

Self-reported sensitivity to chemical exposures in five clinical populations and healthy controls

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Received 22 January 1997; received in revised form 22 September 1999; accepted 15 December 1999

Abstract

Two hundred and twenty-five subjects, including normal volunteers and patients with previously documented seasonal affective disorder (SAD), chronic fatigue syndrome (CFS), Cushing's syndrome, Addison's disease and obsessive-compulsive disorder (OCD), completed a self-rated inventory of reported sensitivity to various chemical exposures. Patients with CFS, Addison's disease and SAD self-reported more sensitivity to chemical exposures than normal controls. In addition, women reported more sensitivity than men. This report suggests that chemical

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sensitivity may be a relevant area to explore in certain medical and psychiatric populations. A possible relationship between reported chemical sensitivity and hypothalamic–pituitary–adrenal (HPA)-axis functioning is discussed. © Published by Elsevier Science Ireland Ltd.

Keywords: Seasonal affective disorder; Chronic fatigue syndrome; Addison's disease; Obsessive–compulsive disorder; Cushing's syndrome; Hypothalamic–pituitary–adrenal axis (HPA); Multiple chemical sensitivity; Chemical exposure

1. Introduction

Enhanced sensitivity to exposures to a wide variety of environmental chemicals has been reported to be a hallmark of a controversial diagnostic entity known as multiple chemical sensitivity (MCS). Chemical sensitivity has also been found to be pervasive in the general population and not just in urban settings. For example, a survey of a rural population in North Carolina reported a 33% prevalence of mild chemical sensitivity, including a daily sensitivity rate of 3.9%, with women reporting higher rates of sensitivity than men (Meggs et al., 1996). Relatively little attention, however, has been paid to the extent to which such sensitivity to exposure to ordinary environmental chemicals is a function of other medical or psychiatric conditions. Indeed, a literature search revealed only a few studies in which various patient groups were surveyed for evidence of chemical sensitivity. In one article, both MCS patients and asthmatics reported higher levels of sensitivity to environmental exposures than a control group (Kipen et al., 1995). Sensitivity was defined by the authors as 'producing symptoms — an awareness of some discomfort or bothersome change'. When all groups were considered, women reported sensitivity to a significantly greater number of substances than men.

Olfactory thresholds have been associated with self-reported sensitivity to chemical exposures, with lower thresholds being associated with higher sensitivities (Henkin and Bartter, 1966). There is evidence that such sensitivity thresholds are related to hypothalamic–pituitary–adrenal (HPA) axis functioning, with higher thresholds occurring in patients with Cushing's syndrome and lower thresholds in patients with Addison's disease (Henkin and Bartter, 1966; Kozak, 1977). When Cushing's syndrome was experimentally induced

in dogs using exogenous steroids, there was a significant elevation in the olfactory threshold and diminished olfactory capacity (Ezeh et al., 1992). Other conditions have been found or hypothesized to be associated with alterations in HPA-axis functioning as well. For example, melancholic depression has been associated with overactive HPA functioning while atypical depressive symptoms, such as those which occur in patients with chronic fatigue syndrome (CFS) (Demitrack et al., 1991) and seasonal affective disorder (SAD) (Joseph-Vanderpool et al., 1991), have been hypothesized to involve underactive HPA-axis functioning.

In preliminary HPA studies involving chemical sensitivity, Bell (1994) found low HPA axis functioning in one study and apparently increased HPA activation and instability in a second study. In the first, a low dose dexamethasone suppression test done on elderly subjects with and without chemical sensitivity found that chemically sensitive individuals had lower post-dexamethasone 08.00 h cortisol levels. In the second, elevated and labile plasma beta-endorphin levels were found in a different group of elderly subjects with chemical sensitivity when blood samples were taken 90 min following ingestion of milk or soy.

Not all chemically sensitive groups have been found to have altered olfactory thresholds. Doty et al. (1988) found that MCS patients may not have altered olfactory detection thresholds. This raises the possibility that chemical sensitivity could arise via different mechanisms in different populations.

In the present study, we evaluated self-reported sensitivity to chemical exposures in several groups with medical and psychiatric diagnoses as well as healthy controls. We discuss the practical and theoretical implications of such symptoms.

