A Prospective Study of Tender Points and Fibromyalgia During and After an Acute Viral Infection

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Background: Tender points (TPs) and fibromyalgia (FM) may be precipitated by infections, but the frequency, associated characteristics, and predictors of these outcomes are unknown.

Objectives: To determine if acute infectious mononucleosis (AIM) is associated with the development of TPs or FM acutely or during the subsequent 6 months; if demographic, clinical, or psychosocial features predict TPs or FM; and if TPs or FM correlate with nonrecovery.

Methods: A total of 150 subjects diagnosed as having AIM were assessed with physical examinations (including palpation of 18 TPs), laboratory tests, and measures of psychosocial and somatic functioning at enrollment and at 2 and 6 months. Subjects also completed a structured psychiatric interview at the initial evaluation.

Results: At presentation and at 2 and 6 months, the mean TP counts were 7.5, 4.6, and 3.0, respectively; at these time points, 19%, 3%, and 1% of subjects also met modified criteria for FM. Tender points and degree of pain diminished over time following AIM. Acutely, TPs were associated only with higher temperature ($P<.001$). Baseline features that predicted more TPs at 2 and 6 months were female sex, older age, less family social support, and more TPs at presentation. Neither initial laboratory tests nor psychiatric disease or distress predicted TPs. Differences between those who had and had not recovered at 6 months were found for the mean number of TPs ($P<.008$), the proportion of subjects with 11 or more TPs ($P<.002$), and the degree of pain.

Conclusions: Tender points are a common, transient finding associated with AIM, but FM is an unusual long-term outcome. Demographic, social, and physical examination features predicted TPs.

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FIBROMYALGIA (FM) is a nonarticular rheumatic condition characterized by widespread pain, multiple tender points (TPs) at specific musculoskeletal sites,[1] and significant functional impairment. It accounts for 15% of rheumatology clinic visits, comprises up to 5% of primary care appointments, and has a prevalence of 2% in the general population.[2,3] Indeed, persons with FM use more allopathic and alternative health resources, incur greater medical expenses, and have higher unemployment rates than the general population.[4-9] Although FM is associated with well-recognized occupational, social, and familial dysfunction[4-10] and can be diagnosed using explicit, validated criteria published by the American College of Rheumatology (ACR),[1] its cause is not well understood.

Psychological, neurohormonal, and immunological factors, sleep disturbances, and abnormalities of muscle metabolism have all been implicated as causal factors in FM.[11-16] Recently, an association between infectious diseases and FM has been found by some[17-24] but not all investigators.[25,26] For example, FM has been reported to develop following Lyme disease,[17] in patients with human immunodeficiency virus[18,19] and hepatitis C,[20,21] and in association with parvovirus and Coxsackievirus.[23,24] However, most of these studies have been relatively small, retrospective, and conducted in specialty centers or unique populations or have examined only a limited number of biological or psychosocial factors or not assessed the predictive value of baseline subject characteristics.[17-24]

Thus, to examine the association of TPs and FM with a documented viral infection, we followed a population-based cohort enrolled in a large health maintenance organization for 6 months after the onset of acute infectious mononucleosis (AIM), serologically confirmed as infection with Epstein-Barr virus (EBV). At ill-

SUBJECTS AND METHODS

STUDY SETTING

The setting for this study was a large health maintenance organization in the Puget Sound area that provides prepaid health care through 2 hospitals, 23 outpatient medical clinics, 3 specialty centers, and a progressive care facility. This plan serves a heterogeneous socioeconomic population whose age and sex composition reflect the region as a whole.

