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REVIEW

Chyluria: the state of the art

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ABSTRACT

Chyluria is the passage of chyle in the urine. The cause seems to be the rupture of retroperitoneal lymphatics into the pyelocaliceal system, giving urine a milky appearance. This communication is caused by the obstruction of lymphatic drainage proximal to intestinal lacteals, resulting in dilatation of distal lymphatics and the eventual rupture of lymphatic vessels into the urinary collecting system.

This condition, if left untreated, leads to significant morbidity because of hematochyluria, recurrent renal colic, nutritional problems due to protein losses and immunosuppression resulting from lymphocyturia.

In this review, we summarize the state of the art of this condition and the newest treatments available.

Keywords: Chyluria, Endourology, Sclerotherapy, Renal pedicle lymphatic disconnection

Introduction

Chyluria has been described since the time of Hippocrates (400BC) as the passage of milky appearing white urine due to the presence of chyle composed of albumin, emulsified fat and fibrin in varying proportions that are absorbed by intestinal lacteals.

Although rare in the West, chyluria is a common problem in subtropical and tropical countries where filarial parasitic infestation is endemic (1). In these areas, approximately 10% of the population are infested, 10% of who eventually develop chyluria (2).

In this review, we summarize the state of the art of this condition and the newest treatments available.

Definition, classification and epidemiology

The passage of large amounts of chyle in the urine is known as chyluria. Chyle is a combination of proteins, emulsified fat and fibrin. The cause seems to be the rupture of retroperitoneal lymphatics into the pyelocaliceal system, giving urine a milky appearance (3). This communication is caused by the obstruction of lymphatic drainage proximal to intestinal lacteals, resulting in dilatation of distal lymphatics and the eventual rupture of lymphatic vessels into the urinary collecting system (4). Chyluria is classified as parasitic and nonparasitic (3). The disease is significantly higher in males (86%) than in females (14%) (5) and it is more common at the left side (2).

Parasitic chyluria

Parasitic chyluria is seen most commonly in endemic areas such as India, China, Japan, Southeast Asia, tropical sub-Saharan Africa and South America (6, 7). Lymphatic filariasis is caused by infection with three species of parasite, *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. Currently, there are an estimated 1.34 billion people living in endemic areas in 72 countries with 120 million people infected. More than 90% of infections are caused by *W. bancrofti*for which humans are the only natural host (6).

Nonparasitic chyluria

Other nonparasitic causes of chyluria include congenital anomalies, lymphangioma of the urinary tract, stenosis of the thoracic duct, retroperitoneal lymphangiectasia, post-surgery trauma (iatrogenic lymphangiourinary fistulae) and other causes (e.g. malignancy, pregnancy, tuberculosis, hypolabuminemia) (8). In particular, congenital anomalies are associated with chyluria: Singh et al (9) and Liu et al (10) described two cases of chyluria in fused renal ectopia, both successfully treated with sclerotherapy.

In the group of iatrogenic lymphangiourinary fistulae, recently, some cases of chyluria due to post-surgical complications were described. A recent published review on this theme (11) implies that chyluria is more common after nonradical renal surgery. The renal capsule and cortex are supplied with

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generous lymphatic drainage with an abundance of lymph vessels. A fistulous connection from the capsule or cortex to the collecting system logically would be a more common event, especially after partial nephrectomy with violation into the collecting system. The cause of the disease seems to be due to the obstruction and the rupture of the lymphatic system into the urinary system: the fistulous communication can occur at the renal pelvis, ureter, bladder or the prostatic urethra. The most common site is the renal fornix (12); renal capsule and parenchymal lymphatics drain to the renal hilum on their way to interaortocaval nodes or lateral aortic nodes, depending on laterality (13). For these reasons, the pathological causes require the formation of a fistulous connection from the transected hilar lymphatic vessels to the remaining urinary system, either to the ureteral stump or the bladder itself.

