

Responses to Panic Induction Procedures in Subjects with Multiple Chemical Sensitivity/Idiopathic Environmental Intolerance: Understanding the Relationship with Panic Disorder

Susan M. Tarlo,¹ Naveen Poonai,¹ Karen Binkley,¹ Martin M. Antony,² and Richard P. Swinson²

¹Gage Occupational and Environmental Health Unit, University of Toronto, Toronto, Ontario, Canada; ²Anxiety Treatment and Research Centre, St. Joseph's Hospital, and McMaster University, Hamilton, Ontario, Canada

Idiopathic environmental intolerance (IEI), also known as multiple chemical sensitivity, is a clinical description for a cluster of symptoms of unknown etiology that have been attributed by patients to multiple environmental exposures when other medical explanations have been excluded. Because allergy has not been clearly demonstrated and current toxicological paradigms for exposure-symptom relationships do not readily accommodate IEI, psychogenic theories have been the focus of a number of investigations. A significantly higher lifetime prevalence of major depression, mood disorders, anxiety disorders, and somatization disorder has been reported among patients with environmental illness compared with that in controls. Symptoms often include anxiety, lightheadedness, impaired mentation, poor coordination, breathlessness (without wheezing), tremor, and abdominal discomfort. Responses to intravenous sodium lactate challenge or single-breath inhalation of 35% carbon dioxide versus a similar breath inhalation of clean air have shown a greater frequency of panic responses in subjects with IEI than in control subjects, although such responses did not occur in all subjects. Preliminary genetic findings suggest an increased frequency of a common genotype with panic disorder patients. The panic responses in a significant proportion of IEI patients opens a therapeutic window of opportunity. Patients in whom panic responses may at least be a contributing factor to their symptoms might be responsive to intervention with psychotherapy to enable their desensitization or deconditioning of responses to odors and other triggers, and/or may be helped by anxiolytic medications, relaxation training, and counseling for stress management. **Key words:** idiopathic environmental intolerance, multiple chemical sensitivity, panic response. *Environ Health Perspect* 110(suppl 4):669-671 (2002).

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Idiopathic environmental intolerance (IEI), also known as multiple chemical sensitivity (MCS), is a clinical description for a cluster of symptoms of unknown etiology that have been attributed by patients to multiple environmental exposures when other medical explanations have been excluded. There are no specific physical or laboratory findings, and the diagnosis is usually one of exclusion. Consensus is lacking with respect to IEI's prevalence, diagnostic criteria, etiology, and therapeutic strategies. There is substantial heterogeneity in exposure, illness history, and presentation among persons with this diagnosis (1-6).

On average, IEI patients seen clinically are between 40 and 50 years of age, with approximately 4 times as many women affected as men. No single chemical or psychosocial situation has been defined as more prevalent than any other for the onset of symptoms (5). Symptoms often include anxiety, lightheadedness, impaired mentation, poor coordination, breathlessness (without wheezing), tremor, and abdominal discomfort (6). IEI patients attribute these symptoms to various environmental chemicals (3,6).

Several hypotheses have been generated regarding the mechanisms contributing to IEI. A central question has been whether individuals characterized with IEI suffer from a toxic or allergic disorder or whether

psychological factors cause at least some to develop physical symptoms that they attribute to allergy or toxic mechanisms. Because allergy has not been clearly demonstrated and current toxicological paradigms for exposure-symptom relationships do not readily accommodate IEI, psychogenic theories have been the focus of a number of investigations (7-9).

Several investigators found increased psychiatric morbidity among IEI patients (7-12). Simon et al. (8) reported a greater prevalence of current anxiety or depressive disorders among patients with IEI than among controls with chronic musculoskeletal injuries. Black et al. (12) found a significantly higher lifetime prevalence of major depression, mood disorders, anxiety disorders, and somatization disorder among patients with environmental illness than among controls. Fiedler et al. (11) compared psychiatric morbidity among patients with IEI, chronic fatigue syndrome (CFS), and healthy controls. Current diagnoses of a major depressive episode were significantly higher among IEI and CFS patients than in controls.

