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Category III Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Insights from The National Institutes of Health Chronic Prostatitis Collaborative Research Network Studies

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Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) remains an enigmatic medical condition. Creation of the (NIH) Chronic Prostatitis Collaborative Research Network (CPCRN) funded by the National Institutes of Health has stimulated a renewed interest in the research and clinical aspects of CP/CPPS. Landmark publications of the NIH-CPCRN over the last 10 years document a decade of progress. Insights from these CPCRN studies have improved our management of patients diagnosed with CP/CPPS and offer hope for continued progress.

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Introduction

The Prostatitis Consensus Workshop sponsored by the National Institutes of Health/National Institute of Diabetes/Digestive/Kidney Diseases (NIH/NIDDK) in December 1995 was a major landmark event in the history of prostatitis research. This meeting resulted in the general acceptance of the NIH classification system for the prostatitis syndromes. This classification system recognized that our understanding of the etiology for most patients previously diagnosed with chronic prostatitis is limited and raised the possibility that structures other than the prostate gland may be important in the pathogenesis of chronic prostatitis. The “new” NIH classification system [1] re-named the traditional classification of acute and chronic bacterial prostatitis respectively as categories I and II. Category III (chronic prostatitis/chronic pelvic pain syndrome or CP/CPPS) recognized that pain was the main symptom characterizing the “non-bacterial chronic prostatitis” syndromes and was defined as “the presence of genito-urinary pain in the absence of uropathogenic bacteria detected by standard microbiological methodology”. This category was further categorized into inflammatory (category IIIA) and non-inflammatory (category IIIB) CP/CPPS. A completely new category, asymptomatic inflammatory prostatitis (category IV) addressed an important inflammatory condition that had been more or less ignored in the previous classification system. The pivotal 1995 NIH/NIDDK Workshop also indirectly led to the formation in 1997 of the NIH Chronic Prostatitis Collaborative Research Network (CPCRN). The network is a multi-institutional, collaborative research endeavor whose mandate is to further define the disease and its etiology and epidemiology, describe its natural history, develop validated outcome measures, and determine better methods of treatment and prevention. [2]. The purpose of this article is to summarize the progress and challenges in meeting the ambitious CPCRN agenda

Development of a Validated Outcome Index

The first step in accomplishing the CPCRN agenda was to develop a reliable and valid index of symptoms and impact on quality of life for the evaluation of patients with CP/CPPS. The CPCRN conducted a structured literature review of previous work to provide a foundation for the new instrument and then conducted a series of prostatitis patient focus groups. From these efforts, the most important symptoms and effects of the condition were identified. Based on formal cognitive testing, expert panel review, and formal validation testing in a large group of chronic prostatitis patients and 2 control populations of benign prostatic hyperplasia patients and healthy men, the initial draft of 55 items eventually yielded an index of 9 items that addressed the 3 most important parameters of a chronic prostatitis patient's experience. The primary component was pain, which was captured in 4 items focused on location, severity and frequency: urinary function was captured in 2 items (1 irritative and 1 obstructive) and quality of life was captured with 3 items related to the effect of symptoms on daily activities. The NIH-CPSI provided a practical but comprehensive evaluative instrument that was easily self-administered, psychometrically robust and highly discriminative [3].

The CPCRN assessed the responsiveness of the NIH/CPSI to changes over time and defined thresholds for changes perceptible to patients [4]. The NIH-CPSI total score, pain and quality of life scores were highly responsive in the improved group, although the urinary score showed minimal responsiveness. A 6 point decline in the NIH-CPSI total score proved the optimal threshold to predict treatment response that was meaningful to the patient. The NIH-CPSI has also proven useful in clinical practice [5]. Physicians have successfully used the NIH-CPSI to identify prostatitis patients' specific symptoms, determine relative severity and most importantly, track response to clinical therapy over time. The NIH has sponsored a translation and linguistic validation of the NIH-CPSI into Spanish [6] and French Canadian [7]. The Spanish and French Canadian version of the NIH-CPSI has proven acceptable for clinical use with Spanish and French Canadian speakers inside North America (and have also been used

outside North America for Spanish and French speakers) and has allowed inclusion of these populations into clinical studies.

