Trifecta Nerve Complex: Potential Anatomical Basis for Microsurgical Denervation of the Spermatic Cord for Chronic Orchialgia

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Purpose: We identified structural abnormalities in the spermatic cord nerves that may explain how microsurgical denervation of the spermatic cord provides pain relief in patients with chronic orchialgia.

Materials and Methods: We retrospectively reviewed a prospective database to compare spermatic cord biopsy specimens from 56 men treated with a total of 57 procedures for microsurgical denervation of the spermatic cord for chronic orchialgia vs a control group of men without pain treated with cord surgery, including varicocelectomy in 4 and radical orchiectomy in 6. Tissue biopsies were obtained from mapped regions of the spermatic cord in all cases. Biopsies stained with hematoxylin and eosin were examined by an independent pathologist. Three human cadaveric spermatic cords were dissected to confirm localization of the nerve distribution identified on pathological mapping.

Results: We identified a median of 25 small diameter (less than 1 mm) nerve fibers in the spermatic cord. Of the 57 procedures for orchialgia 48 (84%) showed wallerian degeneration in 1 or more of these nerves but only 2 of 10 controls (20%) had such degeneration ($p = 0.0008$). In decreasing order of nerve density the 3 primary sites (trifecta nerve complex) of these changes were the cremasteric muscle fibers (19 nerves per patient), perivasal tissues and vasal sheath (9 nerves per patient), and posterior cord lipomatous/perivessel tissues (3 nerves per patient). Cord nerve distribution mapped by the biopsies was confirmed by cadaveric dissection.

Conclusions: In men with chronic orchialgia there appears to be wallerian degeneration in reproducible patterns in the spermatic cord nerve fibers. Transection of these nerves may explain the effect of the denervation procedure.

Key Words: testis, chronic pain, nerve degeneration, spermatic cord, biopsy

Abbreviations and Acronyms

CO = chronic orchialgia

MDSC = spermatic cord microsurgical denervation

WD = wallerian degeneration

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CHRONIC orchialgia is defined as intermittent or constant unilateral or bilateral testicular pain more than 3 months in duration.[1,2] Although the etiology is frequently idiopathic, it is linked to possible nerve irritation or injury after inguinal hernia repair, scrotal surgery, vasectomy, varicocele or trauma.[3–12] CO is not common but it is estimated to affect up to 100,000 men per year due to the mentioned etiologies, including 6% to 12% after vasectomy, up to 18% after inguinal hernia repair, up to 5% after scrotal surgery and up to 1% to 2% after abdominal or groin surgery.[3–14] Not all of these men may require treatment. However, in many patients the pain can be relentless and create a significant impact on quality of life. This

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condition is frustrating and difficult to deal with, not only for the patient but also for the treating physician since there is a paucity of literature on the pathophysiology of this kind of pain.

Treatment options include conservative medical measures, such as nonsteroidal anti-inflammatory drugs, antibiotics, antidepressants and anticonvulsants. If they fail, surgery may be done, including nerve block, epididymectomy, varicocelectomy in varicocele cases, vasectomy reversal for post-vasectomy pain, orchiectomy and MDSC.[2–12,15] Epididymectomy and orchiectomy may be suboptimal due to a variable pain relief success rate and the risk of phantom pain, while it can have lifelong physiological and psychological impacts.[2]

MDSC is a minimally invasive option for CO with a published success rate of more than 70% for durable pain relief and 20% for partial pain relief on long-term followup.[16] An attractive advantage of this procedure is the ability to spare the testicle and epididymis while potentially alleviating pain.

Altered or hyperactivated nerve sensation in and around the spermatic cord is considered a major factor in the CO mechanism. MDSC is postulated to alleviate pain by ablating these altered or hypersensitive afferent nerve pathways in the cremasteric musculature, perivasal fascia, peri-arterial tissue and surrounding pericord lipomatous tissues.[17,18] However, definitive evidence is lacking of these abnormal nerves and the rationale for the postulated nerve distribution.[19] We sought to provide anatomical and pathological mapping of nerve fibers in and around the spermatic cord, and improve our understanding of how the MDSC technique may provide pain relief in men with CO.

Afferent innervation of the scrotum originates via somatic nerves in the genital branch of the genitofemoral nerve, ilioinguinal nerves and autonomic branches from T10-L1 parasympathetic ganglia.[20] These 2 nerves provide anterior scrotal wall and thigh innervation, while the perineal branch of the pudendal nerve innervates the posterior scrotum. Rauchenwald et al also noted an alternative autonomic pathway between the pelvic plexus and testis via the vas deferens, which explains the chronic scrotal pain response of local anesthesia injection to the pelvic ganglia.[21] Hyperactivity or hypersensitivity in any of these nerves could be a cause of CO.

