

Progress in the Research of Reflux Nephropathy

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Abstract

Reflux nephropathy (RN) is a renal disease caused by Vesicoureteral Reflux (VUR) and Intrarenal Reflux (IRR), resulting in renal cortical scar (localized atrophy) and focal glomerulosclerosis. RN is one of the important causes of end-stage renal diseases (ESRD). The most basic pathological feature of RN is kidney scarring. Common clinical manifestations are persistent or recurrent urinary tract infection, albuminuria, hypertension, nocturia, polyuria, lumbago, urinary calculi, etc. Due to the hidden condition of RN, doctors in various departments, especially in pediatrics, nephrology and urology, must strengthen their understanding and understanding of this disease, so as to facilitate the early detection and diagnosis of this disease. Correct conservative treatment of Western medicine, surgical treatment when necessary, and reasonable integrated treatment of Chinese and Western medicine are of great significance for the prevention and treatment of the progression from RN to ESRD.

Keywords: renal disease, reflux nephrosis, end stage renal disease, diagnosis, clinical manifestations, treatment

1. Introduction

Reflux nephropathy (RN), first proposed by Bailey in 1973 (Bailey R R., 1973) to replace the original name "Chronic atrophic pyelonephritis". It refers to a kind of disease caused by vesicoureteral reflux (VUR) and intrarenal reflux (IRR), which lead to renal scar formation, causing hypertension, proteinuria, and even eventually developing into end-stage renal failure (Fillion M L, Watt C L & Gupta I R., 2014).

2. Pathogenesis of Reflux Nephropathy

The cause of reflux is due to abnormal Waldeyer's sheath. This sheath is a one-way valve formed by the detrusor muscle of the bladder at the end of the ureter and acts as a vesicoureteral valve. When normal people urinate, the ureterovesical junction (UVJ) is closed, which can prevent the pressure in the bladder from increasing during urination and the urine from the bladder to the kidney through the ureter. Impaired anti-reflux mechanism caused by various factors can lead to VUR, and severe VUR can lead to increased renal pelvis pressure and urine reverting into

the renal interstitium from the weak part of the renal pelvis (Fillion M L, Watt C L & Gupta I R., 2014). According to the etiology, VUR can be divided into primary and secondary types.

(1) Primary VUR is relatively common. It is caused by the congenital dysfunction of UVJ caused by gene mutation or hypoplasia. It is mainly seen in children and can be reduced or even disappeared with age. This is because the bladder bottom continues to develop, which is conducive to the further improvement of the sheath (Edwards D, Normand I C, Prescod N, et al., 1977).

(2) Secondary VUR is caused by bladder neck or urethra obstruction due to various reasons, neurotic bladder, bladder tuberculosis and after bladder surgery.

1) Urinary Tract Infection: Animal experiments have confirmed that urine regurgitation carries bacteria from the lower urinary tract to the kidney and causes pyelonephritis. It is believed that aseptic VUR has no effect on renal growth and renal function, so VUR and IRR must be treated with urinary tract infection to produce renal scar formation (Roberts J A., 1992; Ransley P G & Risdon R A., 1975), even though infection is not necessary for renal scar formation. However, it can promote the formation of kidney scar (Hodson C J., 1981).

2) Urodynamic changes: Although there may not be IRR in the presence of VUR, severe VUR can lead to IRR, which can lead to renal function damage through stress factors (Johnston J H., 1966).

3) Immune injury: Reflux of urine leaking into the renal interstitium can induce immune reaction of the body. Some RN patients can find IgM and IgG deposits in the glomerulosclerotic area and mesangial area, confirming that immune injury is the cause of glomerulosclerosis, and the pathogenic antigen may be bacteria in the reflux urine or Tamm-Horsfall protein (Ragnarsdóttir B, Lutay N, Grönberg-Hernandez J, et al., 2011).

3. Diagnosis of Reflux Nephropathy

(1) Methods for the examination of reflux nephropathy: ① Isotope renal imaging: Currently, 99tcm-dithioglucolic acid static renal imaging is considered to be the gold index for the diagnosis of RN, and this method can detect renal scar even before the appearance of typical anatomical changes (Westwood M E, Whiting P

F, Cooper J, et al., 2005). ② Intravenous pyelography: as a traditional RN diagnostic method (El-Khatib M T, Becker G J & Kincaid-Smith P S., 1987), it can be manifested as clubbing deformation of the kidney, cortical atrophy and corresponding full-layer local cortical scar. Renal parenchyma was generally thinner and complex papillae changed. A high dose of IVP plus X-ray is more likely to show renal scarring. ③ CT and MRI: renal contour, length, cortical thickness and renal scar are more sensitive (Wong I Y, Copp H L, Clark C J, et al., 2009). ④ Renal biopsy: Some VUR patients could not find parenchymal scar by intravenous pyelography, while renal biopsy showed characteristic RN histological changes. However, kidney biopsy is not easy to penetrate scar tissue, so its diagnostic value is questionable (Kincaid-Smith P S., 1984). ⑤ Ultrasonic examination: the scope of renal scar can be observed, but only obvious renal scar can be displayed, and it is extremely unreliable for detecting the upper kidney, which can be used for follow-up observation.

