

Approach to patients with unexplained multimorbidity with sensitivities

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Abstract

Objective To explore the underlying causation of unexplained multimorbidity with sensitivities and to discuss the management of patients who present with this perplexing condition.

EDITOR'S KEY POINTS

- Multimorbidity with sensitivities is frustrating for both physicians and patients. Investigations typically reveal no objective abnormality, and clinical management with psychiatric intervention is usually unsuccessful.
- The pathophysiologic mechanism toxicant-induced loss of tolerance or *TILT* is the pathognomonic feature of sensitivity-related illness and the disordered pathway to a clinical presentation of multimorbidity with sensitivities.
- Resolution of multimorbidity follows appropriate assessment and intervention. Treatment is directed into 3 broad categories: resolution of inflammation by incitant avoidance; remediation of biochemistry; and toxicant burden elimination to resolve immune dysregulation and the hypersensitivity state (toxicant-induced loss of tolerance).

POINTS DE REPÈRE DU RÉDACTEUR

- La multimorbidité avec sensibilités est un problème frustrant à la fois pour les médecins et les patients. Les investigations ne révèlent habituellement aucune anomalie objective et la prise en charge clinique au moyen d'interventions psychiatriques échouent la plupart du temps.
- Le mécanisme pathophysiologique de la perte de tolérance induite par des substances toxiques, ou «TILT» en anglais, est la caractéristique pathognomonique de la maladie liée aux sensibilités et la voie désordonnée menant à une présentation clinique de multimorbidité avec sensibilités.
- Le règlement de la multimorbidité fait suite à une évaluation et à une intervention appropriées. Le traitement se divise en 3 grandes catégories: l'élimination de l'inflammation par l'évitement des déclencheurs, la restauration de l'état biochimique et l'élimination du fardeau toxique pour remédier à la dysrégulation immunitaire et à l'hypersensibilité (perte de tolérance induite par des substances toxiques).

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Cet article a fait l'objet d'une révision par des pairs.

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Sources of information Medical and scientific literature was used from MEDLINE (PubMed), several books, toxicology and allergy journals, conference proceedings, government publications, and environmental health periodicals.

Main message Multimorbidity with sensitivities has become an increasingly common and confusing primary care dilemma. Escalating numbers of debilitated individuals are now presenting to family physicians and specialists with multisystem health complaints, including sensitivities and fatigue, with no obvious causation, a paucity of laboratory findings, and a lack of straightforward solutions. In the recent scientific literature, there is discussion of sensitivity-related illness, an immune-mediated disorder that frequently manifests with multisystem symptoms, commonly including sensitivities and fatigue. This condition appears to be originally caused by adverse environmental exposures and toxicant bioaccumulation—an increasingly prevalent and well-documented problem in contemporary culture.

Conclusion Various toxic exposures and their bioaccumulation within the body frequently manifest as sensitivity-related illness. In clinical settings, patients with this disorder often present with otherwise unexplained multimorbidity and sensitivities. The health status of patients with this condition can be ameliorated by removing triggers (eg, scented products), optimizing biochemistry, removing further sources of toxicant exposures, and eliminating the internal dose of persistent toxicants.

Approche envers les patients ayant une multimorbidité inexpliquée avec sensibilités

Résumé

Objectif Explorer les causes sous-jacentes d'une multimorbidité inexpliquée avec sensibilités et discuter de la prise en charge des patients qui se présentent avec ce problème singulier.

Sources des données La documentation médicale et scientifique est tirée de MEDLINE (PubMed), de divers manuels, de revues spécialisées en toxicologie et en allergies, de comptes rendus de conférences, de publications gouvernementales et de périodiques sur la santé environnementale.

Message principal La multimorbidité accompagnée de sensibilités est devenue un dilemme de plus en plus fréquent et déroutant en soins primaires. Un nombre grandissant de personnes affaiblies se présentent maintenant chez des médecins de famille et d'autres spécialistes en raison de problèmes de santé multisystémiques, y compris des sensibilités et de la fatigue, sans cause évidente, avec des résultats de laboratoires peu concluants, sans qu'il y ait de solutions simples. Dans la documentation scientifique récente, on traite des maladies reliées aux sensibilités, un trouble à médiation immunitaire qui se manifeste fréquemment par des symptômes multisystémiques, incluant habituellement des sensibilités et de la fatigue. Ce problème semble être causé à l'origine par des expositions environnementales néfastes et une bioaccumulation de substances toxiques, un phénomène de plus en plus prévalent et bien documenté dans la culture contemporaine.

