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The “UW-LPHS Test”: A New Test to Predict the Outcome of Renal Autotransplant for Loin Pain Hematuria Syndrome

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Abstract

Objectives: The objectives of this pilot study were twofold. First, we aimed to elicit whether the “UW-LPHS test” definitively localizes pain from patients’ loin pain hematuria syndrome to the ureter and thus proves our hypothesis. Second, we aimed to understand whether a positive UW-LPHS test predicts a successful outcome after renal autotransplant.

Materials and Methods: The UW-LPHS test is described in detail in this manuscript. Briefly, 0.5% bupivacaine is injected into the ureter of the affected side and kept there using a balloon catheter for 5 minutes.

Results: All six patients studied had complete pain relief at a mean follow-up of 9.2 months after renal autotransplant. All patients were successfully weaned from opioids and have returned to a normal lifestyle.

Conclusions: The UW-LPHS test can be used to predict renal autotransplant outcomes and should be applied to all patients who are being considered for this operation.

Keywords

Groin pain; Kidney stones; Ureter; Ureteral bupivacaine infusion

Introduction

Loin pain hematuria syndrome (LPHS) is a rare disease with a low estimated prevalence of 0.012%.¹ The most prominent and characteristic features include severe persistent or intermittent unilateral or bilateral deep pain in the flank that radiates to the groin. In about 80% of patients, some degree of hematuria is present. Loin pain hematuria syndrome was first described by Little and associates in 1967.² Since then, about 500 cases have been reported in the literature, but it is not clear whether these cases have included patients with a diagnosis of kidney stones and/ or Nutcracker syndrome (NCS). A cluster of 100 cases was reported from the state of Ohio in the United States, suggesting environmental factors.³ A summary of the clinical manifestations of LPHS is shown in Table 1.⁴

Loin pain hematuria syndrome was first described in women in 1967, followed by the first report in men in 1981.^{2,5} Initially, LPHS did not include patients with kidney stones and NCS but focused on patients who did not demonstrate any physical findings. In a multitude of studies, and thus not infrequently, patients with LPHS have been often labeled as drug seeking or displaying a somatoform pain disorder. In our own experience, the number of physicians who believe the syndrome does not exist remains substantial. Based on our clinical observations, we suggest differentiating between type 1 and type 2 syndromes. Type 1 LPHS results from readily identifiable causes such as frequent kidney stones, polycystic kidney disease, recurrent renal papillary necrosis with ureteral obstruction, recurrent renal thromboembolism, renal artery dissection, or NCS. In our patient population, we estimate that NCS causes the syndrome in 40% of patients, nephrolithiasis in 30%, and by the other above-named causes in 20%. In 10% of patients where an extensive diagnostic work-up does not identify any potential cause, we term the syndrome as type 2 LPHS. The possible pathophysiology of type 2 LPHS has been described in detail by Taba Taba Vakili and associates.^{4,6} The puzzling aspect of LPHS, regardless of the cause, is the fact that the pain pattern is identical. Nevertheless, the origin of the pain has remained a matter of discussion, and, in many cases of type 2 LPHS, patients have been left to rely on pain medication or undergo a variety of procedures with the hope of finding pain relief (Table 2).

With the exception of renal autotransplant, no other procedure has provided long-term reliable pain relief. However, there are reports of good success rates with left renal vein transposition in cases where NCS is the cause of LPHS.⁷ To find a reliable therapeutic method, it was essential to understand the underlying cause for what has been described as “possibly the worst pain known in medicine.” The first clue for our current understanding of the disease came from a case report describing a male patient with the classical symptoms of LPHS. The patient was treated with tadalafil (Cialis, Lilly USA, Indianapolis, IN, USA), which is known to relax the smooth muscle cells of the urogenital tract.⁸ The patient’s pain score improved dramatically, which led us to the hypothesis that, regardless of the cause of LPHS, the ureter is the final target organ. To prove our hypothesis, we developed the “UW-LPHS test.” Here, we describe the diagnostic procedures of LPHS in 6 patients who underwent the UW-LPHS test followed by renal autotransplant.