In summary, the NIH-CPSI total score and pain and quality of life scores (but not necessarily the urinary score) provide valid and reliable indicators of disease severity, are responsive to improvement over time, and are appropriate endpoints for clinical trials and can be utilized as a clinical instrument for the following CP/CPPS patients in clinical practice.

Epidemiology of CP/CPPS

Important epidemiological goals of the CPCRN were to characterize men with CP/CPPS and to determine the natural treated history. The CPCRN developed a prospective longitudinal chronic prostatitis cohort (CPC) study in which patients with CP/CPPS were comprehensively studied and then followed over time. Baseline analysis of the first 488 men screened into the CPC study allowed an important description of the patient diagnosed with CPPS. The patients underwent extensive demographic and clinical baseline screening assessment, symptom and quality of life data collection employing the NIH-CPSI, various clinical procedures including physical examination, the standard four-glass test, uroflowmetry, and semen sample analyses. The CPC study represented the largest comprehensive study of a cohort of men with CP/CPPS recruited specifically for the evaluation and study of this condition. The CPC study confirmed that CPPS is an important multi-factorial problem that affects men of all ages and demographic sub-groups. It results in a serious and significant detrimental impact on the quality of life and despite the many treatments undergone by CPPS patients, it appeared that many benefited minimally from empiric therapy [8].

In a separate analysis, the CPCRN investigated the importance of leukocyte and bacterial counts in the patients enrolled in the CPC study. Significant leukocytosis was noted in the expressed prostatic secretion (EPS) samples in 31% (10+ white blood cells/high powered field) to 49% (5+ white blood cells/high powered field). Eight percent of the men had at least one localizing uropathogen based on prostate-specific and/or semen cultures. One of the most interesting findings in this study was that leukocytes and bacterial counts did not correlate with severity of symptoms. These findings suggested that factors other than leukocytes and bacteria could also contribute to symptoms associated with CPPS [9].

Men enrolled in the CPC study were followed for 2 years to determine the natural treated history of this condition [10]. The findings suggested that CP/CPPS was, indeed, a chronic condition, however, a group of men who participated in the study had a tendency to improve during the 2 years of follow-up. More than 30% of these subjects (who averaged more than 7 years since diagnosis) reported on the global response assessment that they were moderately or markedly improved at 2 years. Individual patients had experienced dramatic waxing and waning of symptoms. No baseline demographic or clinical factors predicted which men were more or less likely to improve during the 2 years of follow-up.

In an attempt to identify characteristics that might be associated with CPPS, 463 men enrolled in the CPC study were compared to 121 asymptomatic age-matched controls [11]. Compared to controls, men with CPPS reported a significantly greater lifetime prevalence of non-specific urethritis, cardiovascular disease, neurological disease, psychiatric conditions, and hematopoietic, lymphatic, and infectious disease. More importantly, the study failed to support a widely postulated idea that many behavioral risk factors for CP/CPPS play a role in the etiology of the syndrome. Medical conditions such as cardiovascular and neurological diseases might be more important in the etiology and certainly further study and investigation of these areas could provide insight into the causes of CP/CPPS.

Because little information existed on the economic impact of CP/CPPS, the CPCRN undertook a study to determine the medical costs associated with chronic prostatitis. The average total cost (direct and indirect) for 167 study participants was determined to be $4,397.00 [12]. This was considerably higher than the total annual medical costs for rheumatoid arthritis, peripheral neuropathy, or low back pain. The study did not evaluate the economic impact of CP/CPPS on reported lost time from paid work and reduced work productivity. The only predictor of resource consumption was the severity of symptoms (particularly pain and quality of life) determined by the NIH-CPSI.

Quality of Life in CP/CPPS

The measurement of quality of life (QOL) which describes how well an individual functions in life and his perceptions of well being is extremely important for understanding the impact of CP/CPPS on individual patients. The CPCRN evaluated 278 men in a cross sectional study to determine the impact of CPPS on QOL using validated generic and condition specific indices and to identify the factors associated with worse CP/CPPS symptoms [13]. The Short Form 12 Mental Component Summary scores (SF 12 MCS) were lower than those observed in the most severe sub-groups of patients with congestive heart failure and diabetes mellitus while the Short Form 12 Physical Component Summary scores (MSF 12 PCS) were worse than those among the general US male population. Decreasing scores (poorer quality of life) were seen in both the mental and physical domains with worsening symptom severity. A history of psychiatric disease in younger age was strongly associated with worse mental QOL scores where as history of rheumatologic disease was associated with worse physical QOL scores. The 2 year follow-up of men enrolled in the CPC study [10] showed that mean changes in the SF 12 MCS and PCS during the 2 years of follow-up were proportionally smaller than changes observed by the symptom severity scores.

