Prospective Observational Study on Loin Pain Hematuria Syndrome Complicating Symptomatic Nephroptosis and the Results of Renal Sympathetic Denervation and Nephropexy Surgery

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Abstract

Objective: To report the results of a 10 years prospective observational study on loin pain hematuria syndrome (LPHS) complicating symptomatic nephroptosis (SN) and results of renal sympathetic denervation and nephropexy (RSD&N) surgery.

Patients and methods: All patients presenting with loin pain with or without hematuria during 10 years were entered into a prospective observational study and underwent thorough clinical, laboratory and imaging investigations. Repeated standard imaging was invariably normal, when supine. However, 190 patients demonstrated SN of > 1.5 vertebrae on repeating intravenous urography (IVU) with erect film. Of whom 36 (18.9%) patients suffered LPHS.

Results: Of the 190 SN patients analysed 182 were females. The mean age was 28.8 years. All patients showed renal drop of >1.5 vertebrae (>5 cm) on erect IVU film. Of the 190 patients, 108 (56.8%) had right and 82 (43.2%) had bilateral nephroptosis, of whom 36 (18.9) patients suffered LPHS. Stretch/rotation of renal pedicle causing neuro-ischaemic pain was demonstrable on the right side in 72 (37.9%) and bilaterally in 7 patients- as depicted from the new IVU 7 sign. Open surgical treatment was used in 28 patients for severe LPHS; 10 had simple nephropexy and 18 had RSD&N. Patients who had RSD&N were all cured.

Conclusions: The presented evidence demonstrates that LPHS has real patho-etiology of pedicle stretch /twist neuro-ischemia. The new IVU 7 sign on erect IVU is used for detecting neuro-ischaemia. Renal sympathetic denervation and nephropexy offer the best chance of curing LPHS complicating SN.

Keywords: LPHS; Nephroptosis; Ischemia; Neuropathy; Nephroplegia

Abbreviations

LPHS: Loin Pain Hematuria Syndrome;
SN: Symptomatic Nephroptosis;
RSD&N: Renal Sympathetic Denervation and Nephropexy;
IVU: Intravenous Urography;
RGP: Retrograde Pyelography;
MASS: Multiple Associated Sympathetic Symptoms
Introduction

Loin pain with or without hematuria is most serious and a difficult clinical problem. It affects mostly young females of at their 2nd-4th decade of life. A series of 190 patients prospectively studied over 10 years, representing the largest single group of patients referred to the Urology Department, King Khalid Hospital, Najran, at a rate of 1.76 cases per month. Najran is in the southern province of the Kingdom of Saudi Arabia at the border of Yemen with mixed population from both countries and expatriates. The hospital provides the main urology service in the region. This report reflects the author’s experience based on reviewing the findings of the observational study that aimed at understanding the disorder, verifying its genuineness and identifying its real patho-etiology. A preliminary report was published [1].

The main management problem of loin pain was the lack of demonstrable pathology on repeated imaging, when supine. The underlying SN though well-known [2], was disparaged [3] and LPHS though well documented, its existence may be doubted [4] and both are extremely problematic to manage [4-7]. Demonstrable renal pathology of loin pain and hematuria was invariably lacking on all supine imaging of the received protocol [4-7]. Urinary tract infections (UTI) may affect a few patients during the occasional episodes but UTI and stones play no role in the pathogenesis of LPHS [4,7]. Many complex ramifying management problems of SN and LPHS are well known [4-7] but have no solutions. Some of the problems were communicated [3,8] and the illusive overlooked link of SN with LPHS was pointed out recently [1,8,9]. This article aims to demonstrate the patho-etiology features and complications of SN causing LPHS as genuine causes of loin pain and hematuria. The reported evidence demonstrable on upright imaging and RGP is visible and reproducible by other researchers and colleagues. Identifying the patho-etiology of loin pain and hematuria may revive interest to help future adequate management of young patients suffering from the incapacitating genuine pain of SN and LPHS. This is evidenced by the most successful results of RSD &N for SN and LPHS reported here.

