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Pain in Older Individuals and Its Association with Latent Epstein-Barr Virus Reactivation

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Abstract

Objective: Immunosenescence is a natural process of aging. Pain, a severe stressor, is associated with immune dysregulation. Latent herpes virus reactivation is an indicator of poor cellular immune function. The present study examined the association between pain, latent Epstein-Barr Virus (EBV) reactivation, and markers of inflammation in older individuals.

Methods: Eighty-two individuals ($\overline{x}_{age}$ = 67.0; range 36 - 85 years) examined for pain (SF-36 pain subscale), EBV Viral Capsid Antigen (VCA) IgG antibody titers, C-reactive protein, interleukin-6, and tumor necrosis factor-alpha. Pearson correlation coefficients were calculated to identify potential associations between pain, EBV VCA IgG antibody titers and inflammation. Hierarchical linear regression models were conducted using the PROCESS macro for SPSS to examine the association between age, EBV VCA IgG antibody titers and markers of inflammation.

Results: Older age (B = .033; p = .024) and higher pain (B = .354; p = .004) were associated with greater latent EBV reactivation. A moderation model suggested that pain and EBV VCA IgG antibody titers were associated with older age among individuals with higher pain ($B_{interaction}$ = .013; p = .025), but not among those with lower pain ($B_{interaction}$ = -.004; p = .60). Specifically, older age (≥ 59 years) was associated with more EBV VCA IgG antibody titers among those who reported higher pain levels (SF-36 pain subscale ≥ 54.1; 13% of the sample). No significant relationship between EBV VCA IgG antibody titers and markers of inflammation were identified.

Discussion: The current study extends prior work on EBV reactivation by suggesting that older age (≥ 59 years) is associated with increased EBV VCA antibody titers among those individuals who reported higher pain levels. Continued research is needed to clarify the complexity of age-related symptoms associated with latent EBV infection and immune dysregulation.

Keywords: Epstein-Barr virus; Pain; Inflammation; Age

Abbreviations

ACTH: Adrenal Corticotropin Hormone

BMI: Body Mass Index

CRH: Corticotropin Releasing Hormone

CRP: C-Reactive Protein

EBV VCA IgG antibody titers: Epstein-Barr virus viral capsid antigen (VCA) IgG antibody titers

ELISA: Enzyme-Linked Immunosorbent Assay

HPA: Hypothalamic-Pituitary-Adrenal Axis

HPATG system: Hypothalamic-Pituitary-Adrenal-Thyroid-Gonadal System

IL-6: Interleukin 6

RAND SF-36: The RAND 36-Item Short Form Health Survey

TNF-a: Tumor Necrosis Factor Alpha

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Introduction

Pain is common in older adults and is associated with impaired activities of daily living, decreased quality of life, and increased risks of emotional distress and depression [1]. Importantly, pain is twofold higher among those over age of 60, compared to those under age 60 [2]. Aging is associated with a natural decline in immune function (termed immunosenescence), which is amplified when it occurs in the context of stress [3]. Because immunosenescence occurs in persons with increasing age, resulting in deterioration of the innate immunity and elevations in inflammation, older individuals may be especially susceptible to the potentially negative effects of stress on immune function [4].

Herpes-viruses are ubiquitous among adults with close to 95% of the population worldwide being Epstein-Barr Virus (EBV) seropositive [5]. Individuals are typically exposed to EBV during the first few years of life. After primary infection, EBV continues to reside in B lymphocytes and white blood cells throughout the individual's life [6]. Reactivation and replication of the EBV virus is controlled by the cellular immune response, largely by specific-memory cytotoxic T cells and natural killer cells [7]. Individuals who are seropositive for EBV generally remain asymptomatic; however, under stressful conditions, suppressive immune activity may be reduced, resulting in reactivation of the virus which induces the production of EBV antibodies [7]. Thus, higher EBV virus capsid antigen (VCA) IgG antibody titers indicate poorer control over the latent virus and this can be measured and used as a marker of immune dysregulation [8,9].

