RESEARCH REPORT IN MYALGIC ENCEPHALOMYELITIS (ME)/ CHRONIC FATIGUE SYNDROME (CFS)

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There is now so much literature from so many varying aspects of biology in ME/CFS that it is simply not possible to summarise it all in a paragraph or two. By calling the illness CFS we start with a conundrum - the name.

This is a small point to many academics and clinicians but to sufferers and researchers alike it is at the hub of the enigma in terms of treatment and management and, also, for the researcher, in the classification and definition of cohorts - the hallmark of good science.

Working definitions are necessarily obscure when there is no definitive test for an illness but, whichever definition one uses (nine definitions are in current use), there are clearly subgroups of patients within it. This may take the form of illness onset (slow or sudden), severity and expression of symptoms (for example with or without neurological signs, sensitivity to drugs, chemicals, household goods etc.), age, gender, length of illness or, more specifically, on the basis of immune markers as recently demonstrated.

Currently there is a drive to rename and to reclassify and until this is complete the literature will continue to be awash with poorly defined reports on causality, aetiology, epidemiology and most importantly, treatments which may in some cases be simply wrongly applied but in others may lead to harm and irreversible damage. The present focus by many Health Boards and health planners on cognitive behavioural therapy (CBT) and physical rehabilitation therapy (PRT) may be seen as a response to pressure from patients organisations and members of Parliament besieged with complaints of inaction and charges of disenfranchisement from health care facilities.

Such treatments stem from psychological and behavioural models of illness and, by definition, they ignore all evidence of biological abnormalities. The literature is replete with papers on the claimed efficacy of CBT and PRT in CFS but not in ME; these papers are almost exclusively from a very small group of UK psychiatrists whose inclination is not only to exclude biological research but also to omit to inform readership that patients with ME are excluded from their studies.

This confusion in nomenclature is at the heart of the huge variation in quoted prevalence rates for the illness, from as much as 1-2% of the population with CFS down to 0.1-0.2% for the more serious condition ME.

ME is a neurological illness (WHO ICD 10 G93.3) with evidence of immunological and toxicological signs, clear disturbances to the neuro-endocrine stress axis, impairment of the autonomic nervous system, irregularities in perfusion to the brain and indeed to the peripheral vascular system confounded by red blood cell abnormalities with recent evidence suggesting a hypercoaguable state - all of these are extensively documented findings yet one could be excused for not knowing anything about such biological indications given the plethora of psychological based reports which pepper the UK literature. To quote Dr Andrew

Wright,**"the one disease, one diagnosis, one treatment approach does not apply to this group of illnesses**".

There is a very recent excellent clinical review on neurological dysfunction in ME/CFS which examines evidence for the epidemic and sporadic forms of the illness, reports on the possible aetiology of both physical and mental fatigue along with sleep difficulties, motor and sensory symptoms and impairment to the autonomic nervous system resulting in many complex symptoms most especially affecting temperature regulation, blood pressure control and gastrointestinal function.

In this paper, the authors postulate on a complex interaction between ion channels, neurotransmitters and specific neuroanatomic areas in the brain as being responsible for central fatigue in ME/CFS which could explain the symptoms of both physical and mental fatigue. This is not a new model since comparable mechanisms of pathogenesis are currently accepted for common migraine, Post Polio Syndrome (PPS) and idiopathic epilepsy, the latter having been considered to be a psychiatric illness until the second half of the twentieth century.

A better understanding of the anatomy and neurotransmission of the basal ganglia pathways would be extremely important in the therapeutic management of central fatigue. Unravelling the neurobiology of basal ganglia and their interaction with ion channels and neurotransmitters integrating motivation, motor and emotional activities will have important connotation not only in the treatment of CFS but also in Parkinsons Disease, Post Polio Syndrome and Multiple Sclerosis.

