Focal Segmental Glomerulosclerosis in a Child with Prader-Willi Syndrome : A Case of Obesity-associated Focal Segmental Glomerulosclerosis

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= Abstract =

Obesity-associated focal segmental glomerulosclerosis(OB-FSGS) has been known to progress into advanced renal insufficiency, and its clinicopathological features include obesity, FSGS lesions with glomerulomegaly and, nephrotic-range proteinuria without edema. A 14-year old girl with Prader-Willi syndrome showed nephrotic-range proteinuria without hypoalbuminemia or edema. The renal biopsy revealed focal segmental glomerulosclerosis together with glomerular hypertrophy and an increased mesangial matrix. We report here a case of OB-FSGS as one of the renal problems of Prader-Willi syndrome, and we came to the conclusion that Prader-Willi syndrome is one of the possible disease entities that can lead to renal insufficiency through obesity. **(J Korean Soc Pediatr Nephrol 2004;8:244-249)**

Key Words : Prader-Willi syndrome, Focal segmental glomerulosclerosis, Obesity, Renal insufficiency

INTRODUCTION

Prader-Willi syndrome(PWS) is characterized by diminished fetal activity, muscular hypotonia, mental retardation, short stature, obesity, hypogonadotropic hypogonadism and small hands and feet[1, 2]. This condition can be considered to be an autosomal dominant disorder, and it is caused by deletion or disruption of a gene(s) on the proximal long arm of the paternal chromosome 15 or by maternal uniparental disomy 15, because the gene(s) on the maternal chromosome(s) 15 are virtually inactive through imprinting[1]. Renal diseases are rare in PWS[2] and the reported cases of renal problems were renal tubular acidosis[3], unilateral renal malmigration, membranoproliferative glomerulonephritis[4], Wilms tumor[5], and hydronephrosis combined with hydroureter and vesicoureteral reflux[4]. Obesity can cause cardiorespiratory problems, diabetes mellitus, or obesity-related glomerulopathy such as focal segmental glomerulosclerosis(FSGS)[2, 6, 7]. Obesity-related glomerulopathy has a low incidence of nephrotic syndrome and the consistent presence of glo-

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merulomegaly, which are clinical distinctions marking it from primary FSGS[7, 8]. We report here on a case of PWS in a 14 year old patient that was complicated by obesity-associated FSGS(OB-FSGS).

CASE REPORT

The patient was spontaneously delivered at 43 weeks gestation with a birth weight 2.2 kg. Her family history was non-contributory. At birth, the infant was profoundly hypotonic and had a poor sucking reflex. She was a poor feeder during infancy and had delayed psychomotor development. She sat at 15 months and walked alone at 5 years. Her muscle tone was improved to about a normal level at 26 months. From 3 to 5 years of age, she developed hyperphagia and gained a large amount of weight. At the age of 8 years, the physical examination revealed a severely obese child(44 kg, BMI 28.9) with, short stature(123.4 cm), short hands and feet, and an open, inverted, V-shaped mouth. At the age of 9 years, chromosome analysis showed a deletion of one chromosome 15 {46, XX, del(15) q11-q13} and the diagnosis of PWS was established. At the age of 14 years, her body weight was 70 kg(BMI 37.9), and the onset of polyuria and polydipsia started. She was diagnosed as having type 2 diabetes mellitus and was treated with insulin and metformin. At that time, she had nephrotic-range proteinuria without hypoalbuminemia or edema. Her blood pressure was 134/72 mmHg. Urinalysis revealed proteinuria(3+), but no hematuria. The serum concentration of creatinine was 1.1 mg/dl, urea nitrogen 20 mg/dl, total protein 6.8 g/dl, albumin 3.5 g/dl, and cholesterol 382 mg/dl. The C3 and C4 level were within normal ranges. Her daily protein excretion was 4.0 g and the creatinine clearance was 44 ml/min/1.73m^2. Ultrasonography examination showed no abnormality in both kidneys. The light microscopic examinations of a renal biopsy specimen showed segmental sclerosis of 13 of 25 glomeruli(52%). Most of the glomeruli showed moderate to severe increases in size and there was segmental hypercellularity with mesangial cells. The mesangial matrix was also increased to some degree, and the epithelial foot processes showed focal effacement. The tubules revealed focal atrophy or loss with some interstitial fibrosis(Fig. 1). Immunohistochemistry did not show any deposition of immune complex or autoantibodies. These changes were compatible to the diagnosis of OB-FSGS and glomerular hypertrophy. She has been treated with angiotensin-converting enzyme inhibitor(ACEI) and HMG-CoA reductase inhibitor. During the follow-up period, the proteinuria has persisted

