The patient who presents with vague psychiatric somatic complaints may, in fact, be suffering from chemical sensitivities. Such sensitivities are tied to lower incidences of certain psychiatric disorders while correlating with the higher prevalence of others. Neurogenic inflammation, limbic kindling and psychiatric co-factors are discussed.

Much media attention and professional controversy has focused on the approximately 6% of the population who have multiple chemical sensitivity (MCS) (Kreutzer et al., 1999), i.e., severe low-level chemical intolerance (CI), multisystem chronic symptomatology, extreme chemical avoidant behaviors and associated disability. Chemical intolerance involves negative symptoms such as headache, dizziness, difficulty concentrating and/or nausea in response to the odors of low levels of environmental chemicals that the majority of people tolerate with neutral or even positive hedonic effects (Bell et al., 1996a, 1995). The triggering chemicals include multiple substances such as pesticides, solvents, perfumes, new carpets, automotive exhaust and tobacco smoke. A large proportion of people with chemical sensitivities also report multiple intolerances to common foods. Rates of immunoglobulin-E-mediated allergies per se are not necessarily elevated in MCS, although some patients may have immunoglobulin-G-mediated adverse food reactions. Thus, despite popular references to “chemical allergies,” evidence for immune system disturbances as the primary mediator of MCS has not been persuasive, beyond possibly secondary adverse effects of chronic psychological and physical stress on cellular and humoral immune function (Winder, 2002).

Figure 1 illustrates the point that all MCS patients have CI, but only a subset of people with CI meet diagnostic criteria for MCS.

Sixty percent of solvent-exposed workers reported CI (Morrow et al., 1990). Up to half of patients with chronic fatigue syndrome (CFS) and fibromyalgia (FM) (Aaron et al., 2001; Buchwald and Garrity, 1994) as well as a subset of Gulf War veterans (Bell et al., 1998e) present with CI. Numerous surveys show that mild CI is a symptom in 15% to 30% of the population (Bell et al., 1998b). The demographics of CI suggest that the majority with either MCS or subclinical presentations are women (80%) (Levy, 1997).

Comorbid psychiatric symptoms and disorders are primarily anxiety, especially panic disorder and depression (Fiedler et al., 1996). Psychosis is rare. People with CI report histories of physical, sexual and emotional abuse at increased rates (Bell et al., 1998a), but the psychophysiological electroencephalographic patterns of women with CI diverge from those of depressed or sexually abused women without CI (Bell et al., 1998b; Fernandez et al., 1999). Although some investigators have proposed that MCS is a variant of posttraumatic stress disorder (PTSD), systematic evaluations of patients with MCS have not found increased rates of PTSD. Unlike the general psychiatric patient population, patients with MCS report an inability to tolerate alcoholic beverages and many drugs (Miller and Prihoda, 1999). As a result, few patients with MCS have comorbid alcohol problems. Interestingly, however, the family histories reveal elevated rates of substance abuse, especially alcoholism (Bell et al., 1999a; Black et al., 1999).

Many physicians, finding normal clinical laboratory tests, conclude that such patients have a somatoform disorder with or without other Axis I or II psychopathology, and refer these patients to psychiatrists for ongoing care. However, the patients, who may acknowledge that psychological stress can worsen their condition, generally perceive their condition as a medical, rather than psychiatric, problem (Bell, 1994). **Differentiating MCS Subtypes**