The two previous studies strongly suggest that the impact of CP/CPPS on quality of life must be addressed in the development of any treatment strategy. The CPCRN has undertaken a number of major multi-center, as well as single-center ancillary studies, to evaluate the bio-psychosocial parameters associated with symptom severity and quality of life in CP/CPPS patients. Using a cross sectional retrospective analysis of the CPC study population, the unique contributions of pain, urinary dysfunction and depressive symptoms were examined as predictors of QOL in CP/CPPS patients. This study showed that depressive symptoms and pain intensity significantly predicted a poor QOL in patients with CP/CPPS and that these effects were independent of partner status, age and urinary status. In this particular study, pain intensity was the most robust predictor of poor quality of life [14].

Recognizing that further data relating to pain, quality of life and psychological factors are essential if empirically guided efforts to manage the patient's pain and quality of life are to progress, the CPCRN undertook a prospective bio-psychosocial study to explore physical, cognitive-behavioral, and environmental predictors of pain and disability in CP/CPPS patients [15]. This study of 253 men with CP/CPPS showed that the cognitive/behavioral variables of catastrophizing and pain contingent rest respectively predicted greater pain and disability. Catastrophic thinking about pain includes 3 components of catastrophizing: rumination (“I can't stop thinking about how much it hurts”), magnification (“I worry that something serious may happen”), and helplessness (“There is nothing I can do to reduce the intensity of pain”). Pain contingent resting as a pain coping measure assesses the extent to which patients use rest as a means of coping with pain. This coping style was shown to be a maladaptive behavior in that it contributed to greater pain and pain related disability. A subsequent analysis of the same cohort of men in the bio-psychosocial study [16] showed that poorer SF 12 PCS scores were predicted by worse urinary function and increased use of pain contingent resting as a coping

strategy. Further, poorer SF 12 MCS scores were predicted by greater pain catastrophizing and lower perceptions of social support.

The previous generic and disease specific studies exploring QOL in patients with CP/CPPS did not evaluate the impact of sexual and relationship issues on QOL and symptoms in men with CP/CPPS. In an ancillary CPCRN study funded by the NIH, 38 patient couples (CPPS man with partner) were compared to 38 matched controlled couples [17]. Sexual functioning marital functioning scales and psychological functioning were assessed in the index patient, his matched control, and their sexual partners. Patients differed significantly from control men on several aspects of sexual functioning and depression (desire, erectile functioning, orgasmic functioning, intercourse satisfaction, and non-sensuality). Female partners of men with CP/CPPS differed on some aspects of sexual functioning, martial satisfaction and depression compared to partners of men without CP/CPPS (specifically pain on vaginal penetration and difficulty with penetration). In a further analyses of CP/CPPS couples, the sexual and relationship data was analyzed to predict sexual and relationship functioning in couples in whom the male has CP/CPPS [18]. Findings included the fact that pain severity significantly predicted sexual and relationship functioning among couples, however, sexual and relationship variables were the strongest predictors of patient and partner functioning over and above that of pain severity. These sexual and relationship observations must be addressed in evaluating and treating patients with CP/CPPS.

The data from these 6 important CPCRN studies support a bio-psychosocial model for QOL and CP/CPPS, suggesting that specific coping and environmental factors are significant in understanding CP/CPPS patient adjustment. The NIH has sponsored an ongoing CPCRN ancillary pilot study to develop a specific, evidence based, cognitive behavioral program for men with CP/CPPS refractory to standard medical therapy (J.C. Nickel, personal communication).

