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MUSCLE TENDERNESS IN MEN WITH CHRONIC PROSTATITIS/ CHRONIC PELVIC PAIN SYNDROME: THE CHRONIC PROSTATITIS COHORT STUDY

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Abstract

Introduction—Myofascial pain is a possible etiology for category III chronic prostatitis/chronic pelvic pain syndrome (CPPS), either secondary to infection/inflammation or as the primary cause. We wished to document tenderness on physical exam in a large multicenter cohort of CPPS patients, and compare to controls.

Methods—Data were reviewed from the NIH Chronic Prostatitis Cohort study on 384 men with CPPS and 121 asymptomatic controls who had complete unblinded physical exam data, from 7 clinical centers between 10/98 - 8/01. Tenderness in 11 sites including prostate, genitals, abdomen and pelvic floor together with prostate size and consistency was evaluated. Data was correlated with cultures and symptoms.

Results—Overall, 51% of CPPS patients and 7% of controls had any tenderness. The most common site was prostate (41% CPPS, 5% controls), followed by external and internal pelvic floor (13% and 14% CPPS, 0 controls) and suprapubic (9% CPPS, 0 controls). In CPPS patients, 25% had 1 tender site, 11% had 2 and 6% had 3. Tenderness did not correlate with inflammation or infection in the prostate fluid. Prostate consistency was normal in 79% of CPPS patients and in 95% of controls, and did not correlate with symptom severity. CPPS patients with any tenderness had significantly higher CPSI scores at baseline, and at 1 year (24.1 vs 21.2 and 20.2 vs 17.5, $p<0.0001$), compared to patients without tenderness.

Conclusions—Abdominal/pelvic tenderness is present in half of CPPS patients, but only 7% of controls. Extraprostatic tenderness may identify a cohort of patients with a neuromuscular source of pain.

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§Please include CPCRN Study Group List of Participants in Appendix 1

Introduction

Chronic Pelvic Pain Syndrome (CPPS) or NIH Category III prostatitis ("nonbacterial prostatitis") is a common clinical syndrome with multiple potential etiologies, including infection, autoimmunity, and neuromuscular spasm [1]. Several groups have suggested that a myofascial pain syndrome with abnormal pelvic muscle spasm is the primary source of the symptoms of CPPS, although such spasm could be secondary to local infection or inflammation [2]. In patients with a myofascial pain syndrome, the affected muscles palpation elicits pain, typically the pain that patients attribute to their "prostatitis". There have been no large scale/multicenter studies that have assessed the incidence and distribution of such muscle tenderness.

The NIH Chronic Prostatitis Cohort (CPC) Study examined 488 CPPS patients and 121 controls, and followed their treated natural history for up to 3 years at 7 clinical centers [3]. As part of the initial evaluation, the physical exam included assessment of muscle tenderness in the abdomen, genitals, and pelvis, including the prostate. Tenderness was elicited by the physician performing the physical examination during palpation. This database represents a unique opportunity to study muscular pain and tenderness in men with CPPS that have been fully evaluated for symptoms, cultures, and microscopy, as well as comparing these findings to asymptomatic controls.

Materials and Methods

Data for the CPPS participants were obtained from the CPC study, based on a prospective, longitudinal cohort design, that recruited 488 eligible, consenting participants at 7 clinical centers, described further in Schaeffer et al [3]. An asymptomatic control group of 121 men were also enrolled at these clinical centers, and followed under the same protocol, as described in further detail in Nickel et al [4]. Since the full physical exam was instituted after the first 79 subjects were enrolled, we have complete data on 384 men with CPPS and 121 asymptomatic controls. Tenderness was recorded as present or absent in the following locations: prostate, abdomen, flank, coccyx, pubis, suprapubic, external pelvic floor, internal pelvic floor, cord/inguinal area, epididymis and testes. The prostate exam was reported as normal or enlarged, consistency as normal, firm or soft, and nodularity as absent or present. All patients filled out an NIH Chronic Prostatitis Symptom Index (CPSI), and the questions from the pain domain were analyzed according to number and location of pain sites.