A potential cause of this hypersensitivity could be WD in these peripheral nerves. WD is characterized as an autodestructive change in the proximal and distal nerve axon that produces an environment clear of inhibitory debris, and supportive of axon regrowth and functional recovery. Also, an immune cell response initiated by neutrophils, and cytokines and macrophages are subsequently activated.[22–25] It was hypothesized that WD leads to an inflammatory environment and nerve hypersensitivity. WD could be initiated in these nerves after some type of trauma to the nerve. However, the exact mechanism of WD activation remains unclear in cases in which no direct trauma is evident.

MATERIALS AND METHODS

This study was approved by the University of Florida institutional review board as part of an ongoing, prospective outcome database of men with CO treated at our facility. We retrospectively reviewed the results of spermatic cord biopsy routinely performed in men undergoing MDSC, subinguinal microsurgical varicocelectomy or radical orchiectomy (for tumor) between May 2009 and January 2010. Men with CO (MDSC group) were the test group and men without CO (varicocelectomy and radical orchiectomy groups) served as the control.

Spermatic cord biopsies were obtained in mapped fashion in 56 patients with CO at a total of 57 MDSC procedures (fig. 1). Similar sampling was done in 10 controls without CO undergoing elective inguinal/cord surgery for other reasons, such as varicocele or testicular tumor. All procedures were performed by a single fellowship trained microsurgeon, as previously described.[26] A single pathologist blinded to patient medical history reviewed all specimens.

Using basic hematoxylin and eosin staining, specimens where examined for the number of nerve fibers at each location, nerve size and any evidence of a pathological condition such as WD. Based on these mapped biopsies, the nerve distribution in the cord was analyzed and compared in the 56 patients with denervation and CO, and the 10 controls without CO.

After the nerve distribution in the spermatic cord was identified based on the described pathological study, spermatic cord anatomical dissections were subsequently performed in 3 human cadavers to confirm the localization of the previously identified nerve distribution.

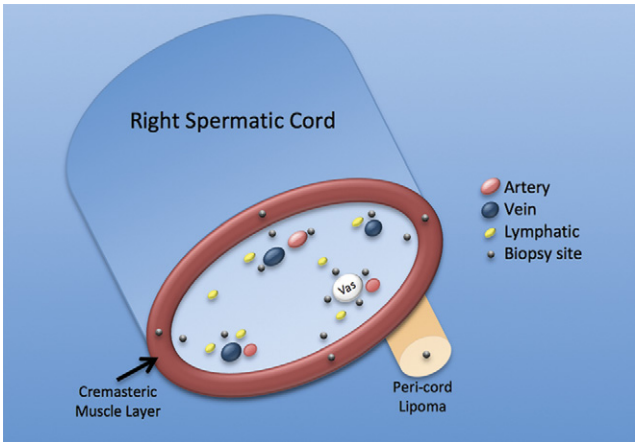

Figure 1. Sites of spermatic cord mapped biopsies

Table 1. *Demographics of patients in CO denervation and control groups*

CO denervation		
Median age (range)	44 (16–70)	
No. procedure side (%):		
Lt	31	(54)
Rt	26	(46)
No. etiology (%):		
Idiopathic	29	(51)
Inguinal hernia repair	13	(23)
Vasectomy	5	(9)
Sports injury or trauma	5	(9)
Varicocele	4	(7)
Bilat nephrectomy for polycystic kidney disease	1	(1)
Control		
Median age (range)	41 (25–78)	
Procedure type (%):		
Varicocelectomy	4	(40)
Radical Orchiectomy	6	(60)
No. procedure side (%):		
Lt	8	(80)
Rt	2	(20)

RESULTS

Median patient age was similar in the CO group and controls (44, range 16 to 70 and 41 years, range 25 to 78, respectively). MDSC was performed in 56 patients for a total of 57 targeted cord denervations, including on the left side in 30 patients, on the right side in 25 and bilaterally in 1. Controls included 4 patients undergoing varicocelectomy and 6 undergoing radical orchiectomy for testicular masses.

