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Original Article

Use of a specific questionnaire and perineal electromyography to assess neuropathic pain after radical retropubic prostatectomy

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Abstract *Objective:* Prostate cancer is the most frequent cancer in men and radical retropubic prostatectomy (RRP) is one of the first-line treatment. However, RRP has some side effects and can lead to chronic perineal pain. The objective of the study was to determine in patients suffering from perineal pain after RRP the possibility of a neurogenic damage by means of a specific questionnaire dedicated to track down neuropathic pain.
Methods: Forty patients were explored by a specific and validated questionnaire, the Neuropathic Pain Symptom Inventory (NPSI). Patients were divided into two groups: Group A with an NSPI score $\geq$4 was considered as suffering from neuropathic pain, and Group B was considered as a control group without neuropathic pain (NSPI score $<$4). All patients had a perineal electrophysiological testing to confirm the possibility of a neurogenic damage.
Results: Group A was composed by 13 men and Group B by 27 men, with mean age 72.45 years and mean duration of pain 2.7 years. In Group A, the most frequent symptoms were burning sensation, electrical shock and numbness. Location of the pain was global perineal area (8/13), anus (10/13), penis (5/13) and glans penis (2/13). Electromyography (EMG) findings confirmed the presence of denervation and neurogenic damages compared with controls ($p < 0.001$).
Conclusion: One third of the patients consulting for chronic pain following RRP had probably a neuropathic lesion leading to a chronic perineal pain as suggested by an NSPI score $\geq$ 4 and EMG alterations.

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1. Introduction

Prostate cancer is the most frequent cancer in men, with more than 240 000 patients newly diagnosed per year in the United States alone [1]. In these patients, radical retropubic prostatectomy (RRP) is the most common technique for removing the prostate gland. Morbidity related to this procedure is quite low [2], however long-lasting pain is not generally reported after RRP. Pelvic and perineal pain persisting more than 3 months after surgery has been yet described [3], with a serious impact on patient's quality of life. It could be speculated that some, or a part, the persistent pain occurring after RRP could be secondary to a neurogenic damage due to the surgical procedure. Indeed, alterations of peripheral nervous system following RRP are well known [4—7] and such neurogenic lesions (beside other consequences of neurogenic damage urinary incontinence, erectile dysfunction) can lead to neuropathic pain. The aim of the study is to determine in patients underwent RRP and suffering from perineal pain the possibility of a neurogenic damage by means of a specific questionnaire dedicated to track down neuropathic pain, and then, to confirm neurogenic damage by a perineal electromyographic (EMG) testing.

2. Patients and methods

Forty patients admitted for perineal pain following RRP for prostate cancer were enrolled in the study. Pain was at least persistent for 6 months postoperatively. They were all well informed about the project and gave their written consents to participate. We have obtained the agreement of local ethics committee (ID-RCB: 2015-A00125-44). The patients had no neurological disorders and none had been treated by radiotherapy.

All the patients were referred to the Neuro-urology Department for EMG examination to track down a neurologic cause related to their chronic pain, especially a pudendal nerve lesion. They underwent a full clinical examination. Perineal skin sensation, anal and bulbo-cavernosus reflexes, voluntary contraction and tone of the anal sphincter were examined in lithotomy position. For all patients, urinary incontinence was evaluated by a specific questionnaire (Urinary Symptom Profile, USP) and erectile dysfunction by the International Index of Erectile Function (IIEF-5). To demonstrate neurogenic changes, an EMG needle electrode was inserted in the following perineal muscles: Urethral sphincter, bulbocavernosus muscle and finally external anal sphincter. Sacral reflex (bulbocavernosus reflex) was elicited by means of stimulations of the dorsal nerve with a record of the motor potentials by means of a needle electrode inserted into the bulbocavernosus muscle. Measurements of right and left latencies were performed at the onset of the motor responses (normal latency $<$ 44 ms). Cortical evoked responses following repetitive stimulation of the pudendal nerve were recorded (normal latency $<$44 ms).