Most of the analytical variables were binary or categorical, and are summarized by proportions and compared among groups using standard chi-square tests of association, and generalized Mantel-Haenszel (MH) methods, to accommodate both nominal and ordinal measurement scales. Small sample methods, such as Fisher's exact test, were used in cases where large sample assumptions were not satisfied. The CPSI scores were analyzed as continuous variables. These analyses were performed to characterize tenderness using number of tender areas, overall CPSI scores and pain subscores, prostate exam variables and colony counts of localization of uropathogens. For our analyses, uropathogens were considered Gram negative bacilli (eg. E. coli, Klebsiella sp.) as well as the Gram positive Enterococcus species. Expressed Prostatic Secretion (EPS) or VB3 (post prostate massage urine) cultures were considered localized if the bacteria identified were not found in the urine culture or if the bacterial counts in EPS were at least 2 log counts higher than in urine. Statistical analyses were performed using SAS version 8.2. For the frequencies of tenderness locations and prostate exam variables, we simply tabulated the number of subjects in each category, and displayed the results. No formal tests of significance were performed because our interest was primarily in descriptive measures. In comparing baseline CPSI scores, the nonparametric Wilcoxon rank sum test was used for comparison between groups, since it is robust with respect to departures from the assumption of normality required by the usual t-test. Comparisons of baseline and 12-month CPSI scores

were made using a generalized estimating equations (GEE) model. For comparison of localization frequencies between groups, a binomial test of difference of proportions was used, since we have a large enough sample, and all observed proportions are sufficiently far from 0 and 1.

Results

As summarized in Table 1, the most common site of tenderness was the prostate (41% of cases and 5% of controls). The next most common site among cases was the internal pelvic floor (14%), followed by the external pelvic floor (13%). All other sites were tender in fewer than 10% of the cases. Two controls had epididymal tenderness, and one had testicular tenderness. Table 2 shows the number of tender sites per subject (out of a possible 11 sites). For the cases, 49% had no sites of tenderness, 25% had 1 tender site, 11% had 2 tender sites and a total of 15% had 3 or more tender sites. In the controls, 93% had no tenderness, 6% had 1 tender site and 1 patient had 2 tender sites. Evaluating the eleven individual sites of possible tenderness, no consistent combinations emerged. Indeed, of the 66 combinations seen, 41 were unique, and no unique combination was seen in more than 3% of patients. Given this lack of consistent pattern, we next grouped the tenderness sites into 4 geographic combinations: i) prostate, ii) trunk (abdomen, flank, coccyx, pubis, suprapubic), iii) genital (cord, epididymal, testes) and iv) pelvic (internal/external pelvic floor). As seen in table 3, prostate tenderness was the most common (41%) followed by pelvic (19%).

We next wanted to correlate tender sites with degree of symptoms, as measured by the CPSI scores. As summarized in table 4, when patients with tenderness are compared to those without, those with tenderness had a statistically significantly higher CPSI total score and pain subscore than those who did not report tenderness. Interestingly though, the absolute difference in average CPSI score was small, ranging from 2.8 (prostate) to 5.0 (trunk). We then compared the change in baseline CPSI to the CPSI at one year for patients with or without tenderness in any of the geographic areas, using a Generalized Estimating Equations (GEE) analysis to accommodate the longitudinal measures within patients. As seen in Table 5, the negative coefficient for the patients with tenderness indicates that those with tenderness at baseline started at a higher CPSI (and pain subscore). The negative coefficient for time indicates that all patients had a lower CPSI (and pain subscore) at one year. There was no differential improvement over time between those with and without tenderness, as reflected by the highly non-significant interaction term between tenderness and time.