Interestingly, some observers have differentiated two general subclasses of MCS: those who can identify a specific peak chemical exposure, usually at higher levels, that initiated their chronic susceptibility to low doses of many other chemicals (approximately 60%) and those who cannot identify such an initiating chemical agent but nonetheless now have adverse reactions to various exposures (approximately 40%) (Fiedler et al., 1996). Of note, patients without an identified initiating chemical exposure have higher rates of lifetime psychopathology than do those with identified initiating chemicals (69% versus 43%). Other studies have found that at least 25% of MCS
patients have no current psychiatric diagnosis (Simon et al., 1993). Moreover, although standard batteries of neuropsychological tests for memory, naming and attention vary in outcomes with MCS (Bolla, 1996), Bell et al. (1999b, 1996b) have repeatedly demonstrated that people with CI exhibit deficits in performance of a visual divided-attention task, a finding similar to patients with CFS (Ross et al., 2001). In solvent-exposed workers, the presence of CI symptoms accounts for a significant portion of the variance in poorer performance on tests of learning and memory (Ryan et al., 1988). Taken together, the specific phenomenological and psychophysiological evidence in MCS indicates that affected individuals diverge from the clinical pictures of typical psychiatric patients, despite some overlaps. The Misattribution Model

A number of skeptics of MCS as a discrete diagnosis have proposed that patients are somatizers with anxiety and depression who are misattributing their symptoms to chemical exposures (Staudenmayer, 2000). The evidence in support of the misattribution model is limited. Studies in which patients with MCS believe that they have been exposed to chemicals in the laboratory reveal increased symptoms of anxiety and panic. The designs of these studies are largely unsophisticated from the perspective of recruitment bias or cognitive set research.

Better-controlled studies have screened MCS patients for those with panic disorder symptomatology and have shown that, like other panic patients, the panic-prone MCS subgroup develops panic symptoms at increased rates during single-blind lactate infusions (Binkley and Kutcher, 1997) or carbon dioxide exposures (Poonai et al., 2000). Follow-up genetic investigations of the panic-prone MCS subset have demonstrated a significantly increased prevalence of the panic disorder-associated cholecystokinin (CCK) receptor allele 7 compared with controls (41% versus 9%) (Binkley et al., 2001). Thus, genetic factors may play a role in vulnerability to MCS.

The findings of biological and genetic overlaps between MCS and panic disorder are especially striking from an interdisciplinary perspective. In industrial hygiene, carbon dioxide levels in indoor environments are one nonspecific marker of poor air quality. Studies on panic disorder demonstrated the ability to provoke panic attacks in the laboratory, even with levels of CO₂ at 5% (Sanderson et al., 1989), similar to those in certain indoor air settings (Lee and Chang, 1999). Therefore, environmental factors such as carbon dioxide could play a clinically meaningful role in triggering symptoms in indoor environments where panic-prone people with CI spend time.

Models

The symptom profile of MCS reveals that almost all patients have subjective dysfunction in the central nervous system (McKeown-Eyssen et al., 2001), with the majority also reporting respiratory and gastrointestinal (GI) disturbances (Fiedler and Kipen, 1997). Cardiovascular symptoms, endocrine dysfunction and musculoskeletal complaints vary from study to study (Miller and Prihoda, 1999). Some clinicians indicate that a subset of patients exhibit an atypical form of porphyria as a mechanism for their symptoms (Ziem and McTamney, 1997). Porphyria is a disorder of heme metabolism that can manifest with neuropsychiatric and GI symptoms. Only certain highly sensitive tests can detect this postulated abnormality in MCS patients. To date, no controlled studies are available to confirm or disprove the porphyria hypothesis for MCS.

A better-studied mechanism in MCS for which there are replicated findings in controlled human and animal studies is that of time-dependent or neural sensitization (Antelman, 1994; Bell et al., 1999a; Pall, 2002). Sensitization is the progressive amplification over time of host responses to repeated, intermittent exposures to an exogenous stimulus. Drugs, volatile organic chemicals and stress can all initiate sensitization and cross-sensitize with each other. Some sensitization involves the mesolimbic system, including the well-studied nucleus accumbens, a key structure in CNS responses to drugs of abuse. A special case of neural sensitization is limbic kindling, which is an animal model for temporal lobe epilepsy. On a scale assessing limbic system symptomatology, those with CI score higher than do normals on derealization, "spaciness" and memory problems (Bell et al., 1995).

