
 - a. Ligament damage from post infectious/toxin exposure induced inflammation, combined with congenital tethered cord, leads to craniocervical instability. The cervical instability leads to brainstem compression.
<https://medium.com/@jenbrea/onset-part-ii-mold-damage-9f9b37cf5a80>
 - b. Csf flow is blocked either by chiari or cci, causing high intracranial pressure. Csf flow blockage also leads to impairment of brain detoxification, especially during sleep [The Role of the Craniocervical Junction in Craniospinal Hydrodynamics and Neurodegenerative Conditions](#)
 - c. Brainstem compression from cci
 - i. Causes global hypoperfusion?
 - ii. Causes hypometabolism?
 - iii. Causes inflammation both directly (by injury activating glia) and indirectly (by causing impaired detoxification, blocking csf flow, and causing an inflammatory response to the toxins the body hasn't dealt with)
 - iv. Causes autonomic issues, pots, OI, apnea of various kinds, hypoxia, gut motility issues

- v. Causes PEM as a result of impaired blood flow/autonomic function?
 - vi. Causes gaba/glutamate imbalance
 - vii. Causes headaches/coat hanger pain
 - viii. [summary of all of the above here](#)
 - d. Chiari
 - i. Similar to cci--both cause [cervicomedullary syndrome](#) and csf flow blockages
 - e. Tethered spinal cord
 - i. Causes hypoperfusion of spinal cord
 - ii. Causes bladder issues
 - iii. Causes fatigue
 - iv. Causes hypometabolism
 - v. Causes PEM, impaired oxygen extraction from muscles
 - vi. <https://medium.com/@jenbrea/pathology-part-ii-could-pem-be-a-symptom-of-neural-strain-f5be69175e1>
2. Micro (cellular level/molecular)
- a. Inhaled toxins/pollutants/irritants lead to brainstem *inflammation*. This explains the subset of people without cci who nevertheless are similar in severity and symptoms to cci patients. <https://www.pnas.org/content/115/27/7087> , <https://www.sciencedirect.com/science/article/pii/S1748013218306364> , <https://www.frontiersin.org/articles/10.3389/fneur.2018.01033/full> (last study showing brainstem inflammation in me/cfs patients as well as commenting on and critiquing methodology of brainstem imaging)
 - b. Hypometabolism as a protective response to oxidative stress? Is this incompatible with mechanical issues causing hypometabolism? Dont think so, Naviaux has mentioned CCI as something that could cause the [cell danger response](#), which is coordinated through pathways in the brainstem
 - c. Specifically, as a result of brainstem compression/neural stretch injury, glial activation and whatnot.
 - d. The problems in metabolism are not a primary issue and not solvable through thyroid hormone or supplementing any cofactors of the Krebs cycle. They are adaptive. <https://www.pnas.org/content/113/37/E5472>
 - e. Inflammation from the innate immune response to novel toxins/pollutants, in the absence of a robust adaptive immune response. Allergies are [adaptive](#)
 - f. Immune profile, in general?
 - g. High brain glutamate/lactate --due to physical trauma OR bio toxins (like domoic acid! Or penitrem a): <https://www.sciencedirect.com/science/article/abs/pii/030439409190792R>

Fun bonus? [Glutamate receptors in the brainstem mediate sound sensitivity](#). Actually it's not so fun. For me, as a former musician, sound sensitivity has been the worst part of my ME/CFS.

Interesting to learn indirectly that both toxic exposure and brainstem injury could contribute to sound sensitivity.

In conclusion: a simplified model:

Someone born with tethered cord (not necessary but it helps) , gets an infection while living in an **environment with toxins**. Becomes one of the substantial minority of the people with that infection who have a chronic illness. The infection and **environmental exposure** lead to inflammation in the brainstem and globally, which in some patients damages ligaments, leading to craniocervical instability. So most or all patients end up with either inflammation in the brainstem or mechanical compression of this. This leads to very severe ME, the brainstem compression in turn blocks csf flow, which prevents the brain from proper detoxification, especially during sleep. Brainstem compression , cord stretching , and inflammation cause all or most of the autonomic issues, blood flow problems, and PEM in this illness. Csf flow blockage causes a vicious cycle in which the brain cannot properly detoxify, and thus the environmental toxins which caused the initial inflammation become even more of an issue, causing an inflammatory response while trying to expel them (cite recent research rethinking the allergy theory of it being adaptive not just against parasites).

And one last thought: I believe that despite the role of other things, such as infection and trauma, in this disease, the role of *as of yet unknown environmental toxins/pollutants* is , very underrated. Connective tissue damage as a sequelae of infection is not unheard of, but , we don't have good epidemiological data on how frequent these conditions are, and I believe them to be increasing. The environmentally caused inflammation may be the main difference separating those who have me/cfs post infection and those who dont. I would have high confidence in the ability to make an animal model of me/cfs based on these factors, if only we knew what the *unknown environmental toxin* was. That variable, *agent x*, needs to be found. Otherwise we will know how to treat ME/CFS but not cure it or prevent relapse.

My most plausible idea of what agent x is, is some kind of slurry of mold spores or mycotoxins, stuck to nanoparticles that are ubiquitously floating around as a result of industrial production of various sorts. But honestly, scientists should just be starting with the idea that we know nothing, and go hunting with air samples and mass spectrometers or NMRs.