We then compared the findings on prostate exam between CPPS patients and controls. As seen in table 6, prostate size was enlarged in 14% of cases vs 5% of controls (p=0.01). The mean age of CPPS patients with a normal size prostate gland was 41.7 yearsvs. 46.4 years for CPPS patients with enlarged prostates (p=0.001). The mean age for controls with normal sized glands was 38.7vs. 51.9 years for controls with enlarged glands(p=0.004). Prostate consistency was different, with a soft/boggy prostate felt in 17% of cases vs 3% of controls (p=0.001). Of notehowever 79% of CPPS patients had normal prostate consistency.

Finally, we compared tenderness with culture results for bacteria that localized to EPS or VB3. Overall, 8.0% of CPPS patients and 8.3% of controls had localization of uropathogens. Of the 37 CPPS patients with bacterial localization, 15 (41%) had no sites of tenderness and 11 (30%) had prostate tenderness. These numbers are similar to those without positive cultures (50% no tenderness and 43% prostate tenderness). As seen in table 7, when comparing tenderness in each of the geographic regions, there was no difference in positive cultures for uropathogens. Similarly, there was no difference in prostate fluid inflammation in patients with or without tenderness.

Discussion

CPPS is a common and enigmatic condition of uncertain etiology. The confusion over etiology was highlighted when an NIH consensus conference developed the current diagnostic categories, which were based only on the presenting symptoms [5]. Attempts to distinguish CPPS patients from controls have found few significant differences apart from symptoms. Commonly measured factors, such as cultures and WBC counts in urine, EPS, and semen have failed to distinguish these groups[4], and we continue to search for biomarkers to make CPPS a diagnosis of inclusion rather than exclusion. Since organic pain is often associated with tenderness, it would be a reasonable assumption that patients with pelvic pain and inflammation would also have pelvic locations tender to the touch, and yet there has never been documentation of the characteristics of tenderness sites in a large scale or multicenter study. Indeed, in clinical practice, many patients receive a diagnosis of "prostatitis" based on prostatic tenderness during a digital rectal exam, regardless of symptoms.

Our findings confirmed the heterogeneity of patients with CPPS. While tenderness was the most discriminating factor between cases (51%) and controls (7%), it is important to note that half the CPPS patients, while suffering from pain, had no sites of tenderness whatsoever. No distinct pattern or combination of tenderness sites emerged. Of the 194 patients who did have tenderness, there were 66 different combinations of sites. There are several possible explanations for sites of extraprostatic tenderness. One is that locations in direct contact with the prostate may have elicited prostate tenderness. Indeed, while 3% of patients had pelvic floor tenderness without prostate tenderness, 11% had pelvic floor tenderness plus prostate tenderness. Another possibility is that extra-prostatic muscle spasm may mimic the symptoms of CPPS in the absence of current prostate pathology[2]. Another possibility is that CPPS patients have greater sensitivity to pain, and may report pain during an exam as opposed to a control patient, who might report it as simply unpleasant[6]. Central neural sensitization is a common feature of many chronic pain conditions and could be the final common pathway through which the pain in CPPS becomes autonomous from it's initial trigger, whether that trigger is infection, inflammation, trauma or neuromuscular stress. Finally, since neither patient nor examiner was blinded to who had CPPS and who was a control, operator and reporter bias may have influenced the results, with a belief that a patient who has pain "should" have or report tenderness in the area. While subgroup analysis was not statistically possible due to low numbers, all examiners reported heterogeneous findings in the patients. There were no sites with "true believers" who reported everyone with tenderness, nor were there "hyper-skeptics" who reported tenderness in nobody. Nevertheless, this examination is, by its nature, objective, and a challenge for future research is the development of stimulation techniques that could be used objectively across examiners. Furthermore, as symptoms typically wax and wane in this disorder, multiple assessments in future studies could help address reproducibility.

