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Posterior urethral valves in patients with Down syndrome

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Abstract. Renal and urological anomalies in Down syndrome (DS) have received little attention compared with the nephrourological findings described in other chromosomal abnormalities. Renal hypoplasia, hydroureteronephrosis, ureterovesical and ureteropelvic junction obstruction, and vesicoureteral reflux, but not posterior urethral valves, have been associated with DS. We report the occurrence of posterior urethral valves in three male infants with DS at a single institution. All had multiple urological procedures for correction or palliation of obstruction. Children with DS may have an increased risk for developing posterior urethral valves and obstructive uropathy. Furthermore, they may also develop chronic renal failure secondary to posterior urethral valves. Therefore, we suggests that infants with DS be screened with ultrasonography for renal and urological abnormalities early in life and, if abnormal, a contrast voiding cystourethrogram be performed to rule out posterior urethral valves or other bladder or urethral abnormalities. A review of the renal and urological anomalies in DS reported in the literature since 1960 is presented.

Key words: Obstructive uropathy – Renal failure – Hydronephrosis – Chromosomal – Urethra

Introduction

In 1960, Berg et al. [1] described five patients with Down syndrome (DS) and renal malformations: four with renal agenesis or hypoplasia and one with horseshoe kidney. Since then, different nephrourological anomalies, including hydronephrosis, vesicoureteral reflux (VUR), ureteropelvic junction and ureterovesical junction obstruction, have been described in association with DS [3–25]. We report three cases of DS associated with posterior urethral valves (PUV) followed at a single institution. We have also reviewed the renal and urological anomalies in patients with DS reported in the literature since 1960.

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Case reports

Case 1

A 22-year-old white male with DS had chronic renal failure secondary to obstructive uropathy. A voiding cystourethrogram (VCUG) demonstrated PUV. He underwent multiple surgical procedures to overcome the obstruction during his 1st year of life, including bilateral pyeloplasties and bilateral nephrostomies, suprapubic excision of the urethral valves, bilateral cutaneous ureterostomies, and a suprapubic cystostomy. He had recurrent episodes of urinary tract infections. He also developed hyperuricemia and symptomatic gout. Serum creatinine has remained in the 2.5–3.0 mg/dl range.

Case 2

The patient is a 3-year-old black male child with DS. The diagnosis of DS was made prenatally by amniocentesis performed for oligohydramnios. Prenatal ultrasonography revealed bilateral hydronephrosis and an enlarged bladder. A VCUG showed PUV and a markedly trabeculated bladder with numerous diverticuli. He had multiple hospitalizations for management of the urethral obstruction. He underwent cystoscopy, transurethral fulguration of PUV, and a percutaneous suprapubic cystostomy. He developed a stricture in the area of the prior valvular resection. Renal function has remained relatively stable with a creatinine clearance of 80 ml/min per 1.73 m^2.

Case 3

The patient is a 3-year-old Oriental child with DS. A prenatal ultrasound at 35 weeks' gestation showed severe fetal hydronephrosis and oligohydramnios. A VCUG showed PUV and a trabeculated bladder with multiple diverticuli. He underwent multiple urological procedures to overcome the obstruction, including a cutaneous vesicostomy, antegrade fulguration of the PUV, bilateral percutaneous nephrostomy tubes, and a cutaneous left pyelostomy. He also developed a grade 4 VUR on the right side and a vesicocutaneous fistula. His renal function is moderately decreased, with an estimated creatinine clearance of 55 ml/min per 1.73 m^2.

Discussion

The pattern of characteristics we now recognize as DS was first described by John Laughton Down in 1866 [2]. In 1960, nearly a century later, Berg et al. [1] described the first cases of DS with renal and urological malformations. Malformations of the kidney and urinary tract have received little attention in association with DS, compared with the nephrourological findings described in other chromosomal abnormalities [3–5]. We present three patients with DS and PUV. PUV were diagnosed by VCUG in all cases. The diagnosis of hydroureteronephrosis was made prenatally by ultrasound in the young patients and postnatally, by intravenous pyelogram, in the oldest. Our finding of three patients with PUV and DS at a single institution suggests that this entity may be more frequent than previously shown. Berg et al. [1] reported one case of urethral valves in 141 cases with DS. Lenz et al. [6] described one case of DS and distal urethral valves, who underwent intrauterine treatment to relieve pressure on the kidney parenchyma, but died 3 h after birth at 34 weeks'. Ahmed [7] described one patient with PUV in a series of four cases of VUR in DS. More recently, Webb et al. [8] have reported two cases of DS and chronic renal failure secondary to PUV.

