Sympathetic Nervous System Dysfunction in Fibromyalgia, Chronic Fatigue Syndrome, Irritable Bowel Syndrome, and Interstitial Cystitis

A Review of Case-Control Studies

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Background: Fibromyalgia often coexists and overlaps with other syndromes such as chronic fatigue, irritable bowel syndrome, and interstitial cystitis. Chronic stress has been implicated in the pathogenesis of these illnesses. The sympathetic nervous system is a key element of the stress response system. Sympathetic dysfunction has been reported in these syndromes, raising the possibility that such dysautonomia could be their common clustering underlying pathogenesis.

Objective: The objective of this study was to carry out a review of all published comparative case-control studies investigating sympathetic nervous system performance in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis.

Methods: Online databases PubMed and EMBASE were accessed using the following key words: autonomic (OR) sympathetic (AND) fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. All entries up to December 10th 2012 were reviewed by 2 independent investigators searching for case-control studies in humans. The Method for Evaluating Research and Guidelines Evidence adapted to the Scottish Intercollegiate Guidelines Network was used to rank the level of evidence contained in the selected articles.

Results: A total of 196 articles are included in this review. The most often used methods to assess sympathetic functionality were heart rate variability analysis, sympathetic skin response, tilt table testing, and genetic studies. The majority of studies (65%) described sympathetic nervous system predominance in these overlapping syndromes. In contrast, 7% of the studies found parasympathetic predominance.

Conclusions: This review demonstrates that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. This concordance raises the possibility that sympathetic dysfunction could be their common underlying pathogenesis that brings on overlapping clinical features. The recognition of sympathetic predominance in these 4 syndromes may have potential clinical implications. It may be worth exploring the use of nonpharmacological measures as well as drug therapies aimed to regain autonomic balance.

Key Words: fibromyalgia, chronic fatigue syndrome, irritable bowel, interstitial cystitis, systematic review, sympathetic nervous system, stress

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Fibromyalgia often coexists and overlaps with other controversial syndromes such as chronic fatigue, irritable bowel syndrome, and interstitial cystitis.[1] These syndromes are very frequent in different clinical settings. The pathogenesis of these illnesses has not been elucidated. Chronic stress has been implicated in the development of fibromyalgia,[2,3] chronic fatigue syndrome,[4] irritable bowel syndrome,[5] and interstitial cystitis.[6] An acceptable physiological definition of stress could be "any stimuli, physical, or emotional that threatens homeostasis."[2]

The sympathetic nervous system is a key element of the stress response system. Sympathetic dysfunction has been reported in the 4 syndromes under discussion, raising the possibility that such dysautonomia could be their common clustering underlying pathogenesis.[1]

OBJECTIVE

The objective of this study was to carry out a review of all published comparative case-control studies investigating sympathetic nervous system performance in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis.

METHODS

Online databases PubMed and EMBASE were accessed using the following key words: autonomic (OR) sympathetic, (AND) fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. All entries up to December 10, 2012, were reviewed by 2 independent investigators searching for case-control studies in humans.

Included were articles written in English containing case-control studies in patients with fibromyalgia, chronic fatigue syndrome, irritable bowel, or interstitial cystitis. Articles on patients with presence of comorbid conditions other than the 4 syndromes under discussion were excluded.

Two independent investigators reviewed, tabulated, and ranked each article. If there were ranking discrepancies between these 2 investigators, a third independent researcher moderated the differences.

The Method for Evaluating Research and Guidelines Evidence (MERGE)[7] adapted to the Scottish Intercollegiate Guidelines Network (SIGN)[8] was used to rank the level of evidence contained in the selected articles. For each article, the following items were evaluated: internal validity, selection of subjects, assessment methods, and confounding factors. Each item was ranked as "well covered," "adequately addressed," "poorly addressed," "not addressed," "not reported," or "not applicable." Reviewed articles were classified as "high quality" when all or most of MERGE checklist items were fulfilled; "medium quality," when some checklist criteria were fulfilled, but those items not fulfilled were thought unlikely to alter the conclusions; and "low quality," when few or none criteria were met.