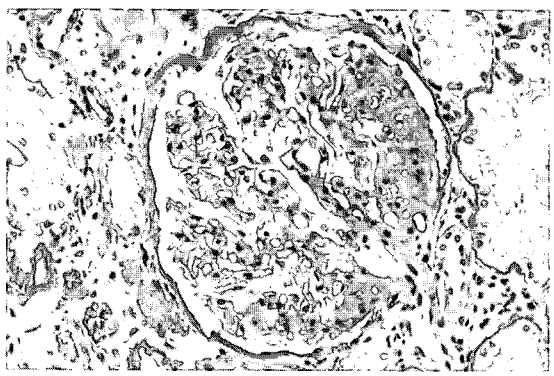

Fig. 1. Light microscopy of renal specimen showing focal and segmental glomerulosclerosis with glomerulomegaly and increase in mesangial matrix (H&E, ×100)

but the renal function remained normal.

DISCUSSION

We report here on a girl with Prader-Willi syndrome who presented with nephrotic-range proteinuria without edema under the diagnosis of OB-FSGS. Regarding the renal involvements in PWS, there are two possible explanations. One explanation is the disease was due to FSGS secondary to obesity and the other explanation is that this is a case of primary FSGS as a simple complication of PWS. It is difficult to state for sure whether the renal manifestation displayed here is from primary or secondary FSGS, but the latter holds more possibility because the patient had severe obesity, and she had no hypoalbuminemia or edema[2, 6-13]. Recent reports have shown that OB-FSGS patients do not develop hypoalbuminemia and they lack the other characteristic features of nephrotic syndrome despite the massive proteinuria[6, 8, 11, 13], and that the glomerular diameters are significantly greater than those of primary FSGS[7, 8, 10, 11, 13]. Other pathologic findings supporting secondary FSGS in this case are the glomerular hypertrophy and increased mesangial matrix.

Severe obesity has a high association with increased systemic arterial blood pressure, high renal plasma flow(RPF), an increased glomerular filtration rate(GFR), and an enhanced albumin excretion rate[8, 9]. Obesity-associated proteinuria has been reported for the first time in 1974[6, 8], and FSGS together with glomerulomegaly were the most common pathological findings in these patients[6-8, 10]. The typical renal histologic features of OB-FSGS include glomerular hypertrophy, FSGS, an increased mesangial matrix and cellularity, relatively preserved foot process morphology, and no evidence of inflammatory or immune-mediated pathogenesis[8]. There have been some hypotheses suggested to explain the causes of FSGS in obese patients. First, obese patients show characteristic hemodynamic changes of glomerular hyperfiltration, including vasodilation of the glomerular afferent arteriols with an increased GFR and am increased filtration fraction[2, 6, 8, 11]. FSGS also occurs in other clinical conditions associated with hyperfiltration such as reduced renal mass, severe vesicoureteral reflux, or for patients with a solitary kidney[6]. The glomerulomegaly and glomerular hypertrophy are known to be common findings in renal diseases mediated by hyperfiltration[8, 13]. Second, the characteristic insulin resistance and hyperinsulinemia of these obese patients could increase the synthesis of several growth factors that induce glomerular sclerosis and hypertrophy [6-8, 11, 14]. There are some evidences that hyperinsulinemia itself can induce preglomerular vasodilation and also activate the renin-angiotensin system(RAS)[6-8, 11, 14]. Third, hyperlipidemia can contribute to renal injuries. In obese Zucker rats, which is valuable animal model for studying kidney disease associated with obesity and diabetes, correction of the hyperlipidemia decreased or prevented the development of FSGS[6, 8, 11]. In addition, some reports have suggested that obese patient with FSGS, compared to those obese patients without FSGS, had higher blood cholesterol

and larger glomeruli[6, 8, 11]. Fourth, some reports have suggested that FSGS in obese patients is not due to hyperfiltration, but to renal venous hypertension[11]. The conditions associated with increased right atrial pressure and the presumed renal venous hypertension such as tricuspid atresia, constrictive pericarditis, and pulmonary hypertension have also been associated with proteinuria and nephrotic syndrome[15]. In a rat model of renal vein constriction and contralateral nephrectomy, urinary protein excretion was markedly increased, whereas the serum albumin and cholesterol levels remained normal [11]. The proteinuria seen in renal vein constriction may be due to changes in the glomerular transcapillary hydraulic pressure, which is mediated by angiotensin II and is largely reversed by an infusion of angiotensin II antagonist[11]. Fifth, sleep apnea can induce sympathetic activation of RAS to the glomerular hypertension, and FSGS lesions with glomerulomegaly are the eventual result[6, 8, 11]. Oxygen treatment has been shown to decrease the proteinuria in patients with sleep apnea syndrome[6]. Sixth, recent experimental studies have shown that leptin, a hormone produced by adipocytes and the serum level of which has a close relationship with body weight, can induce proteinuria, glomerulosclerosis, and the increased synthesis of glomerular transforming growth factor-β and deposition of type IV collagen[7, 8, 10].