SUBJECT IDENTIFICATION AND ENROLLMENT

All patients who met the following criteria were considered eligible for the study: (1) at least 16 years of age; (2) positive heterophile antibody result; (3) no record of a previous heterophile antibody; (4) onset of symptoms within 14 days of having the heterophile antibody; (5) no chronic, disabling medical condition; (6) not being treated with steroids for AIM; and (7) serological evidence of acute infection with EBV. First, using triweekly review of laboratory records, we prospectively identified all enrollees from outpatient sites who had a heterophile antibody performed. Second, potential subjects were screened for eligibility criteria using a computerized record system, then telephoned and asked to participate in a study of medical and psychological factors involved in recovery from viral infections. At that time, they were also screened for eligibility criteria 4 through 6. Finally, medical records were reviewed to confirm the absence of a prior positive heterophile antibody result or a chronic medical condition. Final determination of eligibility occurred after enrollment and considered information from the chart review and the EBV serological profile performed at the initial evaluation (see below). Thus, we used the initial heterophile antibody result to identify probable cases of AIM and a single subsequent serological profile to diagnose acute EBV infection and, hence, eligibility. Subjects without serological evidence for acute infection were dropped from the study at this point.

Follow-up visits at 2 and 6 months included readministration of selected baseline self-report measures and reassessment of laboratory and physical examination findings. All study protocols were approved by the institutional review boards of the University of Washington, Seattle, and the health maintenance organization.

MEASURES OF SYMPTOMS AND BIOLOGICAL DISEASE ACTIVITY

The presence and severity of symptoms were assessed on a scale of 0 to 4 at each visit using a self-report checklist of symptoms characteristic of acute EBV infection (eg, fatigue, sore throat). A complete physical examination was performed at each visit that included ascertainment of oral temperature and the presence of pharyngitis; cervical, axillary, and inguinal adenopathy; hepatosplenomegaly; and TPs. A complete blood cell count with differential and serum transaminases was obtained using standard laboratory methods. A manual review of the differential was performed by the laboratory's pathologist to ensure that atypical lymphocytes, if present, were detected and accurately quantified. Each participant also had serological tests for EBV performed to detect antibodies to viral capsid antigen (IgG and IgM), early antigen, and nuclear antigen. Subjects without viral capsid antigen IgM were considered to have a serological profile inconsistent with AIM and were therefore ineligible for further study.

MEASURES OF TPs AND PAIN

Subjects underwent an examination that entailed systematic palpation of the 18 musculoskeletal sites specified by the ACR[1] and forearm control sites. Tender points were considered positive when they evoked greater pain or discomfort than the control sites. Tender points were assessed manually by a physician (D.B.) or personnel trained and experienced in TP evaluation who were supervised to ensure standardization and consistency throughout the study. Fibromyalgia was diagnosed using a modification of the ACR case definition and required the presence of 11 or more TPs and pain. Pain was appraised using the Body Pain subscale of the Short-form General Health Survey (SF-36,[27] see below). Specifically, patients were asked how much body pain they had experienced during the past 4 weeks. Possible responses included "none," "very mild," "mild," "moderate," "severe," or "very severe." For the purposes of this study, only those with at least moderate pain satisfied the pain criteria for FM.

MEASURES OF PSYCHOSOCIAL AND FUNCTIONAL STATUS

Validated instruments included the SF-36, an instrument derived from items developed and validated in the Medical

ness onset and at 2 and 6 months, we obtained measures of clinical status and psychosocial functioning. This study sought to answer the following questions: (1) Is AIM associated with the presence of TPs or FM acutely or during convalescence? (2) Do subject or illness characteristics predict TPs or FM following AIM? (3) Are TPs or FM associated with nonrecovery from AIM?

RESULTS

Of the 150 subjects who were enrolled in the study, 144 (96%) and 142 (95%), respectively, completed the 2- and 6-month follow-up visits. As seen in **Table 1**, 53% were women and most were students, young (age range, 16-47 years), white, and single. Subjects averaged 12.6 years of education. Table 1 also displays participants' initial physical examination findings, laboratory results, and selected measures of functional and psychosocial status. Subjects generally had experienced a clinical illness typical of AIM. Fever, pharyngitis, and posterior cervical lymphadenopathy occurred in most, while hepatosplenomegaly was less common at presentation. More than half of subjects had hematological evidence of hepatitis, although usually of mild clinical severity (mean aspartate aminotransferase level, 51 U/L; mean alanine aminotransferase level, 90 U/L). Atypical lymphocytes (>5%) were observed in almost 90% of subjects on the peripheral blood smear. The SF-36 scores reflected functioning during the 4 weeks before the initial assessment and therefore were probably influenced by AIM: most subscale scores were lower than would be expected in a group of young, healthy individuals. Initial SCL scores were in-