Aging is associated with elevated antibody titers to latent herpesviruses, such as EBV [10,11], suggesting poorer cellular immune control over these viruses [5,12]. Furthermore, elevated antibody titers to herpesviruses can induce inflammatory markers such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-Reactive Protein (CRP) [11,13]. It is likely that elevated antibody titers to latent herpesviruses partially promote age related increases in inflammation [3]. This study sought to examine the association between age and reactivation of latent Epstein-Barr Virus (EBV) among older individuals and to investigate whether this association was moderated by pain. Our primary hypothesis was that pain, a significant stressor, might exacerbate the association between age and latent EBV reactivation, given work suggesting that chronic stress promotes immunosenescence [3]. In ancillary analyses, we aimed at examining the association between pain, latent EBV reactivation and markers of inflammation.

Materials and Methods

Study design and procedures

The present study is a secondary analysis of a larger prospective observational study examining the relationship between bereavement and cardiovascular risk [14]. In the period between October 2015 and May 2017, study participants were enrolled from the Baylor College of Medicine and the general community of Houston. Individuals who recently experienced the loss of a spouse were contacted and recruited from obituaries, flyer distribution, online posting, support groups, and community events.

Research associates conducted assessments in the Bioscience Research Collaborative Community Research Center in the Texas Medical Center or at the participants' home. During these study visits, study participants completed a set of questionnaires. In addition, anthropometric measurements, including weight, height, and waist circumference and non-fasting blood samples were collected between 7:30 and 11:00 AM to control for diurnal variation. All study procedures performed were in accordance with the Helsinki Declaration of the World Medical Association. The study was reviewed and approved by the Institutional Review Board at Rice University(IRB-FY2016-813). All subjects provided written informed consent prior to their participation.

Participants

Participants who had lost a spouse within the past three months were considered eligible for inclusion unless they: (1) were unable to read and write in English; (2) had significant visual or auditory impairment; (3) were pregnant or nursing; (4) had autoimmune and/or inflammatory disease (including rheumatoid arthritis and ulcerative colitis); (5) experienced the loss of a loved one in addition to their spouse (e.g., mother, child, etc.); (6) had divorced within the past year; or (7) were currently undergoing surgery, chemotherapy, and/or radiation to treat cancer. Sex and age-matched controls were deemed ineligible if they had lost a spouse within the preceding five years. Furthermore, study participants who were EBV-seronegative were excluded from the analysis.

Measures

Determination of EBV VCA IgG antibody titers in plasma: EBV VCA IgG antibody titers were assessed following standard protocol [15]. Ninety-six well microtiter plates, coated with virally infected cells, were obtained from EuroImmun (Morris Plains, NJ). Antigen source for VCA plates were inactivated cell lysates of lymphocytes infected with the P3HR1 strain of EBV. Plasma samples with high IFA-scored antibody titers (i.e., 2560), obtained from past studies, were used as the top standard for EBV-VCA. Eight two-fold serial dilutions of the top standards were made with PBS in separate tubes. After diluting, the VCA standards were 2560, 1280, 640, 320, 160, 80, 40, and 20. One hundred microliters of positive and negative controls, standards, and diluted patient samples (all dilutions were at 1:101) were pipetted in duplicate into individual microplate wells followed by a 30 min incubation (all steps were carried out at room temperature). The plates were then washed 3 times with 350ul wash buffer (provided) using an Embla microplate washer (Molecular Devices, Menlo Park, CA). Next, 100ul of enzyme conjugate (peroxidase labeled anti-human IgG) was pipetted into the wells followed by another 30 min incubation period. The plates were then washed 3 times, and 100ul of chromogen substrate (TMB/H_2O_2) was pipetted into the wells. The plates were then covered to protect from direct light and incubated for 15 min. One hundred microliters of 0.5 M sulphuric acid) was added to each well to stop the reaction. Absorbance was then read at 450nm (reference wavelength 590nm) using a SpectraMax Plus 384 (Molecular Devices). Values from unknown plasma samples (from study subjects) were compared to a standard curve (two-fold dilutions of standards made from a calibrator standard - in this case a sample tittered to 2560). In this study, all subjects were seropositive for EBV. Since we were able to dilute the plasma, there is no upper limit in our method.

