

Acupuncture for Symptom Management in Patients with Hyper-IgE (Job's) Syndrome

Adeline X.Y. Ge, MD, LicAc,¹ Mary E. Ryan, MLS,² Steven M. Holland, MD,³ Alexandra F. Freeman, MD,³ Victoria L. Anderson, RN, MSN,³ Fei Wang, PhD,⁴ and Jim W. Fleshman, PhD²

Abstract

Objectives: The objective of this study was to investigate the effects of acupuncture treatment for symptom management in patients with hyper-immunoglobulin E (IgE) syndrome (HIES).

Design: This was a retrospective case series.

Setting/location: The study was conducted at the The Clinical Research Center of the National Institutes of Health.

Subjects: There were 8 adult patients with HIES ages 23–56 with varying symptoms in the study.

Intervention: Acupuncture treatments were given from May 29, 2001 to February 17, 2009.

Outcome measures: Acupuncture treatment efficacy was measured and evaluated using a 0–10 assessment instrument pre- and post-treatment.

Results: The 8 patients with HIES suffered from a wide variety of symptoms related to the disease. Acupuncture treatments uniformly decreased the self-reported severity of symptoms.

Conclusions: This case series demonstrates that acupuncture is a clinically useful and safe therapy for symptom management in patients with HIES.

Introduction

HYPER-IMMUNOGLOBULIN E (IgE) syndrome (HIES), also known as Job's syndrome, is a rare immunological disorder that was first reported by Davis et al. in 1966. Noting recurrent, "cold" staphylococcal abscesses in two redheaded girls, he used a biblical reference to describe these cases, "So went Satan forth from the presence of the LORD, and smote Job with sore boils from the sole of his foot unto his crown." (Job 2:7)¹ In 1972, Buckley et al. observed an association of these manifestations with elevated levels of immunoglobulin E antibody and proposed the alternative name of hyperimmunoglobulin-E syndrome.² The primary conditions associated with HIES are recurrent eczematous dermatitis, skin abscesses, and lung infections. Other common infections include sinusitis, otitis media, and mastoiditis, and less frequently invasive staphylococcal infections such as osteomyelitis or deep-seated abscesses. The genetic etiology of autosomal-dominant HIES has been determined to be mutations in the STAT3 gene. In addition to infections and eczema, these patients have associated skeletal and connective tissue

abnormalities, such as scoliosis, frequent bone fractures, decreased bone density, joint hyperextensibility, degenerative spine disease, and retained primary teeth.^{3–5} Mutations in the DOCK8 gene have recently been linked to autosomal-recessive HIES,^{6,7} and has a mutation in tyrosine kinase 2, which was reported in a single patient.^{4,8} There remain other patients with similar distinct clinical presentations without identified genetic etiologies as yet.

Due to the frequency of infections and the multiple manifestations of the disease, patients with HIES may complain of many symptoms, may not consider themselves as "normal," and may experience a lower quality of life (QOL).⁹ Young patients with immunodeficiency disorders similar to HIES are reported to have a poor perception of their health, limitations in social and physical activities, and a lower health-related QOL.^{10,11} Standard therapies, both pharmacologic and surgical, have been used to treat the recurrent infections,^{3–5,12–14} but the side-effects associated with these interventions may have an unintended impact on patients' QOL.

To our knowledge, there is no published study on self-reported symptoms in patients with HIES, or on the

¹National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD.

²NIH Library and National Library of Medicine, National Institutes of Health, Bethesda, MD.

³National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.

⁴KAI Research, Inc., Rockville, MD.

management of these symptoms, or on QOL improvement for patients with HIES. Acupuncture has been used for multiple symptoms, such as pain, fatigue, anxiety, depression, headache, and pruritus, with few side-effects.^{15–27} There have been no reports on the use of acupuncture for patients with HIES or for other primary immunodeficiency disorders. This is the first case series report of symptom management using acupuncture treatment for improvement of QOL of patients with HIES with supporting statistical data.

