

Hypothesis

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Hypothesis

Connecting the Dots Between ME/CFS, HSD/hEDS, Abnormal Fascia, Lymphatic and Glymphatic System Impairment, and Craniocervical Instability

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Abstract

This hypothesis paper encourages a comprehensive approach to studying Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) that connects the dots between Hypermobility Spectrum Disorders (HSD) and Hypermobility Ehlers Danlos Syndrome (hEDS), fascial abnormalities, impaired lymphatic and glymphatic systems, spinal conditions like craniocervical instability and Chiari Malformation, and ME/CFS. In particular, this paper encourages more research into biomechanical processes that may contribute to ME/CFS and ME/CFS-like presentations of Long COVID among individuals with HSD/hEDS.

Keywords: ME/CFS; lymphatic system; glymphatic system; fascia; hypermobile ehlers danlos syndrome; hypermobility spectrum disorders; craniocervical instability; chiari malformation

In 2025, two articles appeared in separate special issues of the International Journal of Molecular Sciences (IJMS); while they do not reference each other, they would benefit from being considered together as each sheds light on an important piece of the complicated puzzles posed by Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID. This article considers the interrelationship of the subjects covered by these articles in light of the experience of my daughter, who has been diagnosed with Hypermobility Ehlers Danlos Syndrome (hEDS), ME/CFS, craniocervical instability, Chiari Malformation, and POTS. (More background on my daughter's case may be found here. [1]) I propose connections between these chronic conditions mediated by disorders of the fascia and lymphatic and glymphatic systems. More research is needed on the role these biomechanical processes may play in ME/CFS and ME/CFS-like presentations of Long COVID.

At first blush, the two IJMS articles seem unrelated: one examines disorders of the fascia, [2] thin layers of connective tissue that surround the muscles and other organs, while the other considers the role that disorders of the glymphatic system, [3] which clears waste from the brain, may play in the pathophysiology of ME/CFS. The first clue that the papers may be related comes from the focus in the first article on the fascial pathophysiology of people with Hypermobility Spectrum Disorders (HSD) and Hypermobility Ehlers Danlos Syndrome (hEDS), a population disproportionately represented among people with ME/CFS. [4,5] Another sign of a potential connection lies in the fact that the glymphatic system drains (in part) to lymphatic vessels located within the dura mater, a connective tissue layer, [6] that pass through the crowded craniocervical junction [7] where they could plausibly become vulnerable to mechanical narrowing or impaired flow due to abnormalities in the deep fascia of the upper cervical region. Considered together, a better understanding of the processes described in these articles may help to clarify the connections between hypermobility and ME/CFS and ME/CFS-like presentations of Long COVID. [8]

The first paper describes a range of abnormalities observed in the fascia of people with HSD/hEDS, including "increased fascial thickness, reduced glide between fascial planes, and altered tissue stiffness" and discusses a potential mechanism (elevated TGF- β 1) through which these abnormalities could contribute to chronic fatigue. [2] There are a number of other potential processes through which impaired fascia could contribute to symptoms in people with HSD/hEDS. [9] In

particular, given that lymphatic vessels are located within the fascia [10] and that abnormal fascia functioning could affect lymphatic flow, [11] I would encourage exploration of the possibility that impaired lymphatic functioning contributes to ME/CFS symptoms in people with HSD/hEDS. I've seen parts of this mechanism at work in my daughter, in which fascial tightness in the skull and around the axillary and popliteal nodes appears to obstruct the lymphatic flow, as suggested by symptoms that improve when the tightness is alleviated and we undertake manual lymphatic drainage. These include a localized sensation of trapped fluid and (when untreated or undertreated) systemic symptoms of increased fatigue and overall malaise.

One potential pathway through which impaired lymphatic function could contribute to some of the symptoms seen in people with ME/CFS and ME/CFS-like presentations of Long COVID begins with vascular damage and/or inflammation stemming from a virus, a systemic inflammation event (such as a mast cell activation or ischemia/reperfusion) or exposure to an environmental irritant. This increases vascular permeability, leading to an influx of protein-rich fluid into the interstitium. [12] If thick and disordered fascia disrupt the efficient functioning of the lymphatic system, it may be unable to keep pace with and remove all the extracellular matrix (ECM) fragments produced during vascular repair, potentially contributing to a chronic state of low-grade inflammation and endothelial activation that may delay or impair the completion of the vascular repair and the efficient removal of pro-inflammatory cytokines. [11,12] This is consistent with the findings of elevated proteins associated with vascular repair in proteomic studies of people with ME/CFS. [13] The ECM fragments themselves may contribute to further lymphatic dysfunction, [14] further reinforcing the feedback loop. Increases in vascular filtration during physical or mental exertion could exacerbate the problem by significantly increasing the volume of protein-rich fluid entering the interstitium and needing drainage through an impaired lymphatic system. [15] This could potentially play a role in post-exertional symptom exacerbation and post-exertional malaise.