Diagnosis and Evaluation of CP/CPPS

The NIH sponsored CPCRN studies have led to significant changes in our understanding of CP/CPPS and subsequent changes in the way we diagnose and assess these patients. The development of the 9 question, self-administered NIH-CPSI [3], which has been described in a previous section, was a significant milestone in the development of assessment strategies for CP/CPPS patients. The NIH-CPSI discriminates patients with CP/CPPS [3], is responsive to change over time [4], and can be successfully used in clinical practice [5]. The NIH-CPSI has certainly simplified the initial assessment and follow-up of patients with CP/CPPS for the clinician and has proven invaluable in clinical trials. The CPCRN case control study [11] strongly suggested that history should include documentation of previous sexual activity, urethritis, cardiovascular disease, neurological disease, psychiatric conditions, and hematopoietic, lymphatic and infectious disease. A unique finding from a sub-analysis of the CPCRN CPC study showed that the pain or discomfort associated with ejaculation was one of the most important discriminatory symptoms of CP/CPPS and one of the strongest predictors of pain and quality of life severity [19]. Analysis of the baseline demographics of the CPC study indicated that leukocytes and bacteria did not correlate with severity of symptoms [9]. A CPCRN study which compared 463 men enrolled in the CPCRN CPC study and 121 age matched controls determined that while men with CP/CPPS had statistically higher leukocyte counts in all segmented urine samples in EPS (but not in semen) compared to asymptomatic control men, the control population also had a high prevalence of leukocytes [20]. The difference in the average leukocyte count of the various prostate specific specimens in men with CP/CPPS did not appear clinically significantly different than asymptomatic control men. Localization of uropathogenic bacteria in EPS, post prostatic massage urine specimens and/or semen was similar in men with CP/CPPS (8%) and asymptomatic men (8.3%). The higher

prevalence of white blood cells and positive bacterial cultures in the asymptomatic control population raises questions about the clinical uses of the standard four-glass test as a diagnostic tool in men with CP/CPPS [20].

Although the value of localizing leukocytes and bacteria to prostate specific specimens remains controversial, particularly in chronic heavily pre-treated patients, this data may help direct therapy (anti-inflammatory or anti-microbial) when obtained at first presentation or in patients with recurrent urinary tract infections. The CPCRN evaluated the simple two glass pre- and post-massage test and compared it with the Meares-Stamey four glass test to detect inflammation and bacteria in 353 men with CP/CPPS [21]. There was a strong ability for microscopic evaluation of the post-prostatic massage urine sediment to predict the inflammatory status of the EPS. In terms of bacterial culture, the pre-massage and post-massage test predicted a correct diagnosis in more than 96% of subjects [21]. Certainly in clinical practice, the pre- and post-massage test appears to be a reasonably accurate screening test to rule out uropathogen infection. Whether the leukocyte status of the lower urinary tract needs to be addressed in routine clinical practice, remains controversial.

While it is generally accepted that the PSA may be elevated in patients with category I (acute bacterial prostatitis) and category II (chronic bacterial prostatitis), the effect of CP/CPPS on PSA levels remains unclear. The CPCRN undertook an evaluation of 421 patients enrolled in the CPCRN CPC study and 112 age-matched controls to determine whether PSA (or any of its isoforms) may be used as a diagnostic marker for CP/CPPS [22]. Although PSA, free PSA, and pPSA were slightly elevated in men with CP/CPPS, the low sensitivity and specificity does not warrant using them as biomarkers for CP/CPPS. Men with elevated PSA values and CP/CPPS should be treated as one would any other patient screened for prostate cancer with an elevated PSA level [22].

Treatment of CP/CPPS

Many researchers have been concerned about the lack of standard study design or treatment trials in CP/CPPS. The International Prostatitis Collaborative Network (NIH sponsored group which included many members of the CPCRN) developed preliminary guidelines for clinical research in CP/CPPS [23]. Several years later, the CPCRN [24] described study design and rational for the first placebo-controlled, randomized clinical trial to be conducted by the CPCRN. The design of this clinical trial provided guidelines and a template for future clinical trials in CP/CPPS.