Table 1 lists CO patient demographics and etiology. All patients with CO had a pain duration of least 3 months. Of the 56 patients 45 (80%) achieved transient pain relief response to a prior spermatic cord block at our center or as done by the referring physician before MDSC. The remaining 11 patients (20%) elected no prior block (6) or had had no response to a prior block (5). These men had pain only in the testicle and/or groin area. We used a pain classification system to characterize pain distribution in each patient (fig. 2). All patients with CO had a type 1 to 4 pain distribution. They had no pain in other areas, such as the prostate or perineal region.

Table 2 shows nerve density and WD results of the mapped spermatic cord biopsies in the CO group. On pathological analysis we noted a median of 25 reproducible, 0.5 mm diameter nerve fibers per patient (range 11 to 56) in the spermatic cord. Of the 56 patients with CO 48 (84%) had WD in at least 1 or more of these nerves but only 2 of the 10 controls (20%) had WD ($p = 0.0008$). There were 3 primary locations (trifecta nerve complex) for significant WD in the CO group (fig. 3). In decreasing order of nerve density they were 1) cremasteric muscle fibers (mean 19.1 nerves per patient with 33% to 67% WD), 2) perivasal tissues and vasal sheath (mean 9.4 nerves per patient with 63% WD) and 3) posterior peri-arterial/lipomatous tissue (mean 3.3 nerves per patient with 35% WD). Another area of interest was the pericord (extra-cord) sheath and veins with a mean of 2.4 nerves per patient with 23% WD. Figure 4 shows a biopsy in which hematoxylin and eosin staining revealed a normal nerve in the control group, in

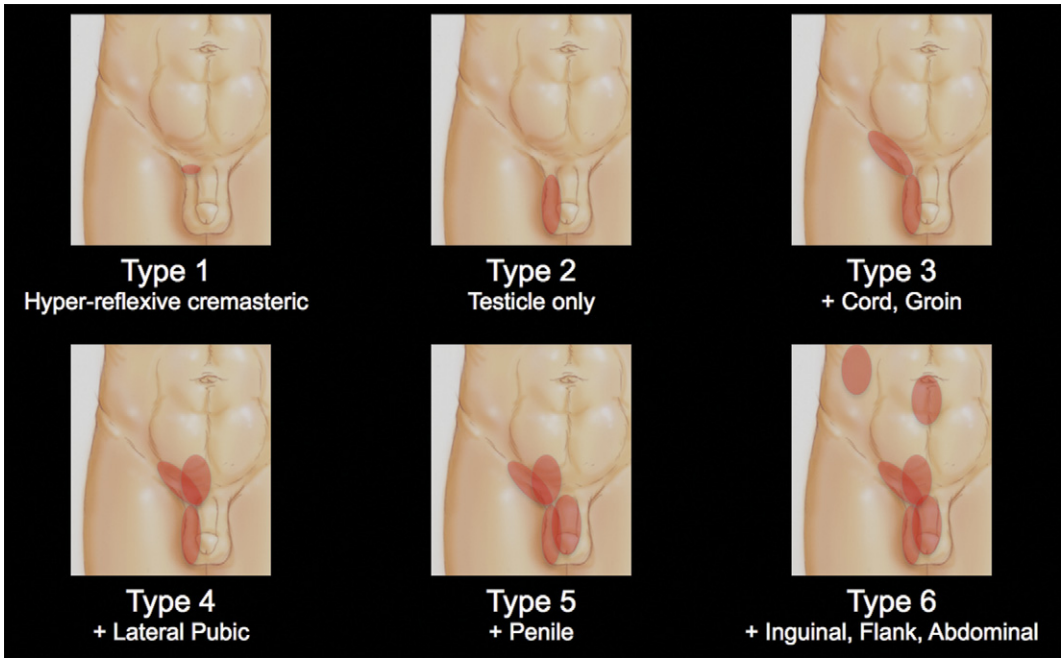

Figure 2. Pain distribution classification system for patients with chronic testicular and/or groin pain

Table 2. *Nerve distribution and mapped spermatic cord biopsy findings in CO denervation group*