Methods

Patients

From May 29, 2001 to February 17, 2009, 8 adult patients with HIES, ages 23–56, were referred for treatment to the Acupuncture Consult Service of the National Center for Complementary and Alternative Medicine, National Institutes of Health (NIH). These patients were enrolled in three National Institute of Allergy and Infectious Diseases (NIAID) protocols related to HIES. These research protocols were approved by the NIAID Institutional Review Board. Our study was approved by the NIH Office of Human Subjects Research (OHSR Exempt #4469). Oral informed consent was obtained and recorded in the medical record for each patient.

Acupuncture

In accordance with Traditional Chinese Medicine, acupuncture points were selected based on the symptoms (Table 1).^{28,29} A 30-minute acupuncture session was administered. Strict sterilization procedures were followed prior to insertion of disposable 32-gauge, 0.25-mm×40-mm (diameter×length) sterile steel needles. Hand manipulation was employed to elicit the *de qi* response, such as soreness, numbness, and heaviness. No electrical stimulation was applied.^{28,29}

Measurements

The Multiple Symptoms Assessment Instrument (MSAI), which was adapted from the NIH Clinical Research Center

Pain Intensity Scale,³⁰ was used to measure the severity of symptoms reported by patients with HIES. Patients were asked to rate the severity of their symptoms on a 0–10 numerical rating scale, ranging from 0 for “no symptoms” to 10 for “worst symptoms.” Patients were informed that a rating of 1–3 would be considered “mild” symptoms, that is, nagging, annoying, but interfering little with activities of daily living (ADL); 4–6 would be considered “moderate” symptoms, that is, interfering significantly with ADL; and 7–10 would be “severe” symptoms, that is, disabling and unable to perform ADL. The MSAI was administered immediately before and after each acupuncture session. Patients were also asked to rate their sense of well-being on a 0–10 scale, with 0 representing “no feelings of well-being” and 10 representing the maximum level of well-being. The well-being assessment was adapted from the Brief Fatigue Inventory, Question 1.³¹ The highest pretreatment symptom scores (HPSS) from the MSAI were used to assess symptom impact on patients’ ADL and QOL. A follow-up evaluation using the MSAI was conducted 1–5 days later. Additional treatments were scheduled according to patient needs. A patient received no further acupuncture treatment if (1) the symptom severity score was 0, (2) he or she was discharged from the hospital, (3) the medical condition did not allow continued acupuncture, or (4) acupuncture would conflict with other protocol objectives. An evaluative questionnaire for each acupuncture consult request was administered during the first treatment.

Data analysis

The primary objective was to assess the difference in symptom scores immediately before and after acupuncture treatment. The change from baseline was calculated as the post-treatment value minus the pretreatment value. Simple descriptive analysis was used.³²

Results

Of the 8 patients with HIES, 4 were male and 4 were female; 7 were white and 1 was Asian. They came from di-