2. Methods

2.1. Subjects

Study populations were as follows:

1. Forty-six patients with seasonal affective disorder (SAD), diagnosed according to Rosenthal's criteria (Rosenthal et al., 1984). Of these, 36 were women and 10 were men; age range: 23–52 years with mean age of 40.1 years (S.D. = 7.2). Four patients had been treated using light therapy.
2. Seventy-three patients with chronic fatigue syndrome (Holmes et al., 1988), 51 women and 22 men; age range: 26–55 years with mean age of 42.3 years (S.D. = 8.0). No patients had been treated.
3. Twenty-seven patients with obsessive–compulsive disorder (OCD), diagnosed according to DSM-III-R criteria (American Psychiatric Association, 1987), 14 women and 13 men; age range: 21–62 years with mean age of 37.3 years (S.D. = 10.6). No patients had been treated.
4. Twenty-one patients with Addison's disease (Thorn, 1951), 14 women and 7 men; age range: 21–63 with mean age of 42.7 years (S.D. = 11.3). Seven patients had been treated with steroid replacement.
5. Nineteen patients with Cushing's syndrome (Carpenter, 1986), 13 women and 6 men; age range: 27–65 years with mean age of 39.0 years (S.D. = 9.6). No patients had been treated.
6. Thirty-nine healthy volunteers, 23 women and 16 men; age range: 20–53 years with mean age of 40.1 years (S.D. = 9.5). No patients had been treated.

Patients in the different groups were specially evaluated and managed in a variety of ways under separate approved clinical research protocols at the National Institutes of Health, the full delineation of which is beyond the scope of the present report.

2.2. The instrument

The self-report questionnaire used in this study was a modification of one used to evaluate chemical sensitivities in Gulf War Veterans and patients with self-reported MCS (Miller, 1994; Miller and Mitzel, 1995). In this questionnaire, subjects were asked to report on a Likert scale of 0 (no sensitivity) to 3 (marked sensitivity) their sensitivity to a variety of chemical exposures. Sensitivity was defined as experiencing any symptoms (e.g. headache, nausea, breathing difficulty, dizziness, and aftermeal discomfort) when smelling certain odors or chemicals. The following list of 36 items was based on those substances that are commonly reported as unpleasant by patients reported to have MCS: engine exhaust, tobacco smoke, oil paint or paint thinner, disinfectants, insect repellents, hairspray, hot tar or asphalt, pesticides or insecticides, nailpolish or nailpolish remover, gasoline or other fuel, certain perfumes and fragrances, open-flame gas heaters or stoves, felt-tip marking pens, chlorine, new carpeting, freshly printed newspapers, books or magazines, new automobile interiors, detergent aisle in grocery store, malls or certain stores, smoke from burning leaves, wood or barbecue grills, caffeine, alcohol, particular foods and beverages. The questionnaire also inquires about usual alcohol intake, smoking habits, adverse reactions to medications or medical procedures such as: penicillin, sulfa antibiotics, aspirin, Tylenol[®], general anesthetics, local anesthetics, decongestants, opiate drugs, X-ray contrast dyes, implants, and vaccines. A category for 'other substances' was also included.

The questionnaire has not been studied for test–retest reliability or any psychometric analysis, nor has it been validated by comparing self-reported symptoms to symptom induction following chemical exposures. A copy of the questionnaire is available to interested readers on request.

2.3. Procedure

Questionnaires with self-addressed stamped

envelopes were mailed to subjects between August 1994 and March 1995. An exception was Cushing's patients who were given questionnaires while being evaluated at the NIH Clinical Center. A cover letter accompanied the questionnaire, informing subjects of the intention to assess sensitivity to a variety of chemicals in different subject populations. No mention was given as to predicted responses. Subjects were drawn from past and present NIH research studies and were diagnosed (clinically and/or with structured interviews) prior to administration of the questionnaire. Reminder notices were sent to subjects who did not respond within 8 weeks.

2.4. Statistical analysis

The scores on all items were added to reach a composite sensitivity score, which could range from 0 to 108 (36 items with a maximum per item subjective response of 3 on the Likert scale). All items were given equal weight and consideration. In addition to determining composite sensitivity scores, the number of items positively endorsed (i.e. given a score > 0) by each subject was also noted. The sensitivity scores of all groups were compared by ANOVA using two grouping factors: diagnosis and sex. The Student–Newman–Keuls test was used to determine intergroup differences when the ANOVA was significant. Outliers were eliminated from the analysis if greater than 3 S.D. from their respective group mean. Individual *t*-tests were used to compare male and female scores. Insofar as we sought to generate, rather than to test, hypotheses in this article, we have not constrained ourselves with corrections for multiple comparisons in order not to miss possible differences between groups.