Moreover very few studies have been carried out on the potential role of peripheral aspects of fatigue a notable exception being recent work demonstrating early fatiguability of leg muscles after exercise with very significantly delayed recovery following aerobic challenge. Clarification and reproducibility of Dr W.H.M. Behan's studies (Dept of Pathology, University of Glasgow) on abnormal mitochondria in ME/CFS remains to be done but the door is at least open for specific structural and functional studies of the neuromuscular junction to be attempted. Studies on the metabolism of acetylcholine in muscle have yet to be carried out despite evidence for impairment of acetylcholine pathways within the vascular endothelium where it is a major nitrovasodilator.

A review of the literature on the immunology of CFS reveals that people who have more strictly defined Chronic Fatigue Syndrome (CFS) equating with ME have two basic problems with immune function that have been documented by most research groups:

1. immune activation, as demonstrated by elevation of activated T lymphocytes, including cytotoxic T cells, as well as elevations of circulating cytokines;

2. poor cellular function, with low natural killer cell cytotoxicity (NKCC), poor lymphocyte response to mitogens in culture, and frequent immunoglobulin de>These findings have a waxing and waning temporal pattern which is consistent with episodic immune dysfunction (with predominance of so called T-helper type 2 and pro-inflammatory cytokines and low NKCC and lymphoproliferation) that can be associated as cause or effect of the physiological derangement and/or activation of latent viruses or other pathogens. The interplay of these factors can account for the perpetuation of disease with remission-exacerbation cycles.

Besides external stimuli, intrinsic imbalances in neurotransmitter levels affect the immune system either directly by acting on immunocompetent cells or indirectly via induction of hormonal secretions. For instance, whilst some neurotransmitter imbalances are indeed associated with depression and several studies have documented the existence of physiologic, neuroendocrine, metabolic, and pharmacological abnormalities in both depressed subjects and in severely ill ME/CFS subjects, the fact is that the results are predominantly and very significantly in opposite directions in the two populations.

Although the causes of ME or CFS remain to be elucidated, many studies provide evidence for abnormalities in immunological markers among patients. A clear picture has not been achieved because of the variability in the nature and magnitude of the findings reported by different groups who have been studying differently defined cohorts. Moreover, little scientific support has been garnered for an association between the abnormalities and the diverse physical and health status changes in the ME/CFS population.

For instance, although a subset of patients with immune system activation can be identified, serum markers of inflammation and immune activation are said by the advocates of the psychiatric aetiology to be of limited diagnostic usefulness in the evaluation of patients with ME/CFS because changes in their values may also reflect an inter-current, transient, common condition, such as an upper respiratory infection, or may be the result of an ongoing illness-associated process.

On the other hand ME/CFS patients can be categorised by immunological findings. It is also worth noting that although the degree of overlap between distributions of soluble immune mediators in ME/CFS and controls has fuelled criticism on the validity or clinical significance of immune abnormalities in ME/CFS, the latter degree of overlap is not unique to ME/CFS and is also present, for instance, in sepsis syndrome and HIV-1 associated disease, clinical entities where studies of immune abnormalities are providing insight into pathophysiology.

While this is an incomplete picture of current research into a very complex illness it does at least try to bridge the huge divide between two entirely polarised schools of thought. In the UK at least ME/CFS is often viewed as a manifestation of dysfunctional illness behaviour or psychological frailty although the individual psychiatrists who so assiduously promote this view go to great lengths to express the notion that all illnesses have both psychological and physical aspects to them and that such dualism about physical versus psychological aspects of illness is irrelevant in modern medical practice.

This is true up to a point but when endorsing this perspective the same psychiatrists carelessly or expediently ignore the increasing evidence for the physical case for ME or CFS. There is little dispute that ME/CFS patients are predisposed to psychological symptom expression just like patients with other chronic health problems, most especially those with a neurological component, but these symptoms have to be seen and treated in the light of other, more dominating and certainly far more alarming physical manifestations of the whole illness picture.

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