TABLE 1. ACUPUNCTURE POINTS FOR TREATED SYMPTOMS REPORTED BY PATIENTS WITH HYPER-IMMUNOGLOBULIN SYNDROME

Symptoms	Acupuncture points
Anxiety, distress	Shenmen (HT 7), Baihui (GV 20), Neiguan (P 6), Shenting (GV 24), Zusanli (ST 36), Sanyinjiao (SP 6)
Discomfort	Hegu (LI 4), Shenmen (HT 7), Baihui (GV 20), Zusanli (ST 36), Taichong (LR 3)
Fatigue	Hegu (LI 4), Zusanli (ST 36), Baihui (GV 20), Guanyuan (CV 4), Qihai (CV 6)
Headache	Hegu (LI 4), Baihui (GV 20), Taiyang (EX-NH 5), Yintang (EX-NH 3), Taichong (LR 3)
Insomnia	Shenmen (HT 7), Zusanli (ST 36), Sanyinjiao (SP 6), Neiguan (P 6), Yintang (EX-NH 3)
Pain, neck	Hegu (LI 4), Fengchi (GB 20), Ashi-point, Houxi (SI 3)
Pain, back	Shenshu (BL 23), Weizhong (BL 40), Ashi-point, Dachangshu (BL 25), Ciliao (BL 32), Mingmen (GV 4)
Pain, body	Hegu (LI 4), Zusanli (ST 36), Sanyinjiao (SP 6), Dabao (SP 21)
Pain, foot	Jiexi (S 41), Taixi (KI 3), Taichong (LR 3), Zusanli (ST 36), Zulinqi (GB 41)
Pain, hand	Hegu (LI 4), Sanjian (LI 3), Houxi (SI 3), Wangu (SI 4)
Pain, leg	Zusanli (ST 36), Yanglingquan (GB 34), Sanyinjiao (SP 6), Tiaokou (ST 38), Chengshan (BL 57)
Pain, skin	Hegu (LI 4), Quchi (LI 11), Xuehai (SP 10), Zusanli (ST 36)
Pain, shoulder	Hegu (LI 4), Jianyu (LI 15), Jianzhen (SI 9), Jianliao (TE 14)
Pruritus	Hegu (LI 4), Zusanli (ST 36), Fengshi (GB 31), Quchi (LI 11), Xuehai (SP 10)
Stiffness, back	Shenshu (BL 23), Yaoyangguan (GV 3), Ashi-point, Dachangshu (BL 25), Ciliao (BL 32)
Stiffness, neck	Fengchi (GB 20), Ashi-point, Houxi (SI 3), Xuanzhong (GB 39)
Lack of well-being	Hegu (LI 4), Zusanli (ST 36), Guanyuan (CV 4), Baihui (GV 20), Taichong (LR 3), Neiguan (P 6)

For a given symptom, all relevant acupuncture points were not necessarily used. The selection of points depended on the severity of symptoms and the number and type of multiple symptoms.

verse sociodemographic backgrounds. Seven (7) patients had the STAT3 genetic mutations; the genetic etiology of the remaining patient was neither STAT3 nor DOCK8 and has not yet been described. Patients presented with multiple symptoms. Nine (9) of these symptoms (pain, fatigue, anxiety/distress, discomfort, headache, joint stiffness, pruritus, insomnia, and lack of well-being) were measured by the MSAI and treated by acupuncture (Table 2). The mean HPSS reported by the patients were as follows: pain 6.9, fatigue 5.1, anxiety/distress 7.2, discomfort 6.8, headache 5.8, joint stiffness 7.5, pruritus 8.0, and insomnia 8.0. The symptoms data show that the disease interfered significantly with ADL or rendered the patient unable to perform ADL, thereby decreasing the patients' QOL.

Records indicate that 44 consults were requested for acupuncture treatment for the 8 subjects from 2001 to 2009. Eleven (11) consults were initially recommended by NIH physicians; 33 subsequent consults were requested by the patients themselves, with their physicians' concurrence. From these 44 consult requests, the 8 subjects received a total of 66 individual acupuncture treatments. The number of

treatments for a single consult request ranged from one to five. Note that one treatment might address a single symptom (12 treatments, 18%) or multiple symptoms (54 treatments, 82%). Symptoms treated per subject ranged from four to eight, with a mean of six. The number of days between treatments ranged from one to seven, with a mean of three (Table 3).

Descriptive statistics summarizing the effects of acupuncture treatments on a variety of symptoms are presented in Table 4. In the first treatment, post-treatment scores uniformly decreased from pre-treatment scores. The largest decreases were seen in measurements of pain (mean: 3.4, 52%); discomfort (mean: 2.9, 45%); anxiety/distress (mean: 2.3, 34%); headache (mean: 3.8, 69%). Patients also reported an improved sense of well-being (mean: 2.3, 76%). Fatigue was reduced post-first treatment (mean 1.3, 26%). In case-patient 1, neck and back stiffness was reduced by an average of 2.5 over five treatments. In case-patient 6, pruritus was reduced from 7 to 4 and from 8 to 3 in two treatments. In case-patient 3, insomnia did not show much improvement in one treatment (8 to 7). None of the subjects

