The Pathobiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Case for Neuroglial failure

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A brief summary of our research, available at:
https://www.frontiersin.org/articles/10.3389/fncel.2022.888232/

Our work on the role of glia in ME/CFS is now published in Frontiers cellular neuroscience. In this publication, we explain why ME/CFS research may benefit from a closer look at the role of neuroglia. The term "neuroglia" or "glia" describes a network of cell populations mainly in the central nervous system which is important for brain health and brain function. In its core this network constitutes the immune system of the brain.

Why should we take this network into focus in ME/CFS?

Many biological systems are affected in ME/CFS. There is, for example, evidence for immune dysfunction (including autoimmunity), for metabolic, mitochondrial and possibly peroxisomal dysfunction, for endothelial or vascular dysfunction, for inflammatory activation and for dysfunction of the autonomous nervous system (and the central nervous system in general).

But it is still unclear how these dysfunctions fit together and how they conspire to cause the symptoms of ME/CFS.

We think that these processes can directly or indirectly affect a very important regulatory system of our biology: the neuroglia, and thus the innate immune system of our central nervous system (CNS). This non-neuronal system is mainly based on cells called microglia, which cooperate with other glial cells, called astrocytes and oligodendrocytes (the latter are responsible for maintaining the myelin sheaths of the nerve cells). The main task of this glial network is to protect the functionality and integrity of the brain. Whenever the health of the brain is challenged these cell population will be called to action. The glial cells are also very important for the cooperation with the immune system outside the brain.

In a more detailed look, the neuroglial network plays an important role especially in the regulation of cerebral blood flow, in protecting the blood-brain barrier and in maintaining functional connections within the brain. The glial cells are thus very important for motor functions, autonomous regulation, sleep, sensory gating, memory, mood and cognition – all functions that are to some extent "broken" in ME/CFS. Also, glial cells work in close concert with mast cells.

Therefore, theoretically, the glial network could play an important role in the pathobiology of ME/CFS.

Our work step by step

We therefore reviewed the whole ME/CFS literature for details about a possible contribution of glia in the many pathways that are dysregulated in ME/CFS. Here, we put the main focus especially on two features of ME/CFS: post-exertional malaise, and the reduced cerebral blood flow.

We picked these two features for two reasons: both are present in all ME/CFS patients (at least if stringently diagnosed and examined), and they have been exceptionally well studied. Also, they seem to somehow jive together (for example, exercise leads to reduced cerebral blood flow).

What we found is that both of these features can be plausibly explained as a manifestation of malfunctioning glia (some more details below).

We then examined through which ways the other pathobiological features of ME/CFS (e.g., endothelial dysfunction, immune dysfunction, mitochondrial/metabolic dysfunction) could affect the functionality of this biological hub between brain and body. Endothelial dysfunction, for example, can alter the permeability of the blood-brain barrier so that peripheral immune cells can enter the brain and cause inflammation. This in turn activates the glia. Mitochondrial dysfunction (or any other cause of metabolic dysfunction) goes along with abnormal metabolites; these can also activate the glial cells (which are especially vulnerable to many toxic substrates). The same aggravation can happen from severe inflammation (which also floods the body with abnormal metabolites) or from signals from a revved-up immune system. Autoantibodies, for example, may not only act on the blood vessels but may also directly or indirectly influence the immune system outside and inside the brain (for example, if the blood-brain barrier is not working properly).

Finally, we reviewed the ME/CFS experimental record for evidence from e.g. imaging studies or from laboratory studies (proteomics, transcriptomics, metabolomics, etc.) that may point to glial dysfunction in ME/CFS. Here, we identify and present many findings from different fields and different research teams which suggest that the function of glia may indeed be affected in ME/CFS. For example, all the findings of abnormal brain function in ME/CFS can plausibly be explained as manifestations of glial dysfunction:

- broken neurovascular coupling
- decreased cerebral blood flow
- altered functional connectivity between brain areas
- raised intracranial pressure
- altered cellular metabolism in several brain areas and nuclei
- vagal dysfunction.

The Jeykyll ond Hyde face of glia

In our explanation of why glia may be central in the regulatory desaster of ME/CFS we especially highlight a unique property of this group of cells: they can shift between an “aggravated” (= hyperreactive) and a more “quiescent” state.

- Aggravation happens by any form of stress (including inflammation)
- As already mentioned, glia can also become activated by abnormal metabolites and also by oxidative or nitrosative stress
- If repeatedly or pervasively aggravated, the glial cells become ever more reactive, i.e. prone to overreaction. This creates a vicious circle.
- This also means that the threshold for becoming aggravated can fluctuate and differ over time.

We propose that this flexible response of glia could explain the typical PEM features, i.e., the delayed onset, the typical duration of days (to weeks) and also the different threshold for PEM between patients. We also think that the central role of glia in PEM could explain why PEM can happen even without any muscular exertion (i.e., alone from thinking hard or from watching a movie).

No “alternative” theory

Our explanations are not meant to replace or contradict the many theories about ME/CFS, like mitochondrial dysfunction, endothelial dysfunction, the role of autoimmunity, the role of reactivation of endogenous microbes, etc. To the contrary: With our theory we try to add a layer which may provide a better or finer-grained understanding of the many broken pieces in ME/CFS. Also, this added piece may be valuable when it comes to understanding how some drugs may work for ME/CFS, or which drugs or interventions may be hopeful candidates.

Also, with this work, we were able to benefit from the knowledge of a world expert on glia, Marie Eve Tremblay, who co-authored this publication (so far ME/CFS research has not had that much access to this field of neuroscience). What she could highlight, for example, was that we may need to think more stringently about the concept of *neuroinflammation* (which some ME/CFS researchers embrace and others dismiss). Glial dysfunction can be caused by many processes, some of which may not necessarily be *inflammatory*. Also, glial dysfunction may not necessarily cause an inflammatory response. For instance, dysfunctional glia may “just” disrupt neurovascular coupling, i.e., the process which matches local perfusion in the different brain areas to local demand. We should probably become less zealotic in this regard.

And, finally, we have used this review of the ME/CFS literature to again and again regard ME/CFS from a system´s perspective: how may the pieces fit together? How may they be orchestrated? This gave rise to an “apple graph” which is part of the publication and shows how intervowen and resonant the many aspects of ME/CFS are.