Panic Responses in Idiopathic Environmental Intolerance

Evidence also suggests that panic responses may play a role in the symptoms of IEI

patients (13,14). In a study by Leznoff (13), 11 of 15 IEI patients exposed to their purported trigger in an open fashion developed hypocarbia and experienced their usual IEI symptoms. In contrast, 4 of the 15 did not develop hypocarbia or reproduce their symptoms. The association of hypocarbia with reproduction of symptoms suggested that anxiety-driven hyperventilation resulting in hypocarbia may have contributed to IEI symptom production. In a pilot study, Binkley and Kutcher (10) reported that all five IEI patients who were challenged with intravenous sodium lactate infusion experienced a symptomatic panic response. This is a challenge shown to trigger panic attacks in patients with panic disorder (PD) but not in most normal controls (15). Independent psychiatric assessment resulted in the diagnosis of PD on the basis of *Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV* (16) criteria in each of the five IEI patients (10). In response to this pilot study, a larger study was performed by our group (17) using inhaled carbon dioxide (CO₂) as a less invasive trigger to panic (18,19). Inhaled CO₂ has been shown to trigger panic symptoms in 48-92% of patients with PD and approximately 5% of normal controls (20,21). In our study, responses to a single-breath inhalation of 35% CO₂ and a single breath of air alone (delivered in a single-blind manner) were compared in 36 subjects with IEI [fulfilling criteria described by Simon et al. (8)] and 37 healthy controls. Subjects given a diagnosis of IEI were excluded from the study if they had a previous psychiatric diagnosis or were taking psychiatric medications. Despite these exclusions, *DSM-IV* (16) criteria for a panic attack were elicited after CO₂ inhalation in significantly more IEI subjects than controls (71 vs. 26%, $p < 0.001$). In addition, IEI subjects scored significantly higher than controls on the Anxiety Sensitivity Index (ASI), a self-report

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Address correspondence to S.M. Tarlo, Gage Occupational and Environmental Health Unit, 223 College St., Toronto, Ontario, M5T 1R4, Canada. Telephone: (416) 978-5883. Fax: (416) 978-2608. E-mail: susan.tarlo@utoronto.ca

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questionnaire (22) completed by the study subjects prior to their visit for air and CO₂ challenges. The ASI measures the extent to which people are fearful of the physical sensations associated with arousal and anxiety. People with PD have higher ASI scores than people with other anxiety disorders and normal controls (23). Among IEI subjects who fulfilled panic attack criteria following the CO₂ challenge, the initial self-reported questionnaires indicated a higher frequency of panic attacks in the preceding month (mean 2.1) compared with the other IEI subjects (mean 0.1, $p < 0.05$) (17).

The IEI subjects in this study also scored significantly higher than controls on other self-completed questionnaires for anxiety and agoraphobia (24). These included the Mobility Inventory for Agoraphobia (MI), a self-report questionnaire in which individuals rate the extent to which they avoid 26 common agoraphobic situations when they are alone (MI-Alone) and when accompanied (MI-Accompanied) (25,26). The MI has been proven to be a sensitive measure of agoraphobia per se rather than a reflection of anxiety disorders in general (25,26). Scores for IEI subjects were significantly higher than those for controls for agoraphobic indices (25) both alone and accompanied, as well as on the Agoraphobia Cognitions Questionnaire (27), a questionnaire designed to measure thoughts related to agoraphobia and the consequences of panic. They also scored significantly higher on anxiety and stress subscales of the Depression Anxiety Stress Scales (DASS) (24), a self-report questionnaire designed to measure dysphoric mood (depression subscale), symptoms of fear and autonomic arousal (anxiety subscale), and symptoms of general nervousness and agitation (stress subscale) (28,29). IEI subjects scored higher than controls on the depression subscale of the DASS as well, a difference that was marginally significant (24). The 22 IEI subjects who fulfilled panic attack criteria after 35% CO₂ inhalation had significantly higher scores than IEI subjects who did not panic on the MI-Alone component of the MI, as well as the depression subscale of the DASS.

Therefore, evidence from these studies supports an association between panic symptoms and IEI. In addition there was a trend to an increase in other psychiatric morbidity consistent with other reports (7,8,12). Further support for an association with panic response comes from subsequent genetic analyses of DNA samples taken from IEI subjects (30). Samples from MCS subjects were compared with those from normal controls and showed the presence of the PD-associated cholecystokinin B receptor allele 7 in 9 of 22 (41%) subjects with MCS compared with 2 of 22 in control subjects.