In addition to comparing the individual subject categories to one another, categories were also grouped according to putative HPA-axis functioning. According to this a priori classification, Cushing's patients were regarded as falling into the high HPA-axis activity group, the healthy volunteers and OCD patients (Altemus et al., unpublished) into the normal HPA-axis activity group, and Addison's disease (Kozak, 1977), SAD (Joseph-Vanderpool et al., 1991) and CFS (De-

mitrack et al., 1991) into the low HPA-axis group. The HPA-axis functioning categories used in this survey are admittedly somewhat hypothetical as they were developed on the basis of the literature on the conditions in question rather than as a function of direct measurement.

3. Results

Of the 290 targeted subjects, 225 (77.6%) completed and returned the questionnaire. Returns were as follows for the various groups: Cushing's syndrome, 20 of 21 (95.2%); seasonal affective disorder, 49 of 53 (92.5%); chronic fatigue syndrome, 73 of 91 (80.2%); Addison's disease, 21 of 28 (75.0%); and obsessive–compulsive disorder, 27 of 55 (49.1%) ($\chi^2 = 36.4$, d.f. = 5, $P < 0.0001$). One patient with Cushing's syndrome was an outlier (sensitivity score > 3 S.D. from mean) and was thus excluded from analysis.

When composite sensitivity scores were evaluated, patients with chronic fatigue syndrome, Addison's disease, and seasonal affective disorder reported the greatest sensitivities to chemicals (mean \pm S.D. = 26.5 ± 21.5 , 20.7 ± 18.1 , and 19.9 ± 13.8 , respectively) followed by obsessive–compulsive disorder (14.1 ± 14.5), Cushing's syndrome (13.0 ± 8.1), and healthy controls (7.4 ± 5.9) who claimed to be least sensitive ($F = 8.34$, d.f. = 5, $P < 0.0001$). Post-hoc analysis revealed that patients with CFS, Addison's disease, and SAD were statistically different from normal controls ($P < 0.0001$, $P < 0.005$, $P < 0.005$, respectively), but not from each other. In addition, patients with CFS reported significantly more sensitivity than those with OCD or Cushing's syndrome ($P < 0.005$), but these latter two conditions did not differ from each other or from normal volunteers. There was a trend towards greater sensitivity in Addison's and SAD patients compared with Cushing's patients ($P = 0.06$; $P = 0.09$, respectively).

Women with CFS, Addison's disease, and SAD reported significantly more sensitivities than the women with Cushing's disease ($P < 0.005$, $P < 0.05$, $P < 0.05$, respectively). Although it appears

from Fig. 1 that a higher proportion of women than men with Addison’s disease, CFS and SAD reported being sensitive to environmental exposures, no significant gender × diagnosis interactions emerged from the ANOVA.

Subjects suspected of having low HPA-axis activity (CFS, Addison’s, SAD) described significantly more sensitivity than both the high HPA group (i.e. Cushing’s) ($F = 16.32$; $d.f. = 2$; $P < 0.01$) and the normal HPA group (normal subjects, OCD) ($F = 16.32$; $d.f. = 2$; $P < 0.001$). No

differences were found between the normal and high HPA groups ($P = 0.4$). There was a significant interaction between gender and HPA axis group ($F = 3.3$; $d.f. = 2$; $P < 0.05$), with women reporting greater chemical sensitivity than men in the low HPA-axis group only (Fig. 2).

The items most consistently reported as producing symptoms with all groups considered were tobacco smoke (65.8%), engine exhaust (60.9%), oil paint (56.9%), certain perfumes and fragrances (54.2%), and pesticides or insecticides