The incidence of renal and urological anomalies in DS has been reported to vary between 3.5% and 21.4%. Berg et al. [1] described 5 cases in 141 autopsies of DS (3.5%). Egli and Stalder [4] reported a 6.7% incidence in 103 autopsies of DS. Kravtzova et al. [5] found an incidence of renal and urinary tract anomalies of 12.5%. The incidence of hypospadias was reported to be 6.5% in a sutdy of 77 males with DS [9]. More recently, Ariel et al. [10] found renal hypoplasia in 18 of 84 autopsies [21.4%) and obstructive uropathy in 8 of 124 autopsies (6.4%) of DS patients. Furthermore, an increased incidence of intrauterine pyelectasis was observed in patients with DS [11, 12]. Benacerraf et al. [11] showed that 25% of fetuses with DS have mild fullness of the intrarenal collecting system seen prenatally, compared with only 2.8% of fetuses with normal karyotypes. When fetal pyelectasis was detected, the incidence of DS was 3.3%. It has been suggested that obstructive uropathy may be associated with DS [10]. Furthermore, we suggest that PUV may be specifically associated with DS. Data from the New York State Department of Heath Congenital Malformations Registry [13] suggest a significant risk of urethral obstruction in DS, similar to our finding. For 1983–1990, the incidence of bladder outlet or urethral obstruction including PUV was 0.17 per 1,000 births in New York State. The incidence in DS during the same period of time was 2.0 per 1,000 births ($P < 0.01$). Furthermore, the incidence of any kidney or urinary tract anomaly was 2.1 per 1,000 births in the general population, while it was 13.9 per 1,000 births with DS ($P < 0.01$).

Table 1 describes the renal and urological abnormalities in cases of DS reported in the literature since 1960 [1, 4–7, 9–25]. Benda [23] found small kidneys in DS. A decrease of approximately 10% and 14% in renal weight was described by Naeye [14] and Ariel et al. [10] respectively. Naeye [14] has also shown a decrease in the number of glomeruli of approximately 55%–60%. Fitzsimmons et al. [24] have described growth retardation of the kidneys during the second trimester of pregnancy. Microscopic renal abnormalities in DS include glomerular microcysts, tubular dilatation, and immature glomeruli [10, 25].

Glomerular diseases in DS patiens include mesangiocapillary glomerulonephritis [26], and immunotactoid glo-

Table 1. Kidney and urinary tract anomalies in patients with Down syndrome (DS)

Author (year)	Pathology	Material of study
Berg et al. [1] (1960)	Unilateral renal agenesis Renal/bladder hypoplasia Horseshoe kidney Urethral valves	5/141 DS autopsies (3.5%)
Naeye [14] (1967)	Hydronephrosis Ureteropelvic junction stenosis Horseshoe kidney Small kidneys	4/21 DS autopsies (16.6%)
Johnston and Coimbra [15] (1970)	Megalourethra	1 DS in 4 cases of megalourethra
Egli and Stalder [4] (1973)	Renal cysts-megacystis Hydroureteronephrosis Ureteral stenosis	7/103 DS autopsies (6.8%)
Ozer [16] (1974)	Hydronephrosis Ureteropelvic junction stenosis	1 DS autopsy
Kravtzova et al. [5] (1975)	Renal hypoplasia-dysplasia Hydroureteronephrosis Atresia of ureters	14/112 DS autopsies (12.5%)
Al Saadi et al. [17] (1984)	Obstructive uropathy Renal dysplasia	1 DS in 21 renal dysplasia autopsies
Curry et al. [18] (1984)	Obstructive uropathy Hypospadia	1 DS in 80 Potter's syndrome autopsies
Zerres et al. [19] (1984)	Prune-belly anomaly Cystic disease-hydroureter	1 case of DS
Lenz et al. [6] (1985)	Distal urethral obstruction Cystic dysplasia	1 DS in 4 urethral obstruction autopsies
Amacker et al. [20] (1986)	Prune-belly anomaly Cystic kidney-hydroureter Urethral atresia	2 cases of DS and prune-belly anomaly
Lang et al. [9] (1987)	Hypospadia-micropenis Dorsal urethral duplication	5/77 DS males (6.5%)
Passerini-Glazel et al. [21] (1988)	Hydronephrosis Vesicoureteral reflux Urethral hypoplasia/atresia	1 DS in 8 urethral hypoplasia autopsies
Ahmed [7] (1990)	Vesicoureteral reflux Ureterovesical obstruction Posterior urethral valves Urethral diverticulum Hypospadia	4 cases of DS and vesicoureteral reflux
Ariel et al. [10] (1991)	Hydroureteronephrosis Ureterovesical stenosis Bladder neck obstruction Renal cystic dysplasia Double pelvis and ureter Ureterocele	8/124 DS autopsies (6.4%)
Kupferman et al. [22] (1993)	Posterior urethral valves	3 cases of DS

