Chronic fatigue syndrome: Is it one discrete syndrome or many? Implications for the “one vs. many” functional somatic syndromes debate

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Abstract

There is a current debate as to whether “functional somatic syndromes” (FSSs) are more similar to or different from each other. While at the same time, there is evidence of heterogeneity within single syndromes. So, it could be that these syndromes are all part of one big process/illness, are discrete in their own right, or that they are heterogeneous collections of different illnesses lumped together by common symptoms but separated by uncommon pathophysologies. The example of chronic fatigue syndrome (CFS) is instructive. There is evidence to support all three models of understanding. Three recent large studies have suggested that FSSs are both similar and dissimilar at the same time. The solution to the debate is that we need to both “lump” and “split.” We need to study both the similarities between syndromes and their dissimilarities to better understand what we currently call the FSSs.

Keywords: Functional somatic syndromes; Chronic fatigue syndrome; heterogeneity; homogeneity; risk markers

Introduction

In order to understand the cause or pathophysiology of an illness or disease the usual first step is to define the phenotype of that illness and then seek associations with putative risk markers. Without doing that, no amount of markers will be shown to be consistently associated with one distinct illness or disorder. The example of one particular “functional somatic syndrome” (FSS), namely, chronic fatigue syndrome (CFS), provides insights into the difficulties of trying to define the phenotype in the absence of the biomarkers that usually help us to define a disease phenotype in the first place. The literature about CFS also provides the possible solution to this problem for both CFS and for all FSSs in general.

Does a phenotype of CFS exist?

There are several operationalized criteria used for defining CFS [1–3]. These criteria provide reliability across different studies [4], but the tests of validity suggest that they do not “cleave nature at the joint” [5], omitting more patients that have chronic unexplained disabling fatigue than they include. At the same time, large empirical studies suggest that there is a more broadly defined phenotype of chronic unexplained fatigue with associated symptoms (thus a CFS) with good cross-cultural and international empirical data supporting the broad phenotype of CFS [5–8]. In addition to these cross-sectional studies, cohort studies of at-risk populations, such as patients with incident infections, suggest that a CFS exists independently of mood disorders, the most common alternative diagnosis [9,10]. Therefore, there is good evidence that CFS exists as a discrete illness phenotype.

Is CFS homogeneous or heterogeneous?

There have been several attempts to test the heterogeneity of CFS, using symptoms and demographic data to define the phenotypes [5,6,11–15]. Some studies used principal components or other factor analyses to define the syndromes themselves, whereas others used latent class analysis to seek clusters of patients. The early studies found a broad phenotype in the majority and a separate polysymptomatic phenotype in the minority, labeled as a somatization disorder.
[11,12]. Later studies, mainly using latent class analysis, found between three and five subphenotypes, some clustering with comorbid mood disorders and other clusters labeled musculoskeletal and infectious on the basis of symptoms [5,13–15]. Although similar clusters of symptoms are found across studies, no work has looked at the validity of these empirically defined subphenotypes, such as longitudinal studies with risk marker associations. We therefore cannot be sure that these symptom clusters define valid subphenotypes. A second problem is that these attempts to define the heterogeneity of CFS have relied on symptoms and demographic variables alone, excluding associated biological abnormalities, such as down-regulated hypothalamic-pituitary-adrenal axis activity [16]. Adding such biomarkers might reveal subphenotypes that are defined by the underlying biological processes, which are called endophenotypes [17].