Spermatic Cord Biopsy Site	Nerves (Range)		Overall % WD
	Overall No.	Diameter (mm)	
Pericord:			
Medial lipoma	0 (0–10)	0.5	0
Extra-cord sheath + veins	1.5 (0–9)	0.5	23
Anterior intraspermatic cord perivenous tissue	0 (0–1)	0.5	0
Cremasteric muscle:			
Anterior	1.5 (0–8)	0.5	54
Medial	5 (0–15)	0.5	33
Lateral	3.5 (0–17)	0.5	48
Posterior	5 (0–12)	0.5	67
Medial tissue:			
Spermatic cord/ perivascular	0 (0–6)	0.5	0
Perivenous	0 (0–4)	0.5	7
Perivasal (vas deferens) tissue	9.4 (1–20)	0.5	63
Residual vas deferens after denervation*	0 (0–3)	0.5	0
Central peri-arterial + perivenous tissue	0 (0–10)	0.5	7
Testicular artery†	0		0
Lateral tissue:			
Perivascular	0 (0–2)	0.5	0
Perivenous	1 (0–4)	0.5	9
Posterior tissue:			
Perivascular	2 (0–2)	0.5	0
Perivenous	1 (0–5)	0.5	13
Peri-arterial/lipomatous	3 (0–12)	0.5	35

* Short segment removed in initial 6 patients.
† In 1 patient intraoperative testicular artery injury was successfully repaired/reconstructed intraoperatively with short injured segment removed to perform anastomosis.

contrast to a biopsy from a similar area with a WD nerve in the CO group.

We identified a complex network or distribution of nerves 0.5 mm in diameter using the described mapped biopsy scheme (trifecta nerve complex). To further reassess this nerve distribution, 3 cadaveric

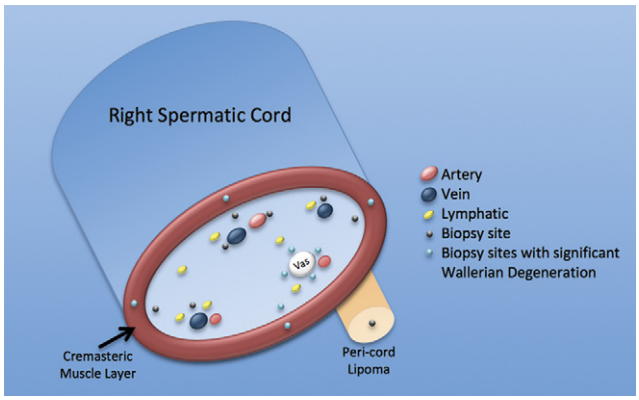

Figure 3. Mapped biopsy scheme shows significant WD sites

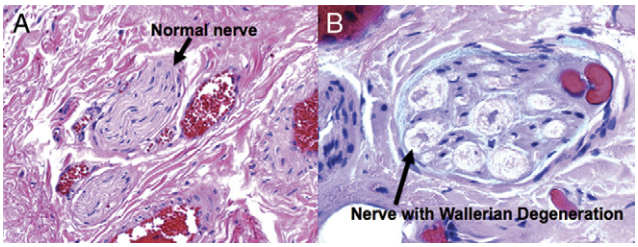

Figure 4. Pathological staining of biopsies reveals normal control nerve (*A*) and nerve from similar site with WD from patient with CO (*B*). H & E, reduced from ×20 (*A*) and ×40 (*B*).

spermatic cord dissections were done, which confirmed the presence and localization of the described nerve plexus (fig. 5).

DISCUSSION

We identified a statistically significant difference in the prevalence of WD in the spermatic cord nerves in men with CO compared to controls. Interestingly, the WD distribution was heavily focused in 3 main areas, including the cremasteric muscle layer (the posterior part was the area with greatest WD), perivasal tissues and posterior peri-arterial/lipomatous tissues. Nerve ligation in these areas during MDSC may explain the success of the procedure in eliminating pain in these men. It suggests that perhaps more targeted ligation or denervation of only these areas may provide sufficient pain relief. It also implies that perhaps we should give particular attention or care to these areas during elective procedures, such as vasectomy and inguinal hernia repair, to ensure that we avoid any unnecessary irritation or trauma to these nerves and minimize the risk of future pain in the groin/testicle.

Knowledge of this nerve distribution may also allow us to perform more effective nerve cord blocks in patients with CO in whom medical treatment fails. If patients have a partial or complete response to the cord block, they may then be candidates for targeted microsurgical denervation.

