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Developmental Influences on Medically Unexplained Symptoms

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Key Words
Medically unexplained symptoms · Prenatal programming · Epigenetic modulation · Chronic disease

Abstract
Background: Medically unexplained (or 'functional') symptoms (MUS) are physical symptoms that prompt the sufferer to seek healthcare but remain unexplained after an appropriate medical evaluation. Examples of MUS also occur in veterinary medicine. For example, domestic cats suffer a syndrome comparable to interstitial cystitis, a chronic pelvic pain syndrome of humans. ***Method:*** Review of current evidence suggests the hypothesis that developmental factors may play a role in some cases of MUS. Maternal perception of a threatening environment may be transmitted to the fetus when hormones cross the placenta and affect fetal physiology, effectively 'programming' the fetal stress response system and associated behaviors toward enhanced vigilance. After birth, intense stress responses in the individual may result in similar vulnerability, which may be unmasked by subsequent stressors. ***Results:*** Epigenetic modulation of gene expression (EMGEX) appears to play a central role in creation of this 'survival phenotype'. The recent development of techniques to identify the presence of EMGEX provides new tools to investigate these questions, and drugs and other interventions that may reverse EMGEX are also under active investigation. ***Conclusion:*** Viewing MUS from the perspective of underlying developmental influences involving EMGEX that affect function of a variety of organs based on familial (genetic and environmental) predispositions rather than from the traditional viewpoint of isolated organ-originating diseases has at least two important implications: it provides a parsimonious explanation for findings heretofore difficult to reconcile, and it opens whole new areas of investigation into causes and treatments for this class of disorders.

Introduction

Medically unexplained (or 'functional') [1, 2] symptoms (MUS) are a major public health problem. They have been defined [3] as 'physical symptoms that prompt the sufferer to seek healthcare but remain unexplained after an appropriate medical evaluation'. The MUS are also common, affecting as many as one third of people seeking medical care [4]. They may be disabling to those afflicted by them, and often result in increased health resource utilization, loss of productivity, and frustration on the part of both the patient and the clinicians caring for them. Most of the medical subspecialties are presented with patients suffering at least one MUS [5], although controversy concerning the definition and categorization of these disorders exists [6]. Commonalities across the different MUS include over-representation of females, history of adverse early experiences, sudden onset (often

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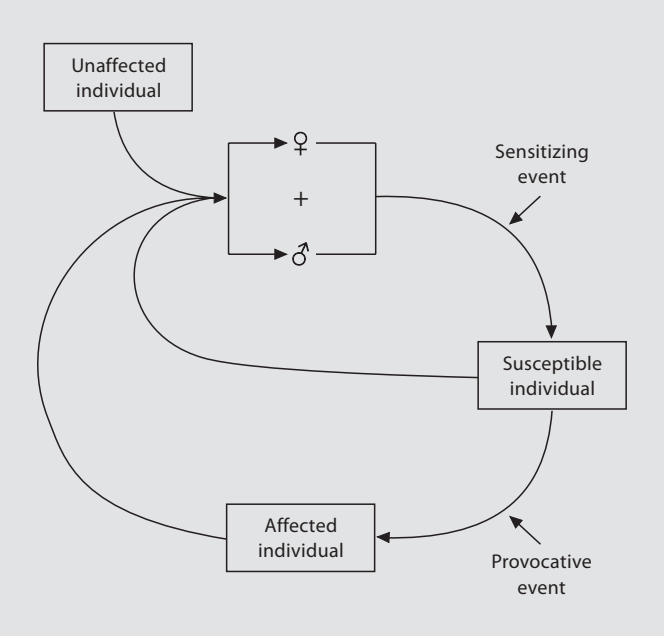

Fig. 1. Proposed pathways to development of medically unexplained symptoms. An unaffected individual mates with another individual, which results in a pregnancy. Either parent may transmit stress susceptibility if it is present in their genome, or it may appear from the resultant genome of the offspring. Additionally, genetic predisposition of the mother to stress susceptibility may increase the likelihood of her transmitting her response to a sensitizing event to the fetus. This pregnancy may result in susceptible offspring, whose stress response to a provocative event may result in an affected individual. This cycle may be repeated and even amplified across generations by these offspring, who have an increased likelihood to pass their vulnerability on to succeeding generations.

after a precipitating event such as an injury or infection), multiple comorbid MUS in the same individual with no obvious pattern or order of onset, waxing and waning course, altered stress response system function (generally including altered adrenocortical and sympathetic nervous system function during stressful periods), and resistance to current therapeutic approaches. These commonalities have led some to suggest the presence of a common underlying cause for the MUS [1, 7, 8].