Patients and Methods

All patients presenting with loin pain with or without hematuria during 10 years were entered into a prospective observational study and underwent thorough clinical, laboratory and imaging investigations. Repeated standard imaging was invariably normal, when supine. However, 190 patients demonstrated SN of > 1.5 vertebrae on upright imaging of IVU. Of whom 36 (18.9%) patients developed recurrent episodes of painful hematuria for which no organic pathology was detected on all standard and ancillary imaging, when supine. The study aimed to affirm genuineness of loin pain and hematuria and identify its real patho-etiology.

Reviewing the data of 10 years study revealed many clinical and radiological findings that is indeed incredible for a discarded disorder but may be easier to believe when the underlying patho-etiology of pain and hematuria is demonstrated on imaging photographs using new methods. Imaging included grayscale ultrasound (US) and IVU and were carried out repeatedly on all patients. Ancillary imaging was carried out on all cases suffering from severe loin pain and hematuria episodes and included computer axial tomography (CAT), magnetic resonance imaging (MRI) or arteriography (MRA), doppler ultrasound, and 99mTc DTPA isotope renography (IR) scans. Grayscale ultrasound, IVU and IR were carried out at supine and upright postures. Cystoscopy and RGP were carried out for localizing the side and site of hematuria in cases who gave informed consent. Upright IVU and IR imaging and RGP demonstrated the overlooked pathoetiology features and complications causing pain and hematuria while all other imaging missed the detectable pathology.

Long term follow-up observations identified the illusive overlooked anomalies of SN complicated into LPHS. Investigations included regular urine analysis and culture that were mostly negative for UTI, so were the tests for Tuberculosis and Brucellosis. Renal function tests were always normal. Serum immunoglobulin’s, complement factors C3 and C4 were normal in all but 5 of the 36 LPHS cases. Consumption coagulopathies affected 3 cases presenting with life-threatening hematuria episodes and requiring massive blood transfusions. All cases were thoroughly investigated at multiple specialist clinics, both at our hospital and elsewhere, for the bizarre MASS that accompany loin pain and hematuria. Attending physicians excluded all relevant organic causes of pain and hematuria, and possible causative personality and psychiatric disorders.

The figure of 7, with its horizontal and vertical segments visually simulated the renal pedicle at supine and erect IVU films, respectively. It was used for measuring renal pedicle stretch. The change in calyx shape from supine to erect IVU films represents the rotation/ twist of renal pedicle.

The rubber tube stretch hypothesis: To illustrate how stretch and rotation of renal artery in pedicle may cause ischaemia, the middle segment of rubber Foley’s catheter of the same diameter and twice the length of renal artery was used; fold the segment into two equal halves and stretch one to twice its length to resemble the IVU 7 sign, then twist it to 90ο; Total obliteration of the tube’s lumen occurs.

The kidney was explored by open surgery, placing the kidney at ptosed position caused stretch of renal pedicle causing ischaemic cyanosis of the kidney. This confirmed the IVU 7 sign and tube stretch hypothesis; representing the renal pedicle stretch ischaemia.

**Results**

This prospective observational study lasted 10 years. Patients presenting with loin pain were 236; of whom 46 were excluded and 190 patients had SN of > 1.5 vertebrae. Of the 190 SN patients analyzed 182 were females and 8 were males; 140 of Saudi origin and 47 were Yamani. Of the females 69 were single and 113 were married. The mean body weight of singles was 47.7 and of married 66 kg. The mean age (range) was 28.8 (12-70), duration of symptoms 15.7m (3-46) and hospital follow up 6.6 (3-19) years. The age distribution is shown in (Figure 1). The patient presented via Accident and Emergence department with loin pain and hematuria were 36 (18/9%) and with severe loin pain only were 64 (33.7%). Patients who were seen at Outpatient department with mild to moderate pain were 90 (47.4%). The rate of presentation was 1.76 cases per month. In addition to the main presentation of loin pain, patients also had MASS including: Backache and sciatica like pain affected 96 (51) and 24 (63%) patients respectively. Dysuria and interstitial cystitis affected 96 (51%) and 10 patients respectively. Gastrointestinal symptoms affected 94 (49%) patients.

