

Rapid communication

Panic response to sodium lactate infusion in patients with multiple chemical sensitivity syndrome

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Background: Many patients who are first seen with what has been called multiple chemical sensitivity syndrome (MCS) experience symptoms suggestive of panic disorder including chest tightness, shortness of breath, palpitations, paresthesias, lightheadedness, and mental confusion. Although such patients are often convinced that these symptoms reflect toxic effects of environmental "chemicals," direct evidence of this is lacking. To the contrary, a previous study has shown that some of these individuals exhibit hyperventilation responses on exposure to non-noxious stimuli, and it has been suggested that the resulting hypocarbia accounts for their symptoms. We postulated that some patients with self-identified MCS had an underlying condition similar to panic disorder and would therefore demonstrate similar responses to provocative challenges, such as sodium lactate infusion.

Methods: Patients referred to an allergy and clinical immunology service for evaluation of "chemical sensitivity" were investigated to rule out underlying medical conditions, including asthma, as a cause of their symptoms and were enrolled for study after giving informed consent. After a standardized psychiatric assessment was performed, patients underwent single-blind intravenous infusions of normal saline solution (placebo) and sodium lactate (which reproduces symptoms in individuals with underlying panic disorder). All patients were referred for independent psychiatric assessment.

Results: The standardized psychiatric assessment identified four of five patients as meeting *DSM III-R* diagnostic criteria for panic disorder along with other depressive and/or anxiety-related disorders. All five patients with self-identified chemical sensitivity exhibited a positive symptomatic response to sodium lactate compared with placebo infusion. Independent psychiatric assessment confirmed the diagnosis of panic disorder on the basis of *DSM III-R* criteria in each of the five patients.

Conclusions: These results suggest that MCS may have a neurobiologic basis similar, if not identical, to that of panic disorder. We speculate that treatments with demonstrated efficacy in panic disorder may also be of benefit in MCS, and

conversely, treatments that reinforce anticipatory anxiety and avoidance behavior in patients with MCS may be detrimental. (*J Allergy Clin Immunol* 1997;99:570-4.)

Key words: *Environmental hypersensitivity, multiple chemical sensitivity, panic disorder, sodium lactate infusion*

Controversy surrounds the nature of multiple chemical sensitivity syndrome (MCS),¹ also called *environmental hypersensitivity* and various other terms. Stringent diagnostic criteria have not been developed, but features include anxiety, irritability, difficulty concentrating, poor memory, shortness of breath, chest pain or tightness, palpitations, nausea, abdominal cramping, and polyuria, which individuals with these symptoms attribute to various "chemicals" in their environment.² Many of these individuals demonstrate anticipatory anxiety and phobic avoidance of common substances, often going to extreme lengths to avoid exposure.

Direct evidence to support these claims and behaviors is lacking.³⁻⁶ In fact, a previous study has shown that some of these patients exhibit hyperventilation responses on exposure to their purported triggers, suggesting that the resulting hypocarbia accounts for their symptoms.⁷

Panic disorder is a serious psychiatric disturbance that affects 3% to 5% of the population.⁸ It comprises three elements: panic attacks, anticipatory anxiety, and phobic avoidance. Episodic panic attacks are characterized by symptoms of intense anxiety, shortness of breath, dizziness, lightheadedness, palpitations, chest pain, abdominal upset, urinary urgency, dry mouth, and clammy skin.⁹ Occasionally, panic attacks may become paired with nonnoxious stimuli, which the patient may come to consider as actually causing the symptoms. Patients may then experience anticipatory anxiety regarding these otherwise nonnoxious stimuli and exhibit phobic avoidance of them.

The diagnosis of panic disorder is made on clinical grounds. However, various neurochemical stimuli, including intravenous sodium lactate infusion, will reproduce symptoms in approximately 80% of individuals with clinically diagnosed panic disorder.¹⁰ Only approximately 20% of individuals without panic disorder experience panic symptoms during sodium lactate infusion.

Given the similarities in symptoms, we hypothesized

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Partial support for Dr. Kutcher was provided by a Senior Scientist award from the Ontario Mental Health Foundation.

Received for publication Nov. 11, 1996; revised Jan. 6, 1997; accepted for publication Jan. 10, 1997.