Some studies have demonstrated that patients with OB-FSGS exhibit distinctive clinical profiles that differ from those usually seen in primary FSGS[6, 13]. First, the appearance and progression of the markers for renal disease(proteinuria, increasing serum creatinine levels) are slow to develop in these OB-FSGS patients[6, 13]. Second, the typical clinical findings of nephrotic syndrome are seldom manifested despite the heavy proteinuria in these OB-FSGS cases [6, 13]. The reasons why patients with OB-FSGS have a lower incidence of nephrotic syndrome compared to primary FSGS patients are not yet known, but there are some possible explanations for it. One of them is the slow increase in proteinuria that is, observed in FSGS secondary to obesity, which may allow compensatory mechanisms to counterbalance the proteinuria[6, 13]. Another possible explanation is that the patients with massive proteinuria and hypoalbuminemia have shown significantly higher urinary excretions of N-acetyl-B-glucosaminidase and β2-microglobulin than those patients with similar levels of proteinuria without the hypoalbuminemia[6, 8, 13]. These results may suggest that an altered tubular handling of the filtered proteins could have certain biochemical repercussions for the proteinuria in OB-FSGS[6, 8, 13]. However, whether the existence of glomerular hyperfiltration could influence the tubular handling of filtered proteins has not been yet investigated.

Distinguishing OB-FSGS from primary FSGS holds important implications both for the prognosis and treatment of the disease [10]. OB-FSGS has better renal survival compared to primary FSGS[8, 13, 15]. Whereas primary FSGS may respond to immunosuppressive treatment, OB-FSGS should be managed with weight reduction[8-11, 13, 15],

lipid lowering agents[8], and ACEI or angiotensin receptor antagonists[7, 8, 11, 13, 15], and these treatment have shown a remarkable capacity to halt the progression toward advanced renal insufficiency[11]. Corticosteroids, the mainstay of therapy for primary FSGS, are contraindicated in OB-FSGS because they may exacerbate the obesity[15]. Several cases have been reported in which extensive reduction of body weight markedly reduced the GFR and RPF, and it reduced or eliminated the proteinuria[6,11-13]. The favorable prognosis for OB-FSGS despite not using steroids treatment provides solid proof that this condition is a distinct and separable clinicopathologic entitiy[8]. Recent reports suggest that ACEI may halt the progression of renal insufficiency in patients with OB-FSGS[6, 11], but only if such treatment is initiated when the renal function is still normal[6]. It is not clear whether the action of ACEI in OB-FSGS is related to hemodynamic changes in the efferent arteriolar resistance or to non-hemodynamic factors, or to the combination of the two. It's also not clear how chronic ACE inhibition may affect the long-term course of FSGS[11]. A case of PWS combine with unilateral renal agenesis that, later developed FSGS and end-stage renal failure at an age of 16 years was reported by H. Mochizuki et al.[2]. In that case, the combination of unilateral renal agenesis with obesity appeared to be a main driving force in the progression of FSGS[2]. We made sure that our patient had OB-FSGS, and we put her exclusively on ACEI and a lipid lowering agent. The patient was later complicated with diabetes mellitus, and it could be possible that the renal injury may be exacerbated by type 2 diabetic nephropathy. We come to the conclusion that severe obesity, even in children, should be monitored carefully for the appearance of proteinuria, because early diagnosis is the best way to prevent OB-FSGS from progressing to far advanced renal insufficiency.

한 글 요 약

비만성 사구체경화증(obesity-associated focal segmental glomerulosclerosis)은 비만과 부종이 없는 신증후군 범위의 단백뇨, 사구체 비대 및 경화 등의 임상상을 보이는 질환으로, 다수의 환자에서 신부전으로 진행되는 것으로 알려져 있다. 연구자들은 부종 없이 심한 단백뇨와 저알부민혈증을 보인 14세의 Prader-Willi 증후군 여아에서 신생검을 통하여 사구체비후와 메산지움 증식이 동반된 국소성 분절성 사구체경화 소견을 관찰하였다. 이로써 소아의 Prader-Willi 증후군에서도 비만성 사구체경화증에 의한 신부전으로의 진행 위험이 있음을 알리는 바이다.

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