**Figure 1.** Shows Age Distribution of 190 SN Patients

Patients showed no abnormality on IVU or ancillary imaging when supine. All patients showed renal drop of >1.5 vertebrae (>5 cm) on erect IVU film. Of the 190 patients, 108 (56.8%) had right and 82 (43.2%) had bilateral nephroptosis with a total of 272 kidneys involved. Nephroptosis distribution is shown in (Figure 2). Other demonstrable pathology on erect IVP film included: pelviuretric junction kink affecting the right kidney in 116 (61.1%) and bilateral in 19 (10%) of patients. Stretch/rotation of renal pedicle causing neuro-ischaemic pain was demonstrable on the right side in 72 (37.9%) and bilaterally in 7 patients. Right renal pedicle twist (900 rotation) was demonstrable in 45 (23.7%) of right kidneys. A combination of PUJ kink and pedicle stretch and twist may affect the same kidney affecting the right kidney in 77 (44.7%) and bilaterally in 17 (9%) patients.

**Figure 2.** Shows Nephroptosis Distribution According to Renal Drop in Vertebrae

Complications of SN detected on IVU erect film included both obstructive and neuroischaemic: obstructive complication included ballooned renal pelvis in 15 right kidneys and 3 bilateral, hydronephrosis in 4 right and 3 bilateral and right upper pole diverticulum in 7 patients. Neuroischaemic complications induced by pedicle rotation (Figure 3) and Stretch (Figure 4) were hematuria of the LPHS affecting 36 (18.9%), auto nephropexy affecting 12 right kidneys, upper pole calyctiasis with extravasation affecting 28 (15.8%) right kidney and 2 bilateral is best shown on RGP.
Renal atrophy affected 4 right kidneys. Upper pole infarction affected 2 kidneys and glomeruonephritis in one kidney. Retrograde pyelography (RGP) also demonstrated upper pole calyctiasis with extravasation in 9 patients, all calyx extravasation in 5 right kidneys and 2 bilateral, bilateral calyctiasis affected 9 patients off those who consented to cystoscopy and RGP (Figure 5).

Systemic complications included arterial hypertension in 4, renal failure in zero, anaemia in 46 patients. The following complications occurred before the diagnosis of SN was made. False diagnosis during an episode of the acute abdomen caused unnecessary surgeries included appendectomy in 28, intervertebral disc removal in 3 and cholecystectomy in 4 patients. False labelling included depression in 18, opioid dependency in 13 and malingering in 3 patients.

Open surgical treatment was used in 28 patients suffering from severe LPHS; 10 had simple nephropexy and 18 had RSD&N; skeletonising the right renal artery. Four of those treated with simple nephropexy had recurrence of LPHS while those who had RSD&N were all cured of pain and hematuria.

Discussion

The reported evidence demonstrates heterogeneous organic causes of SN pain in which ureteral kink obstruction and stretch and torsion of renal pedicle causing neuroischemia on IVU erect film is shown in (Figures 3 and 4). Retrograde pyelography demonstrates the organic pyelocalyctaisis (Figure 5) as the patho-etiologic of painful hematuria, caused initially by intermittent renal ischemia of pedicle ptotic stretch or torsion [10,11]. This affirms that SN may complicate into LPHS. Definition of LPHS is fulfilled as standard imaging still lacks a demonstrable pathology [3,4], when supine. Other ischemic renal complications included renal infarction, nephron loss and atrophy. Renal atrophy of ptosed kidneys occurred insidiously over a few years, affirmed by serial imaging.

The reported patho-etiologic of SN pain is heterogeneous with obstruction, ischemia and neuropathy components that have reversible and organic stages. Although, these causes, and rarely UTI, may contribute to the establishment of pyelocalyctaisis [12-14], the lesion seems primarily ischemic [10-12]. The link of SN with LPHS was illusive and overlooked, particularly when the ischemic complications of auto-nephropexy, auto-nephrectomy and sympathetic nephroplegia involving the normal contra-lateral kidney occurred insidiously over many years. Auto-nephropexy, made the link of SN with LPHS most illusive erasing the evidence on renal mobility, but demonstrated that surgical [14-16] or spontaneous nephropexy alone may neither cure the loin pain of SN nor abort its complication into LPHS.