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0091-6749/97 \$5.00 + 0 1/1/80298

Abbreviations used

API:	Acute Panic Inventory
DSM III-R:	<i>Diagnostic and statistical manual of mental disorders. 3rd ed., revised</i>
MCS:	Multiple chemical sensitivity syndrome
SCID:	Structured clinical interview for DSM III-R
VAS:	Visual analog scale

that some patients with self-identified MCS may be experiencing panic symptoms, which have been paired with nonnoxious environmental stimuli. As a first step in testing this hypothesis, we conducted a pilot study that included a self-reported psychiatric diagnostic survey and a single-blind placebo (normal saline solution) versus sodium lactate infusion challenge in individuals with self-reported hypersensitivity to environmental "chemicals." All patients were referred for independent psychiatric assessment.

METHODS

Our protocol involving single-blind sodium lactate infusion in patients with self-reported chemical sensitivity was approved as ethically acceptable on August 31, 1994, by the Research Ethics Board of Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada. Recruitment began at that time and concluded in 1996.

Patients with self-identified chemical sensitivity were referred to an allergy and clinical immunology clinic for assessment. Allergy testing (prick method) was performed with a panel of common allergens (Bencard Laboratories, Mississauga, Ontario, Canada) including dust mite, tree, grass, ragweed, *Alternaria* spp., *Aspergillus* spp., *Cladosporium* spp., dog, cat, and cockroach. The patients underwent pulmonary function testing including histamine and/or methacholine challenge. Patients with underlying medical conditions that would contribute to anxiety (e.g., thyroid toxicosis, stimulant abuse) were excluded.

The patients were concerned that they were developing allergies or sensitivities to "chemicals" and were otherwise typical of patients self-identified as having this problem. In all cases the patients had gone to substantial lengths to avoid the presumed environmental "toxins." All had been referred by their general practitioner for allergy assessment.

Patients were considered for study if they met all of the following criteria: (1) had characteristic symptoms as described above, (2) were able to give informed consent, (3) had no medical contraindication to sodium lactate infusion, (4) had not been previously diagnosed as having panic disorder, (5) were not taking psychotropic medications during the preceding 2 months, and (6) had no evidence of airway hyperreactivity on histamine or methacholine challenge.

All patients identified olfactory stimuli (perfume, tobacco smoke, and unpleasant odors) as triggers; patient 1 also identified tactile stimuli ("fuzzy" or textured fabrics) as triggers.

Patients were involved in a discussion regarding the potential role of anxiety and consequent hyperventilation in producing their symptoms and were asked to participate in a research protocol designed to evaluate whether anxiety might account in part for their symptoms. The first five patients who gave

informed consent and participated in this study protocol are reported here.

After informed consent was obtained, patients underwent standardized psychiatric evaluation consisting of a clinical interview and a semi-structured diagnostic self-report scale (Mini Structured Clinical Interview for DSM III-R [SCID]).¹¹ Baseline psychologic distress was evaluated by using three self-report instruments: the Symptom Checklist-58,¹² the Beck Depression Inventory,¹³ and the Hamilton Anxiety Rating Scale.¹⁴ Beck Depression Inventory scores greater than or equal to 11 are consistent with depressive or dysphoric symptoms; Symptom Checklist-58 scores greater than 60 are often consistent with significant emotional distress; and Hamilton Anxiety Rating Scale scores greater than 8 are often consistent with significant anxiety. All five patients completed this assessment and did not exhibit either current or lifetime history of the following psychiatric disorders: bipolar disorder, schizophrenia, anorexia nervosa, bulimia, obsessive compulsive disorder, or stimulant abuse.

Infusions were performed on an outpatient basis in a single-blind fashion with normal saline solution infused intravenously over 40 minutes, followed by a 0.5 mol/L solution of sodium lactate^{10, 15} infused at a rate of 10 ml/kg over an additional 40 minutes. These infusions were carried out with the patient in bed in a sitting position. The primary self-report outcome variable was the Acute Panic Inventory (API), modified to reflect DSM III-R criteria and completed at 10-minute intervals during the entire procedure. The API is an 18-item inventory of panic symptoms designed for patient self-report used in the study of panic attacks in laboratory settings.¹⁶⁻¹⁸ Additionally, each subject completed a visual analog scale (VAS) of "anxiety symptoms" at 10-minute intervals during the procedure. The primary observer report outcome variable was the presence or absence of a panic attack as observed by the attending clinicians in which an abrupt and escalating onset of fear or apprehension was accompanied by at least five of the 12 symptoms of panic attack listed in the DSM III-R.

Alprazolam was available to each patient on request at any point during the procedure. Patients 1 and 5 requested alprazolam; the others did not. After the procedure, each patient was evaluated by a physician before discharge.