TABLE 2. SYMPTOMS REPORTED BY PATIENTS WITH HYPER-IMMUNOGLOBULIN SYNDROME

Self-reported symptoms	No. (%) of pts. (N = 8)	Case-patient							
		1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^b	7 ^a	8 ^a
Anxiety, distress	6 (75)	X ^c	X ^c		X ^c	X ^c		X ^c	X ^c
Depressed mood	7 (88)	X	X		X	X	X	X	X
Diarrhea, blood in stool, constipation	3 (38)	X	X		X				
Discomfort	8 (100)	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c
Eczema, dermatitis, pruritus, rash	8 (100)	X	X	X	X	X	X ^c	X	X
Fatigue, low qi	7 (88)	X ^c	X ^c	X ^c	X ^c	X ^c		X ^c	X ^c
Fever	3 (38)			X		X		X	
Gait dysfunction, decreased mobility, leg weakness	3 (38)	X		X		X			
GI reflux, abdominal irritation, dysphagia, heartburn, poor appetite	4 (50)	X	X		X			X	
Headache, migraine	4 (50)	X ^c		X ^c			X ^c		X ^c
Hearing loss	2 (25)	X			X				
Hypermobility, inability to extend fingers, laxity	3 (38)	X		X	X				
Insomnia, sleep apnea	4 (50)	X		X ^c			X		X
Joint stiffness, feelings of dislocation, popping, swelling, tenderness, weakness	3 (38)	X ^c		X		X			
Lack of well-being, malaise	7 (88)	X ^c	X ^c	X ^c	X ^c	X ^c		X ^c	X ^c
Lung-bacterial or fungal infection, congestion, cough, sputum, hoarseness, breathing difficulty	7 (88)	X	X	X	X		X	X	X
Mouth ulcers and fissures, angular cheilitis, bleeding gums, candidiasis, dry mouth, toothache	4 (50)	X	X	X		X			
Muscle cramping, spasm	2 (25)			X	X				
Night sweats	1 (13)							X	
Numbness or tingling—fingers, toes	3 (38)	X		X	X				
Pain—back, body, flank, feet, hands, hips, knees, legs, neck, shoulders, skin	8 (100)	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c	X ^c
Sweating of hands and feet	1 (13)				X				
Swelling of hands and feet, puffy hands, weakness in hands	4 (50)	X	X	X		X			
Urinary frequency	1 (13)					X			

^aPatient(s) had STAT3 genetic mutations.

^bPatient had unknown genetic mutation, not STAT3 or DOCK8.

^cMeasured by Multiple Symptoms Assessment Instrument and treated by acupuncture.

GI, gastrointestinal.

in this study reported any adverse effects from the acupuncture, as evaluated by the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (grade 0).³³

For each of the 44 consult requests, a questionnaire was administered following the first treatment to assess patients' satisfaction with treatment efficacy. In 43 of 44 responses, patients "strongly agreed" or "agreed" that the acupuncture treatment was helpful; that they would use acupuncture again; and that they would recommend acupuncture to others. One (1) patient was initially "undecided" but "agreed" that acupuncture was helpful for his back pain after successful second and third treatments.

Discussion

This case series points out that acupuncture can be useful for the management of symptoms reported by patients with HIES. The mechanisms underlying acupuncture's efficacy in treating some symptoms have been reported. Evidence suggests that acupuncture stimulates the neuroendocrine system and produces an increase in the levels of neurotransmitters, such as endomorphin-1, β -endorphins, enkephalin, and serotonin, resulting in analgesia and

sedation.^{34,35} Studies on headache have shown that acupuncture provides direct or indirect inhibition of the trigeminal nucleus caudalis and dorsal horn neurons through increases in endogenous pain-modulating substances, such as β -endorphins, serum magnesium, and cerebrospinal fluid met-enkephalin, with positive effects on migraine and headache.^{36–38} The effects on pruritus are also thought to be related to the endogenous opioid peptides released through acupuncture treatment or to acupuncture stimulation of specific brain regions involved in the central processing of pruritus or to suppression of IgE production.^{24,39} Another study found that stimulation of acupoint P6 reduced corticosterone-induced depression and anxiety, possibly through modulation of the hypothalamic–pituitary–adrenal axis.⁴⁰ A link between fatigue and serotonin has been proposed, and changes in serotonin levels following acupuncture have been documented.⁴¹

