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Prevalence of Relative Deficiencies in Testosterone and Vitamin B12 Among Patients Referred for Chronic Orchialgia: Implications for Management

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Abstract

Chronic testicular pain (CTP) is a complex pain syndrome that is widely variable in presentation and etiology. Many cases of CTP are thought to be associated with neuropathy and recent data suggest an inflammation-mediated process is more common among patients with CTP. Deficiencies in vitamin B12 and testosterone are common in chronic pain syndromes may play a role in CTP. A retrospective review of men treated for CTP by a single provider over a 2-year period was performed. Patients with serum screening of testosterone and B12 were selected. Patients with total testosterone below 300 ng/dl, free testosterone below 46 pg/ml, or B12 below 400 pg/ml were deemed deficient and offered repletion. Efficacy of treatment was measured based on patient report with a minimum follow-up of either 3 months or resolution of pain symptoms. One hundred and fifty-four (154) men with CTP were identified, with 125 assessed for testosterone and B12 levels. Of these, 95 patients (76%) were deemed deficient. Fifty-six (56) patients elected to receive B12/testosterone replacement. In patients with sufficient follow-up, 24 patients (65%) reported significant improvement of symptoms, 6 patients (16%) reported some improvement, and 7 patients (19%) reported no improvement. The prevalence of testosterone and B12 deficiencies in this study is much higher than that reported for the general population. In addition, when chemical deficiencies were corrected, greater than 80% of patients with sufficient follow-up reported some improvement in pain. This suggests that screening of B12 and testosterone should be incorporated into the assessment of patients with CTP.

Keywords

chronic testicular pain, orchialgia, testosterone deficiency, B12 deficiency

Introduction

Chronic testicular pain (CTP) is a complex pain syndrome that is widely variable in presentation and etiology. In the literature, CTP is defined as intermittent or constant pain, either unilaterally or bilaterally, in the testicles or scrotum that lasts for greater than 3 months and is severe enough to prompt the patient to seek medical attention (Davis, Noble, Weigel, Foret, & Mebust, 1990). An acute episode of trauma, ischemia, inflammation, or infection of some parts of the male genitalia including the testicles, epididymis, prostate, urethra, and scrotum often precedes the development of CTP (Masarani & Cox, 2003). The factors that determine which men develop CTP have not been clearly identified.

Recent histologic data confirm a higher incidence of Wallerian degeneration within the spermatic cord among CTP patients undergoing microscopic denervation than in patients undergoing cord surgery for other reasons (Parekattil et al., 2013). Wallerian degeneration is an inflammation-mediated process normally seen after peripheral nerve trauma and serves to clear debris in preparation for axonal regrowth (Rotshenker, 2011). The inflammatory process is usually complete within days to weeks (Rotshenker, 2011) following an acute injury. Chronic inflammation can lead to aberrant axonal regrowth and nerve hypersensitivity (Levine, 2010).

Similar to other chronic pain syndromes, CTP is commonly associated with depressive symptoms such as low energy, easy fatigability, and depressed mood (Quallich & Arslanian-Engoren, 2013). This association has prompted the inclusion of antidepressants (e.g., nortriptyline) and neuroleptics (e.g., gabapentin) in treatment algorithms for

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Table 1. Testosterone and Vitamin B12 Deficiencies Among Men With Chronic Testicular Pain.

	Isolated testosterone deficiency	Isolated B12 deficiency	Combined B12 and testosterone deficiency	Total testosterone deficiency	Total B12 deficiency	Total
Number (% of total)	32 (25.6)	27 (21.6)	36 (28.8)	68 (54.4)	63 (50.4)	125
Age in years: mean (range)	50.3 (29-81)	42.9 (20-70)	46.7 (21-72)	48.4 (21-85)	45.0 (20-72)	45.3 (18-85)
Average total testosterone in ng/dl	270.4 (144-491)	531.0 (367-808)	275.1 (104-447)	272.9 (104-491)	383.1 (104-808)	391.8 (104-939)
Average serum B12 in pg/dl	518.5 (416-1,078)	289.4 (148-405)	275.7 (128-398)	358.6 (128-1,078)	281.3 (128-405)	389.7 (128-1,078)

CTP, with some benefit (Sinclair, Miller, & Lee, 2007). Side effects such as drowsiness, dry mouth, and weight gain are problematic and can result in noncompliance. While there is a well-documented relationship between depression and various chemical deficiencies, such as thyroid hormone, vitamin B12, vitamin D, and testosterone, the same relationship has not been explored in CTP.

Biochemical deficiencies of agents such as vitamin B12 and testosterone could explain both the aberrant persistence of Wallerian degeneration and the prevalence of depressive symptoms in patients with CTP. B12 is essential in the production of myelin, and deficiency can lead to peripheral neuropathy (McCaddon, 2013). Testosterone has been linked to improved muscle tone, increased energy (Tsujimura, 2013), and reduction of inflammation (Schooling, 2013). In addition, evidence suggests that testosterone serves as a neuroprotective agent in models of neurodegeneration involving oxidative stress, beta amyloid toxicity, and heat shock (Fargo, Foecking, Jones, & Sengelaub, 2009; Garcia-Segura & Balthazart, 2009). The local conversion of testosterone to estrogen or 5α-dihydrotestosterone within neural tissue has also been reported to have neuroprotective effects (Saldanha, Duncan, & Walters, 2009). No prior studies have evaluated the prevalence of relative deficiencies of B12 and testosterone among patients with CTP.