Individual difference factors that favor sensitization include characteristics that overlap markedly with MCS and CI, e.g., female gender, sucrose preference, behavioral hyper-reactivity to novelty, early life stress and genetic traits (e.g., parental vulnerability to drug self-administration) (Bell et al., 1999a).

Patients with CI have exhibited sensitization of heart rate, blood pressure, resting EEG α activity and EEG Δ activity after chemical exposures (Bell et al., 1999a, 1999c, 1998b; Fernandez et al., 1999). Animal researchers have also found evidence for behavioral sensitization to environmental chemicals such as toluene (von Euler et al., 1994) and formaldehyde (Sorg et al., 1998). In other words, people who become ill from low levels of environmental chemicals may be unusually sensitizable individuals to a wide range of exogenous influences such as chemicals, drugs, foods, noise and stress (Bell et al., 1999a). Their addictive-like features may fall in the arena of food cravings, rather than drug...
cravings (Miller, 2001). As in animals, such sensitizability may manifest as amplification in numerous psychological, behavioral and physiological parameters in the clinical situation (Bell et al., 2001).

Another potentially interactive model for the somatic symptoms of MCS is that of neurogenic inflammation (NI) (Bascom et al., 1997). Neurogenic inflammation is a form of nonimmunological inflammation initiated by stimulation of peripheral c-fiber sensory neurons. The inflammation results from neuropeptide release as part of a peripheral axon reflex response, e.g., via actions of substance P, calcitonin gene-related peptide, neurokinin A and other mediators. The CNS receives the signal that such inflammation and related pain have developed. In turn, areas of the spinal cord and limbic system are required for the initiation of chronic susceptibility to subsequently amplified pain, experienced at the peripheral site originally injured. Neurogenic inflammation plays a role not only in chronic pain, but also in irritant rhinitis, asthma and arthritis. Consistent with an inflammatory model, Bell et al. (1998c, 1998d) observed a significant correlation between serum neopterin, a general marker of inflammation, and scores on standardized scales of somatization in women with CI, but not in depressives without CI or normals. Taken together, neural sensitization and neurogenic inflammation provide models for mechanisms that could account for much of the phenomenology in MCS and CI.

Treatment Issues

Even when patients accept psychiatric treatment with psychotherapy and psychiatric medications for a comorbid depression or anxiety disorder, they often report that their sensitivities to chemicals and foods are at best dampened, but not resolved (LeRoy et al., 1996). Theoretically, inhibitors of substance P and blockers of other mediators of neurogenic inflammation could also be beneficial (Di Sebastianio et al., 1999). Many patients with MCS report intolerance to most medications, however. Psychiatric interventions for somatization per se emphasize improving case management more than providing definitive treatment (Bass et al., 2001; Sharpe and Carson, 2001). Notably, one of the few treatment outcome studies in this area recently showed significant improvement in a small sample of patients with MCS and CFS on the SF-36 measure of health-related functional quality of life (Lacour et al., 2002). The treatment involved an eight-week interdisciplinary intervention that included a self-help program, acupuncture and a psychosomatic supportive therapy group. In addition, other patient-centered interventions that support the patient’s efforts to regain a sense of control over their health and their world may be beneficial, e.g., with journal writing, guided imagery and/or biofeedback.

Conclusions

Patients with multiple chemical sensitivity report an average of 23 health care provider visits per year (Buchwald and Garrity, 1994). Lost U.S. worker productivity associated with related conditions such as sick building syndrome (workplace-specific illness, elicited in part by indoor pollutants at low levels) has been estimated at $10 billion/year. Society is puzzled over how to address the growing number of workers’ compensation claims, disability cases and personal injury lawsuits associated with alleged chemical injury at work and at home. Given the high stakes, neuropsychiatric researchers have many promising leads that demand exploration. In the meantime, clinicians have tools to provide compassionate and supportive care for people with MCS and CI.

References: References


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