Immune assays

Blood samples were drawn between 8:00 AM and 11:00 AM. Serum samples were frozen and maintained at -80°C until assayed. Standardized Enzyme-Linked Immunosorbent Assay (ELISA) methods were utilized to measure serum C-Reactive Protein (CRP), interleukin 6 (IL-6) and TNF-alpha (TNF-α). Particle enhanced immunoturbidimetric assay (Cobas5S Roche) was utilized for the

Table 1: Sociodemographics and medical characteristics of study population.

	%	Mean (SD)	Range
Demographic			
Age	-	67.0 (11.5)	36 - 85
Sex, % female	63	-	
Race			
White	76	-	
Black	24	-	
Ethnicity			
Hispanic/Latino	8	-	
Education			
≤ High school degree	20	-	
≥ Bachelor Degree	80	-	
Income			
<$25,000	16	-	
≥$25,000	84	-	
Marital status			
Married	37	-	
Not married	15	-	
Widowed	47	-	
Risk factors			
Smoking, yes	7		
Alcoholic drinks/week	-	4.3 (5.9)	0 - 30
BMI	-	28.3 (5.7)	17.9 – 47.2
Biomarker			
CRP	-	0.21 (.4)	-0.7 – 1.0
EBV	-	2.8 (0.5)	1.4 – 3.8
IL-6	-	.001 (0.4)	-0.8 – 1.0
TNF-α	-	-.02 (0.2)	-0.3 – 0.4
Health Outcomes			
SF-36 Pain (reversed)	-	77.0 (20.7)	20 - 100
CES-D	-	13.5 (10.8)	0 - 52

M=Mean; SD=Standard Deviation; BMI = Body Mass Index; CRP = C-reactive protein; EBV = Epstein-Barr Virus; IL-6 = interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; SF-36 Pain = RAND 36-Item Short Form Health Survey Pain subscale; CES-D = The Center for Epidemiological Studies-Depression
Note: For easier interpretation, SF-36 Pain subscale was reversed. Lower SF-36 Pain values indicate lower pain; higher SF-36 values indicate higher pain.

in vitro quantitative determination of high sensitive CRP. Subjects with CRP levels greater than 10 mg/L were excluded, since this could have reflected acute systemic inflammation. IL-6 was measured using high sensitivity human IL-6 ELISA kit (cat # HS600B; detection range 0.156 to 10 pg/mL) and TNF-α was measured using high sensitivity human TNF-a ELISA kit (cat # HSTA00E, detection range 0.156 to 10 pg/mL).

Pain

The RAND 36-Item Short Form Health Survey (SF-36) is a 36-item measure containing eight multi-item subscales: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; pain; general well-being; social functioning; and general health. The SF-36 is a widely-utilized measure for which robust psychometric properties have been documented [16]. The SF-36's bodily painsubscale was used to assess pain severity and impact over the last four weeks via two items (e.g. 'how much bodily pain have you had?'; 'how much did pain interfere with your normal work?'). The response scale ranges from 0 to 100, with higher scores indicating less severe, lower impact pain. The SF36 bodily pain subscale showed good internal consistency, with a Cronbach's alpha of .80. For ease of interpretation, the SF-36 Pain subscale was reversed, so that lower SF-36 values indicated less pain, while higher SF-36 values indicated more pain.

Depression

The Center for Epidemiologic Studies Depression Scale (CES-D) [17] was used as a measure to assess prevalence of depression and also included in regression models as a control variable due to its close association with inflammation. The CES-D is a widely utilized measure of depression and has been validated across populations. Higher scores on this scale indicate greater depressive symptomatology. The clinical depression cut-score for MDD is 16.

Covariates

Demographic factors (i.e.,sex, race, and income), mental health (CES-D), Body Mass Index (BMI), and group (bereaved versus non-bereaved) were included into the model as covariates. Demographic information was collected via self-report questionnaires. BMI was calculated from height and weight data collected during each assessment.

