EDITORIAL

Differing case definitions point to the need for an accurate diagnosis of myalgic

encephalomyelitis / chronic fatigue syndrome

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterised by unexplained and persistent or recurrent incapacitating fatigue accompanied by a variety of symptoms and substantial reductions in previous levels of occupational, educational, social and/or personal activity [1, 2]. Given the absence of biomarkers for diagnosis, ME/CFS is defined by a combination of symptoms, most of which are non-specific and common to a number of diseases and conditions.

Over 20 case definitions have been proposed, leading to large variations in sensitivity and specificity of diagnosis. These diverse sets of diagnostic criteria and distinct ways in which they have been applied pose significant problems, as research results may vary considerably according to which definition is used. A particular problem occurs when overly inclusive criteria are used, since their lack of specificity may lead to considerable selection bias [3, 4]. Unfortunately, many studies, clinical trials in particular, have used broad case definitions such as the Oxford criteria [5], which requires little more than the presence of persistent significant fatigue for over 6 months and the exclusion of conditions that could explain symptoms, for a diagnosis to be made.

This problem has been highlighted by the Agency for Healthcare Research and Quality (AHRQ) review of evidence for the NIH Pathways to Prevention Workshop [4], which showed significant changes to the interpretation of evidence for treatment, when studies using broad case definitions, such as the Oxford criteria, are excluded from the analysis. The implications for clinical practice suggest that fit-for-all management approaches to ME/CFS, although more applicable to those who fit such broadly inclusive criteria, may be inadequate for patients who fulfil better targeted case definitions.

For patients selected using more restrictive definitions, cognitive behavioural therapy (CBT), graded exercise therapy (GET) and other forms of non-drug management approaches to ME/CFS, are most appropriate as adjunct therapies rather than restorative treatments, when provided by therapists with a good understanding of ME/CFS. These forms of behavioural intervention have been shown to support the well-being and rehabilitation of those suffering from many chronic and disabling conditions [6]. However, it is very important that the use of behaviourally based management strategies does not deter researchers, physicians, and other health professionals from the overarching goal of investigating the causes and pathophysiology of ME/CFS in various sub-groups and the development of specific treatments.

Disease Misclassification

The impact of disease misclassification is well known in the epidemiological research field [7]. In observational studies and clinical trials, such misclassification can lead to significant under- or over-estimation of association or effect. For instance, in therapeutics, misclassification can lead to missed opportunities when it results in an under-estimation of effect in clinical trials. Over-estimation of effect from misclassification can lead to the implementation of costly and less effective service practices and possible patient harm.

Best epidemiological practice dictates that specificity, not sensitivity, of diagnostic criteria is more important in ensuring the validity of research studies [7]. This should encourage the use of more restrictive case definitions, which are more likely to capture genuine cases, with fewer "false-positives" and a lower risk of significant misclassification. Savitz and Wellenius point out that "*bias in measures of association should be least when using the most stringent, restrictive case definitions and greatest for the more uncertain, inclusive categories*" [8]. This assumes that the most restrictive case definitions relate to higher diagnostic certainty and has the added

advantage of usually reducing research costs. However, the subsequent testing of hypotheses in groups with less restrictive case definitions is also desirable, costs allowing, as part of a stepwise rational strategy for improving case definitions and refining hypothesis testing [9].

Restrictive Case Definitions and Bias

The relationship between restrictive case definitions and lower level of bias has been studied in other conditions such as febrile convulsions in relation to vaccinations [10] and in fertility and smoking. More current ME/CFS definitions such as the Canadian Consensus [1] (revised as International Consensus [12]) and Institute of Medicine (IOM) [2] criteria, address some of the problems of previous less stringent criteria. These newer definitions require a combination of specific symptoms for diagnosis, in addition to the presence of incapacitating chronic fatigue. For example, the IOM criteria require post-exertional malaise and unrefreshing sleep, and either cognitive impairment or orthostatic intolerance for diagnosis confirmation [2], whilst the Canadian and International Consensus criteria require the combination of a larger number of symptoms indicating impairments in a number of proposed body systems, e.g. neurological and immune systems [1, 12].

Using more specific case definitions only begins to address the complexities of studying ME/CFS. Like most diseases in clinical medicine, ME/CFS is heterogeneous in presentation and identified pathophysiology. Multi-causality and variations in disease mechanisms may require different approaches for diagnosis and treatment of sub-groups of cases. In the absence of a robustly validated case definition, the use of sound combined criteria can help to avoid significant selection bias, and advance the discovery of biomarkers for diagnosis, sub-grouping, and personalised treatments.

Symptoms vs. Diagnosis

While symptoms such as fatigue, pain and cognitive dysfunction can be described a representing a continuum of severity, to advance the discussion of disease entities such as ME/CFS (as opposed to description of symptoms), it is good clinical and research practice to dichotomise individuals according to diseased and non-diseased status. Using two simple examples, hypertension and diabetes would be difficult to identify as diseases without dichotomising the continuous variables of blood pressure and glycaemia. Determining the right cut-off points for disease status is more feasible once we have identified a small number of key variables. We argue that a reasonable starting point for this type of research in ME/CFS should be compliance with multiple criteria as indicated above.

Finally, it is difficult for both researchers and those with ME/CFS not to be left with a sense of frustration and loss when reflecting on the time and resources invested in studies using more generalized, and we argue, less productive criteria such as that contained in the Oxford definition. If ME/CFS participants who are more likely to be "true cases" are recruited with standardised procedures and robust data collection for clinical phenotyping across research groups, significant advances in the understanding of ME/CFS are likely to follow.

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