merulopathy [27]. Recently, Robson and Leung [28] reported a case of DS with chronic renal failure due to chronic glomerulonephritis. Tubular defects such as cystinuria have also been reported in DS patients [29, 30]. Patient 1 developed hyperuricemia and gout. An increased serum uric acid level in DS [31, 32], and the possibility of developing gout [33, 34], have been previously documented. The mechanism for the hyperuricemia appears to be a decreased urinary clearance of uric acid [32]. In addition, there is a decreased fractional excretion of uric acid in patients with DS compared with controls with other types of mental retardation [31].

Morbidity related to renal and urological anomalies may be significant. Our patients also developed different degrees of chronic renal failure secondary to PUV. The estimated creatinine clearance was approximately 30, 80, and 55 ml/min per 1.73 m^2, in patients 1, 2, and 3, respectively. Morbidity should also be considered in association with treatment. In our patients, multiple urological procedures were needed for correction or palliation of the obstruction. This led to frequent or prolonged hospitalizations. Patients are at greater risk of developing urinary tract infections and chronic renal failure. Renal replacement therapy in DS has been previously reported [8, 35].

In summary, we have presented three patients with DS and PUV. The incidence of this association is unknown. However, it appears to be an incidence of renal and urological anomalies in patients with DS which is higher than previously reported. Hence, we suggest that infants with DS be screened with ultrasonography for renal and urinary tract abnormalities early in life and, if abnormal, a VCUG be performed to rule out PUV or any other urological abnormality, including VUR. Screening for renal and urinary tract abnormalities should be part of the standard clinical care of children with DS.

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Ask the expert*

What is the actual management of a child with membranous glomerulopathy associated with chronic hepatitis B?

Key words: Membranous nephropathy – Chronic hepatitis B – Management

There is no definite answer to the question for there is still no satisfactory treatment for the condition; however, various treatment schemes have been tried and seem to be encouraging in some circumstances. As the outcome of hepatitis B virus (HBV)-related membranous glomerulopathy in children is usually favourable and many of them have frequent spontaneous remission [1–3], one can afford to observe the clinical course in most patients and give supportive treatment. However, there are some who run a persistent or relapsing course and a small minority may have impairment of renal function [1, 4]; in adults a slow but relentless and progressive course is not uncommonly seen [5]. Thus in older children the prognosis may need to be more guarded [1] and specific treatment may have to be sought if the nephrotic state persists for months.

As in idiopathic membranous glomerulopathy, the usefulness of *steroids* is questionable, and in the HBV-related glomerulopathy it is even thought to be harmful, as activation of viral replication may occur with corticosteroid treatment [6–8] and seroconversion may be delayed or even prevented [6, 7, 9]. Neither is the use of alkylating agents thought to be warranted [10, 11]. Reports of treatment with *interferon* seem a bit more encouraging. Clearance of HBeAg with clinical remission was demonstrated in some trials [12–15]. However, the response has not always been favourable, especially in endemic areas [5], and there is sometimes recurrence. Treatment with interferon is better reserved for older children whose nephrotic syndrome is troublesome and persistent, say for more than a year, with the presence of HBeAg indicating viral activity. Histological stage II–III and focal sclerosis on light microscopy suggesting permanent glomerular damage, and thus less chance of going into spontaneous remission [1], would indicate a trial of interferon treatment [13]. There is no standard regimen, but favourable results have been obtained with a dose of 5 MU/m^2 on alternate days for 16 weeks, with clearance of HBeAg and a decrease in proteinuria [13].

Adenine arabinoside has been used to treat chronic HBV infection, with some patients seroconverting [16, 17]. A recent study used a combination of *adenine arabinoside and thymic factor* (Thymostimulin, Instituto Farmacologico Serono, Rome, Italy) to treat 24 children with HBV membranous nephropathy, with some success [18]. The thymic factor was thought to promote T cell function by enhancing the production of cytokines. Loss of proteinuria with seroconversion and disappearance of both HBsAg and HBeAg were observed. Whether this treatment has a role in the future management of the condition needs further evaluation.

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* The editors invite questions for this section