(2) Diagnostic criteria for reflux kidney disease:

① IVP or high-dose IVP plus X-ray tomography showed club-shaped deformation of renal calyces and cortical scars at corresponding parts; Renal development stopped and/or ureteral calices expanded. ② Vur of different degrees can be found in half of adults, and the detection rate of children is high; Attention should be paid to exclude secondary VUR (Ye Rengao & Huang Fengxian, 1996).

4. Clinical Manifestations of Reflux Nephropathy

4.1 Urinary Tract Infection

Urinary tract infection is the most common clinical manifestation in patients with RN, characterized by persistent or recurrent urinary tract infections that are persistent and difficult to treat. In acute episodes, it can be manifested as typical acute pyelonephritis. However, most patients do not have typical urinary tract irritation symptoms such as frequent urination, urgency of urination, and pain in urination, but only as fever and slow growth and development (Hoberman A, Greenfield S P, Mattoo T K, et al., 2014).

4.2 Proteinuria

Proteinuria is the most important factor affecting the prognosis of patients with RN. It can be the first symptom of RN, or it can occur

years after severe scarring. The persistent occurrence of proteinuria suggests that VUR has led to progressive glomerulopathy with poor prognosis, and even if VUR disappears after surgical treatment, renal function will continue to deteriorate (Yavuz S, Anarat A & Bayazit A K., 2013).

4.3 Hypertension

Hypertension is a common complication in the later stage of RN patients, and it is also the most common cause of malignant hypertension in children. About 20% of children and young patients with RN develop hypertension. As renal scarring progresses, the risk of developing hypertension increases. About 25% of RN patients seek medical advice with hypertension (Dillon M J & Goonasekera C D., 1998).

4.4 Pregnancy-Related Complications

Pregnancy induced hypertension syndrome (PIH) can be the first symptom of RN, and about 4% of patients with severe PIH have RN. Most studies believe that pregnancy in RN patients can cause rapid deterioration of renal function, especially if hypertension, proteinuria, or serum creatinine > 200 μ Mol/L; Some patients with RN have the first manifestation of RN due to preeclampsia, premature delivery, and even miscarriage (Jungers P, Houillier P, Chauveau D, et al., 1996).

4.5 Nocturia and Polyuria

Urine concentration dysfunction is a sensitive indicator of renal tubular dysfunction. In patients with VUR, distal tubular function is first affected, including nocturia, polyuria, fixed low specific gravity urine, and hypotonic urine.

4.6 Others

The common clinical manifestations of RN include low back pain, urinary tract stones, enuresis, chronic renal failure, microscopic hematuria, and gross hematuria.

5. Treatment of Reflux Nephropathy with Traditional Chinese and Western Medicine

The purpose of RN treatment is to terminate VUR, control infection, prevent the formation of kidney scarring and renal function injury. It has been pointed out in the literature that the ultimate goal of VUR treatment is to prevent renal parenchymal injury and renal decline, rather than simply correct urine regurgitation (Brakeman P., 2008).

5.1 Medical Treatment

Medical treatment mainly adopts anti-infection and comprehensive symptomatic treatment to delay the loss of kidney function. Specific measures include: ① Conduct regular urine examination and urine culture, evaluate reflux status, and monitor scar formation. ② Regularly empty the bladder to reduce urine reflux. Develop the habit of drinking more water and urinating frequently. Adopt secondary urination, especially before going to bed every day, to reduce residual urine in the bladder. It is necessary to avoid frequent increase in bladder pressure due to abdominal pressure during defecation due to dry stool, which can aggravate the damage of reflux to the kidney. ③ Treatment of urinary tract infections. In view of the close relationship between the pathogenesis of reflux nephropathy and the formation of renal parenchymal scar and urinary tract infection, the prevention and treatment of urinary tract infection is the key to the prevention and treatment of this disease. ④ Anticholinergic drugs. Some patients with VUR have frequent urination, enuresis, squatting behavior, etc. It is also common for women to have unstable bladder. Some studies have reported that about 40% of children with vesicoureteral reflux have unstable bladder. Concurrent use of anticholinergic drugs in these patients can reduce the incidence of urinary tract infections and increase the self healing rate of reflux (Leclair M D & H  loury Y., 2010). ⑤ After comprehensive treatment, symptoms such as hypertension, proteinuria, and renal dysfunction can occur in the later stage of RN, and corresponding measures can be taken according to CKD. Hormones and immunosuppressants have no clear effects and have prominent adverse reactions, and should be avoided.