Conclusion Diverses expositions à des substances toxiques et leur bioaccumulation dans le corps se manifestent souvent sous forme de maladies reliées à des sensibilités. Dans les milieux cliniques, des patients souffrant d'un tel trouble se présentent avec une multimorbidité et des sensibilités inexplicables autrement. L'état de santé des patients qui ont ce problème peut être amélioré en supprimant les déclencheurs (p. ex. produits parfumés), en optimisant la condition biochimique, en enlevant les autres sources d'exposition à des substances toxiques et en éliminant la dose interne de substances toxiques persistantes.

To prevent disease, to relieve suffering, and to heal the sick—this is our work.

Sir William Osler

As discussed in a commentary in this month's issue of *Canadian Family Physician* (page 511),¹ escalating numbers of exasperated individuals suffering from chronic multisystem conditions, often including chemical sensitivities or food intolerances, are repeatedly presenting to primary care physicians and specialists, as their symptoms remain unresponsive to standard medical treatments and conventional pharmaceuticals. Recent evidence suggests that about

three-quarters of patients in general practice now present with multiple ongoing conditions,² with management of chronic disorders accounting for about 80% of primary care in Canada. As clinical practice guidelines are generally focused on single and distinct disorders, practitioners are often not effectively trained to modify care to manage multimorbidity states.³ The repercussions of this reality are profound, as multimorbidity is associated with increased disability, declining functional status, diminished quality of life, higher mortality, and greater consumption of health care services.⁴

In this clinical review, we describe the clinical state and progressive recovery of a man presenting with chronic multisystem complaints.

Case description

A 59-year-old rabbi experienced episodic headache, dizziness, and muscle discomfort beginning in adolescence. Into adulthood, these symptoms became more frequent and manifestations expanded to include episodic vision and hearing loss, inexplicable rashes, memory impairment, ataxia, profound agitation, and eventual blackouts. He also complained of intractable fatigue, insomnia, recurrent wheezing, musculoskeletal discomfort, and cognitive dysfunction.

The patient saw multiple physicians, but no physiologic cause for his multimorbidity was identified. Various diagnoses were given, but a subsequent psychiatric assessment conferred a diagnosis of "narcissistic, borderline personality disorder with extreme anxiety" to explain the totality of his presentation. As analgesic, asthma, and allergy medications provided minimal sustained benefit, psychotropic medication was employed but to no avail.

On taking an environmental history, the patient described exposure to perfumes and other scents as precipitating and aggravating his varied symptoms. While fervently avoiding all scented locales, many environments were still not trigger free. With worsening hypersensitivity, he reduced social interaction and public activities, and eventually stopped working as a religious leader and teacher.

Marked psychological distress and hopelessness ensued. Contact with his children and grandchildren was greatly curtailed; social gatherings and public events were out of the question; and his health condition put considerable stress on his marriage. Every aspect of his life seemed to be crumbling, and the patient described his quality of life as being exceptionally low.

The patient was referred to a physician who was trained in environmental health sciences for evaluation of his multisystem complaints. History revealed considerable pesticide exposure and street-drug use as a young man. On examination, the

patient was found to have nearly 20 amalgam dental fillings, with elevated serum levels of mercury on laboratory testing. Further biochemical and toxicologic assessment demonstrated high ochratoxin levels, with a subsequent home inspection confirming extensive hidden mold—a well-recognized potential source of myriad health problems.⁵⁻⁷ Considerable levels of lead were found in his urine on toxic metal provocation testing,⁸ but no clear history of lead exposure was identified. The patient was not able to afford laboratory testing for various persistent pesticides and pesticide metabolites; such laboratory analysis is expensive, not readily available, and typically is not covered by health care plans in Canada. Biochemical deficiencies that were identified included low serum levels of copper, manganese, coenzyme Q10, α -tocopherol, and beta-carotene.