MDSC was first described in 1978 by Devine and Schellhammer.[16] Outcomes appear to be improving in terms of decreasing pain scores and durable response rates when done by others.[17,27] Heidenreich et al achieved a 96% success rate in 35 CO cases at a mean followup of 31.5 months.[28] Strom and Levine reported 71% complete durable relief and 17% partial relief in 95 testicular units at a mean 20.3-month followup.[17] Oliveira et al achieved 70% complete and 20% partial relief in 60 CO cases during a 2-year followup.[27] We recently reported an 85% rate (123 of 151 cases) of

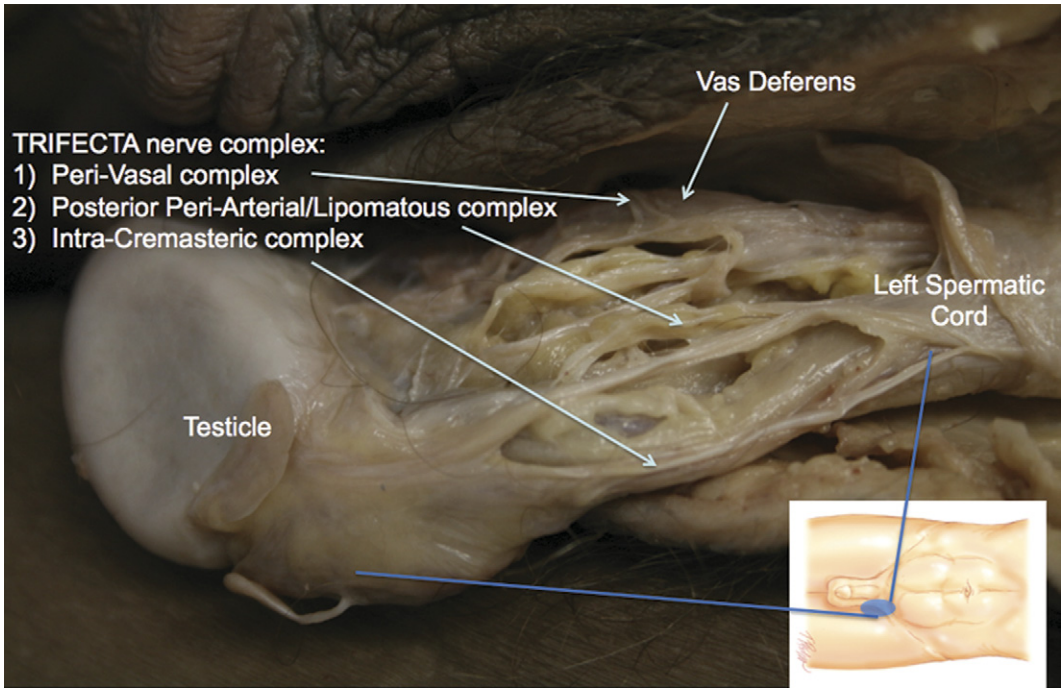

Figure 5. Cadaveric dissection of left spermatic cord confirmed trifecta nerve plexus identified in mapped spermatic cord biopsies

significantly decreased pain, defined as greater than 50% pain reduction, 6 months postoperatively using the externally validated PIQ-6 (Pain Impact Questionnaire) pain impact score.[26] These findings establish MDSC as a promising treatment for CO. Interestingly, we use a less aggressive targeted MDSC technique that focuses on only the 3 primary WD areas mentioned (trifecta nerve complex). We achieve results similar to those in previously published studies using the more aggressive, complete MDSC technique.

A limitation of these MDSC techniques is that we cannot easily visualize all of these small nerve fibers in real time during the procedure. As our technology improves, more accurate visualization of these specific nerve fibers would help create even more targeted, less aggressive versions of MDSC. To this effect, Ramasamy et al identified and ablated nerves in vivo in a rat model using multiphoton microscopy.[29] They identified 10 nerve fiber bundles per spermatic cord in the rat model and focally ablated these nerves by increasing the intensity of laser light and generating a cavitation bubble. There is potential for the future use of this technology to visualize individual nerve fibers and selectively perform real-time ablation in patients with CO.

To our knowledge this study provides the first glimpse of a possible mechanism of the hyperactivity of the peripheral nerves of the spermatic cord in patients with CO. It suggests that WD may have a role in CO.

Although we found an association with WD in these patients with CO, our report does not provide proof of a definite causal relationship, which was beyond the scope of this study. This inference is based on prior studies in the neurology literature linking WD to chronic pain in other peripheral nerves.[24–26] Our series had a small sample size. However, to our knowledge we are the first to seek to identify any association of structural nerve changes in men with CO vs a control group.

CONCLUSIONS

There is a reproducible, distinct anatomical distribution of nerves in the spermatic cord. There appears to be a unique pattern of WD in these nerves. Further future targeting of these specific abnormal nerves may enhance the efficacy of microsurgical cord denervation in patients with CO. This trifecta complex may also provide targeted therapeutic options apart from surgery in the future.

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