Method

Evidence for Early Influences on MUS

Evidence from clinical, epidemiological, and experimental observations has led to development of theories about how evolutionarily conserved developmental processes interact with environmental cues (often transmitted from the mother via the placenta) to attempt to match the physiology of the developing organism to its postnatal environment. Some cases of cardiovascular, type-2 diabetes mellitus and the metabolic syndrome, and respiratory and mood disorders have now been shown to result from a mismatch between the predicted and actual environment an organism inhabits [9], and the available evidence suggests that some of the MUS also may be influenced by early life experiences [10].

Converging lines of research suggest that when a pregnant female is exposed to a sufficiently harsh stressor, the hormonal products of the ensuing stress response may cross the placenta and affect the course of fetal development [11], resulting in durable changes in brain [12], autonomic [13], endocrine [11] and immune function [14]. While of potential survival value, these changes also appear to increase vulnerability to life stressors, putting these individuals at greater risk of developing disorders characterized by pain and discomfort [15, 16] in some environments.

Additionally, genetic variability in the pattern and magnitude of each of these responses occurs among individuals [17–20], so the final pattern of the stress response may be variable in outbred populations [21]. This pattern also may depend on the salience and threat potential of environmental stressors to the individual, and is likely to be more similar to responses in closely related family members than to unrelated individuals with similar symptoms (fig. 1).

Results

Potential Mechanisms of Early Influence

Recent research suggests that one mechanism underlying the sensitization of the stress response system involves a process called epigenetic modulation of gene expression (EMGEX) [22, 23]. EMGEX is a prominent candidate mechanism for the identified differences in stress responsiveness found in patients with MUS because it has been shown to occur in the offspring of pregnant females exposed to stressors [24, 25], and to result in long-term neuroendocrine abnormalities [24, 26].

My introduction to MUS came through studies of interstitial cystitis (IC), a chronic pelvic pain syndrome of unknown cause and no generally accepted treatment [27]. Patients with IC also present with a variety of other medical problems, including chronic pelvic pain [28], irritable bowel syndrome [29], and chronic fatigue syndrome/fibromyalgia [30, 31]. Moreover, a clinical and genetic link between IC and panic disorder, social anxiety disorder and mitral valve prolapse has been reported [32, 33].

A syndrome similar to IC also occurs in domestic cats, which has been called feline IC (FIC) [34]. Cats with FIC meet all of the inclusion and exclusion criteria for diagnosis of IC that can be applied to animals [35]. IC in hu-

mans and FIC in cats are remarkably similar; patients of both species have abnormalities of local bladder factors, visceral afferent pathways, the central nervous system, hypothalamic and gonadal hormone systems, and the sympathetic nervous system [36]. In addition to bladder problems, studies have shown that cats with FIC also have variable combinations of gastrointestinal, metabolic, cardiovascular, autonomic and behavioral symptoms [36–38]. As in humans, no discernable pattern of onset of these symptoms has yet been reported in cats.

We recently found that the adrenal glands of cats with FIC were smaller than those of healthy cats, and less responsive to adrenocorticotropic hormone [39]. Microscopic examination of the glands revealed an absence of hemorrhage, inflammation, infection, or necrosis to explain the reduced size, suggesting the presence of mild primary adrenal insufficiency or decreased adrenal reserve in these cats. These findings provided early circumstantial evidence that vulnerability for IC, and by extension other comorbid MUS, might have developmental antecedents.

In addition to humans and cats with IC, hypocortisolism has also been identified in patients with chronic pelvic pain, chronic fatigue syndrome, fibromyalgia and post-traumatic stress disorder. Hypocortisolism also seems more common in women than in men, although its presence has been reported in a subset of men with metabolic syndrome [40]. It has been suggested that hypocortisolism may be a protective response to reduce the damaging effects of the glucocorticoid response to daily hassles, albeit at the expense of symptoms such as high stress sensitivity, pain, and fatigue [41]. This effect could be exaggerated in individuals with preexisting (developmental) vulnerabilities.