Implications

In conjunction with other reports of psychological and psychiatric assessments in IEI patients, our findings indicate that a significant contribution to symptoms in these patients occurs from psychological and/or psychiatric disorders. Our studies have particularly demonstrated a contribution from panic responses. Conditioning of physical symptoms after neurotoxic exposure was suggested by Bolla-Wilson and colleagues in 1988 (31). Such a response could represent a learned or conditioned reflex response following an initial physical or emotional traumatic event, with subsequent extension to various non-noxious stimuli. Such learned responses were reported in patients by Dager et al. (32), and by Shusterman et al. (33) after solvent or other chemical exposures. Similarly, in an experimental setting, Van den Bergh and colleagues (34) demonstrated that healthy subjects can acquire somatic symptoms and respiratory changes in response to non-noxious odors when these odors are associated with a physiological challenge that originally caused these symptoms. The response to the non-noxious odors could subsequently be reduced in an extinction procedure, which further supports the hypothesis that this was a conditioned response. The same research group (35) subsequently reported that the learned symptoms could also be extended to new odors, particularly in subjects with high negative affectivity. For a classically conditioned fear response to be extinguished would require subsequent pairing of the conditioned stimulus (e.g., a feared substance in the environment) with safety (i.e., a lack of negative consequences) (36). It is not uncommon for patients with IEI to relate the initial onset of symptoms to an accidental exposure to a substance with a strong odor, either at work or in another setting.

It could be argued that although no toxic response has been demonstrated in these patients, hypothetically it is possible that a toxic central neural change may have been induced by such an exposure in subjects. Nevertheless, the preliminary genetic findings in this disorder (30) are more supportive of an underlying predisposition to panic responses. Similarly, reports by Black and colleagues (37,38) suggest preceding psychiatric morbidity in these patients as well as an increased prevalence of psychiatric disease in relatives of MCS patients, which further suggests that this condition occurs in a psychologically susceptible group of individuals.

Although the responses of these patients are similar to those of patients with PD, this psychiatric diagnosis cannot be used in these IEI patients, as the current diagnosis of PD in the *DSM-IV* (16) stipulates that PD cannot be diagnosed if responses occur secondary to a

particular trigger rather than spontaneously. Therefore the history given by IEI patients (that an environmental exposure always triggers symptoms) would exclude a formal diagnosis of PD. Further studies, such as investigation of neurotransmitters, that examine other outcome measures of panic responses in IEI patients may be useful in the future.

The panic responses in a significant proportion of IEI patients open a therapeutic window of opportunity. Patients who accept that panic responses may be at least a contributing factor to their symptoms might be responsive to intervention with psychotherapy to enable their desensitization (deconditioning of responses to odors and other triggers) and/or may be helped by anxiolytic medications, relaxation training, and counseling for stress management. A response to such intervention has been reported anecdotally (39,40,41), although randomized, placebo-controlled studies of such an approach have not been reported. Indeed, although panic responses were common in the group of IEI subjects we studied, only 1 among the 26 study subjects who had panic responses was agreeable to having a referral to a psychiatrist or psychologist. Perhaps such intervention may be more successfully achieved in a less formal manner through the family doctor, although again there are no published studies of such an approach.

Another possible implication of these findings relates to the prevention of IEI. If this response results from a conditioned reflex after an accidental exposure, it would be possible to prevent such responses by appropriately intervening after traumatic events such as accidental chemical exposures in the workplace, as suggested by Shusterman and Dager (42). It may be expected that early, accurate health information and early medical assessment—with reassurance when appropriate—workplace changes to prevent further accidental exposure, and accommodation of the worker's potential need to be gradually reintroduced to the same work area could be helpful.

Finally, panic responses to CO₂ challenges did not occur in all our IEI study subjects, and it is certainly likely that other organic and/or psychiatric disease also contributes to symptoms in some or all patients with IEI. Therefore, it continues to be important that such patients have both a full medical and psychiatric/psychologic assessment to identify other contributing diseases that may respond to specific treatment.

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