5.2 Surgical Treatment

Surgical treatment of RN should be cautious, especially in children, as 80% of young children will automatically disappear with age; Some reflux can heal after treatment for urinary tract infections. On the other hand, complications of ureteral replantation should also be considered. It is generally believed that ureteral replantation should be performed in cases of 4-degree reflux if there is no improvement in reflux after active treatment of urinary tract infection for 6 months. However, before surgery, it is necessary to effectively rule out whether there is urinary tract obstruction caused by posterior urethral valvular disease. If there is urinary tract

obstruction, it should be treated first. If the obstruction has been eliminated, but reflux still does not improve, surgical treatment should only be considered (Ye Rengao, 1985).

Surgical methods include traditional anti reflux surgery and endoscopic injection therapy. The submucosal treatment of reflux ureteral orifice by endoscopic injection of a biomaterial has become increasingly widely used due to its advantages of simplicity, effectiveness, minimal injury, low mortality, short hospital stay, and ease of acceptance by patients and their families. Therefore, the indications for surgical treatment have been broadened. In recent years, there have been reports of using polytetrafluoroethylene or polydimethylsiloxane for injection, with a higher success rate than previous injection materials, and a lower risk of injection migration or granuloma formation. Although the short-term efficacy of endoscopic therapy is acceptable, the long-term effect needs further study (Sung J, & Skoog S., 2012).

5.3 TCM Treatment and Syndrome Differentiation

(1) The following three types of syndromes are most common in clinical practice for those who mainly focus on standard symptoms: 1) Damp-heat accumulation, lower jiao adverse syndrome: to clear heat and purge fire, Li water through shower. The main prescription is the addition and subtraction of Bazheng Powder. If hematuria, white grass root, dry lotus and thistle can be added to nourish Yin and stop bleeding; Urine pain even add honeysuckle and dandelion to clear heat and detoxify. 2) Stagnation of the liver meridian, syndrome of constipation disorder: to treat the drainage of liver qi, exhalation of heat and Tonglin. Shulitonglin Decoction (Lv's) is the main prescription (Liu Huafeng, Anning & Liu Weijing, 2015). Frequent urination urgent urination pain add dandelion, yellow cedar to strengthen the work of clearing heat through rinsing; Waist and knee sour and soft, kidney qi deficiency to rhubarb, plus fairy spleen, cinnamon to tonics kidney qi. 3) Syndrome of stagnation of qi and blood stasis and obstruction of blood vessels: treated with promoting blood circulation and resolving stasis, regulating qi to relieve pain. The prescription is mainly composed of Shixiao Powder and Huoluo Xiaoling Pill. In patients with frequent and astringent urination, black medicine and acute diarrhea are added to regulate qi and dredge lymph (Liu Huafeng, Anning & Liu Weijing, 2015).

(2) In clinical practice, the following two types of syndromes are most common when both the deficiency and excess are evident: 1) Deficiency of spleen and kidney, and downflow of dampness and heat: the treatment is to strengthen the spleen and remove dampness, and benefit the kidney to consolidate astringency. The prescription is mainly composed of matchless yam pills or Buzhong Yiqi Decoction combined with Bazheng Powder. For patients with liver depression and qi stagnation, add bupleurum and turmeric to course the liver and rectify qi. 2) Syndrome of deficiency of kidney yang and stagnation of liver qi: treated with warming and tonifying kidney yang, course the liver and rectify qi. The main prescription is Shenqi Pill and Chenxiang Jiangqi Powder. For those with dizziness and tinnitus, add wolfberry fruit and gastrodia elata to nourish the blood and soften the liver (Liu Huafeng, Anning & Liu Weijing, 2015).

(3) The following two types of syndromes are most common in clinical practice for those with deficiency of the root cause: 1) deficiency of kidney qi and loss of qi due to gasification: the treatment is to warm and replenish the kidney yang and fill up the essence and blood. The prescription is based on the addition or subtraction of Yougui Pill. Those with enuresis and urinary incontinence should be given Suoquan Pill to benefit the kidney and firm astringency. 2) Kidney Yin Deficiency, Kidney Yang Decline Syndrome: Treat with warming and tonifying Kidney Yang, nourishing Kidney Yin. The prescription is mainly composed of Eucommia pills. If there is dampness and heat inside, add wine army and locust flowers to clear the internal organs and relieve heat (Liu Huafeng, Anning & Liu Weijing, 2015).

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