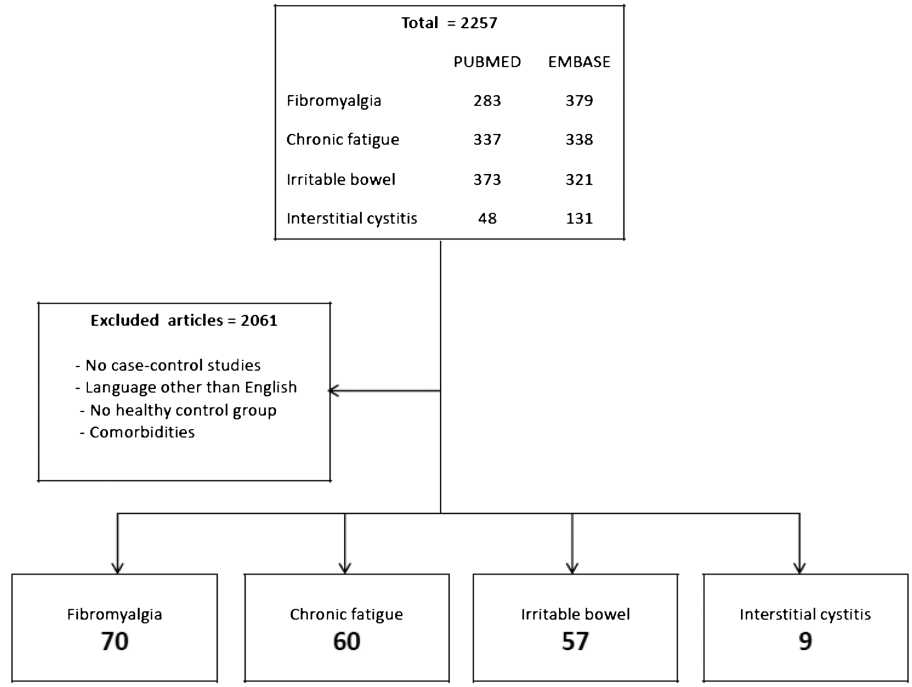

FIGURE. Literature search flowchart.

All reviewed case-control studies were included in the final analysis.

"Sympathetic predominance" was defined as statistically significant data suggesting higher sympathetic activity, decreased parasympathetic activity, or both. A reverse definition was applied for "parasympathetic predominance."

Statistical Analysis

Descriptive statistic was used to summarize overall results. A χ^2 method compared the proportion of studies describing sympathetic predominance versus parasympathetic predominance for each of the 4 groups.

RESULTS

Our search identified 2257 abstracts listed in PubMed and/or EMBASE databases. After review, 2061 were excluded for the following reasons. They were not case-control studies, articles were written in a language other than English, there was no

TABLE 1. SIGN 50 Checklist (n = 196 Articles)

SIGN 50 Assessment Points	Well Covered, %	Adequately Addressed, %	Poorly Addressed, %	Not Addressed, %	Not Reported, %	Not Applicable, %
The study addresses an appropriate and clearly focused question	36.2	53.6	10.2	0	0	0
The patients and control subjects are taken from comparable populations	40.8	40.8	13.3	4.1	0.5	0.5
The same exclusion criteria are used for both patients and control subjects	50	25	18.9	4.6	1.5	0
Comparison is made between participants and nonparticipants to establish their similarities and differences	43.4	24.5	21.9	6.1	2	2
Patients are clearly defined and differentiated from control subjects	34.2	44.4	17.9	3.6	0	0
It is clearly established that control subjects are nonpatients	25	42.9	27	5.1	0	0
Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment	26	49.5	21.9	2	0	0.5
Exposure status is measured in a standard valid and reliable way	27.6	52	16.3	3.1	1	0
The main potential confounders are identified and taken into account in the design and analysis	13.8	48	32.7	4.1	1	0.5