A large population-based study has attempted to elucidate the underlying endophenotypes of the broad phenotype of CFS. That is, the authors used biomarkers in addition to symptoms and demographic variables in an attempt to delineate the endophenotypes. The Centers for Disease Control (CDC), based in Atlanta, GA, in the USA, has produced several epidemiological studies derived from populations. One of these was based in Wichita, KS, chosen as it is demographically representative of the USA [18]. The CDC did a nested case-control study of those with a CFS-like illness and healthy controls. They studied clinical variables, such as symptoms and comorbid disorders, but also biomarkers, measuring immune and endocrine variables as well as polysomnography [18]. The authors first of all used principal components analysis to reduce the large number of variables to the smaller number of only those that contributed to defining the components, and then latent class analysis to seek clusters of individual women (men being too small in number to analyze) [19]. The best statistical solution defined four classes, but interpretations were possible for five and six classes [19]. Interpretation of the six classes is as follows: Class 1 (26% of subjects) was primarily delineated by obesity and sleep disordered breathing (hypnea). Class 2 (24%) was healthy. Class 3 (15%) contained obese and hypneic subjects, but with low heart rate variability during sleep and low 24-h urinary cortisol levels (consistent with physiological evidence of chronic stress). Class 4 (14%) had sleep disturbance and myalgia without obesity or significant depression. The two remaining classes (Class 5 with 14% and Class 6 with 7%) consisted of subjects who reported most symptoms and were depressed, but without obesity or its related hypnea. Class 5 had normal sleep indices. Class 6 was characterized by disturbed sleep, with low sleep heart rate variability, low 24-h urinary cortisol levels, and the subjects were postmenopausal.

It is vital to validate and replicate these findings in order to avoid being sidetracked by spurious findings. The authors tested the validity against variables not used in the original analyses. Firstly, they found that fatigue and disability differentiated ill classes from each other [20]. Secondly, they found that gene expression differentiated three classes out of both the five and six class solutions [21]. Thirdly, they reported that single nucleotide polymorphisms of candidate genes, related to monoamine transmission and cortisol receptors, differentiated three out of six classes [22]. These authors went on to replicate this work in an independent population sample, also studied by the CDC, this time in Georgia, USA. They were not able to directly replicate this work in this replication study because the same biomarkers had not been studied. However, by using proxy variables, they were able to partially replicate this work, finding four out of five classes were similar to those found in the original Wichita study [23].

Testing the heterogeneity of other FSSs is less well developed, but preliminary studies suggest that other FSSs may also be heterogeneous [24–26], as well as sharing commonalities [26].

Is CFS part of another FSS?

A related but seemingly paradoxical issue is the need to explain the clinical associations between the FSSs. Why is CFS strongly associated with both chronic widespread pain ("fibromyalgia") and irritable bowel syndrome (IBS) [13,26–28]? Could it be that there is only one general functional somatic disorder [29,30]? One way to answer these questions was attempted in a primary care prospective case-control study of risk markers of patients with fatigue syndromes (postinfectious and CFSs) matched by age, gender, and general practice with two comparison groups: patients attending primary care of other ill health reasons and patients attending with IBS [31]. These authors used the UK General Practice Research Database and found that, although the fatigue syndromes were heterogeneous, those with CFS had the same predisposing risk markers as those with IBS (primarily premorbid mood disorders and other FSSs). In contrast, triggering risk markers differentiated the syndromes, with systemic viral infections triggering CFS and gastrointestinal infections triggering IBS. Using a cohort study of Epstein-Barr virus and Campylobacter infections, Moss-Morris and Spencer [32] had previously found this specificity regarding triggering infections, with EBV triggering CFS and Campylobacter even more convincingly triggering IBS.

A large study of Swedish twins seems to support this novel conclusion. Kato et al. [33] studied mainly symptom profiles in over 30,000 twins obtained from the population, looking for the latent traits supporting four FSSs: CFS, chronic widespread pain, IBS and recurrent headaches, along with two mood disorders (major depression and generalized anxiety). When examining women, they found that two latent traits explained the main variance, with one loaded with the two mood disorders, and the other (which included all four FSSs) without them. Furthermore, all four FSSs had their own specific heritability, but environmental
risks had more specific influence in determining the individual syndromes. Kato et al. [33] concluded that there are two latent vulnerabilities to develop FSSs, one of which is related to the vulnerability to develop mood disorders, and which is primarily inherited. A second latent vulnerability is primarily acquired and specific to the individual syndromes [33].

These three recent studies suggest that we need to further understand the commonalities across FSSs at the same time as understanding those factors that differentiate both between these syndromes and within them. In other words, we need both to split the FSS and to lump them together, rather than to do one or the other.