Materials and Methods

Only patients who had no prior procedure(s) at our institution were selected. All patients had previously undergone an extensive work-up at various major medical centers. A careful history of pain management was taken, and, for the sake of documentation, pain medications used in the month before renal autotransplant were documented in great detail. Use of pain medications at 3 months posttransplant was monitored by personal calls to the patients and/or their physicians. In addition, the extent and type of physical activities and lifestyle were recorded pretransplant and at 3 months posttransplant (Table 3).

In an attempt to identify patients who would benefit from renal autotransplant, we performed ureteral bupivacaine infusion (identified here as the “UW-LPHS test”).⁹ Most patients are hypersensitive; hence, the infusion is usually performed under deep sedation or, if not tolerated, under general endotracheal anesthesia. Cystoscopy is performed using a 16F

flexible (preferably) or 21F rigid cystoscope, and the bladder is carefully evaluated to rule out anatomic abnormalities, stones, tumors, or features suggestive of interstitial cystitis, which can on occasion mimic symptoms of LPHS. After that, the ureteral orifice of the painful side is cannulated with a balloon-tipped catheter (5.5F dual-lumen Fogarty), and a retrograde ureterogram using 5 cm³ of contrast is performed to assess the anatomy. The catheter is then advanced to the kidney and bupivacaine is instilled, the catheter is pulled back to the ureterovesical junction, and the balloon is inflated to prevent efflux of the bupivacaine. A total of 15 to 30 mL of 0.5% bupivacaine is instilled into the kidney and ureter. The bupivacaine is kept in the ureter for 5 minutes, after which the balloon is deflated and the catheter and cystoscope are withdrawn. The patients are not given any further analgesics or relaxants. Patients are evaluated before discharge from the hospital, which is followed by a phone interview on the same evening. On the day after the procedure, the patient is seen in the clinic, and a detailed history is taken of events since administration of the UW-LPHS test.

Once it has been determined that the patient would benefit from renal autotransplant because of a positive UW-LPHS test, the patient is scheduled for surgery. Autotransplant and nephrectomy are performed via a midline incision. The kidney on the affected side is removed, leaving renal vessels as long as possible. After the nephrectomy, the remaining distal ureter is completely removed to the level of the bladder. The kidney is cooled with University of Wisconsin solution (Belzer solution, Viaspan, Bridge to Life, Columbia, SC, USA), and the vessels are prepared for transplant. The implant is performed on the right side in a standard fashion. The ureteroneocystostomy is performed over a double J stent (Bard Medical, Covington, GA, USA).

Results

Six patients who were previously diagnosed with LPHS underwent the UW-LPHS test as described above. Each of these patients reported vast improvement in their pain after bupivacaine infusion and were subsequently scheduled for renal autotransplant. All patients reported a significant improvement in their pain 3 months postoperatively. Patient characteristics, narcotic usage, and postoperative complications are listed in Table 3.

Patient 231

Patient 231 is a 37-year-old white female with a 19-year history of LPHS. Her past medical history included multiple ectopic pregnancies, including a splenic rupture caused by an ectopic focus. She consulted several specialists, including a urologist who suggested total cystectomy as treatment. The patient underwent the UW-LPHS test at our institution and reported being completely pain free for approximately 24 hours, a first for her in 19 years. Prior to surgery, her pain medication regimen included oxycodone/acetaminophen 10/650 mg (oral dose every 4 hours or as needed) and oxycodone HCl up to 10 mg every 6 hours. The patient was fully employed before surgery but had applied for disability due to her chronic pain. One-year posttransplant, she does not take any pain medications, describes herself as pain free, and is fully employed. She considers the renal autotransplant to be “absolutely life-saving and life-changing.”

Patient 402

Patient 402 is a 28-year-old white female with LPHS diagnosed in high school. Her surgical history includes superior mesenteric artery transposition and cholecystectomy. After the UW-LPHS test, she stated that she was pain free for 10 to 12 hours. She was unable to work before renal autotransplant. Pain medications prior to surgery included oxycodone 30 mg (oral dose every 3 hours or as needed for pain) and oxycodone HCl 30 mg twice daily. At 4 months posttransplant, she has been completely weaned off oxycodone. She remains pain free and does not take pain medication. She is planning to get married.

