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EDITORIAL

The biological challenge of myalgic encephalomyelitis/chronic fatigue syndrome: a solvable problem

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is comparable to multiple sclerosis, diabetes or rheumatoid arthritis in prevalence (∼0.2% to 1%), long-term disability, and quality of life,[1–5] yet the scale of biomedical research and funding has been pitifully limited, as the recent National Institutes of Health (NIH) and Institute of Medicine reports highlight.[6,7] Recently in the USA, NIH Director Francis Collins has stated that the NIH will be ramping up its efforts and levels of funding for ME/CFS,[8] which we hope will greatly increase the interest in, and resources for researching this illness. Despite scant funding to date, researchers in the field have generated promising leads that throw light on this previously baffling illness. We suggest the key elements of a concerted research programme and call on the wider biomedical research community to actively target this condition.

Biological questions

For many with ME/CFS life has effectively stopped – so immediate therapeutic studies are attractive. However, although serendipity can help, as in the observation that some patients may benefit from B-cell depletion,[9] lack of biomarkers or an understanding of the illness has held back development of targeted treatments. Study of mechanism therefore remains a key priority.

Drawing on the experience of one of us (JE) in elucidation of pathogenesis in rheumatoid arthritis, and its application to therapy,[10,11] we favour starting with broad systems analysis of natural history. Following Stastny,[12] we see such an analysis as including the evaluation of internal stochastic factors (e.g. chance immunoglobulin gene rearrangements encoding auto-antibodies capable of evading deletion) as well as genetic and environmental factors. Stochastic factors, although of major importance in cancer (as cumulative random mutations), have often been overlooked in mechanistic explanations of disease and are likely to be relevant in acquired, largely sporadic conditions such as ME/CFS. Additionally, epidemiology provides several clues, most notably the strikingly high proportion of female patients – typically 75% [1,2] – and the apparent bimodal age distribution [13] suggesting an age-dependent susceptibility to initiating events.

There is some family clustering, and sometimes a common history of initial viral or other (chiefly intracellular) infection, occasionally as during an epidemic: examples include Epstein-Barr virus (EBV), Ross River virus and the bacterium *Coxiella burnetii* (which causes Q fever).[14] Either prolonged exposure to a pathogen or adverse environmental

factors, in combination with stochastic factors, could lead biological signalling networks to shift from a healthy steady state into a dysfunctional steady state that perpetuates the illness.[15–17] The occurrence of remission, either spontaneous or following treatment, [9] supports this dysregulatory model rather than one of irreversible damage.

Clues to ongoing mechanism include:

- unconfirmed hints of genetic linkage, including to cytokine [18,19] and human leucocyte antigen genes [20];
- repeated but variable observations of defective natural killer cell populations [21,22];
- variable changes in B and T cell control of EBV reactivation in patients whose illness began with infectious mononucleosis [23];
- reduced physiological performance on the second of a two-day cardiopulmonary exercise test, despite respiratory exchange ratios indicating maximal effort on both days [24];
- substantial changes in leucocyte gene expression of metabolite-sensing adrenergic receptors following physical exertion [25];
- autonomic dysfunction, including orthostatic intolerance and syncope [26];
- altered brain imaging, indicating both microglial activation [27] and structural changes.[28]

These findings have not been replicated sufficiently to provide firm anchor points for further research, but this may reflect lack of opportunities with scant resources and perhaps cohort heterogeneity. In this context a recent report suggests that plasma cytokine levels may be abnormal (including IL-8 and gamma interferon, which have been noticed before), but specifically in illness of under three years' duration.[29]

Potential models

The most productive analysis may involve the systems dynamics of the chronic disease state, assuming that ME/CFS could be the sequel of some sort of 'hit and run' event. Further genetic clues could be helpful but may be hard to identify. The continued search for novel infective triggers may be productive, but so far it seems that no unique microbe is implicated. The central problem is in explaining the ongoing physiological disturbance.

Considering both the clinical picture itself (with widespread cognitive and other global problems such as pain and fatigue), and the likelihood that the chronic disease state may involve a complex regulatory system shifting to an abnormal equilibrium state, it is likely that the pathophysiology involves the central nervous system (CNS), plus or minus the immune system (both with complex regulatory dynamics) in some or all cases. The autonomic nervous system is another potential site for dysregulation. Generalised metabolic abnormalities have been proposed by others,[30] but again these seem likely to be secondary to dysregulation of systemic control mechanisms, since acquired persistent dysregulation purely at a local cellular or mitochondrial level is hard to explain, despite some intriguing findings.[31]

There are many possible models, but three major categories of causal model appear of most interest:

1. The brain is responding normally and symptoms are due to persistent signal input from peripheral tissues, such as cytokines or metabolites, based on persistent immune dysregulation (as in autoimmunity, for example, or, conceivably, low-grade infection).
2. There is a persistent abnormality of 'housekeeping' processes in the brain, such as an increase in activation of microglia following an initial insult, which leads to distorted processing of peripheral signals including autonomic pathway activation.
3. There is a persistent abnormality in neural signalling in sensory pathways. This may be quantitative (comparable to dopamine depletion in Parkinson's disease) or qualitative (comparable to post-concussion amnesia or post-traumatic stress disorder) due to CNS structural or regulatory changes following an initial insult.

