Invited lecture

The Perplexing Problem of Multiple Chemical Sensitivities: A Perspective for Toxicologists

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Background

During the 1980's, occupational and environmental physicians recognized and reported a new syndrome, characterized by respiratory, CNS and other symptoms occurring after exposure to very low levels of diverse irritant or toxic chemicals. Typically this occurred after a well-characterized environmental "event" from which the patient appeared to recover, such as a spill or overexposure. Dubbed by this author multiple chemical sensitivities (MCS) to describe the phenomena, theories arose to explain it, ranging from a new form of allergy, a unique residual form of neurotoxicity, or a psychiatric condition. Because many of the patients became very disabled, and because of the absence of any simple toxicologic explanation, debate became widespread and new cases began to be reported from around the world. In this presentation I will describe a typical case and summarize what has been learned from two decades of research.

Case Study

Mr. M, a 44 year old machine operator, presented to clinic complaining of severe headache, confusion and shortness of breath every time he smelled even the slightest trace of "petrochemical". He had been well until three months before when a ventilation failure occurred at work and he and the others were overexposed to degreasing solvents, largely 1,1,1 trichloroethane. Many had developed headache and nausea, but all the others recovered when the ventilation was fixed after two days. Mr. M, however, remained symptomatic when he returned to work after the ventilation was improved, and could not work his shift. More disturbingly, he began to notice the same thing when he was driving behind a bus or truck, or even at a store. Household products also began to affect him, and he started to wear a respirator. However, over the three months before he came to clinic more chemicals began to bother him, including his wife's perfume. Only after all of the household products were removed from his house did he feel better, and then only when he stayed at home.

At clinic he had a full examination and routine bloodwork, as well as an MRI of the brain and lung function studies. All studies were normal. Examination of his workplace revealed a very clean shop, with all levels of solvent and machining fluid less than 10% of TLV's. He was diagnosed with MCS.

Definition of MCS

There have been many attempts to define this clinical syndrome, but since there is no cardinal finding or laboratory abnormality, all of the definitions rely on the clinical history and the absence of finding other causes. The key features are: 1) the onset after an environmental exposure; 2) the recurrence of *multiple* symptoms in a predictable way after even very low exposures to *diverse* odors and irritants in *multiple* settings; 3) laboratory tests and examinations are all normal, or unable to explain the symptoms; 4) no other major disease—physical or psychiatric– is present to explain the symptoms.

Epidemiology

Although it appeared at first that these cases were very rare, clinical reports in the 1980's and 1990's suggested they were occurring everywhere. Moreover, several large surveys were done, including health surveys of military veterans from the Persian Gulf War of 1990–91 (from which large numbers of cases emerged). These surveys showed that between 2 and 6% of people had minor or more serious variants of MCS based on the evidence they had moved job or house to avoid chemicals causing symptoms. From the military surveys, 2% unexposed to the war had MCS while almost 5% of those in the war had the syndrome, many quite seriously.

Clinical studies have provided some clues: Women are affected about 3 times more than men, most cases occur

between ages 30–50, many patients have also experienced chronic fatigue or fibromyalgia (also poorly understood) and many have had anxiety or depression in the past. Neither atopy nor family background appears relevant, although the clinical cases occur most often in higher social classes than among poorer people at least in the US.

Pathogenesis

The big question of course is the mechanism of injury. Originally MCS was thought to be some sort of allergy or immunologic disturbance, but many studies have proved this false. Likewise, there has been extensive search for a "biochemical" pathway, i.e., some phenotypic deficiency in detoxification pathways such as P-450 or glutathione reductase; this also has proved unlikely. Because of the central role of odor and irritant response in triggering symptoms, more recent attention has turned to first cranial nerve pathways, and patterns of limbic response in the CNS; evidence for disruption of these neural pathways is mixed, and there remains no compelling animal model.

Alternatively, many have construed MCS as an anxiety disorder, either behavior or biochemically mediated. The DSM IV system classifies MCS in this category (Of note there is *no* ICD-10 code for MCS). In favor of this hypothesis is the frequent history of anxiety disorders in the patients, and the pattern of response resembling post-traumatic stress disorder. However, neither pharmacologic nor behavioral interventions have been convincingly useful in treatment, and most psychiatrists resist construing the symptoms in this way.

Natural History

There are now enough cases to demonstrate several key features of MCS: 1) It does not seem to spontaneously resolve, and as yet there is no proved treatment; 2) After the initial presentation it does not appear to progress or lead to any complication, except that many patients will develop more "chronic" complaints such as fatigue or musculo-skeletal pain. Importantly, these observations are true whether the patient chooses extreme isolation, which many do despite the terrible social and economic ramification, or whether they continue to function normally and have repeated symptoms. In fact, overall the latter group appears to do better over time than those who withdraw.

Prevention and Treatment

Although many different clinical and psychologic manipulations have been tried, there appears no way to alter the underlying response to exposure. Most efforts currently are aimed at improving life function in the face of symptoms, rather than controlling or modifying the symptoms themselves.

More usefully, efforts to prevent development of MCS after an over-exposure may be more successful. The key to this are: 1) very close follow-up of every patient who has a noxious chemical exposure, however self-limited or benign it my seem; 2) early exploration for the occurrence of MCS-like reactions; 3) early education to reinforce that the symptoms are not evidence of a more serious toxic reaction to the initial exposure as almost every single patient believes when the first MCS symptoms occur.

The Future

Because of the prevalence and severity of MCS there continues to be research on the mechanism(s), but this work has been hampered by the extreme difficulty of these patients as study subjects, and the absence of any good animal model.

Curriculum vitae

Mark Richard Cullen, M.D.

【Education】

1967–1971	Harvard College
1972–1976	Yale University School of Medicine, received M.D.

【Work Experience】

1980–1985	Assistant Professor of Medicine, Yale University
1980–current	Director, Yale Occupational and Environmental Medicine Program
1985–1993	Associate Professor of Medicine and Epidemiology, Yale University School of Medicine
1993–current	Professor of Medicine and Public Health, Yale University School of Medicine

【Prize & Awards, Advisory Positions】

Campel Prize for Highest Grade in Medical School (1996), Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine (1983–1988), Member of Institute of Medicine (National Academy of Sciences, 1997), Member of Connecticut Academy of Science & Engineering (2002), Harriet Hardy Award (New England College of Occupational and Environmental Medicine, 2007), Medical Consultant of International Chemical Workers Union (1981–current), Member of Scientific Advisory Panel - Semiconductor Industry Association Directors Task Force on Health and Safety (1987–1993, 1999–2002), Member of NIH Study Section (OH, 1988–1991)