The demonstrable pathology on upright IVU [2,3,8-11,13-16], arteriography [10,11] and IRG [2,10,12] are well documented on SN that was discarded long ago [3]. Upright imaging is currently undone and has not been reported previously in LPHS. Retrograde pyelography findings (Figures 5) have not previously been documented in either condition. The use of IVU started early in the 20th century while clinical evidence on the genuineness of SN pain dated back to the 15th
The sympathetic reflex of acute splanchic pain causing nausea, clarification. The role of sympathetic neuropathy is important but requires further analysis. The intermittent ischemia of ptosis [10,11,16] insidiously affects the eye and testes, offering the only scientific explanation for sciatica-like pain and cystitis [8]. These symptoms were documented in SN [2,15,16] and may represent features of sympathetic over-activity or neuropathy that add to the dilemma of diagnosis. Sympathetic neuropathy is known to play an important role in the pathogenesis of LPHS [7], which is identified and affirmed here to complicate SN.

Disputes of historical interest have led to many rises and falls [13], until SN was disparaged and nephropexy was abandoned decades ago [3,8,13,14]. Discarding SN from current textbooks has made it a forgotten and overlooked diagnosis. Upright imaging is not routinely carried out and chance diagnosis of SN and its link with LPHS is impossible to detect on supine imaging [8,9]. The bizarre MASS may present SN patient to urologists but also physicians and surgeons managing these cases. The symptoms are explained when the anatomy of blood and sympathetic nerve supply of the kidneys is considered [17]. The presented data and imaging evidence resolves the main problem of SN and LPHS concerning the lack of a demonstrable patho-physiology on supine imaging. Other renal SN features and complications [10-16] as well as management problems of SN [3,8,13] and LPHS [4-7,8] are documented but require objective evaluation and resolution. Symptomatic nephropexy was discarded when pain was thought imaginary and the disease was thought an invention of keen urologists [1,4-16]. The reported evidence is reproducible when upright imaging and RGP are considered in the management of loin pain with and without hematuria, and calls for reconsideration.

Organic causes of SN and LPHS pain at its early intermittent stage are demonstrated here on upright imaging IVU erect films. Renal-vascular complications of SN shown on arteriography of advanced SN [10] and LPHS [4,10] cases appear much earlier on RGP. However, conventional arteriography is considered obsolete in the current era of MRA and spiral CT scans that are possible only at supine postures. The reported features and complications of SN were thus illusive and overlooked due to the obscure role of “Gravity and Time” detectable only on upright imaging, RGP and long term follow up observations. The intermittent ischemia of ptosis [10,11,16] insidiously progressed into chronic renal-vascular damage, in which the role of sympathetic neuropathy is important but requires clarification.

The sympathetic reflex of acute splanchic pain causing nausea, vomiting, constipation and anorexia is well known. The MASS has cured SN pain and is a rare, unreal and hard to believe. It also confused loin pain presentation with acute abdomen, causing many unnecessary surgeries [3,8]. Chronic MASS of SN included gastro-intestinal symptoms of acid peptic disease and irritable bowel syndrome or constipation, backache with sciatica-like pain and cystitis [8]. These symptoms were documented in SN [2,15,16] and may represent features of sympathetic over-activity or neuropathy that add to the dilemma of diagnosis. Sympathetic neuropathy is known to play an important role in the pathogenesis of LPHS [7], which is identified and affirmed here to complicate SN.

Surgeons who operated early on SN addressing its intermittent heterogeneous patho-etiology before the onset of organic pyelocaliactasis reported results of >90% pain cure [2,15,16]. When surgery was indicated on the basis of demonstrable pyelocaliactasis on IVU, however, nephropexy cured renal pain in <50% of patients [13]. This demonstrates that accurate assessment of the patho-etiology of renal pain and timely interference are mandatory for successful surgical management. The only chance of cure is dependent upon timely dealing with the anomalies at the reversible stage of SN or early LPHS. Addressing sympathetic neuropathy seems important for achieving a cure. Simple nephropexy, reported by Hahn [18] may cure the pain of early intermittent obstruction and pedicle stretch and twist ischemia [2,10,12,15,16], but does not abort sympathetic over-activity and neuropathy or reverse the organic damage of chronic disease. It remains unknown when neuropathy sets in.