Finally, terminal motor latencies of the pudendal nerve following intrarectal stimulations were recorded at the onset of motor potential of anal sphincter (normal latency $<$3.5 ms). Lesion of peripheral nervous system was defined as neuropathic changes in EMG examination (increased rate of motor unit potentials $\geq$20/s presence of spontaneous fibrillation and/or positive sharp waves) with at least alteration of sacral latencies and/or pudendal nerve terminal motor latencies and/or cortical evoked potentials.

All the patients fulfilled a specific questionnaire, the Neuropathic Pain Symptom Inventory (NPSI). The NPSI is a validated questionnaire [8] which allows to speculate a neurogenic cause of a chronic pain in case of a total score $\geq$4 (Supplement file). This cutoff has been used to determine two groups of patients. The first group (Group A) included patients with NSPI score $\geq$4 defining patients with neuropathic pain. The second group (Group B) included patients without neuropathic pain and so, with NSPI score $<$4. All the results of EMG findings were analyzed with a Fisher test and a *p*-Value less than 0.05 was considered as significant. All statistical analyses were performed with the RStudio 1.0.136.

3. Results

The age of the 40 patients was 72.45 $\pm$ 7.45 years (mean $\pm$ SD) and the duration of the chronic pain was 2.7 $\pm$ 2.2 years (mean $\pm$ SD). They also had associated erectile dysfunction (n = 38) and urinary incontinence (n = 9). There were no statistical differences between the two groups. Thirteen patients were classified in Group A (NSPI score $\geq$4) and considered as having neuropathic pain. Twenty-seven patients were classified in Group B (NSPI score $<$4) and considered as without neuropathic pain.

The most frequent symptoms in Group A were burning sensation (10/13 *vs*. 9/27 in Group B), electrical shock (10/13), numbness (10/13) and paresthesia (10/13). Location of the pain was global perineal area (8/13), anus (10/13), penis (5/13), glans penis (2/13), and scrotum (6/13).

In Group A, EMG findings confirmed the presence of a significant denervation in perineal muscles (13/13 *vs*. 3/27 in Group B) ($p < 0.001$). Sacral latencies were delayed in 3/13 (*vs*. 2/27 in Gruop B) and pudendal nerve terminal latencies in 8/13 (*vs*. 2/27 in Group B). Cortical evoked responses were altered in 2/13 Group A and 2/27 in Group B (Table 1).

4. Discussion

This study is the first, to our knowledge, to demonstrate clinically a neurogenic cause of perineal pain following RRP. Moreover, this neurogenic lesion is confirmed by specific neurogenic alterations of EMG testing. In this study, one third of patients consulting for chronic pain following RRP had a neurogenic lesion leading to a chronic perineal pain as suggested by an NSPI score $\geq$4 and EMG alterations.

The first limit of our study is that we could not obtain the overall data on surgical technique of prostatectomy for all included patients, but the primary outcome of our study was to assess neuropathic pain and neurogenic alterations in patients who underwent a radical prostatectomy (RP) regardless of the surgical technique that has been used. Chronic pain following RRP is rarely reported [3,9—11]. Indeed, most of the studies are related to evaluation and therapeutic strategies of the

Table 1 Results of EMG testing and clinical complications on a population of 40 men who underwent RRP.

Patient characteristics	Group A (NSPI ≥4) (n = 13)	Group B (NSPI <4) (n = 27)	p-Value
EMG findings			
Delayed sacral latencies	3 (23%)	2 (7%)	0.3
Delayed pudendal nerve terminal latencies	8 (62%)	2 (7%)	<0.001
Delayed cortical evoked responses	2 (15%)	2 (7%)	0.58
Perineal muscles denervation	13 (100%)	3 (11%)	<0.001
Urinary incontinence	2 (15%)	7 (26%)	0.69
Erectile dysfunction	12 (92%)	26 (96%)	1.00

NPSI, Neuropathic Pain Symptom Inventory (a neurogenic cause of a chronic pain is speculated in case of a total score ≥4). Data are presented as n (%); RRP, Retropubic Radical Prostatectomy; EMG, Electromyography.