TABLE 4. MULTIPLE SYMPTOMS ASSESSMENT INSTRUMENT SCORES

Symptom	ATS	NATPS	Pre/post mean	Change from baseline Mean/percent
Anxiety, distress	1st	13	7.2/4.9	–2.3/–34.0
	2nd	4	6.5/4.2	–2.3/–36.3
	3rd	2	6.5/4.5	–2.0/–31.0
	4th	1	7.0/5.0	–2.0/–28.6
	5th	1	6.0/4.0	–2.0/–33.3
Discomfort	1st	40	6.8/3.9	–2.9/–44.5
	2nd	4	7.8/5.1	–2.7/–36.0
	3rd	2	7.0/5.0	–2.0/–29.2
	4th	1	8.0/6.0	–2.0/–25.0
	5th	1	7.0/5.0	–2.0/–28.6
Fatigue	1st	20	5.1/3.9	–1.3/–26.4
	2nd	4	6.0/4.5	–1.5/–26.5
	3rd	2	6.5/5.0	–1.5/–26.3
	4th	1	8.0/6.0	–2.0/–25.0
	5th	1	7.0/6.0	–1.0/–14.3
Headache	1st	5	5.6/1.8	–3.8/–68.6
	2nd	2	5.8/1.5	–4.3/–81.3
Insomnia	1st	1	8.0/7.0	–1.0/–12.5
Joint stiffness	1st	1	7.0/4.0	–3.0/–42.9
	2nd	1	7.0/4.5	–2.5/–35.7
	3rd	1	6.8/5.0	–1.8/–25.9
	4th	1	7.5/4.5	–3.0/–40.0
	5th	1	6.3/4.0	–2.3/–36.0
Pain	1st	37	6.8/3.4	–3.4/–51.5
	2nd	11	6.4/3.3	–3.1/–51.4
	3rd	6	7.0/3.9	–3.1/–44.2
	4th	4	5.9/3.5	–2.4/–40.3
	5th	3	5.6/3.3	–2.3/–44.8
Pruritus	1st	1	7.0/4.0	–3.0/–42.9
	2nd	1	8.0/3.0	–5.0/–62.5
Well-being ^a	1st	39	3.5/5.9	2.3/75.8
	2nd	4	2.5/4.9	2.4/96.0
	3rd	3	3.0/4.0	1.0/41.7
	4th	1	3.0/4.0	1.0/33.3

^aSymptom scores for well-being range from 0 to 10: 0 = no feeling of well-being; 10 = maximum level of well-being.

Under "Change from baseline" negative scores show symptom reduction; positive scores show improvement in well-being.

ATS, acupuncture treatment session(s); NATPS, number of acupuncture treatment(s) per session.

TABLE 3. TREATED SYMPTOMS

	Subjects (N = 8)	
	n	(%)
Number of subjects per symptom ^a		
Anxiety, distress	6	(75.0)
Discomfort	8	(100.0)
Fatigue	7	(87.5)
Headache	4	(50.0)
Insomnia	1	(12.5)
Joint stiffness	1	(12.5)
Pain	8	(100.0)
Pruritus	1	(12.5)
Lack of well-being	7	(87.5)
Number of symptoms treated per subject		
4	1	(12.5)
6	4	(50.0)
7	2	(25.0)
8	1	(12.5)
	Treatments (N = 66)	
	n	(%)
Number of treatments for symptoms ^b		
Anxiety, distress	21	(31.8)
Discomfort	48	(72.7)
Fatigue	28	(42.4)
Headache	7	(10.6)
Insomnia	1	(1.5)
Joint stiffness	5	(7.6)
Pain	61	(92.4)
Pruritus	2	(3.0)
Lack of well-being	47	(71.2)

^aSubjects may report more than one symptom.

^bIn 82% of acupuncture sessions, multiple symptoms were treated. Therefore, the number of symptoms treated is larger than the total number of sessions (66).