Outcomes Study, which assesses health-related functional status and quality of life.[27] It has 8 subscales that measure physical, role, social, and emotional functioning and vitality, body pain, general health, and mental health. Each scale is scored from 0 to 100, with higher scores indicating better functional status or less pain. To evaluate the presence and severity of somatic and psychological symptoms, we used the somatization, anxiety, and depression subscales of the Symptom Checklist–90 (SCL-90). This survey assesses distress on a scale of 0 to 4. It has good reliability and validity in medical populations and correlates with data from structured psychiatric interviews.[28] The 5-item Barsky Amplification Scale measured an individual's tendency to perceive and report physical symptoms.[29] In a previous cross-sectional study of acute viral illness, this instrument was a strong predictor of symptom severity and disability.[30]

Other self-report data collected included the Perceived Social Support Inventory, which is a 20-item questionnaire that measures support from family and friends with each item scored on a 1- to 5-point scale.[31] This questionnaire has established validity and reliability in a variety of patient and nonclinical samples.[31] The List of Threatening Experiences contains 12 events found to account for 77% of life events rated as being marked or moderate long-term threats.[32] Current threats were defined as those occurring within the 6 months preceding the onset of AIM. The Multidimensional Health Locus of Control is a consistent, reliable, and valid 3-factor inventory that describes beliefs about the source of reinforcements for health-related behaviors.[33] These factors are the beliefs that health is controlled by one's own behavior (internal), that health is a matter of chance (external), or that one's health is under the control of influential persons such as physicians (powerful others).

Several instruments that were not expected to change substantially over time were obtained only at the index visit. The Eysenck Personality Inventory is a true-false questionnaire that has been extensively validated, widely used in personality research,[34] and previously used in studies of distress and infection.[35,36] The extraversion and neuroticism scores were used in our analyses. Coping was evaluated using an abridged version of the Ways of Coping Checklist, which identified cognitive and behavioral strategies used to manage stressful situations.[37] Items are classified as problem-focused efforts to manage the source of the difficulty and emotion-focused strategies aimed at minimizing distress. Finally, the National Institute of Mental Health Diagnostic Interview Schedule[38] was administered at baseline to determine current and lifetime psychiatric diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. The modules on major depression, panic, generalized anxiety, and somatization disorders and alcohol abuse or dependence were administered to subjects by a research assistant trained in their use and supervised by the senior psychiatrist (W.K.).

ASSESSMENT OF RECOVERY

Since there are no well-accepted objective measures to assess the outcome of AIM, recovery was determined by asking subjects at the 2- and 6-month follow-ups to compare their current health to their condition at the time AIM was diagnosed. Possible responses included "worse," "the same," "better but not recovered," or "completely recovered." Persons who replied completely recovered were considered "recovered," while all others were classified as "nonrecovered."

STATISTICAL ANALYSIS

Descriptive statistics were generated and distributions were examined for normality and outliers. Pearson correlations were calculated between the numbers of TPs at the initial, 2-month, and 6-month assessments and the baseline values for the SF-36 and SCL-90 and measures of amplification, social support, life events, locus of control, personality, and coping, as well as physical examination findings and laboratory tests. Three multiple regression analyses were used to examine which baseline variables were related to the number of TPs at the first visit and the 2- and 6-month follow-ups. To minimize type I error, only correlations that were significant at $P<.05$ were used in these multiple regression analyses. First, age and sex were forced into the models. In the models using TP at 2 and 6 months as dependent variables, the number of baseline TPs was also forced into the models. Second, the significant variables from the bivariate analyses were allowed to enter the models in a stepwise manner. The models were examined for statistical outliers, and if found they were removed and the models were refit.

dicative of mild distress. The structured psychiatric interviews revealed low baseline rates of current psychiatric disorders: 7 individuals (5%) and 3 individuals (2%) had current major depression and panic or generalized anxiety disorder, respectively. The frequency of lifetime illness was similarly low, eg, only 16 subjects (11%) were diagnosed as having major depression.