Are the risks for FSSs biological or psychosocial?

The Swedish twin study mentioned in the previous section suggested that risks were both genetic and environmental. Environmental risks can be biological and psychosocial. What are the psychosocial risks for CFS in particular and FSS in general, and are they specific for each FSS? The Swedish twin registry helps us out again in answering these questions. Kato et al. [34] used the registry to examine childhood risks for CFS and found that perceived stress and “emotional instability” are risks for later CFS. This is consistent with birth cohort studies of people who later develop CFS, which show that premorbid psychiatric disorder, particularly depressive and anxiety disorders, are more likely in those who later develop CFS than in those who do not [35]. Furthermore, Heim et al. [36,37] have replicated their original finding that childhood abuse of any kind is more likely to be reported retrospectively by those with CFS compared to those without.

These replicated risks of early life events and psychological distress may be confounded by the higher prevalence of comorbid mood disorders with CFS [7]. In other words, since like predicts like, it may be that these early life difficulties are more related to being depressed as well as to having CFS in adulthood than to CFS alone. At the same time, it is important to remember that early life adversity may affect the physiological stress response, so that an individual reacts physiologically to later adult life events, such as infections, in a different way as a consequence of the early life experience. In other words, the risks are neither psychosocial nor biological, but both. Heim et al. [37] in their replication study of early life adversity and CFS found exactly that. Those who reported early life adversity had lower salivary cortisol levels on waking [37].

There is good evidence that early life adversity is not specific for CFS and is found more often in all FSSs [38], where it has been sought. So, it is likely that early life adversity is a generic risk marker for all FSSs. It may be that this generic risk marker for FSSs is mediated by psychological and physiological changes to both the stress response system and sensitization of the central nervous sensory system [37–39], perhaps mediated by epigenetic changes [40].

How might we seek further knowledge about how FSSs are both similar but different?

It may be possible that not all endophenotypes underlying specific or associated syndromes share the same generic risks for all FSSs, such as early life adversity. The next tranche of studies needs to test this possibility, as well as to test the validity and reliability of these potential endophenotypes in men and to seek etiological risks in a longitudinal study of endophenotypes, such as altered stress response related to early life adversity and its genetic associations. Longitudinal and cohort studies looking at multiple FSS outcomes will help us to confirm and better understand how different triggers bring about both different FSSs and the different subphenotypes within single syndromes. How is it possible to do this when FSSs are hard to define and heterogeneous? The example of obesity is instructive, in that there are many pathophysiologicals that can lead to obesity, and yet there are important single gene polymorphisms (e.g., FTO rs9939609 A allele) that are associated with obesity in general [41]. Therefore seeking associations between risk markers and broad phenotypes, such as having any FSS, may reveal common risks. These risk markers may be biomarkers, such as single nucleotide polymorphisms, or biopsychosocial risk markers such as childhood trauma and their biological consequences.

An additional way to better differentiate the heterogeneity within single FSS is to develop an iterative process between a risk marker and its phenotypic expression. An example of this comes from understanding the genetic associations of restless leg syndrome (RLS), in which an association was found with chromosome 12q and the disease expression of RLS, but the association was strongest in those with prominent periodic leg movements [42]. In other words, the genetic association allowed the better differentiation of the associated phenotype. This iterative process may work for any broadly associated risk marker. All these designs require large studies, so pan-European and other international collaborations are the way forward.

Conclusions

Chronic fatigue syndrome can be considered as a discrete FSS, made up of different subphenotypes, which we are beginning to understand by their underlying endophenotypes. At the same time, CFS shares common risk markers with other FSSs, which are both genetic and environmental. The environmental risks are both psychosocial and biological with interactions between them. This “both separate and combined” approach applies to all FSSs. In order to better understand and treat patients with complex as yet unexplained physical symptoms and disability, we need to consider both generic and individual risks associated with broadly defined phenotypes, their subphenotypes, and the endophenotypes that underpin them.
References