TABLE 2. Quality of Studies According to MERGE-SIGN 50 Checklist

		Topic			
		Fibromyalgia	Chronic Fatigue	Irritable Bowel	Interstitial Cystitis
Quality		n	n	n	n
High quality	(++)	24	27	12	3
Medium quality	(+)	43	31	37	5
Low quality	(−)	3	2	8	1

control group, or the cases had comorbid conditions. The remaining 196 articles are included in this review as shown in the flowchart (Fig.). One hundred three cases were found in both PubMed and EMBASE databases: Forty one articles were found in PubMed, but not in EMBASE. In contrast EMBASE contained 52 papers that were not listed in PubMed. Most of the studies included both women and men (57%). Forty-two percent of the studies were done only in female individuals. The remaining 1% had only male participants. Most research protocols included adult people. Thirteen chronic fatigue syndrome studies were done in teenagers.

Table 1 depicts MERGE-SIGN 50 main checklist points. Most articles had high and medium quality (Table 2). A wide variety of methods were used to assess sympathetic nervous system functionality. The most often used were heart rate variability analysis, sympathetic skin response, tilt table testing, and genetic studies, as listed in Table 3. A brief explanation of the most often used methods follows: Heart rate variability analysis is a noninvasive method to estimate autonomic nervous system performance. This method is based on the fact that the heart rate is not fixed; rather, it has a constant beat-to-beat temporal variation. Computerized analysis of such variability yields a good estimation of parasympathetic (or sympathetic) influx on the sinus node. The autonomic nervous system is challenged during the tilt table test. Symptoms, blood pressure, and heart rate are analyzed under controlled conditions. The development of hypotension, tachycardia, or syncope unveils a dysfunctional autonomic nervous system. Sympathetic skin response is a method of measuring the electrical conductance of the skin, which varies with its moisture level. The sweat glands are controlled by the sympathetic nervous system. Skin conductance is used as an indicator of sympathetic activity. Several groups of investigators have studied different genetic polymorphisms of key sympathetic elements. They have focused on catechol-*O*-methyltransferase enzyme that is in charge of clearing catecholamines from the system and the adrenergic receptor that maintains cardiovascular homeostasis.

Additional methods were used to assess sympathetic nervous system performance. In cases of interstitial cystitis, bladder biopsies are done to estimate sympathetic innervation of the bladder wall. There are validated questionnaires such as the COMPASS questionnaire to evaluate the presence of dysautonomia symptoms.

The bottom of Table 3 includes 43 studies in the "other" category. This number reflects single techniques that were used to test autonomic performance such as pupil response to stimuli, ocular sympathetic innervation, photoplethysmography, blood pressure and/or pulse response to diverse stimuli, and norepinephrine injections, among many others. We recognize as a limitation of our studies the fact that the wide variety of studies used to test sympathetic nervous system performance diminishes the consistency of the results.

The majority of studies (65%) described sympathetic nervous system predominance in these painful syndromes (Table 4). In contrast, 7% found parasympathetic predominance. Seventeen percent of reviewed studies described autonomic dysfunction, but the method used was not directed to define the predominant branch of the autonomic system. Only 11% of studies found no differences

TABLE 3. Method Used to Assess Sympathetic Function

	Illness				
	Fibromyalgia	Chronic Fatigue	Irritable Bowel	Interstitial Cystitis	
Method	n	n	n	n	Total
Heart rate variability analysis	21	25	30	0	76
Tilt table	2	14	0	0	16
Hormones	6	2	2	0	10
Sympathetic skin response	12	2	3	1	18
Genetic studies	7	2	1	2	12
Symptom questionnaire	1	1	1	1	4
Electromyography	3	0	1	0	4
Sleep latency test	1	0	0	0	1
Electroencephalographic brain activity	0	0	3	0	3
Urinary bladder biopsy	0	0	0	3	3
Catecholamine levels	3	1	1	1	6
Others	14	13	15	1	43