Evidence of adverse early experiences in patients with IC [42, 43] and other MUS [44–46] suggests the likelihood of environmental instability in the lives of their parents [44], which may have affected the development of their offspring. The small adrenal glands we found in cats and adrenocortical hormone abnormalities present in some patients with MUS during stressful episodes [36, 41, 47, 48] may be stigmata of such events. The effects of stressors on fetal adrenal development in other species seem to depend both on the timing and magnitude of exposure to products of the maternal stress response in relation to the activity of the developmental 'programs' that determine the maturation of the various body systems during gestation and early postnatal development [49]. If exposed before initiation of a developmental program, there may be no effect. During the critical period while the adrenocortical maturation program is running however, studies in rodents [50, 51], carnivores [52], and primates [53, 54] all have found maternal stressors to reduce adrenal size in the affected offspring. If a sufficiently severe stress response occurs after the critical period of adrenocortical development, adrenal size and subsequent adrenocortical responses to stress may be increased [55].

In addition to epigenetic alterations in gene expression, a variety of genetic polymorphisms that affect stress responsiveness also have been identified in humans [56], including the catechol-O-methyltransferase [57], serotonin transporter [58], and α_2-adrenergic receptor genes [59]. Once pregnant, exposure of mothers carrying such polymorphisms to significant salient stressors may increase the risk for exposure of a developing fetus to products of the stress response, enhancing the chances of sensitizing the stress response system of these offspring. Such a mechanism has been identified in other disorders. For example, Beversdorf et al. [60] recently reported that a history of prenatal stress peaking at 25–28 weeks gestation was associated with an increased risk for development of autism. In a follow-up study [61], surveys for a history of prenatal stress combined with genotyping for presence of the long and short alleles of the serotonin transporter gene promoter revealed that the presence of a history of prenatal stress was significantly associated with the presence of the short allele of the promoter in mothers of autistic children, suggesting that the enhanced stress sensitivity associated with the presence of this allele [62] may serve as a maternal stress-response risk factor for the development of autism in their offspring. Such studies are needed in patients with MUS to test the relevance of these provocative findings to this category of disorders.

In addition to alterations in the components of the stress response system distal to the hypothalamus, changes in proximal structures that modulate its activity also may play a role in MUS. For example, the medial prefrontal cortex is known to regulate the neuroendocrine and autonomic output of the hypothalamus [63]. Many critical periods of development occur during brain maturation [64], which have been shown to be affected by maternal stressors [12]. Reser [65] recently proposed that one result of this process is a decrease in cerebral metabolic rates to conserve energy in unpredictable environments.

Cognitive function too is influenced by both genetic [66] and epigenetic [67] factors. Many studies have also shown that cognitive factors, such as classical and operant conditioning, attentional bias and memory, can influence the onset, development and maintenance of MUS

[68–70]. Moreover, studies of the importance of cognitive factors such as attention to behavioral contingencies in situations in which potentially traumatic events occur have shown that it is not the physical event(s) per se that determine the immediate and long-term consequences, but the individual's expectations and ability to cope with the threatening situation [71].

Implications for Therapy

Consideration of developmental influences on MUS may have important therapeutic implications. For example, drugs to reverse the processes of EMGEX also are under active investigation, as cancer chemotherapeutic agents [72–74]. If some of the MUS turn out to have developmental origins, these drugs may be appropriate to consider for their therapeutic potential in these patients. This hypothesis also may explain the effectiveness of such 'central' approaches to therapy as tricyclic antidepressants (which among other actions attenuate catecholaminergic output) [75–78], hypnosis [79, 80], effective doctor–patient communication [81], use of psychiatrists as consultants in the general practice setting [82], and various other psychological approaches to treatment [2, 83–88] that might reduce the perception of threat in amenable patients. We also have successfully used an 'environmental' approach to therapy for cats with FIC [89]; EMGEX is one candidate mechanism for the effects of environmental enrichment [90].

Conclusion

In summary, viewing the MUS from the perspective of underlying developmental influences involving EMGEX that affect function of a variety of organs based on familial (genetic and environmental) predispositions rather than from the traditional viewpoint of isolated organ-originating diseases has at least two important implications. First, it provides a more parsimonious explanation for many findings that have been quite difficult to account for, including the unfortunate lack of beneficial effect of therapies directed at the peripheral organ of interest to a particular medical subspecialty [91, 92], the presence of multiple comorbid disorders in many patients with MUS, but not in patients with other individual organ diseases, the unpredictable order of appearance of the comorbidities, and the altered functioning of the hypothalamic-pituitary-adrenal and autonomic axes of the stress response system. Second, and more importantly, it invites investigation of new areas of therapy that may otherwise escape consideration.

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