Wah described in 2011 a case of chyluria after a radiofrequency ablation of a renal cancer: the patients were asymptomatic and was conservatly treated with good results (14). As already mentioned, nonparasitic chyluria after renal surgery is rare and limited to few cases reported in the literature. Chylous ascites has been reported much more frequently after nephrectomy than chyluria, which is, vary rare. Nevertheless, in one case of radical nephrectomy, Tuck et al described the presence of chyluria in the postoperative follow-up. In that case, a fistula developed between the lymphatics vessels and the distal half of the ureter left in situ (15). This was treated with endoscopic injection of povidone iodine and then with N-butyl-2-cyanoacrylate. Miller et al reported four cases of chyluria after partial nephrectomy; all the patients were asymptomatic and the diagnosis was made thanks to computed tomography (CT) scan that demonstrates fat-fluid level in the bladder (16). Only two of these four patients noted occasional cloudy urine and none had intervention due to their asymptomatic nature. Komeya et al described, as well, a case of chyluria after partial nephrectomy, treated with endoscopic injection of silver nitrate solution (17). Thrasher and Snyder reported chyluria after percutaneous nephrolithotomy, which resolved with total parenteral nutrition and no other surgical intervention (18).

Chyluria classification

Chyluria may be classified as mild, moderate or severe on the basis of symptoms and imaging at the retrograde pyelogram (RGP). Mild chyluria was intermittent milky urine with no clot colic chylous coagulum, urinary retention or weight loss and with the involvement of a single calyx. Moderate chyluria was intermittent or continuous milky urine with occasional clot colic or chylous coagulum but no urinary retention or weight loss with two or more calyxes involved. Severe chyluria was continuous milky urine with clot colic, chylous coagulum, urinary retention or weight loss with the involvement of most of the calyxes with or without the involvement of renal pelvis and/or the ureter (4, 19).

Symptoms

Chyluria has a natural history of exacerbation and remissions and in the majority of the cases presents with passage of milky-white urine along with clots and the symptoms of a renal colic. Other possible symptoms could be dysuria, hematuria and urinary tract infections. In some severe forms, the disease could cause significant weight loss, cachexia, malnutrition, hypoproteinemia and immunosuppression (20). This condition, if left untreated, leads to significant morbidity because of hematochyluria, recurrent renal colic, nutritional problems due to protein losses and immunosuppression resulting from lymphocyturia (20).

Diagnosis

Laboratory tests

The clinical diagnosis is confirmed by an ether test, in which a sample of postprandial urine is mixed with an equal volume of ether, which extracts the triglyceride-rich fatty emulsion into an organic layer, leaving the remaining urine clear. The demonstration of lymphocytes in the urine sediment and estimation of urinary triglycerides can also be helpful in confirming the diagnosis (21-23). Oral ingestion of fat labeled with Sudan III (10 gm butter + 100 mg Sudan red III) causes orange pink coloration of urine in chylurics within 2-6 hours (24). Urinary triglycerides are invariably present in morning sample, 100% sensitive/specific test. Postprandial urine lipids, especially triglycerides ranging from 10 to 1955 mg/dl, might be used as markers for the clinical evaluation of chyluria (23). Urine albumin is also abnormally high in most cases.

Differential diagnosis of turbid urine should include pyuria and phosphaturia. In the first case, in particular, attention must be done to evaluate the possibility of a pyuria due to urinary tuberculosis. Additional investigation as complete blood test is required: Immune function of the patients who present with filarial chyluria is impaired in terms of the changes in T-lymphocyte subsets; the percentage of CD3+, CD4+ cell is significantly decreased, the ratio of CD4+/CD8+ being under 1.0 (25).

Radiological investigations

To exclude other urological anomalies, an abdominal ultrasound can be performed; echolucent areas may be seen within blood clot due to the chylous component, leading to heterogenous character of clot.