Using the NIH-CPSI to assess degree of symptoms, presence of tenderness in any of the geographic areas was associated with a higher symptom score, both for total score and for the pain subdomain. Nevertheless these differences were clinically small, and their average magnitude was below the threshold that patients describe as clinically relevant. Patients in this observational cohort study were treated at each local center according to best local practices, and while overall scores dropped at 1 year on average for all patients, the presence of tenderness did not make this improvement in symptoms any more or less likely. It was not recorded which therapies were used for which patients, and it is possible that treatment selection was tailored to the physical findings, but given the clinical practice at most of the centers, this is not likely.

The lack of correlation between tenderness sites and culture results is not surprising, given the selection criteria of the patients. As category III, none would have had recurrent urinary tract infections (category II) and most patients seen in the primarily tertiary care settings of the study

sites had previously been treated with antibiotics, and almost all would have failed or recurred. It is likely, therefore, that the 8% of patients with cultures of uropathogens that localized to prostatic secretions had colonization with these bacteria and not acute infection, defined as associated local tissue damage with an inflammatory response. Indeed, prostatic inflammation, as measured by counted WBC in a wet mount of EPS, did not correlate with tenderness. However this method of assessing inflammation, while most commonly used in the clinic, may not truly reflect soluble mediators of inflammation within the prostate that do cause tissue injury[7].

The abnormal consistency of the prostate was more often seen in patients with CPPS patients when compared to controls; however, these changes were not common in the CPPS patients as a whole. Indeed, the notion that prostatitis is associated with a soft or “boggy” prostate is pervasive in urologic practice, but without any basis in data. In reality, 79% of the CPPS patients in our study had a normal prostate consistency.

In conclusion, roughly half of CPPS patients have areas of tenderness that are elicited during the physical exam, compared with only 7% of asymptomatic controls. It is noteworthy that half of symptomatic CPPS patients do not. Tenderness is associated with a modest increase in symptom score, but not with prostatic cultures or WBC counts, and does not predict response to therapy. Documentation of tenderness should be a part of the physical exam in men with CPPS, and may aid in the diagnosis. If men with extra-prostatic tenderness truly have a distinct neuromuscular or central chronic pain syndrome, then physical exam may help the classification and treatment stratification for these patients in the future.

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Glossary

CPPS
: Chronic Pelvic Pain Syndrome

CPSI
: Chronic Prostatitis Symptom Index

EPS
: Expressed Prostatic Secretions

WBC
: White Blood Cell count

Appendix 1

Chronic Prostatitis Collaborative Research Network (CPCRN) Study Group

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Table 1

Incidence of Tenderness for Cases and Controls by Tenderness Area

	Cases		Controls	
Tenderness Site	**#**	**% (out of 384)**	**#**	**% (out of 121)**
Prostate	157	41%	6	5%
Trunk				
Abdomen	21	5%	0	0%
Flank	4	1%	0	0%
Coccyx	7	2%	0	0%
Pubis	18	5%	0	0%
Suprapubic Area	33	9%	0	0%
Cord/Inguinal Area	14	4%	0	0%
Genital				
Epididymal	29	8%	2	2%
Testes	31	8%	1	1%
Pelvic				
Internal Pelvic Floor	52	14%	0	0%
External Pelvic Floor	49	13%	0	0%

Table 2

Number of Tender Sites Out of 11 Possible Sites for Cases and Controls

	Cases		Controls	
Number of Tender Sites	**#**	**% (out of 384)**	**#**	**% (out of 121)**
0	190	49%	113	93%
1	95	25%	7	6%
2	43	11%	1	1%
3	24	6%	0	
4	15	4%	0	
5	9	2%	0	
6	4	1%	0	
7	1	<1%	0	
8	1	<1%	0	
9	2	1%	0	

Table 3

Incidence of Tenderness Areas for Cases/Controls

	Cases (N=384)		Controls (N=121)		
Tenderness Area	**Freq**	**Incidence**	**Freq**	**Incidence**	**p-value**
Prostate	157	40.9%	6	5.0%	<0.0001
Trunk	45	11.7%	0	0.0%	<0.0001
Genital	48	12.5%	2	1.7%	<0.0001
Pelvic	72	18.8%	0	0.0%	<0.0001