Statistical analysis

SPSS 23.0 software was used for all statistical analysis. General linear models were utilized to perform all analyses. Values for EBV VCA IgG antibody titers, CRP, IL-6, and TNF-α were log10 transformed to normalize their distribution prior to analysis. All independent variables were grand mean centered. Pearson correlation coefficients were calculated to identify potential associations between pain, EBV VCA IgG antibody titers and inflammation. To test our central hypothesis, we conducted hierarchical linear regression, using the PROCESS macro for SPSS [18]. We examined whether pain was a moderator of the relation between age and EBV VCA IgG antibody titers. For the regression analyses, only individuals above the age of 34 years were included. Age was applied as an independent variable into the analysis. Covariates for the model were sex, BMI, race (White, Black, Asian, other), income (<$25,000; ≥$25,000), and group (bereaved vs. non-bereaved). The Johnson-Neyman technique was used to probe for significant interaction terms [19]. The regression model was constructed based on the significant correlations shown by the univariate analysis. All test were two-sided and any pvalue less than 0.05 was considered statistically significant.

Results

Detailed patient demographics and clinical characteristics are summarized in Table 1. All of the subjects enrolled (N = 82) in the study were seropositive for EBV. Correlation analyses are displayed in Table 2. No statistically significant correlations were found for EBV VCA IgG antibody titers and inflammatory markers. Linear regression analyses revealed no significant association between EBV VCA IgG antibody titers and CRP (B = -.04; p = .74), IL-6 (B = .06; p = .70) and TNF-α (B = .11; p = .35).

Table 3 summarizes the analyses examining the relationship between EBV VCA IgG antibody titers and age among older individuals. Regression analyses indicated that those individuals who

Table 2: Correlational table of immune markers, age, and pain.

	EBV	IL-6	TNF-α	BMI	Age
IL-6	0.07				
TNF-α	0.161	.310*			
BMI	0.054	.340**	0.168		
Age	-0.057	0.002	0.172	-.328**	
SF-36 Pain (reversed)	.325**	.234*	0.062	0.175	-.254*

Abbreviation. EBV = Epstein-Barr virus; IL-6 = interleukin-6, TNF-α = Tumor Necrosis Factor-alpha; BMI = Body Mass Index; SF-36 Pain = RAND 36-Item Short Form Health Survey Pain subscale.
Note: For easier interpretation, SF-36 Pain subscale was reversed. Lower SF-36 values indicate lower pain, higher SF-36 values indicate higher pain.
*p< .05, **p < 0.01

Table 3: Summary of multiple regression analysis for variables predicting EBV VCA antibody titers with estimated coefficients (B, SE), 95% confidence intervals, t and p-values.

Variable	Log10 (EBV VCA IgG) (N=82)				
	B	SE	95% CI	t	p-Value
*Intercept	1.023	0.984	[-.939, 2.985]	1.04	0.3
SF-36 Pain_rev	-0.017	0.011	[-.039, .006]	-1.46	0.15
Age	0.033	0.014	[.005, .061]	2.31	<.05
Sex (Female)	0.082	0.108	[-.133, .297]	0.76	0.45
BMI	-0.006	0.01	[-.027, .015]	-0.58	0.56
CES-D	-0.004	0.005	[-.015, .007]	-0.77	0.45
Race	0.23	0.151	[-.070, .531]	1.53	0.13
Income	0.212	0.149	[-.085, .509]	1.42	0.16
Group	0.052	0.12	[-.187, .290]	0.43	0.67
Age x SF-36 Pain_rev	0	0	[.000, .001]	2.06	<.05

*Intercept = value of y when x is zero.
Sex: 0 = male; 1 = female
Note: CES-D = The Center for Epidemiological Studies-Depression; Group: 1 = bereaved; 2 = control; SF-36 Pain rev = RAND 36-Item Short Form Health Survey Pain subscale reversed.

were older had higher EBV VCA antibody titers (B = .033; p = .024). Furthermore, participants with more pain had higher EBV VCA IgG antibody titers versus those who had less pain (B =.354; p = .004). For the next regression model, we added the interaction between age and pain. A significant interaction between age and pain was identified, such that the association between EBV VCA IgG antibody titers and age was stronger among those who had more pain (B =.000; p = .043). Specifically, at one standard deviation above the mean SF-36 pain subscale (reversed), the association between age and EBV VCA IgG antibody titers was positive ($B_{interaction}$=. 013; t = 2.01;p = .048; CI = .000; .025), while no significant association between age and EBV VCA IgG antibody titers was apparent one standard deviation below the mean ($B_{interaction}$ = -.004; t = -.53; p = .60; CI = -.018; .010).