Concomitant to their participation in the study, each patient was referred for independent psychiatric assessment.

RESULTS

Patient demographics and baseline assessment information are shown in Table I. Mini SCID evaluation suggested the following psychiatric diagnoses in the subjects: panic disorder ($n = 4$), social phobia ($n = 3$), generalized anxiety disorder ($n = 2$), major depressive disorder ($n = 2$), dysthymic disorder ($n = 2$), and alcohol abuse ($n = 1$).

Positive skin prick test responses to grass were observed in patient 4, and positive responses to grass and ragweed were observed in patient 2, consistent with histories of mild seasonal allergic rhinoconjunctivitis (data not shown). Results of skin tests were negative in the other patients.

The results of the infusion with each patient's self-reported API and VAS of anxiety symptoms are reported in Table II. The small number of subjects did not permit statistical analysis of the data. However, the objectively reported intrasubject scores of the API and

TABLE I. Patient demographics and baseline assessment

Patient No.	Age (yr)	Sex	Diagnosis (Mini SCID)	SCL-58	BDI	HARS
1	43	F	PD	80*	1	10†
2	43	M	PD, SP, ETOH	66*	1	0
3	40	M		83*	3	9†
4	29	F	PD, DD, GAD, MDD, SP	168*	19‡	40†
5	57	F	PD, SP, DD, GAD, MDD	150*	37‡	34†

SCL-58, Symptom Checklist-58; BDI, Beck Depression Inventory; HARS, Hamilton Anxiety Rating Scale; PD, panic disorder; SP, social phobia; ETOH, alcohol abuse; DD, dysthymic disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder.

*Suggests significant baseline emotional disturbance.

†Suggests significant baseline anxiety symptoms.

‡Suggests significant baseline depressive symptoms.

TABLE II. Patient self-report response and observer-rated panic attack incidence to normal saline (placebo) and sodium lactate infusion

Patient No.	VAS of anxiety symptoms			API			Observer-rated panic attack with			
	Baseline	Placebo	Lactate	Baseline	Placebo	Lactate	Normal saline infusion		Lactate infusion	
							No	Yes	No	Yes
1	1	1	8	2	5	43	X			X
2	0	0	0	0	1	7	X			X
3	1	1	4	0	0	25	X			X
4	3	3	7	12	11	21	X			X
5	5	0	6	10	5	44	X			X

VAS were compatible with clinically significant symptoms induced by sodium lactate infusion and not by placebo (normal saline solution) infusion.

The clinical diagnosis of the attending clinicians (research nurse and psychiatrist), using *DSM III-R* criteria for the identification of a panic attack, was that each of the patients experienced a panic attack of varying severity during sodium lactate infusion but not during placebo infusion.

In five of the five patients, independent psychiatric assessment confirmed the presence of panic disorder meeting *DSM III-R* criteria (Drs. Peter Stenn and Granville da Costa. Personal communications).

The major findings of this pilot study are:

1. Four of the five studied patients with self-reported chemical sensitivity were diagnosed with panic disorder, comorbid with other anxiety and/or depressive disorders, as identified by a standardized psychiatric assessment.
2. In all five patients, sodium lactate infusion resulted in the induction of a panic-like state with reproduction of their presenting symptoms, which was not induced with placebo infusion.
3. In all patients, independent psychiatric assessment confirmed the diagnosis of panic disorder on the basis of *DSM III-R* criteria.

DISCUSSION

The similarity between symptoms reported by patients with MCS and those with panic disorder prompted us to study the responses of these patients to sodium lactate infusion. We postulated that some patients with MCS have an underlying condition similar, if not identical to panic disorder, and might therefore demonstrate similar panic symptoms on provocative challenge, such as sodium lactate infusion.

Lactate infusion is a useful technique in the study of panic disorder.^{10, 15, 19} Eighty to one hundred percent of patients with a clinical diagnosis of panic disorder may experience a panic attack after an intravenous infusion of sodium lactate compared with about 20% of unaffected control subjects. Panic attacks produced by sodium lactate infusion have been demonstrated to be phenomenologically similar to natural panic.^{18, 19} Although the sodium lactate infusion test is not necessarily diagnostic of panic disorder, it nevertheless may identify a group of individuals with a neurobiologic diathesis consistent with panic attacks. The exact pathophysiology of panic disorder is currently under investigation, but sodium lactate infusion, as a model for inducing panic attacks, is consistent with current neuroanatomic hypotheses.¹⁹⁻²¹