Patient 379

Patient 379 is a 47-year-old white female who first experienced loin pain 2 years prior to presentation. She has a past medical history significant for ovarian cysts and was previously diagnosed with NCS at another facility. She underwent removal of her ovarian cysts; however, her groin pain persisted and resulted in her seeking a second opinion at our institution. Before renal autotransplant, she was taking oxycodone and tramadol for pain control. After the UW-LPHS test, the patient reported being completely pain free for several hours. She underwent autotransplant and has remained pain free postoperatively without the need for additional narcotics. The patient was able to downhill ski 3 months posttransplant.

Patient 412

Patient 412 is a 24-year-old female who had 7 months of loin pain before diagnosis. Her past medical history was significant for superior mesenteric artery syndrome for which she underwent open superior mesenteric artery decompression with a subsequent exploratory laparotomy with adhesiolysis for a small bowel obstruction. She also underwent laparoscopic median arcuate ligament release. She experienced some pain relief with the UW-LPHS test and then underwent renal autotransplant. She stopped pain medications 4 weeks after surgery and is now a fulltime student.

Patient 501

Patient 501 is a 28-year-old white female who was diagnosed with LPHS after 3 years of pain. Before the renal autotransplant procedure, she was on multiple narcotics and was also referred to a pain specialist who placed a spinal cord stimulator. Her pain did not improve with the spinal cord stimulator, and it was ultimately removed due to ongoing severe pain at the site of insertion. She was primarily bed-ridden due to her chronic pain and had run out of disability coverage, which forced her to move back in with her parents. She was pain free for 48 hours after the UW-LPHS test and subsequently underwent renal autotransplant. At her last postoperative follow-up, she was completely off narcotics and remained pain free. She takes no pain medications and is fully employed.

Patient 172

Patient 172 is a 35-year-old white female who had loin pain for 7 years prior to presentation. She has a past medical history significant for endometriosis and pelvic congestion syndrome for which she underwent sclerotherapy with embolization; however, her pain remained unchanged after this procedure. She underwent renal autotransplant with subsequent

resolution of her pain. Before the autotransplant procedure, she was working 40 hours a week. After autotransplant, she continued in her job and added 15 hours a week working as a bartender. She continues to take aspirin 81 mg per day.

Discussion

The pivotal issue in LPHS is the origin of the pain. Loin pain is described as burning or throbbing, localized at the costovertebral angles, and made worse by a gentle punch or even slight bumps such as when riding in a car. The pain may radiate to the abdomen, inguinal area, or medial thigh. Pain is mostly unilateral but can be bilateral either from the beginning or become bilateral over time. The pain score ranges between 5 and 10 (out of 10) in many patients and often ultimately results in the prescription of opioids, which we have observed in more than 70% of our patients. Additionally, LPHS can be associated with nausea, and many patients complain of postural hypotension. Considering the ill-defined nature of the pain, the crucial consideration for the diagnosis and treatment of LPHS is to identify the origin of the pain. Our first clue came from a 2015 publication by Russell and colleagues,⁸ which described a male patient who presented with typical symptoms of LPHS. This patient was treated with tadalafil 5 mg/day, which reduced his pain score by several points. With the understanding that tadalafil relaxes the smooth muscles of the urogenital system, we concluded that the ureter is the most likely target organ. In our program, we routinely place patients on a short course of tadalafil as a diagnostic maneuver. We estimate that 50% to 60% of patients respond with a reduction in pain score, which can last several days or weeks. Two of our patients have opted to use tadalafil as maintenance therapy and have forgone further treatment.

With the hypothesis that the ureter is the target organ, we developed the UW-LPHS test as described above. With the exception of 2 patients, the test resulted in total pain relief. One patient with a negative test was later diagnosed with severe interstitial cystitis, features of which were impressive during cystoscopy, and the second patient was diagnosed with pudendal neuralgia. Therefore, we believe that the UW-LPHS test is helpful, not only in identifying patients who are good candidates for renal autotransplant but also to guide us away from renal autotransplant in patients who would not benefit. The UW-LPHS test indicates that the pain experienced in LPHS results most likely from continued or intermittent spasms of the ureter, which also explains why the pain is similar to a renal stone colic. This explanation is consistent with a relatively high success rate reported for renal autotransplant compared with other treatment methods. The first patient described by Aber and associates in 1982 had long-term pain relief.¹⁰ In 1985 and 1987, Sheil and colleagues reported a study with 3 patients and later a study with 9 patients in which all patients had excellent outcomes.^{11,12} Three patients later required renal autotransplant on the contralateral side of a previously asymptomatic kidney. After this initial success, the first report of a failure came from Hutchinson and associates, with the patient reporting recurrent pain after renal autotransplant, which was followed by a report of bilateral occurrence that required nephrectomy and hemodialysis.^{13,14}