Lymphangiography results in the procedure of choice for identification of fistulous communication, demonstrating the site, the caliber and the number of the fistulae. It can also diagnose vascular dysplasias of the lymphatic vessels (26). Findings generally include lymphaticourinary fistulae at the level of kidney, ureter or bladder; tortuous dilated lymphatics around hilar region (lymphangiectasia) communicating with paravertebral lymphatics; contrast outlining major/minor calyces. Unilateral pedal lymphangiography technique is useful to detect lymphaticorenal fistulae via lymphatic crossover even when the contrast agent has been injected from the opposite side identifying cross-over channels. Nevertheless, for its invasiveness and its complications (local tissue necrosis, fat embolism, hypersensitivity reaction and exacerbation of lymph edema), lymphangiography is not currently used as a diagnostic tool (27, 28). Instead of this technique, a

noninvasive method with equal accuracy is used: lymphoscintigraphy using 99mTc-nanocolloid (29). It is the investigation of choice to localize, lateralize and know the functional extent of reflux and to detect recurrence on follow-up. It can demonstrate abnormal lymphatic drainage in chyluria and allows functional assessment of lymphatic transport and depiction of regional lymph nodes. A [AU: Please check the sentence 'A rapid ... side effects' for correctness, as the intended meaning is not clear] rapid and nontraumatic investigative procedure, it has no known side effects (30,31). Moreover, a recent paper published by Suh et al demonstrated the efficacy of SPECT [AU: Please provide the full forms of SPECT, RPG, DEC.] combined with CT scan to identify abnormal lymphatic drainage to the kidney (32).

Recently, some experiences with CT and magnetic resonance imaging (MRI) have also been useful in making the diagnosis. CT shows dilated vessels resembling a mass of confluent low-density lymph nodes and fat in the bladder secondary to chyluria (16). MRI shows multiple tubular, tortuous, fluid-filled structures in the retroperitoneum corresponding to retroperitoneal and perirenal lymphangiectasia with tortuous and markedly dilated retroperitoneal lymph vessels extending to the renal hilum. In particular, in the T1-weighted images, these structures will be as numerous interconnected small, nodular and streaky intensities and as a cloak of diffuse homogenous hyperintensity on T2-weighted axial images (33). In a new technique described by Goel et al, the association between MRI and RPG seems to be very useful for the evaluation of chyluria due to the simultaneous detailed intra-abdominal evaluation (34). Other important evaluation required is cystoscopy and RPG after a heavy fat meal to confirm the site and side of the lymphatic-urinary fistula and also to make the classification of the chyluria (4).

Management

Nonsurgical management

Medical and conservative treatments

Different types of treatment were tried in patients affected by chyluria. In cases of parasitic chyluria, diethylcarbamazine (DEC) is mandatory that rapidly kills microfilaria and can kill some, but not all adults of both *Wuchereria* and *Brugia*. DEC exerts no direct lethal effect on microfilarae but apparently modifies them so that they are eliminated by host's immune defense mechanism (35).

Other conservative measures to avoid the effects of chyluria, such as bed rest, high fluid intake, low-fat diet, fat-containing medium-chain triglycerides (MCTs), have been described with not always effective results (36). In cases of heavy chyluria, parenteral administration of specialized products with MCT formulas, containing the fat as MCT along with albumin, has also been prescribed. In cases of intractable chyluria, total parenteral nutrition with total enteric rest is advised (37). High protein diet is also suggested to make up for the albumin lost in the form of chyle. Bed rest, anti-inflammatory, analgesics and antipyretics are useful in managing of associated lymphadenitis.

Sclerotherapy

Renal pelvic instillation of sclerosant agents is a minimally invasive treatment for chyluria. Various type of sclerosant agents have been described: silver nitrate 1-3%, sodium iodide 1-25%, potassium bromide 10-25%, dextrose 50%, uro-graffin 76% and hypertonic saline (38-41). These sclerosant agents induce an inflammatory reaction in the lymphatics. Initially, they lead to chemical lymphangitis and edema of lymphatic channels. Later, fibrosis and blockage of lymphatics occur, leading to closure of lymphatic pelvic communication (39). In the past, silver nitrate was commonly used in concentration ranging from 0.1 to 3% (40,41). Although it was effective in 80% of the cases, it was not without complications such as flank pain, nausea, vomiting, interstitial nephritis, chemical cystitis, papillary necrosis, arterial hemorrhage, pelvi-calyceal system cast formation, ureteric strictures, acute renal failure and even death (42-45).