These categories may overlap. Each might predominate in a subgroup of patients but all may use some common pathway causing exertion intolerance and abnormal responses to other stimuli, together with sleep disturbance, which might provide a central pathophysiological concept.

The evidence currently available for contributions from each of these three model categories is limited, but there are some clues. The improvement in 67% of patients at six months following B cell depletion (versus 13% of controls) needs confirmation, but suggests that ongoing immune dysregulation may drive symptoms.[9] The general absence of a significant persistent acute phase response does not preclude an immunological basis since several autoimmune diseases have non-inflammatory effector mechanisms. Studies of respiratory, metabolic and leucocyte gene expression changes following exercise (which often precipitates a relapse in symptoms) hint at persistent peripheral signal sources.[24,25] Two independent research groups are currently examining the possible contribution of gastrointestinal-tract microbiota to persistent immune dysregulation. [32,33]

While the brain is often considered as 'immune privileged', it has been shown that peripheral immune activation can influence the microglia of the brain, with 'sickness behaviour' as a stereotypical example.[34,35] Microglial activation has been implicated in animal models of persistent hyperalgesia,[34] immunologically induced fatigue in animal models [36] and a range of other conditions from major depressive disorder to neurodegenerative diseases.[35] A recent positron emission tomography (PET) study suggests that microglial activation in brainstem and limbic areas may occur in ME/CFS [27]; hopefully replication will follow. There is also a significant literature on possible changes in the hypothalamic–pituitary–adrenal axis that might support a role for 'dysfunctional housekeeping' centrally, but findings are difficult to interpret.[37]

Manipulation of neurotransmitter levels with drugs such as antidepressants has not shown significant benefit, so evidence for a quantitative abnormality in central signalling is currently lacking. However, the full range of transmitters and receptors has probably not been explored sufficiently to exclude this possibility. A report of local structural change in the arcuate fasciculus in ME/CFS [28] is intriguing. Qualitative functional changes in neural pathways are perhaps hardest to address. There are difficulties with direct interpretation of functional magnetic resonance imaging (fMRI). However, Baraniuk's group [38] has

reported differing connectivity patterns on fMRI in subgroups in Gulf War syndrome (which has commonality with ME/CFS) and such internal comparisons may help overcome interpretation problems.

These are beginnings, but they demonstrate that alternative theoretical models are being proposed and tested.

Practicalities

Identifying the biological basis of ME/CFS is challenging but there are now a number of promising findings, with a real opportunity to make progress towards rational therapy. These areas seem most worth highlighting:

(1) *Infrastructure*. Increased collaboration and networking among specialists across the academic and medical disciplines is needed. A combination of views from different fields, along with a broader collection of data can lead to more robust studies and important insights. The problems with classification and the likelihood of subgroups within ME/CFS require improved infrastructure to allow mechanistic research to relate back to population-based cohorts and demographic data. Selection bias due to clinical referral patterns and variable use of criteria threaten to undermine replication attempts. Population-based cohorts will also be essential in reducing selection bias in future genetic studies. Comparison of epidemiological factors with other, better understood diseases within a population could also prove productive.

(2) *Brain imaging*. Given the likely role of the CNS in the symptomatology, brain imaging has potential to provide direct evidence of pathophysiology. Although appropriate techniques may still be under development, both MRI and PET show promise. [27,28,39]

(3) *Immunology*. Mechanisms underlying potential abnormalities in natural killer cell function, cytokine shifts, and immune responses to viruses such as EBV need to be pinned down. A continued search for auto-antibodies to neural components or intercellular signal receptors is worthwhile, following the discovery of novel antibodies in other neurological diseases. Preliminary findings have shown promise for ME/CFS.[40]

(4) *Autonomic/endocrine regulation*. Continued exploration of dysregulation of autonomic and endocrine signalling systems that might explain prominent autonomic symptoms in ME/CFS seems important.

(5) *Stress testing*. The re-emphasis on post-exertional malaise in the Institute of Medicine review [7] highlights the importance of extending documentation of physiological responses specifically in the context of exertion, whether peripherally in muscle or the circulation, or in the CNS.

(6) *Replication*. It is key to replicate immunological, microbiological, imaging and other observations and agree on which findings are robust. A facility for exchange of blinded samples and images from cohorts in different countries would establish confidence in quality control.

(7) *Data presentation*. Data should be presented in forms (such as scatter plots) that allow subgroup analysis. All raw data should be available, even if null or unpublished, so that meta-analyses can be accurate.

In summary, much more biomedical research into ME/CFS is urgently needed to provide hope for improved treatment. Nobody can claim to know at what level the key disorder of physiology occurs, although various levels of brain function appear to be involved. There may be several etiological subgroups, which may require different management. Prognosis is poor and the impact of current care is limited. We now need a more concerted effort for ME/CFS.

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