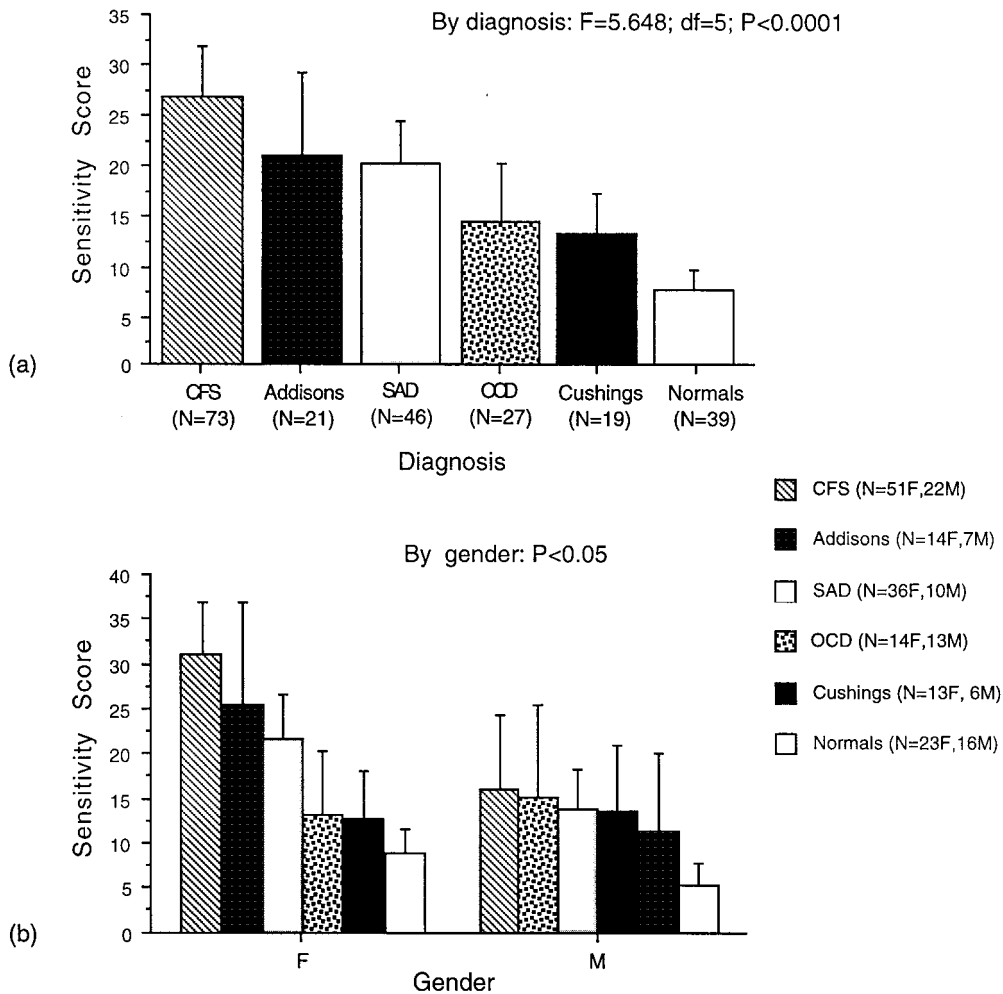


Fig. 1. A comparison of self-reported chemical sensitivity across diagnostic groups for all subjects ($F = 5.648$; $d.f. = 5$; $P < 0.0001$) (a); and for men and women considered separately ($P < 0.05$) (b).

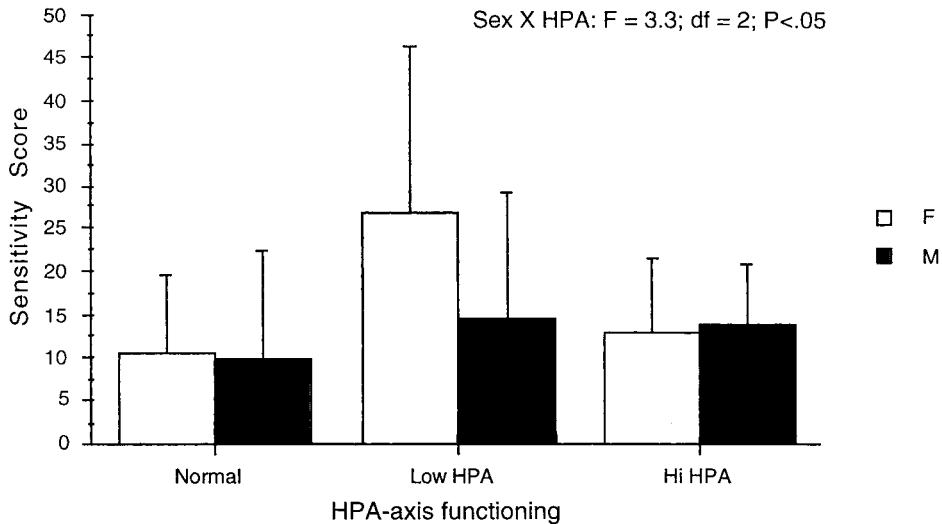


Fig. 2. A comparison of self-reported chemical sensitivity by HPA axis functioning and gender ($F = 3.3$; $d.f. = 2$; $P < 0.05$).

(53.8%). Analyzing the groups according to the number of sensitivity items positively endorsed did not fundamentally affect the results.