TABLE 4. Autonomic Nervous System Performance in 4 Stress-Related Syndromes

	Topic				
Autonomic Nervous System Performance	Fibromyalgia n	Chronic Fatigue n	Irritable Bowel n	Interstitial Cystitis n	Total, n (%)
Sympathetic predominance	47	36	39	5	127 (65)
Parasympathetic predominance	4	3	7	0	14 (7)
Only autonomic dysfunction is mentioned	10	14	6	3	33 (17)
No differences between patients or control subjects	9	7	5	1	22 (11)

between patients and control subjects. For each of the 4 syndromes under review, the difference between sympathetic predominance versus parasympathetic predominance had $P < 0.0001$ according to χ^2 test. $P < 0.0001$ did not change, when the 14 articles classified as "low quality" were excluded from the analysis.

DISCUSSION

Sixty-five percent of the reviewed case-control articles of fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis described sympathetic nervous system predominance. This association does not necessarily imply a cause-effect relationship. The sympathetic dysfunction seen in these syndromes could be secondary to nature or nurture underpinnings. Different publications have associated fibromyalgia with genetically defective catecholamine clearing enzymes.[9] On the other hand, the 4 syndromes under discussion are linked to chronic stress[3–5] that can lead to sympathetic overactivity. The possible role of the sympathetic nervous system in the pathogenesis of these syndromes has been better characterized in fibromyalgia. Sympathetic hyperactivity may explain sleeping problems, dry eyes, dry mouth, anxiety, and also widespread pain.[2] A double-blind study demonstrated that FM patients have norepinephrine-evoked pain.[10] Sympathetic hyperactivity may be one of several predisposing elements to develop fibromyalgia. Trauma, infection, or pain-related sodium-channel structure[11] could be other contributing factors. It is clear that more research is needed to better understand the pathogenesis of fibromyalgia and similar maladies.

We recognize limitations in our analysis. For a formal systematic review, the search strategy was not extensive enough. We explored only PubMed and EMBASE databases. Other sources such as CINAHL, PsycINFO, or ISI Web of Science could theoretically have additional relevant publications. Similarly, we did not conduct forward and backward citation tracking, nor did we search the "gray literature." It seems unlikely, however, that these additional sources would contain numerous case-control studies that could significantly modify our results.

Another limiting factor of our review is the well-known tendency to publish studies with positive results; therefore, our findings of 11% of studies reporting no difference between patients and control subjects are possibly an underestimation. Furthermore, the methods used to assess sympathetic performance were heterogeneous, and some of them may have low specificity value.

For the practicing clinician, it may be important to recognize that sympathetic nervous system dysfunction is frequent in patients who have fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, or/and interstitial cystitis. The sympathetic nervous system is the main component of the stress response system. Along these lines and from a philosophical perspective, the presence of these syndromes could be viewed as a failed attempt of our main complex adaptive system (the autonomic nervous system) to adjust to a hostile environment.[3] Therefore, nonpharmacological therapies aimed to modulate sympathetic tone are recommended. Such therapies include relaxation techniques, breathing exercises, water-based exercises, tai-chi, and cognitive-behavioral therapy. There is evidence that these therapeutic modalities may alleviate patient symptoms.[12]

We are not aware of controlled studies testing the long-term effect of pharmacological sympathetic blocking on these syndromes. However, in a double-blind study done in patients with fibromyalgia, acute adrenergic blockade with intravenous propranolol led to decrease pain and hyperalgesia.[13] Moreover, a controlled study done in another stress-related syndrome, temporomandibular joint dysfunction, showed that propranolol may have a favorable effect on pain.[14] It is surprising that despite growing evidence of autonomic dysfunction in the 4 syndromes under discussion, very few studies evaluate treatment for sympathetic nervous system predominance.

CONCLUSIONS

This review suggests that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis. This concordance raises the possibility that sympathetic dysfunction could be their clustering underlying pathogenesis.

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