Other authors described their experience using instillation of povidone iodine solution alone or combined with dextrose. Shanmugam et al (46) used a single instillation of povidone iodine in five patients; all the patients treated were free of symptoms at the 6-month follow-up. Goel et al (47) in a prospective randomized study on 106 patients divided into three groups (first group treated with 1% silver nitrate, second group treated with 0.2% povidone iodine and third group treated with 50% dextrose, all at 8-hour intervals for 3 days) underwent instillation of the solution at 8 hours for 3 days; the authors demonstrated that povidone iodine was as effective as silver nitrate. Nandy et al have used a combination of 5 ml of povidone iodine with 5 ml of 50% dextrose with complete recurrence in 87% of the patients (19). Ramana Murty et al have used a solution of 2 ml of 5% povidone iodine dissolved in 8 ml of distilled water instilled every 8 hours into the renal pelvis for 3 days. In 21 of 26 patients, complete clearance was noted. Four patients required repeat injection, of whom only two patients responded (48). In a study published by our group, we used 5 ml of 10% povidone iodine dissolved in 5 ml of 10 ml of 10% dextrose solution instilled twice a day into the renal pelvis for 3 days through a monoJ ureteral stent. In two patients, recurrence was noted: in the first case after 6 months and in the other one after 24 months. In both patients a repeat injection was given with complete clearance (49). In another case, we treated after the publication of the first series, a woman of 25 years old with moderate chyluria. She presented milky urine and edema. She was already studied with an abdomen MRI that demonstrated an enlargement of the lymphatics vessels at the bladder level at the right side. The patient underwent cystoscopy that revealed the presence of a right side efflux and a subsequently position of a 7 F monoJ: a retrograde pyelography demonstrated the presence of a communication between the right upper urinary tract and the retroperitoneal lymphatics. Subsequently, an ureterorenoscopy was performed and the presence of a small orifice at the medial tract of the pelvis of the right kidney was found. This area was photocoagulated Ho-YAG Laser. The monoJ attached to a 18 F indwelling Foley catheter was left for the 3 days for the treatment schedule previously described (49). Before removing the ureteral catheter, a retrograde pyleography was performed and it demonstrated the

absence of communication between the lymphatic system and the upper urinary tract. At last follow-up after 2 years from the treatment, the patient had not relapses symptoms.

Surgical treatments

Surgery is the treatment of choice in severe forms of chyluria, for example in case of significant weight loss, hypoproteinemia, anasarca with or without severe anemia, recurrent clot retention with or without hematochyluria and recurrent urinary tract infection. Chyluria refractory to the above-mentioned conservative treatments and to two or more instillations of sclerosants [AU: Please check the sentence 'Chyluria ... apporach' for correctness, as the intended meaning is not clear.] (50) altered immune status and marked psychological disturbance are other indications to a surgical approach.

Surgical treatments for intractable chyluria are represented by renal pedicle lymphatic disconnection (RRPLD). This technique can be perfomed either by laparoscopy or open surgery.

Open surgery

The first described open approach of a RRPLD by Katamine in 1952 consists in a lumbar approach to the kidney after a fatty diet 24-36 hours before surgery and a pedal lymphangiography. The lymphatics at the kidney hilum were isolated and dissected. Subsequently, the areolar tissues containing dilated lymphatics traveling to the kidney in the perirenal and hilar region are dissected and divided between ligatures (51). A modified technique characterized by the only disconnection of abdominal peri-ureteral lymphatics avoiding the ones at the hilum was described in 1977 (52). The omentum to wrap the disconnected lymphatics was then used to reduce the incidence of postoperative lymphatic drainage, lymphocele formation, recurrence, fibrosis and postoperative adhesions (50). Other microsurgical open techniques are described: the aim of these procedures is to reduce the lymphatic pressure that is responsible for chyluria. These results are obtained by lymph-vascular anastomosis made between a single lymphatic vessel and the gonadal vein or between the inguinal lymphatics and the saphenous vein (53,54). A case of recurrency after surgery was treated with kidney auto-transplantation, with good results (55).