For all subjects, the number with 11 or more TPs declined from 42 (29%) at baseline to 11 (8%) at 2 months and 7 (5%) by the 6-month assessment. The mean TP count also decreased over time, from 7.5 initially to 3.0 at 6 months. The proportion of subjects reporting at least moderate pain diminished from 61% to 6% during the study. At the initial, 2-month, and 6-month evaluations, 28 individuals (19%), 4 individuals (3%), and 1 individual (0.7%) fulfilled our modified FM criteria (data not shown). Overall, at the 2- and 6-month follow-ups, 55 subjects (38%) and 17 subjects (12%) had not fully recovered from AIM. **Table 2** presents results on number of TPs, degree of pain, and presence of FM at each study visit for all subjects followed up for 6 months as a function of their recovery at 6 months. In terms of recovery status, there were an inadequate number of subjects who developed FM at follow-up to perform Pearson correlations. However, among those who had not recovered by 6 months, differences at this follow-up were found for the mean number of TPs ($P<.008$) and the number of subjects with 11 or more TPs ($P<.002$). Differences by recovery status were also noted for degree of pain at 2 ($P = .004$) and 6 months ($P = .008$).

In univariate analyses, baseline temperature significantly correlated with the average number of TPs at the

Table 1. Selected Baseline Subject Characteristics

Demographic features	
Age, mean ± SD, y	21.3 ± 6.6
Female, No. (%)	80 (53)
White, No. (%)	135 (90)
Married, No. (%)	10 (7)
Student, No. (%)	87 (64)
Education, mean ± SD, y	12.6 ± 2.6
Physical examination findings, No. (%)	
Temperature >37.5°C	41 (27)
Pharyngitis	109 (73)
Anterior cervical adenopathy	93 (62)
Posterior cervical adenopathy	99 (66)
Hepatosplenomegaly	20 (13)
Laboratory evaluation, No. (%)	
Atypical lymphocytes >5%	113 (88)
Aspartate aminotransferase >42 U/L	57 (38)
Alanine aminotransferase >48 U/L	80 (53)
Total bilirubin >1.3 mg/dL	5 (3)
Functional status means, SF-36	
mean ± SD subscale scores	
General health	69 ± 18
Energy-vitality	33 ± 19
Physical functioning	70 ± 20
Role limitations–physical health	21 ± 30
Emotional well being	66 ± 18
Role limitations–emotional problems	61 ± 42
Social functioning	48 ± 25
Pain	51 ± 25
Psychiatric distress*	
SCL-90 depression scale, mean ± SD score	0.88 ± 0.71
SCL-90 anxiety scale, mean ± SD score	0.49 ± 0.56
Current DIS psychiatric diagnosis, No. (%)	10 (7)
Lifetime DIS psychiatric diagnosis, No. (%)	26 (17)

**SCL-90 indicates Symptom Checklist–90; DIS, Diagnostic Interview Schedule. For current and lifetime DIS, some subjects met criteria for more than 1 diagnosis.*

Table 2. Tender Points, Pain, and Fibromyalgia at Baseline and Follow-up by Recovery Status at 2 and 6 Months*

	Baseline	2 mo	6 mo
≥11 Tender points, No. (%)			
Recovered at 6 mo	34 (27)	7 (6)	3 (2)†
Nonrecovered at 6 mo	6 (35)	3 (18)	4 (24)
Tender points, mean			
Recovered at 6 mo	7.5	4.4	2.7‡
Nonrecovered at 6 mo	7.2	5.8	5.1
At least moderate pain, past month, No. (%)			
Recovered at 6 mo	75 (60)	9 (7)§	4 (3)‡
Nonrecovered at 6 mo	11 (65)	6 (35)	4 (24)
Fibromyalgia, No. (%)‖			
Recovered at 6 mo	20 (16)	3 (2)	0
Nonrecovered at 6 mo	4 (24)	1 (6)	1 (6)

**N = 142 for the total sample; recovered = 125; and nonrecovered = 17.*
†P = .002.
‡P = .008.
§P = .004.
‖Using the modified definition for fibromyalgia described in the text.