Sources of information

This review was prepared by assessing medical and scientific literature from MEDLINE (PubMed), several books, toxicology and allergy journals, conference proceedings, government publications,⁹ and environmental health periodicals. References cited in identified publications were examined for additional relevant writings. Searching techniques included key word searches with terms related to chemical sensitivity, chronic disease co-occurrence, cluster comorbidity, comorbidity, concurrent comorbidity, food intolerance, environmental illness, multimorbidity, and multisystem disease. We found that there was limited scientific literature on the underlying cause of these disorders, the pathogenesis involved, and the management of multimorbidity with sensitivities (MWS). The first author's (S.J.G.) professional observations as an environmental health physician were also incorporated into the discussion of management strategies. The format of an integrated clinical review was chosen, as such reviews play a pivotal role in scientific research and professional practice in emerging medical issues with limited primary study and uncharted clinical territory.¹⁰

Main message

Definition of terms

Multimorbidity: *Multimorbidity* is defined as the co-occurrence of 2 or more ongoing or chronic medical conditions that might or might not interact with each other within 1 person. However, there is ambiguity in the understanding of multimorbidity, as current definitions have been described as simplistic and inadequate¹¹ because the term *multimorbidity* does not delineate between situations of apparently unrelated conditions or multisystem manifestations of a common source that causes illness. For example, while long-term tobacco toxicant exposure might be the single primary

determinant for each condition in an individual with chronic obstructive pulmonary disease, bladder cancer, and intractable sinusitis, the patient is still considered to have multimorbidity.

Sensitivity: *Sensitivity* is a broad term referring to situations in which adverse reactions occur in association with exposure to low concentrations of antigenic stimuli such as foods, inhalants, or chemicals that are well tolerated by most people.¹² It is important to note that direct questioning might be necessary to elicit sensitivities to foods or chemicals; patients often neglect to mention such intolerances because they might seem unimportant compared with other presenting complaints.

Environmental health sciences. What is meant by the "environment" and "environmental health sciences"? In 2000, the Centers for Disease Control and Prevention stated that virtually all human disease represents the interaction between the genome and the environment.¹³ There are essentially 2 parts that make up the functional aspect of the environment in relation to health. In order to thrive, any fully functional system relies on 1) the presence of requisite components and 2) the absence of harmful influences; without these conditions, systems falter. As with any functional system, the human body adheres to this basic scientific principle.¹⁴

A 2010 article in *Science* confirms that most chronic disease results from environmental factors¹⁵; that is, most disease results from individuals missing what they need to thrive or being exposed to toxic factors such as pathogens or toxicants that induce harm. This is hopeful information, as the environment, unlike the genome, is modifiable. So, rather than assuming that chronic illness is solely genetic and masking signs and symptoms with assorted therapies, environmental medical practice endeavours to identify and rectify causal determinants that are the sources of the underlying illness.¹⁴ Dysfunctional systems have potential for remarkable restoration and improved function if the underlying detrimental state is rectified by providing necessary components and eradicating harmful ones.¹⁶

Toxicant damage. The ongoing accumulation of toxic pollutants within the body certainly qualifies as a source of escalating and pervasive harm.^{17,18} Although patients experiencing MWS are often given a psychiatric diagnosis, an expanding body of scientific literature suggests that harm from bioaccumulated toxicant loads from adverse chemical or biologic exposures (eg, mold exposure) might be causally involved in their illness.¹⁹⁻²²

Approximately 85 000 synthetic chemicals have been manufactured over the past few decades, and although only about 2800 are used in high volumes (more than 1 million pounds produced per year), little toxicity information exists for most of these compounds,

including many in common use today.²³ It has been well established that some of these agents can cause serious damage at small doses²⁴ and that myriad toxicants can bioaccumulate and persist within human tissues for many years or even decades.²⁵ In the scientific literature of late, the underlying cause of several disease states and presentations is being linked to such adverse environmental exposures.^{17,24,26,27} Multiple mechanisms of harm have been elucidated, including cytotoxicity,²⁸ endocrine disruption,²⁹ enzyme inhibition,³⁰ oxidative stress,³¹ genotoxicity,³² mitochondrial damage,³³ microbiome disruption,³⁴ autonomic nervous system impairment,³⁵ and epigenetic alterations.³⁶ However, there is emerging evidence that bioaccumulated toxicant burdens frequently induce a phenomenon of immune dysregulation³⁷⁻³⁹ with release of various proteins including pro-inflammatory cytokines frequently resulting in a varied constellation of signs and symptoms involving multiple organ systems.²²