Laparoscopic surgery

The laparoscopic approach has been widely accepted since first reported by Chiu et al in 1995 (56). At present, the procedure can be performed transperitoneoscopically or retroperitoneoscopically. Zhang et al (57) demonstrated that compared with open surgery, RRPLD had the advantages of being minimally invasive and resulting in a shorter postoperative hospital stay and more rapid recovery, without compromising the effectiveness of open surgery. The procedure has a high reported rate of success (57-61). In the largest series of 383 patients who underwent RRPLD, immediate cessation of chyluria was observed in 98%, with improvement seen in another 1% (59). With the optical magnification provided by laparoscopy, small lymphatics can be visibly identified; thus, an excellent outcome can be expected for laparoscopic RRPLD. RRPLD was reported to reach a 100% cure rate in 78 patients with a follow-up of 1-2 years (62). A retroperitonescopic approach has also been described. It consists of different approaches: nephrolympholysis, ureterolympholysis, hilar vessel stripping, fasciectomy or nephropexy out of which the first three are mandatory, while fasciectomy and nephropexy (to prevent renal pedicle torsion and nephroptosis) are not routinely recommended (4). Retroperitoneoscopic RRPLD for chyluria completely ligates the lymphatic vessels and is a safe, effective and efficient surgical procedure with minimal invasion, less pain, less blood loss, lower morbidity, short hospital [illegible] and rapid recovery (63). A robotic approach was recently described by Barman et al in 2016 (64): a right robotic ureterolysis, renal hilar dissection and intraperitonealization of the ureter was performed in a 75-year-old man with persistent chyluria. No intra and peri-operative complications were described and chyluria was not present at last follow-up.

Other treatments

Other annedotic treatments are described in the literature. In a case of post-traumatic chyluria due to lymphorenal fistula, the patient was treated successfully after somatostatin therapy (65). In another case of chyluria, it has been reported to disappear following percutaneous sclerotherapy to the left inguinal lymph nodes with octeotride (66). Gerota's fasciectomy consisting of bilateral excision of the perinephric fascia and fat in two stages has been reported to result in complete resolution of chyluria (67).

Conclusion

The gold standard treatment of acute manifestations of filaria and consequent chyluria is the filariasis eradication by a low dose of DEC-medicated salt for a period of 6 months.

The nonparasitic treatment of mild chyluria is mostly conservative with usually very good prognosis and symptoms remission. In the sclerotherapy group, pure dextrose treatment has been discontinued due to poor success, and povidone iodine 0.2% has been found to be as effective as 1% silver nitrate but with less complications (47,68). In a paper published by Tandon et al, a long-term remission rate of 62% in the conservatively managed group (DEC + fat-restricted diet) but a cure rate of 90% of patients in the operated group was described with a more weight gain and dietary freedom along with a longer chyluria-free period in the operated group (60). In severe or refractory chyluria, definitive surgical ablation of lymphatic urinary fistula is better than conservative medical management because it has a higher success rate, more dietary freedom and better patient acceptability (60). Over 95% success rate has been described with a follow-up of 1 to 9 years following a single microsurgical operation (53). Reno-lymphatic disconnection is the reference procedure, with long-term success rates of 99% (69).

Chyluria is a rare condition in West countries and it is a well known condition in all the countries in which filariasis is endemic. When it happens, it represents a tuft condition to diagnosis and to treat. Nowadays, many different and effective treatment options are available to give the best treatment to our patients.

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