Using the Johnson-Neyman technique, it was determined that older age (≥ 59 years; 78% of the sample) was associated with more EBV VCA IgG antibody titers among those who reported more pain (SF-36 pain subscale-reversed ≥ 54.1; 13% of the sample) ($B_{interaction}$ = .013; t = 2.01; p = .05; CI = .000; .025) (Figure1). Thus, pain was a significant moderator of the relationship between age and EBV VCA IgG antibody titers. We looked also at associations between pain, EBV VCA IgG antibody titers, and inflammation. However, given that there was no significant relationship between EBV VCA IgG antibody titers and markers of inflammation, we did not conduct additional analyses using inflammatory markers.

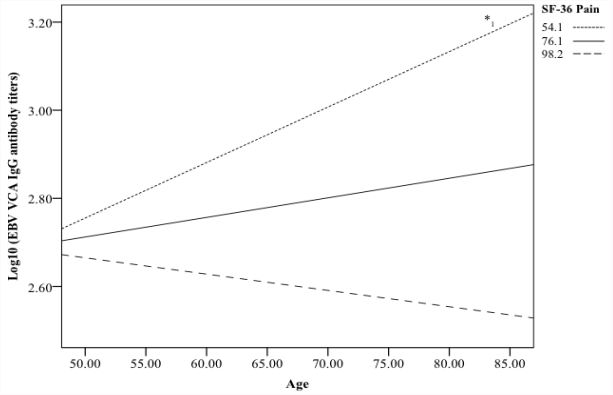

Figure 1: Interaction between age and pain in the model of EBV VCA antibody titers activation.
*1 simple slope: B = .013, t = 2.01, p < .05
The regression analysis used the full range of EBV VCA antibody titers as continuous variables. Age was stratified for graphical purposes using 1/- 1 standard deviation from the mean. The line representing those with a SF-36 pain level of 76.1 and 98.2, respectively did not significantly differ from zero (simple slope: B = .004, t = .83, p = .41; simple slope: B = -.004, t = -.53, p = .60).
Note: Lower SF-36 values indicate higher pain, higher SF-36 values indicate lower pain.

Discussion

In this study, we examined the relationship between age, pain and latent EBV reactivation. As expected, after adjusting for sociodemographic and medical variables, older age was associated with elevated EBV VCA IgG antibody titers. Importantly, this effect was specific to individuals who were 59 years and older and reported higher pain levels (SF-36 pain subscale ≥ 54.1). Changes in immune function after the age of 50 years have received particular attention because of their clinical impact. Such changes have been globally called "immunosenescence", which is associated with diminished effectiveness of the immune system [20].

Pain is a severe stressor and has profound physiological effects on the Hypothalamic-Pituitary-Adrenal-Thyroid-Gonadal (HPATG) system, which is the major stress control mechanism of the body [21]. Specifically, pain signals that reach the brain from the peripheral nervous system activate hormones in the hypothalamus, which promotes Corticotropin Releasing Hormone (CRH) and the subsequent release of serum Adrenal Corticotropin Hormone (ACTH), and ultimately cortisol [22]. Indeed, robust evidence links chronic pain with activation of the HPA-axis, upon which chronic pain acted as a significant stressor [23]. Based on our results, it is plausible that pain and latent EBV reactivation are linked via chronic stress-induced HPA dysfunction. Thus, the relationship between older age and EBV VCA IgG antibody titers among those who reported more pain suggests that pain as a significant chronic stressor has the potential to accelerate the association between age and immune dysfunction in older individuals.

Our results are in accordance with previous research demonstrating that a variety of triggering factors are responsible for disrupting the delicate balance between latency and the reactivation of viral replication [5]. For instance, chronic stress has shown to modulate the virus-specific immune response to latent herpes simplex virus [24]. Our results corroborate with an extensive series of studies demonstrating conclusively the negative impact of environmental and psychological stressors on reactivation of EBV [25-28]. There is

also strong evidence from geriatric studies, documenting impaired cellular immune system control over latent EBV in the older individuals [4,10,12].