Significant increases in interstitial fluid can also contribute to the formation of subcutaneous adipose tissue in some individuals, as is believed to happen in lipedema, which is pro-inflammatory and can become fibrotic and painful, potentially contributing to pain and ongoing inflammation in people with ME/CFS. [16,17] In addition, the fascia play a biomechanical role in supporting muscle and joint movement, which in turn influences venous return, [18] so the potential impacts of abnormal fascia on venous return and dysautonomia also merit exploration.

Given the evidence of blood brain barrier dysfunction and microglia activation in people with ME/CFS, it is not surprising that ME/CFS researchers are particularly interested in the glymphatic system; by exploring how glymphatic system dysfunction could contribute to ME/CFS the recent paper provides an important roadmap for future research. [2] But as the discussion above suggests, disorders of the broader lymphatic system may also lead to profound adverse effects in people with ME/CFS and similarly merit further research. It is also important to recognize the interrelationship of the lymphatic and glymphatic systems. For example, a recent mouse model study found that noninvasive stimulation of superficial lymphatics through the skin doubled outflow of cerebrospinal fluid (CSF). [19] While we cannot document this precise mechanism through our external observations, we have found that vigorous stimulation of my daughter's scalp and massaging of the fascia in her lower skull and upper neck, followed by manual drainage of the accumulated superficial lymphatic / interstitial fluid, markedly improves her brain fog. One possible explanation is that this technique reduces fascial constriction and tissue congestion in the craniocervical region, contributing to improved cerebral perfusion; the same congestion relief could potentially improve the outflow of glymphatic fluid / CSF.

Conceptually, disorders of the lymphatic or glymphatic system could be related to either excess inflow of fluid into the interstitial space or impaired removal of that fluid. I would encourage research on both fronts. On the inflow side, it will be important to understand whether and to what extent (and why) there is a large increase in the volume of fluid entering the interstitial space (e.g., due to inflammation that triggers vascular permeability or vascular damage or both) that overwhelms the lymphatic system of people with ME/CFS. If so, how can this inflow be staunched? It will also be

important to understand the composition of that fluid. For example, we know that during acute vascular permeability, fibrinogen released into the interstitial space converts to fibrin which forms a gel that impedes lymphatic drainage. [20] But what happens when that fibrin has amyloid properties, as we see with microclots? [21] Could amyloid fibrin be clogging both the vascular and lymphatic systems?

While my daughter remains in bed most of the time, her condition has improved over time; among other changes, she had a much more urgent need for manual lymphatic drainage in the months following her last major relapse (in 2020) than currently. From our perspective, it feels like the volume of fluid entering the interstitium has been dramatically reduced (although it's possible that what we're observing is due to improved clearance of fluid instead or some combination.) This raises the question of what contributed to this result. One plausible explanation is that her relapse was caused by vascular damage that occurred during a systemic inflammatory event which created the conditions that allowed an overwhelming volume of fluid to enter her interstitial space. Her real but painfully slow improvement may have been the healing of that vascular damage, potentially slowed by the impaired healing process discussed above related to her hEDS. [22] There could well be other explanations; I offer this anecdote to highlight the kinds of issues meriting further research on fluid inflow.

There are many factors that could impair the removal of interstitial fluid by the lymphatic system including the fascial abnormalities, ECM fragments, and fibrin gel discussed above. With respect to the glymphatic system, one particular issue to consider, as my co-authors and I originally proposed here, [8] is whether spinal conditions like craniocervical instability and Chiari malformation could impede the removal of glymphatic fluid and drainage of CSF through vessels passing through the craniocervical junction. Potentially, people with these spinal conditions might not experience symptoms until the volume of fluid entering the interstitial space markedly increases following vascular damage or increased inflammation stemming from a viral infection, spinal trauma, or exposure to an environmental toxin. When this occurs, congestion at the craniocervical junction may contribute to excess glymphatic fluid build-up, which causes increases in intracranial hypertension and brainstem compression. (A newly published article offers a different mechanical hypothesis linking spinal abnormalities to brainstem compression in people with ME/CFS. [23] It could be useful to integrate these hypotheses.)

There are many other hypotheses that could be explored, but hopefully this discussion is sufficient to underscore the potential of fascial, lymphatic, and glymphatic impairments to tie together many of the diverse findings observed in people with HSD/hEDS and ME/CFS or ME/CFS-like presentations of Long COVID and document the importance of further research on these topics.

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Abbreviations

The following abbreviations are used in this manuscript:

CSF	Cerebrospinal Fluid
hEDS	Hypermobile Ehlers-Danlos Syndrome
HSD	Hypermobility Spectrum Disorders
IJMS	International Journal of Molecular Sciences
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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