4. Discussion

Our findings suggest that rates of self-reported sensitivity to a variety of chemical exposures differ across diagnostic groups. We should emphasize that we cannot address the accuracy of these reports nor comment on their clinical significance as we have no understanding of the biological basis (if any) underlying such self-reported sensitivities. Nevertheless, it is of interest that self-reported sensitivity to chemical exposures was not uniformly reported across groups. In addition, it is possible that such symptoms are meaningful, in that sensitive patients might feel better if they avoid certain chemical exposures. Such efforts at avoidance can be psychologically costly in their own right, however, and need to be balanced against considerations of what is practical, affordable, and socially acceptable, regardless of the putative biological underpinnings of the symptoms.

The tendency for women to report greater chemical sensitivity than men is in line with the

preponderance of women in some of the highly sensitive groups, such as CFS and SAD, as well as the higher percentage of women in previously described chemically sensitive groups (Steinberg and Wall, 1995; Miller and Mitzel, 1995). The reason for this gender difference may be related to estrogen secretion. An increase in sensory detection acuity (particularly olfaction) in females has been found to be most acute during the follicular phase of the menstrual cycle when estrogen levels are highest, and least acute during the luteal phase when estrogen levels are relatively low (Henkin, 1974). Furthermore, studies have shown that hypogonadal women often have poor olfactory acuity which is significantly improved following estrogen administration (Marshall and Henkin, 1971; Steinberg and Wall, 1995). Other possible reasons for the gender differences, such as differences in early learning, verbal ability, anatomy/physiology of nasal airways, and olfactory/neural pathways have also been suggested (Doty et al., 1985). Whether this greater tendency to report sensitivity reflects gender differences in biology, perception, or an ascertainment bias remains to be established.

The suggestion that HPA-axis status might correlate with chemical sensitivity, postulated on the basis of both animal and clinical experience

(Henkin and Bartter, 1966; Kozak, 1977; Ezeh et al., 1992), is supported by the present data. It would seem logical that when under severe stress, the focus of the central nervous system would be geared towards heightened action rather than heightened sensory input. Accordingly, Henkin has suggested that glucocorticoids increase sensory thresholds. The finding that low HPA axis females report greater sensitivity to chemicals may reflect the synergistic actions of estrogen levels with low glucocorticoid levels.

It is of interest that patients with MCS are likely to have experienced traumatic experiences (especially sexual abuse) and are at risk of post-traumatic stress disorder (PTSD) (Staudenmayer, 1996). This is relevant because PTSD is associated with low HPA axis activity marked by lower urinary-free cortisol levels and dexamethasone suppression (Yehuda et al., 1993). Our findings are in agreement with those of Bell (1994) showing low HPA axis functioning in people with chemical sensitivity rather than with a later report of Bell et al. (1996).

It is worth noting that patients with CFS and MCS have remarkable similarities clinically and demographically (Buchwald and Garrity, 1994; Fiedler et al., 1996). Most are relatively well educated adult females with similar mean ages, racial/ethnic distribution, marital status, employment rates, and duration of illness (Buchwald and Garrity, 1994). CFS patients have previously been reported to have greater chemical sensitivity than controls, but this is not as marked as in MCS (Buchwald and Garrity, 1994; Fiedler et al., 1996). Dunstan et al. (1995) found that levels of serum organochlorines are higher in CFS patients compared with normal subjects (whether or not they have a history of toxic chemical exposure) suggesting that chemical exposure may play an etiological role in CFS. Similarly, Gershon and Shaw (1961) published case reports in which chronic exposure to organophosphates led to psychiatric manifestations such as depression, chronic fatigue, and heightened sensitivity to external stimuli.

Our finding of no significant difference in chemical sensitivity between Cushing's patients and controls argues against a simple relationship

between HPA axis status and chemical sensitivity. We cannot explain why Cushing's patients in this article are not less sensitive to chemicals than normal, as we would have predicted. One possible reason is that the stringent criteria used to choose our normal controls might have selected for people who were particularly insensitive to environmental chemical exposures.

We are aware that our HPA axis grouping was not made by direct measurement and our findings must therefore be interpreted cautiously. Our data encourage a systematic investigation of the level of HPA axis functioning in patients who report marked chemical sensitivities. They also suggest that clinicians should inquire about chemical sensitivities in patients with other conditions.

Acknowledgements

The authors thank Drs Sue Carter-Porges, Dan A. Oren, Hans E. Kaiser, John R. Glowa, Jack Yanovski, Alan Ganjei, and Rhonda Voskuhl and the 10 West Patient Care Unit for their invaluable support. Special appreciation goes to Julia Thomas, Sam Angura and Chris Drake for technical assistance, and to Dr John Bartko for statistical consultation.

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