Method

A retrospective review of all men treated for CTP over a 2-year period by a single provider was performed. Patients having undergone serum screening tests of vitamin B12 or testosterone were identified. Patients with total testosterone below 300 ng/dl, free testosterone below 46 pg/ml (Harman et al., 2001), or B12 below 400 pg/ml (Herrmann & Obeid, 2008; Werder, 2010), were deemed deficient. All patients were evaluated for an organic basis of disease, treatment modalities received, and efficacy of treatment. Efficacy of treatment was based on patient report with a minimum follow-up of either 3 months or resolution of pain symptoms.

Results

A total of 154 men with CTP were identified. Of this group, 125 (81%) patients were screened for testosterone and B12 levels, of which 95 (76%) were considered deficient in either B12 or testosterone (Table 1). Fifty-six (45% of those with testosterone or B12 deficiencies) patients elected repletion of B12, testosterone, or both. Thirty-seven (66% of those who elected repletion) patients who received testosterone or B12 repletion met criteria for length of follow-up, and of these, 24 (65%) patients reported significant improvement of their symptoms, 6 (16%) reported some improvement, and 7 (19%) reported no improvement with 1 (3%) progressing on to microscopic denervation (Table 2).

Discussion

The prevalence of depressive symptoms (Hong, Corcoran, & Adams, 2009) and Wallerian degeneration among men with CTP suggests that an underlying biochemical deficiency may exist. In this study, the prevalence of individual deficiencies of testosterone and B12, both around 50%, are much higher in this series than that reported for the general population (Mulligan, Frick, Zuraw, Stemhagen, & McWhirter, 2006). Interestingly, when the identified deficiency was corrected, greater than 80% of patients returning for follow-up reported at least some improvement in pain.

Intramuscular injections were the primary modality for B12 supplementation. While IM supplementation was preferred in this study to avoid issues of absorption, there is a growing body of evidence that oral B12 supplementation may be sufficient for raising levels into the normal range (Bolaman et al., 2003; Kuzminski, Del Giacco, Allen, Stabler, & Lindenbaum, 1998). Anecdotally,

Table 2. Effect of Supplementation of Testosterone and/or Vitamin B12 in Men With Chronic Testicular Pain.

	Significant improvement	Some improvement	No improvement	Total
Number (% of total)	24 (64.9)	6 (16.2)	7 (18.9)	37
Age in years: mean (range)	45.2 (20-68)	52.8 (43-68)	46.0 (26-69)	46.5 (20-69)
Average pretreatment testosterone in ng/dl	324.2 (144-601)	308.4 (104-502)	348.5 (165-579)	325.9 (104-601)
Average pretreatment B12 in pg/dl	329.7 (140-512)	289.6 (170-384)	312.0 (205-385)	323.2 (140-512)

Note. Of the patients with significant improvement, nine received testosterone, nine received B12, and six received both. Of the patients with some improvement, four received testosterone, one received B12, and one received both. Of the patients with no improvement, three received testosterone, two received B12, and two received both. Testosterone and B12 values reported here represent pretreatment levels and were not statistically different between groups.

patients receiving IM supplementation of B12 often noted greater improvement in energy and depressive symptoms than patients receiving oral supplementation. For testosterone replacement, patients were allowed to choose from topical gel, biweekly injection, and pellet implant. Heterogeneity in treatment modality is admittedly associated with variability in serum levels achieved and rates of compliance.

The interaction of steroid hormones and neural tissue is complex and is an area of ongoing investigation. There is evidence that testosterone has multiple neuroprotective effects including protection against motor neuron death, prevention of dendritic atrophy, preservation of presynaptic innervation, and enhancement of axonal regeneration (Fargo et al., 2009). Testosterone is a precursor for estradiol and 5α-dihydrotestosterone, both of which have additional neuroprotective effects (Saldanha et al., 2009). Although the mechanism by which testosterone affects the neurodegeneration in CTP is unclear, the evidence supports a relationship between testosterone and maintenance of neural tissue.

There are limitations to this study beyond the retrospective design. This study was not able to account for potential issues of compliance or a placebo effect, which may be considerable when treating pain-related conditions. In addition, this study was not able to report numerical values for levels of testosterone and/or B12 above which symptom improvement may occur. Granted, there is no established guideline on how to best follow supplementation in this subset of patients. This study did not include a validated questionnaire when assessing for symptom improvement, but there is an ongoing effort to develop a validated questionnaire specific to orchialgia. One could argue that these data are limited by the patients that chose to return for follow-up. It is unclear if patients lost to follow-up were due to lack of improvement or lack of persistent symptoms. The biopsychosocial nature of chronic pain makes it difficult to determine the true efficacy of replacement therapy. It is unclear at this time whether replacement therapy is correcting an underlying pathology, or if therapy is treating depressive symptoms and alleviating the perception of pain. Another potential confounding factor relevant to patients with CTP is the effect of chronic opioid use on the hypothalamic–pituitary–testicular axis. A growing body of literature indicates that long-term opioid use depresses the production of gonadotropins and can result in opioid-induced androgen deficiency (Elliott & Fibuch, 2013; Smith & Elliott, 2012). Future prospective studies using validated assessments of pain and associated symptoms are needed to determine the overall effectiveness of B12 and testosterone replacement. Future histological studies are also needed to evaluate whether replacement therapy can treat the underlying neuropathology.

Conclusion

The treatment of CTP can be challenging and is often frustrating for both patients and physicians due to complex etiology and vague presentation. Unfortunately, no individual treatment modality has been identified to be overwhelmingly successful (Kavoussi & Costabile, 2013; Levine, 2010). In this study, a considerable subset of men presenting with CTP benefit from repletion of B12 and/or testosterone. These data suggest that screening for B12 and testosterone deficiencies should be considered when evaluating men with CTP.

Declaration of Conflicting Interests

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