immediate pain occurring just after the surgery [12]. Few studies are devoted to the long-term post RRP painful syndrome [9,10]. However, this complication may seriously affect the quality of life of these patients [13]. Mirzapour et al. [14] have reported local pain after 12 months following RRP in 28% of patients and 29% after perineal RP. In the same study, 6 months after RRP or perineal RP, one third of the patients complained of their pain in sitting position. These data support firstly the hypothesis that the pain does not depend on the surgical procedures and secondly that the pain is possibly due to a neurogenic cause since it increases in sitting position suggesting a compression of the pudendal nerve against the ischial tuberosity in this position. Data on local postoperative pain after RRP are available in a systematic review conducted by Ficarra et al. [15] in 2009 reporting nine studies. Seven studies compared pain after RRP or laparoscopic radical prostatectomy (LRP) and the most used tool was a validated 10-point visual analogic scale (VAS). All these data concerned acute postoperative pain.

The NSPI has been used to evaluate the type of pain in our 40 patients and suggested a neurogenic cause to this chronic neuropathic pain, if the score was ≥4. EMG was done to assess if these patients also had neurogenic damages and to support the data found allowed by NSPI questionnaire. In 2012 Yiou et al. [16] assessed the penile cold and vibratory sensory thresholds to reflect the cavernous nerve damage after RP and found that some surgical techniques had better results. Indeed, penile sensory threshold for warm and cold sensation increased after Non-Nerve Sparing Radical Prosatectomy (NNSRP) but not after Nerve Sparing Radical Prostatectomy (NSRP). Vibratory threshold only increased after transperineal NNSRP. With the same neurophysiological evaluation, Lefaucheur et al. [17] in 2000 demonstrated that the warm, cold and vibratory threshold was significantly increased after trans urethral resection of the prostate (TURP) and supported the hypothesis of neurogenic damage (penile small nerve fiber) as the primary cause of post operative erectile dysfunction. Thus, all these studies support the hypothesis of a neurogenic damage following RRP. Since then, it can be speculated that these neurogenic lesions can lead not only to urinary incontinence and/or impotence, but also to a neuropathic pain since acute or chronic nerve lesions can determine chronic neurogenic pain syndrome.

Nevertheless, even if changes and neurologic damages could be part of the explanations of a neuropathic pain, other causes could be discussed.

Gerbershagen et al. [10] in 2009 have evaluated the preoperative pain status and its influence on the occurrence of chronic post-surgical pain (CPSP). Mental and physical health regarding CPSP development were analyzed. From 72 patients evaluated after RP, 12 had CPSP and all the patients suffered from preoperative pain (p = 0,003). In this study only one patient suffered from chronic pain at the 6 months follow-up. A systematic review conducted in 2015 by Boogaard et al. [18] assessed pain and tried to find predictive factors. The main factors leading to post-surgical pain were psychological distress, pain at Day 2 (VAS >3) or a higher body mass index. In 2012, the European Association of Urology [19] proposed guidelines on prostate cancer pain management. Pain can be precisely caused by the cancer (77%) or by cancer treatment (19%). Furthermore, the overall incidence of chronic pain in prostate cancer patients was found about 30%—50% [19].

Another key point is the clinical evaluation of cancer pain. VAS usually used to quantify chronic pain is not only inadequate in term of diagnosis, but also imperfect for a complete evaluation since pains that impact the psychological, mental and physical health status are not strictly taken into account with this tool. The use of a specific questionnaire as the McGill Pain Questionnaire [20,21] seems to be better to evaluate such chronic pain. Furthermore, the interest of a specific questionnaire as the NPSI [8] is major, since it can give strong arguments for a neurogenic pain. It characterizes with great accuracy the neurogenic etiology using specific words as "burning" or "electrical shock" or "numbness", all words largely reported by patients suffering from neuropathic pain [22]. The knowledge of such an etiology, *e.g.* neuropathic pain, is important in terms of therapeutic strategies [12].

5. Conclusion

A neurogenic cause of perineal pain following RRP is possible. This can be clinically confirmed by using a specific questionnaire like NSPI and eventually by perineal EMG. The knowledge of such an etiology can be taken into account in adjusting the therapeutic strategies.

6. Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Author contributions

Study concept and design: Nicolas Turmel, Gérard Amarenco.
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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajur.2018.06.004.

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