The first clinical trial undertaken by the CPCRN was to evaluate the two most common treatments employed by physicians to treat patients with CP/CPPS; anti-microbials and alpha-blockers [25]. The objective of the study was to determine whether 6 weeks therapy with ciprofloxacin or tamsulosin was more effective than placebo in improving symptoms in men with refractory, long-standing CP/CPPS. This randomized, double-blind trial with a 2 × 2 factorial design compared 6 weeks of therapy with ciprofloxacin, tamsulosin, both drugs and placebo. One hundred and ninety six men who had received substantial previous treatment, NIH CPSI score of at least 15, and a mean of 6.2 years of symptoms were enrolled. The NIH-CPSI total score decreased modestly in all treatment groups but there was no statistically significant difference in the primary outcome seen for ciprofloxacin or tamsulosin compared to placebo. The conclusion of this trial was that ciprofloxacin and tamsulosin did not substantially reduce symptoms in men with long-standing CP/CPPS who had at least moderate symptoms [25].

Results from small, randomized placebo-controlled trials published in the literature suggested that men with short duration of disease, who are alpha-blocker naïve and who are treated for longer than 6 weeks may respond better to alpha-blocker therapy than patients in the CPCRN

study described previously. The CPCRN has initiated a randomized multi-center double-blind clinical trial to evaluate the efficacy and safety of 10 mg of alfuzosin in the treatment of CP/CPPS in recently diagnosed and/or newly symptomatic alpha-blocker naïve patients [26]. The trial, which is presently enrolling patients (it is expected that the last patient will be enrolled in the study in the 2nd or 3rd quarter of 2007), will be randomizing approximately 270 patients to 12 weeks of alfuzosin or its matching placebo with the NIH-CPSI being the primary endpoint. Further objectives of this study are to characterize newly diagnosed, alpha-blocker naïve CP/CPPS patients with respect to symptom severity, to assess the incidence of depression and anxiety, domains of male sexual function and impact of patient expectations on symptom severity and response to treatment in newly diagnosed alpha-blocker naïve CP/CPPS participants.

Of major concern to members of the CPCRN is the management of patients diagnosed with CP/CPPS who have failed traditional medical therapies (for example, anti-microbials, alpha-blockers, anti-inflammatories, etc.). Based on the recently accepted premise that many cases of CP/CPPS have developed a neuropathic pelvic pain syndrome, the CPCRN has initiated a trial of oral neuro-modulatory therapy using pregabalin. Patients with treatment refractory CP/CPPS (n = 318) will be randomized to 6 weeks of escalating doses of pregabalin or placebo [27]. This trial is presently enrolling and the last patient will have entered the trial in the 4th quarter of 2007. Two very important ancillary studies, funded by the NIH are being carried out by CPCRN members, include development and evaluation of an evidence based cognitive behavioral therapy program (J. C. Nickel, personal communications) and development of a directed physical therapy program (Mary Pat Fitzgerald, personal communication) for men with CP/CPPS refractory to traditional therapy. Future therapeutic trials undertaken by the CPCRN will be built on the foundation provided by these two major multi-centre clinical trials (alfuzosin and pregabalin studies) and the 2 ancillary pilot studies (cognitive behavioral and physical therapy studies).

The CPCRN has primarily focused the dissemination of its findings to the urological community by publishing most of its research in the urology literature. But many CP/CPPS patients are first seen, evaluated and initially managed by primary care physicians. A CPCRN objective was to define the primary care physicians' practice patterns in managing patients with symptoms suggestive of CPCPPS [28]. The data suggested that many primary care physicians have limited experience in managing these patients. The CPCRN plans to target educational efforts, not only for urologists, but also for primary care physicians in its ongoing goal to improve the care of patients with CP/CPPS.

Conclusions

Research and clinical advances in our understanding of CP/CPPS has progressed more in the last decade than in the previous century. The NIH CPCRN has, undoubtedly, provided the driving force behind this remarkable resurgence of interest in this enigmatic condition. Evaluation and clinical management of patients diagnosed with CP/CPPS has improved substantially. Future aims of the CPCRN are to continue progress in unraveling the etiology, natural history, and optimal management strategies for patients with CP/CPPS.

Acknowledgments

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University, Philadelphia, PA. Dr. Anthony J. Schaeffer: Northwestern University, Chicago, IL. Dr. Daniel A. Shoskes: Cleveland Clinic, Cleveland, OH. Drs. John Kusek and Leroy Nyberg: National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

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