Seven (7) of 8 subjects were found to have STAT3 genetic mutations. They reported numerous symptoms associated with dermatitis and infections, as well as skeletal and connective-tissue abnormalities. The patients also suffered depressed mood, anxiety/distress, discomfort, and fatigue (Table 2). The HPSS data indicate that the patients' ADL were significantly impacted or rendered impossible, thereby decreasing patients' QOL. The number and severity of self-reported symptoms in patients with HIES indicate the need for medical attention. Pharmacologic interventions are not always successful, may cause adverse effects, or may not be permitted by the research protocols. Four (4) of 8 subjects in this case series had drug allergies. For example, case-patient 4 presented with allergic reactions to 21 drugs prescribed for bacterial infections, respiratory disorders, asthma/bronchospasms, coughing, pain, depression/anxiety, insomnia, and pruritus. Acupuncture has the potential to be a safe alternative therapy for symptom control. It has been demonstrated to rapidly increase patients' comfort level and feelings of well-being with few side-effects, which pharmacologic or surgical interventions might be unable to do. There are no publications that specifically address HIES-associated pain and its management, but all 8 subjects in our case series reported pain (HPSS mean 6.9-severe) due to HIES-related bone fracture, scoliosis, degenerative spine disease, and dermatitis. Acupuncture treatments reduced this pain from 40% to 52% (Table 4).

There is no cure for HIES at the present time. The multiple manifestations of the disease result in complicated physical and mental symptoms, and death often occurs in the second and third decades of life, usually due to pulmonary disease.¹² Acupuncture can be a useful therapy to reduce symptom severity, improve patients' QOL, and support the efforts of conventional medicine to prolong patients' lives. For example, case-patient 3 requested acupuncture treatments during each outpatient visit to the NIH to control his symptoms of pain, headache, fatigue, discomfort, insomnia, and generally improve his well-being and QOL. He also continued acupuncture after his return home. With the combined regimen of conventional and complementary and alternative medicine care, this patient was able to maintain a full-time job and family and did not succumb until age 50. Like HIES, the majority of rare diseases are genetic in origin; are usually chronic and incurable; and are accompanied by numerous debilitating and life-threatening symptoms. Our study suggests that acupuncture may be a significant modality for symptoms management in other rare, chronic disorders.

Acupuncture has been in clinical use for 3000 years in China, and its popularity in the United States and other parts of the Western world has been increasing since the late 1970s.⁴² Acceptance of acupuncture by patients with HIES was also investigated in this study. The results of the evaluative questionnaire indicated that the acupuncture treatments were viewed favorably by patients of varied sociodemographic backgrounds. The safety of acupuncture was monitored in this case series and no serious adverse events occurred, including no acupuncture-associated infections. Considering that patients with HIES are at increased risk of infection from acupuncture needles because of their underlying primary immunodeficiency disorder, strict attention to hygienic techniques, including adherence to sterile

procedures, must be emphasized. Two (2) previous articles, one a study of the adverse effects of 32,000 acupuncture consultations and the other a prospective audit of acupuncture treatments of 1848 professional acupuncturists, have demonstrated that acupuncture is safe.^{43,44} In 1997, an NIH Consensus Development Conference on Acupuncture concluded that dental pain and nausea could be successfully treated with acupuncture.⁴⁵ Statements issued in 2003 by the World Health Organization provided a longer list of indications for acupuncture, including pain, headache, pruritus, insomnia, and stiff neck.⁴² This study suggests that patients with HIES should be informed that acupuncture may be helpful for symptom management and their QOL improvement.

Conclusions

This study demonstrated that acupuncture is a useful and safe therapy for symptom management in patients with HIES. Further research is needed to better understand the mechanisms of action.

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Disclosure Statement

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Address correspondence to:

Adeline X.Y. Ge, MD, LicAc

National Center for Complementary and Alternative Medicine

National Institutes of Health

Building 10, Room 4-1741

9000 Rockville Pike

Bethesda, MD 20892

E-mail: age@mail.nih.gov