In contradiction to the current literature, suggesting that reactivation of latent herpes viruses can drive inflammation [29], we did not identify a significant relationship between latent EBV reactivation and inflammation in the current sample. This apparent lack of correlation can be justified by the fact that the association between a stressor, herpes virus reactivation, and inflammation is likely complex and multifaceted. While research has shown that a greater herpes virus burden is associated with higher levels of inflammation [30,31], evidence demonstrates that only a specific combination of multiple herpes viruses can lead to systemic inflammation. Specifically, seropositivity for both EBV and Cytomegalo Virus (CMV) has been found to be significantly associated with elevated levels of CRP and IL-6 [11]. Another possible rationalization for the missing relationship between EBV VCA IgG antibody titers and inflammatory markers is that only a single blood test per study participant was conducted, while the half-life of immunoglobulin (IgG) is 23 days but much shorter for TNF-α and IL-6. This problem becomes prominent particularly in studies with small sample sizes. A recently published study confirmed this assumption by demonstrating a significant association between latent herpesvirus reactivation and inflammation in a much larger subject number (N = 1208) [32]. Assessing a broader area of herpesviruses (e.g. CMV, herpes-simples virus type 1 [HSV-1]) could give us a clearer picture of the relationship between herpesvirus latency and inflammation. Finally, it may be possible that EBV reactivation may actually be a better marker of inflammatory processes than inflammation because EBV VCA IgG antibody titers are more stable. A major limitation of the use of circulating cytokines is that their levels are often below the limit of detection [33].

It is possible that the management of chronic pain may help to reduce immune dysregulation [34]. The standard approach to managing pain in older individuals is generally symptom-oriented and multidisciplinary, including modalities like pharmacotherapy, psychotherapy, and physical rehabilitation [35]. Psychological treatment to the management of chronic pain aims at increasing self-management of pain, improving pain-coping resources, and reducing pain-related disability and emotional distress [36]. Such interventions have been demonstrated to reduce pain and improve quality of life in older adults with chronic pain [37,38]. Interestingly, psychological interventions can modulate certain features of the immune response [39-41]. However, only little research has been conducted in a population of older adults suffering from chronic pain, and therefore needs to be further investigated.

Study Strengths and Limitations

We investigated cross-sectional baseline data, which limited our ability to determine causality. It is likely that periodic stress-induced viral reactivation contributes to an increase in EBV-specific T cells over time [10]. Adopting a longitudinal approach to study the aforementioned associations might reveal more information on immune dysfunction in older individuals. Second, as our study sample was predominantly white, it will be important for future researchers to examine the relationship between pain and EBV reactivation in more racially-diverse samples. Future work would benefit from investigating relationships between pain and additional markers of immune dysregulation (e.g., cytomegalovirus; IL-1β, IL-6, Natural Killer (NK) cells) to provide a more comprehensive understanding of how pain may adversely affect immune function in seniors. Third, the inclusion of individuals who have recently lost a spouse could have affected the results. However, in the current study, we found no reliable differences between bereaved and non-bereaved individuals on the predictors or outcomes of interest.

Conclusions

The current study extends prior work on latent EBV reactivation by suggesting that increased latent EBV VCA IgG antibody titers is associated with older age among those individuals who reported higher pain levels. A better understanding of different physiological and molecular pathways of herpes virus reactivation and its association with immune dysregulation in older individuals could aid in the development of novel strategies to predict disease susceptibility, target novel therapies and, ultimately, develop new approaches to preventing many chronic age-associated disease. Continued research is needed to determine the reliability and generalizability of these findings and to help clarify the complexity of age-related symptoms associated with latent EBVreactivation and immune dysregulation.

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The specific roles of the authors are articulated in the 'author contributions' section.

Author Contribution

Conceptualization: Annina Seiler, Kyle W. Murdock, Christopher P. Fagundes

Funding acquisition: Annina Seiler, Christopher P. Fagundes

Methodology: Annina Seiler, Kyle W. Murdock, Raymond P. Stowe, Christopher P. Fagundes

Determination of EBV VCA IgG antibody titers: Raymond P. Stowe

Supervision: Christopher P. Fagundes

Writing – original draft: Annina Seiler

Writing – review & editing: Annina Seiler, Kyle W. Murdock, Raymond P. Stowe, Christopher P. Fagundes

Competing Interests

The authors do not have any conflict of interests to declare. The affiliation with Microgen Laboratories, La Marque, TX does not alter our adherence to all Annals of Pain Medicine policies on sharing data and materials.

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