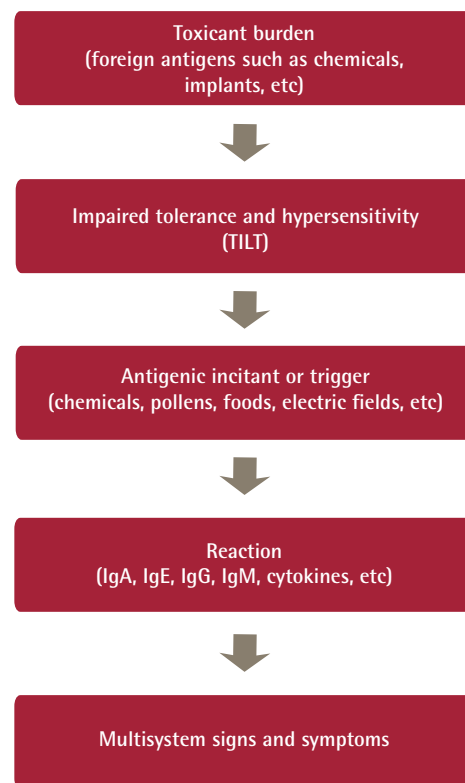
Figure 1 presents this common pathophysiologic mechanism of multimorbidity.

Toxicant-induced loss of tolerance. By toxicant-induced loss of tolerance (TILT), an intriguing mechanism of illness described in the literature since 1997,^{19,22,37,40} accrued toxicant burdens in humans and animals⁴¹ seem to evoke immune dysregulation, leading to hypersensitivity and consequent adverse reactions to commonly encountered compounds in the environment.^{22,40} A resulting sensitivity-related illness (SRI) ensues with multisystem response to the release of proteins from immune sources, often including antibodies and cell-regulating pro-inflammatory cytokines.^{22,39}

To further expound, the accrual of toxicant compounds foreign to the human body instigates a pathologic hypersensitivity state called *TILT*, with ensuing inflammation in response to antigenic stimulation.^{22,37} The toxicant burden might be caused by varying agents including stockpiled chemical compounds stored in tissues, implants, dental materials, chronic infections, and radioactive materials. The toxicant burden does not appear to be agent specific, but myriad types of toxicants alone or in combination have potential to induce SRI.^{22,42,43} The resulting immune dysregulation manifests as a profound hypersensitivity to commonly encountered substances such as specific foodstuffs, inhalants (eg, pollens), and various chemicals in the environment.⁴⁴

Multimorbidity presentation. Upon exposure to such inciting triggers, individuals with SRI might experience reactions leading to many apparently unrelated signs and symptoms. These reactions might include allergic-like responses, respiratory compromise, neurologic dysfunction, gastrointestinal damage, fatigue, musculoskeletal impairment, psychiatric difficulties, and other

Figure 1. Common pathophysiologic mechanism of multimorbidity



IgA—immunoglobulin A, IgE—immunoglobulin E, IgG—immunoglobulin G, IgM—immunoglobulin M, TILT—toxicant-induced loss of tolerance.

signs and symptoms.^{19,22,45} The reactions might be immediate or delayed and usually abate after 3 to 5 days in the absence of further exposure. In clinical practice, symptoms often persist for much longer, likely owing to recurrent exposure with insufficient recovery time. If exposure to triggers occurs habitually, inflammation persists and manifests as chronic ongoing body system impairment. It is generally observed that the greater the total toxicant burden, the more severe the hypersensitivity state. Biochemistry is frequently compromised from gastrointestinal dysfunction and malabsorptive states associated with inflammation.

The ensuing multisystem morbidity frequently drives individuals to their primary health providers with apparently inexplicable multisystem health complaints. Most people with such multisystem complaints go from caregiver to caregiver over many years desperately trying to find answers for their various health struggles; these individuals certainly fall into the World Health Organization category of having *chronic conditions*, described as “health problems that require ongoing

management over a period of years or decades.⁴⁶ A diagnosis of SRI should be considered whenever a presentation of plural diagnoses or multisystem complaints exists with associated food or chemical sensitivities.