Table 4

Comparison of Mean CPSI and Pain Subscores for Tenderness Areas

CPSI Mean Scores: Baseline				
Subgroups	**N**	**Total Score (max 43)**	**N**	**Pain Sub-score (max 21)**
Any Tenderness	192	23.89	192	11.14
No Tenderness	192	21.23	192	9.8
Difference(p-value)		**2.66 (0.003)**		**1.35 (0.005)**
Any Prostate Tenderness	155	24.14	157	11.34
No Prostate Tenderness	227	21.41	227	9.87
Difference(p-value)		**2.83 (0.001)**		**1.47 (0.002)**
Any Trunk Tenderness	45	26.93	337	12.84
No Trunk Tenderness	45	21.97	339	10.15
Difference(p-value)		**4.96 (<0.001)**		**2.69 (<0.001)**
Any Genital Tenderness	48	25.52	334	11.85
No Genital Tenderness	48	22.13	336	10.27
Difference(p-value)		**3.39 (0.015)**		**1.58 (0.023)**
Any Pelvic Tenderness	72	24.96	310	12
No Pelvic Tenderness	72	22	312	10.12
Difference(p-value)		**2.96 (0.008)**		**1.88 (0.001)**
CPSI Mean Scores: 12 Month Follow-up				
Subgroups	**N**	**Total Score (max 43)**	**N**	**Pain Sub-score (max 21)**
Any Tenderness	133	19.65	133	9.28
No Tenderness	111	17.53	111	8.29
Difference(p-value)		**2.12 (0.057)**		**0.99 (0.068)**
Any Prostate Tenderness	151	19.88		9.24
No Prostate Tenderness	93	17.63		8.35
Difference(p-value)		**2.25 (0.051)**		**0.89 (0.128)**

Table 5

Generalized Estimating Equations Models of CPSI and Pain Subscore vs. Time (12 months vs. Baseline) and Presence of Tenderness (None vs. Any)

	CPSI Index		Pain Subscore	
No Tenderness Vs. Any	**Estimate**	**p-value**	**Estimate**	**p-value**
Intercept (value at baseline)	23.75	<0.0001	11.13	<0.0001
Tenderness - None vs. Any (1 vs. 0)	−2.63	0.0022	−1.39	0.0022
Time - 12 mo. vs. Baseline(1:0)	−3.92	<0.0001	−1.66	<0.0001
Tenderness * Time	0.2448	0.809	0.02	0.9709

Table 6

Prostate Exam Results for Cases and Controls

	Cases		Controls		
Prostate Exam Result	**#**	**% (out of 463)**	**#**	**% (out of 121)**	**p-value**
Size					
Normal	397	86%	115	95%	0.01
Enlarged	66	14%	6	5%	
Consistency					
Normal	367	79%	115	95%	0.0002
Firm	20	4%	3	3%	
Soft	76	17%	3	3%	
Nodularity					
No	448	97%	120	99%	0.2
Yes	15	3%	1	1%	
Tenderness					
No	280	60%	115	95%	<0.0001
Yes	183	40%	6	5%	

Table 7

Comparison of the Incidence of Localization of Uropathogens by Tenderness Area

Variable	Frequency Localized	N	Proportion	p-value
Prostate Tenderness	11	157	7.01%	0.6245
No Prostate Tenderness	19	227	8.37%	
Trunk Tenderness	6	45	13.33%	0.1419
No Trunk Tenderness	24	315	7.62%	
Genital Tenderness	3	48	6.25%	0.6663
No Genital Tenderness	27	336	8.04%	
Pelvic Tenderness	6	72	8.33%	0.855
No Pelvic Tenderness	24	312	7.69%	