Burke and Chin presented a series of 48 renal autotransplant procedures in which an initial success rate of 70% of patients becoming pain free was reported.^{15,16} In their series, 3

autotransplanted kidneys had to be removed because of persistent pain. In contrast, a few smaller centers have reported pain recurrence of up to 70% (Table 4).^{17,18} This difference could be attributed to the fact that statistically it is difficult to evaluate smaller patient sample sizes; however, one could also argue that they did not have the experience for proper patient selection.

In our view, the UW-LPHS test is a simple and valuable diagnostic tool for patients with suspected LPHS and can be employed at smaller centers with limited experience in evaluating or treating LPHS patients. Based on our findings, a positive UW-LPHS test predicts a successful outcome after renal autotransplant.

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Table 1.

Clinical Manifestations of Loin Pain Hematuria Syndrome

Hematuria	•Hematuria can be microscopic, but most LPHS patients have experienced at least 1 episode of gross hematuria
Kidney function	•In the majority of patients, kidney function is normal
Loin pain	•Loin pain is described as burning or throbbing,localized at the costovertebral angles, and made worse by a gentle punch •Pain may radiate to the abdomen, inguinal area or medial thigh •Pain may be unilateral or, less often, bilateral, although the majority of LPHS patients eventually develop bilateral pain •The onset of pain often is associated with nausea and vomiting, and patient may be unable to manage pain with oral opioids ^{6,19}

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Table 2.

Treatments for Loin Pain Hematuria Syndrome

Intervention
1. Implantable intrathecal pump-implantable drug delivery systems (IDDS)
2. Ureteric bupivacaine infusion
3. Pulsed radiofrequency
4. Celiac plexus block
5. Retrograde capsaicin infusion
6. Percutaneous renal nerve sympathetic ablation
7. Kidney auto-transplantation (AT)
8. Surgical renal denervation; renal neurectomy
9. Sodium thiosulfate infusion

Summary of Patients Undergoing Renal Autotransplantation for Loin Pain Hematuria Syndrome

Table 3.

Patient Number	Age at Autotransplant	Pain Duration Pretransplant	Pain Medication				Current	Posttransplant Complications	Return to Work?
			1 month Pretransplant	3 months Posttransplant					
231	37 y	19 y	- Oxycodone/acetaminophen 10/650 mg every 4 h or as needed - Oxycodone HCl up to 10 mg every 6 h	Acetaminophen 1 g every 4 h, tapering narcotics			None	Urinary tract infection	Yes
402	28 y	12 y	- Oxycodone 30 mg every 3 h or as needed - Oxycodone HCl 30 mg twice daily	Minimal narcotic usage			None	None	Preparing to get married
379	47 y	2y	- Oxycodone 5 mg every 6 h or as needed - Tramadol 50 mg every 6 h or as needed	None			Ibuprofen	None	Working in real estate
412	24 y	7 mo	- Tylenol (does not tolerate narcotics)	Ibuprofen			None	Readmission,pain	Student
501	28 y	6 y	- Tylenol	None			None	None	Full time
172	35 y	A	- Ibuprofen	Tylenol, ibuprofen			None	None	Two jobs

Table 4.

Summary of Follow-up After Renal Autotransplant in Patients with Loin Pain Hematuria Syndrome

Study	No.	No. of Autotransplants	Pain Recurrence
Sheil et al ¹¹ (1985)	3	3	33%
Harney et al ²¹ (1994)	4	4	75%
Parnham et al ²² (1996)	11	12	73%
Karvelas and Ramsey ²⁰ (1996)	4	4	None
Spitz et al ²² (1997)	2	2	None
Chin et al ¹⁶ (1998)	22	26	31%
Sheil et al ¹⁰ (1998)	30	40	24%
Eisenberg et al ¹ (2008)	19	19	31.5%
Almaiman et al ²⁴ (2013)	4	4	50%