Management. Resolution of multimorbidity follows appropriate assessment and intervention. Treatment is directed into 3 broad categories^{22,47}: resolution of inflammation by incitant avoidance; remediation of biochemistry; and toxicant burden elimination to resolve immune dysregulation and the hypersensitivity state. With alleviation of the TILT state by diminution of the toxicant burden, intolerance of foods and chemicals gradually abates with resumption of normal functioning. Left unrecognized, individuals with SRI often flounder with ongoing symptoms. Detailed information regarding pathophysiologic mechanisms and management strategies can be found in recent scientific literature.^{19,21,22,25,38,48}

Case resolution

The patient's presentation was consistent with a diagnosis of SRI. Removal of inciting agents was meticulously carried out. In the early stages, the patient initially wore a filter mask designed to preclude particulate and volatile exposures both indoors and outdoors as required. The indoor air environment was initially addressed through a home inventory and associated high-efficiency particulate air filtration. Professional mold remediation was undertaken and follow-up mold testing was clear. Commercial scents, perfumes, and fresheners were eliminated. Common food triggers such as gluten, casein, refined fructose, nightshades, artificial sweeteners, and flavouring agents were temporarily eliminated from the diet.²²

With these measures, the patient's symptoms began to abate steadily and attention was directed to remediating his nutritional biochemistry.⁴⁹ An organic, traditional whole food diet to minimize further toxicant and pesticide or herbicide exposure was implemented, along with directed supplementation to target specific biochemical deficiencies. With ongoing improvement, elimination of his total toxicant burden was commenced.


Amalgam removal employing exposure precautions and safe replacement materials was systemically done by a dental professional.⁵⁰⁻⁵² A saline nasal rinse with sodium bicarbonate was used for 3 weeks to eliminate residual mold from the sinus area, and detoxification measures were used to facilitate removal of residual mycotoxin.⁵³ General measures to facilitate toxicant elimination were undertaken, including exercise and regular transdermal depuration.^{25,54,55} High serum levels of trans fatty acid were addressed with dietary counseling.

With incitant avoidance, biochemical remediation, and toxicant elimination, the patient continued to steadily improve. His sensitivities continued to decrease, with diminished frequency and intensity of reactions, and there was dramatic improvement in overall physical and psychological functioning. His multisystem problems including chronic pain and asthma subsided, and all medication was discontinued. The patient recommenced work as a teacher and religious instructor, and he resumed his ability to enjoy daily activities without constant fear of debilitating reactions.

Conclusion

It has been said that "chronic disease is the great epidemic of our time."⁵⁶ Most patients with chronic illness now present with multimorbidity and many of these individuals experience associated sensitivities. Multimorbidity with sensitivities generally results in much frustration for both physicians and patients, as no cause is usually found and results of routine laboratory testing are unremarkable.^{57,58} Psychiatric attribution is commonplace; outcomes are generally poor; and associated health care costs are enormous.

Over the past 4 decades, a plethora of potentially adverse anthropogenic agents have been inadvertently unleashed into the environment for reasons of convenience, beauty, financial gain, safety, and other perceived needs within our culture.¹⁷ Increasing evidence indicates that some of these agents, as well as certain biotoxins and toxic elements, might bioaccumulate within the human organism and, after surpassing a certain accrued threshold, disrupted physiology ensues.^{19,21,22,48} Many adverse effects of toxicant accrual have been recognized, one of which is TILT,^{37,59} a pathognomonic feature of SRI and the disordered pathway to a clinical presentation of MWS.²²

The case we presented illustrates how various toxic exposures and their bioaccumulation within the body can manifest as SRI with associated MWS. Many primary care practitioners and specialists are not yet familiar with this common mechanism of illness or the required interventions to address this affliction. The protocol of removing triggers, optimizing biochemistry, removing future sources of exposure, and eliminating the stockpile of existing toxicants^{25,60} can be successfully employed to ameliorate the health status of countless patients with previously inexplicable multimorbidity. 

Dr Genuis is Clinical Professor and **Mr Tymchak** is a medical student, both in the Faculty of Medicine and Dentistry at the University of Alberta in Edmonton.

Contributors

Both authors contributed to the literature search and to preparing the article for submission.

Competing interests

None declared

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