All five patients studied demonstrated panic symptoms typical of their presenting complaints with sodium

lactate infusion but not with placebo infusion. Although sodium lactate infusion is usually less sensitive than clinical assessment in identifying panic disorder (up to 20% of patients with clinically diagnosed panic disorder will have no response to sodium lactate), the results of the infusions are particularly compelling because they are less likely than clinical assessments to be distorted by bias. Our study involved a small number of patients, but our data nonetheless suggest that at least some patients with MCS may actually have panic disorder or a similar condition, perhaps hypersensitivity of brain stem chemoreceptors.¹⁹

Additional support for our hypothesis comes from the results of the standardized psychiatric diagnostic interview, which provided suggestive evidence that four of the five patients met the criteria for a *DSM III-R* diagnosis of panic disorder. These patients also exhibited concurrent psychiatric disturbances within the anxiety and depressive spectrum. In all five cases independent psychiatric assessment confirmed the diagnosis of panic disorder on the basis of *DSM III-R* criteria. Whether these psychiatric conditions account in full or in part for these patients' symptoms remains to be determined.

Panic disorder is a serious psychiatric disturbance that affects 3% to 5% of the population.⁸ In addition to episodic panic attacks, which can be spontaneous or triggered, this disorder usually involves anticipatory anxiety and phobic avoidance. Neutral stimuli can become paired with panic symptoms, thus becoming conditioned stimuli, which may then be considered by the patient to be causes of the attacks. These otherwise neutral stimuli may then act as independent triggers of panic symptoms, leading to incapacitating phobic avoidance and agoraphobia, which severely limit social and occupational functioning.⁸ The conceptualization of MCS as a type of phobic disturbance has recently been detailed elsewhere^{22,23} and is compatible with the panic disorder hypothesis we advance. In fact, underlying panic disorder with conditioned phobic responses to "chemical" triggers could account for the full clinical picture in at least a subset of patients with MCS. The presence or absence of a variety of comorbid psychiatric or other conditions could lead to the observed heterogeneity of clinical presentation.

The patients described in this study exhibited many of these fear and avoidance patterns with regard to non-specific "chemical" triggers, which we postulate had become conditioned stimuli. Some of our patients had sought or had considered seeking assistance from practitioners who supported their view that "chemical sensitivity" was the underlying cause of their symptoms. If these patients indeed have a panic-type disorder, external reinforcement as to the harmful effects of environmental "chemicals" may inadvertently lead to strengthening of the psychologic pairing of relatively nonnoxious environmental stimuli (typically "chemical" odors), with panic symptoms. We speculate that this could then increase anticipatory anxiety and phobic avoidance. Thus contact of these patients with "alternative" thera-

pies, models, or belief systems that reinforce a "chemical sensitivity" paradigm may actually increase the spectrum of perceived triggers, symptoms, and functional disability. Similar concerns have been expressed by others.²²⁻²⁴ Additionally, cognitive modeling, in which an individual complaining of MCS may have particular symptom complexes found in others with MCS (which are a priori attributed to environmental "chemicals") may occur.

In summary, we have presented preliminary evidence that some patients with MCS may have panic disorder. These patients may have a psychiatric diagnosis of panic disorder (with or without comorbid anxiety, depression, or other psychiatric disorders) but attribute their symptoms, not to a primary psychiatric disturbance, but to environmental "toxins," which we postulate have become psychologically linked with panic symptoms. This perspective, reinforced by "alternative" care givers, could result in increased anticipatory anxiety, production and maintenance of panic attacks, phobic avoidance, and a reluctance to seek potentially helpful psychiatric treatments.²⁴

Although these results need to be replicated in larger studies that include Axis I and Axis II psychiatric disorders, the diagnostic and therapeutic implications arising from this report are considerable. The importance of considering primary psychiatric disorders in patients with self-identified chemical sensitivity⁶ is highlighted. These results have led us to speculate that treatments including pharmacotherapy (e.g., serotonin reuptake inhibitors, tricyclic antidepressants, benzodiazepines) and psychotherapy (cognitive and behavioral), which have demonstrated efficacy in the treatment of panic disorder and comorbid psychiatric conditions, may be of benefit in the treatment of patients with MCS. Further such investigations are in progress.

We thank Betty Rychlewski for preparation of the manuscript, Bridgette Ward and Dr. George Papatheodorou for their assistance with this study, and our patients for their participation.

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