initial ($r = 0.21$, $P = .007$), 2-month ($r = 0.30$, $P<.001$), and 6-month ($r = 0.20$, $P = .02$) visits. Other baseline variables associated with more TPs at 2 months included lower viral capsid antigen IgG ($r = -0.20$, $P = .01$), worse social functioning ($r = -0.16$, $P = .049$), and less social support from family ($r = -0.16$, $P = .049$). A higher TP count at 6 months was related to poorer health ($r = -0.17$, $P = .047$). Thus, baseline variables used in the regression included the SF-36 social and general health subscales, the family social support measure, temperature, and viral capsid antigen IgG titers. After controlling for age and sex, the multiple regression analyses were significant for TPs at baseline ($F_{3,145} = 6.70$, $P<.001$, $R^2 = 0.12$), 2 months ($F_{4,137} = 23.12$, $P<.001$, $R^2 = 0.40$), and 6 months ($F_{4,136} = 11.27$, $P<.001$, $R^2 = 0.25$). The only variable associated with TPs at presentation was initial temperature ($t = 3.57$, $P<.001$), with higher temperatures being associated with more TPs. After also controlling for baseline TPs, social support from family at illness onset predicted TPs at both 2 ($t = -2.73$, $P = .007$) and 6 months ($t = -2.36$, $P = .02$), with less support associated with more TPs. Female sex was associated with more TPs at 2 ($t = 2.93$, $P = .004$) and 6 months ($t = 2.17$, $P = .03$), as was age ($t = 3.54$, $P<.001$, and t = 2.88, $P<.005$). Finally, baseline TP count was significant in the 2-month ($t = 7.61$, $P<.001$) and 6-month ($t = 5.13$, $P<.001$) models.

COMMENT

Fibromyalgia has been associated with a variety of triggers or stressors such as motor vehicle crashes, psychological distress, sexual and physical abuse, and infections.[39-42] Such stressors have been postulated to precipitate or facilitate the onset of FM by altering normal sleep patterns and causing immune activation and neuroendocrine dysregulation.[16,43] These processes, in turn, may lead to local muscle disease,[15] activation of peripheral nociceptors, release of substance P, and development of TPs.[15,43] Since acute infection alters sleep cycles, provokes the immune system, and stimulates the neuroendocrine axis,[44-46] its role in FM deserves closer examination.

In retrospective series, up to 50% of adults with FM report that their illness was precipitated by a flulike illness.[25] Several other nonprospective studies also have linked infectious agents with FM.[17-21] For example, FM has been reported to develop following Lyme disease in 8% of a large specialty clinic population[17] and, in case reports, after infection with parvovirus or Coxsackievirus.[23,24] In 2 studies of human immunodeficiency virus–infected patients, FM was present in 11% and 29% of subjects, respectively.[18,19] Similarly, FM was observed significantly more often in a hepatitis C–infected cohort (16%) than in a healthy control population (0%) or a group with non–hepatitis C–related cirrhosis (3%).[20] On the other hand, some investigators have not substantiated an association of FM with infectious agents.[25,26]

A prospective study during the acute and convalescent stages of a well-characterized infectious illness that also examined the contribution of baseline demographic, clinical, and psychosocial factors could offer insights into the pathogenesis of FM. AIM associated with EBV is a common and readily examined infectious disease that lends itself to such a study for several reasons. First, for most infections there is no commonly available screening test. However, for AIM a positive heterophile antibody result indicates a high likelihood of in-

fection with EBV. Second, in patients with a positive heterophile antibody result, primary EBV infection is readily confirmed by the presence of viral capsid antigen IgM antibodies. Third, AIM typically affects younger populations, hence the frequency of medical conditions (eg, prior FM or a preexisting chronic infection) that could confound results is low.

We found that 19%, 3%, and 1% of subjects fulfilled our modified FM criteria at the baseline, 2-month, and 6-month evaluations, respectively, suggesting that FM only rarely persists after AIM. Interestingly, in prior cross-sectional studies of chronic active viral infections, namely, human immunodeficiency virus and hepatitis C, the proportion of subjects with FM (10%-29%) was similar to that observed in our population during the acute illness.[18-21] The decrease in the frequency of FM over time coincides with immune control of EBV infection, as reflected by the serological and clinical markers measured at follow-up (data not shown). One possible explanation for our findings is that ongoing immune stimulation in the form of active infection must be present for FM to persist. Alternatively, our study population consisted primarily of young, single, healthy students who did not possess many of the psychosocial or age characteristics that might predispose them to develop FM.