In 1989, Blacklock reported renal sympathetic denervation for the treatment of LPHS [19]. Unfortunately, neither sympathectomy nor renal auto-transplantation cured LPHS [4-7]. This may be due to the fact that surgery was delayed until irreversible renal damage had occurred. Sympathetic neuropathy is particularly important for explaining the ischemic complication of SN into LPHS affecting the contralateral kidney. Loin pain hematuria syndrome is known to affect both kidneys [4-7]. It is demonstrated here that LPHS may affect both the ptosed right kidney as well as the contra-lateral normally situated left kidney. “Sympathetic nephroplegia” is neuropathic damage of a contralateral normal organ with its twin organ pathology, akin to the known condition that affects the eye and testes, offers the only scientific explanation for the involvement of a normal kidney with LPHS. Many patients reported left loin pain contra-lateral to the right ptosed kidney, well before organic renal complications affected either kidney. The bizarre pain of SN and its MASS become easier to understand when sympathetic patho-physiology is considered.

Sympathetic nerves synapse at the celiac plexus [17] and over-stimulation may explain the cross-referred renal pain and MASS, in addition to the fact that some patients also...
have visceroptosis [2,15]. The problem of which kidney is the original site of painful hematuria is resolved by cystoscopy and RGP, but to determine which kidney is the origin of pain, and when sympathectomy should be carried out with nephropexy, is extremely difficult.

The patients’ main problem was being disbelieved and falsely labelled [5,8,9], mainly due to the lack of demonstrable pathology on the invariably normal supine imaging. Lack of objective tests to affirm pain genuineness, renal origin and severity has also compounded the problems of diagnosis [3,8]. The bizarre MASS made SN pain sounds unreal. Patients look absolutely normal after an agonizing episode of functional “renal angina” pain is settled. Some may use hospital time to make up for their lost social life outside, leaving an impression of malingering but this does not explain the hematuria.

Doctors’ perception of malingering, opiate dependency and psychological pain [5] has lead to labelling with these disorders that may occur as iatrogenic complications later perhaps as a result of prolonged suffering from the undiagnosed and untreated disorders. Believing that these patients suffered from genuine pain implanted a belief that initiated this research to find and demonstrate a patho-etiology of LPHS that is evidenced by the presented data. The importance of evidence is to overcome medical and patients problems of disbelief and false labelling. Increased awareness may help such unfortunate patients both in the Kingdom of Saudi Arabia and elsewhere to be taken seriously, properly investigated and appropriately treated. This may prevent adding the insult of false labelling to injury of the incapacitating pain, allowing adequate analgesia until an effective cure for the diseases is found. Awareness of the precise patho-etiology of renal pain at its reversible and organic stages may moderate expectations of colleagues, patients and relatives of a successful therapy that may cure pain and hematuria but cannot reverse an established pyelocalciactasis or renal atrophy.

For predicting precise prognosis, objective evaluation before therapy must segregate intermittent features from organic irreversible complications of SN. In order to achieve the highest possible chance of cure, therapy must address the mixed patho-etiology of pain at an early stage of SN and LPHS. This has important implications on taking the consent, particularly for explaining any post-therapy residual symptoms or possible renal atrophy. Renal atrophy was reported in 2 of 10 patients after intraureteric capsaicin injection [5] and the loss of 75% kidneys of LPHS patients that was reported after previous surgery [7] may in fact be complications of advanced renal disease rather than surgery as renal atrophy may occur spontaneously in patients who remain on conservative therapy.

The obstructive features and complications of PUJ kink explain some of SN pain while neuroischaemia due to pedicle stretch/rotation explain the LPHS. The IVU erect film demonstrates these features of SN while all ancillary imaging remain normal being supine. The IVU 7 sign and calyx deformity are used for detecting neuro-ischaeimic and obstructive pathology respectively. The condition goes through two stages; a reversible stage which is curable and an irreversible stage which is incurable. Renal sympathetic denervation and nephropexy offer the best chance of curing SN and LPHS.

References