Previous studies have found TPs to be the most powerful discriminator between patients with FM and healthy subjects.[1] Indeed, some authors have suggested that it may be more useful to study TPs and their distribution rather than FM when investigating nonarticular pain syndromes.[47,48] In epidemiological studies, TPs are markers of general distress and correlate directly with symptoms of depression, fatigue, and pain in the general population.[47,48] Although we could not demonstrate an association of TPs with distress, we did find differences in the degree of pain and number of TPs between subjects with a prolonged convalescence and those who recovered quickly. Consistent with the decrease in the frequency of FM, we found that among all subjects mean TP counts declined from 7.5 during the acute illness to 4.6 at 2 months and 3.0 at 6 months. At presentation, TP count correlated only with higher temperature. Interestingly, baseline predictors of TPs present at the 2- and 6-month evaluations were identical: older age, female sex, less family social support, and more TPs at the initial examination.

There are several explanations for these findings. In the setting of acute illness, fever is a crude marker of immune stimulation. Thus, perhaps an FM-like syndrome is unveiled in febrile subjects through the production of acute-phase reactants, such as interleukin 6, that are known to cause fever and induce fatigue.[49,50] Although the findings are not readily understood, other studies in both general and clinic populations have consistently observed that TP counts and frequency of FM increase with age and female sex.[3,51,52] Furthermore, strong social support can favorably affect a variety of medical conditions, including rheumatoid arthritis.[53-56] The few studies of social support in FM have revealed conflicting results; 1 investigation revealed "restricted" social networks in FM,[57] while others have suggested adequate social support.[58,59] However, these studies described social support among clinic patients with established FM and did not examine predictors of TP or FM in a community-based sample like ours.

Finally, it is noteworthy that neither baseline laboratory tests nor any measure of psychological distress predicted TPs or FM. To our knowledge, this is the first prospective investigation to examine the association of infection with TPs, pain, and FM; hence, our findings need confirmation. Several previous studies have identified psychosocial characteristics, including mood and anxiety disorders, that appear to be associated with FM and an "at-risk" population.[11,60,61] Other work in community and clinical settings has also demonstrated an association of TPs and FM with psychiatric disease, specifically depression.[3,10,42,47] One possible explanation for our findings is that distress and psychiatric disorders develop as a consequence of TPs, chronic pain, or FM. Alternatively, TPs and FM are transient signs of sleep disruption and/or immune activation in most persons with AIM; more chronic disturbances of sleep as seen in psychiatric disorders and chronic infection[62,63] may develop among those in whom symptoms persist.

This study has several limitations. First, in contrast to the ACR criteria, our modified FM definition did not explicitly ask about either diffuse pain or a duration of 3 months.[1] Thus, our pain assessment probably overestimated the proportion of subjects with FM at the initial and 2-month visits. However, since the single subject meeting our case definition at 6 months also reported pain at all previous visits, this subject most likely would have met the ACR criteria. Second, because our population was young and otherwise healthy, TPs in our study may not reflect the same clinical constructs demonstrated in previous work.[47,48] Finally, we enrolled subjects from a population seeking health care, thereby excluding those with AIM who did not receive medical attention. Consequently, our results may only be applicable to patients with AIM in clinical settings.

In summary, this prospective, population-based study found that although a significant proportion of subjects had TPs and pain at presentation, persistent FM infrequently follows AIM. Tender points were correlated with an elevated temperature at presentation and, in follow-up, were predicted by older age, female sex, less family social support, and more baseline TPs. Neither baseline laboratory tests nor psychiatric or psychological distress predicted TPs. Subjects who had not recovered from AIM at 6 months had significantly greater pain at 2 and 6 months and more TPs at 6 months. Further prospective studies are needed to determine whether our findings are generalizable to other infections, settings, and populations.

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