Severe Intimal Thickening of Interlobular Arteries Revealed by a Renal Biopsy in an Adult with Prader-Willi Syndrome Complicated by IgA Nephropathy

Takayasu Ito, Eiji Ishikawa, Mika Fujimoto, Tomohiro Murata, Norikazu Yamada and Masaaki Ito

Abstract

Renal complications are rare in patients with Prader-Willi syndrome (PWS). We herein experienced a 31-year-old woman with PWS, in whom a renal biopsy showed IgA nephropathy and severe intimal thickening of the interlobular arteries. The patient was admitted to our hospital due to proteinuria and microscopic hematuria after an upper respiratory infection. The occurrence of cardiovascular events has been reported as a cause of death in obese PWS patients. Because chronic kidney disease is generally a risk factor for cardiovascular disease, early detection checkups are essential in obese PWS patients to monitor the possible development of cardiovascular disease.

Key words: Prader-Willi syndrome, IgA nephropathy, atherosclerosis

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Introduction

Prader-Willi syndrome (PWS) is characterized by fetal muscle hypotonia, obesity from childhood, hypogonadotropic hypogonadism, mental retardation, and small hands and feet. Renal complications are rare in patients with PWS (1). Conversely, cardiovascular disease has been reported as one of the causes of death after 15 years of age in PWS patients with obesity (2). However, there have been few reports to date discussing the arteriosclerotic changes in the vital organs of obese patients with PWS syndrome. We herein present an adult obese patient with PWS complicated with IgA nephropathy. Importantly, a renal biopsy showed severe arteriosclerosis in this patient.

Case Report

A 31-year-old woman with PWS visited our hospital due to proteinuria and microscopic hematuria. She had been diagnosed with PWS at 2 years of age. She had had no proteinuria or hematuria until she was 30 years of age. One year previously, after an upper respiratory infection, proteinuria and microscopic hematuria (not gross hematuria) persisted. A physical examination revealed features of PWS, including obesity (body weight 57.4 kg; body mass index 30.0), short stature (height 139 cm), short hands and feet, almond-shaped eyes, and an open, inverted, V-shaped mouth. Her blood pressure was 120/70 mmHg, and her pulse rate was 80 bpm. She had no leg edema or purpura. The laboratory data revealed the following: white blood cell count 9,070/μL; hemoglobin 13.0 g/dL; platelets 35.5×10^4/μL; blood urea nitrogen 14 mg/dL; creatinine 0.81 mg/dL; total protein 6.9 g/dL; albumin 3.8 g/dL; blood glucose 107 mg/dL; HbA1c 5.0%; total cholesterol 329 mg/dL; low-density lipoprotein 229 mg/dL; high-density lipoprotein 70.8 mg/dL; IgA 395 mg/dL; C3 132.5 mg/dL. A urinalysis showed the following: uric protein, 5.7 g/gCre; occult blood, 3'; beta 2-microglobulin, 362 μg/L. The urinary sample showed granular casts and red blood cell casts. Although the patient did not have diabetes mellitus, an oral glucose tolerance test using 75 g revealed borderline diabetes. The size of each kidney was within the normal range, as observed on ultrasound. Her ankle-brachial index (ABI) was normal.
Figure 1. A renal biopsy shows glomeruli with diffuse mesangial matrix expansion, mesangial cell proliferation, cellular crescent (red arrow), and fibrocellular crescents (white arrow).

Figure 2. A renal biopsy shows severe intimal thickening in the interlobular arteries and arteriolar hyalinosis (red arrow).

(right: 1.18; left: 1.25); however, her pulse wave velocity (PWV) was significantly high (right: 1,330 cm/sec; left: 1,344 cm/sec). There was no plaque in the arteries of either of her lower limbs or in her carotid arteries, as seen on ultrasonography. A fundus examination showed no abnormal findings including hypertensive or diabetic changes in her eyes.

Renal biopsy

A light microscopic examination of the patient’s renal biopsy specimen identified 33 glomeruli, with the collapse of 12, 1 cellular crescent, and 5 fibrocellular crescents (Fig. 1). Mesangial matrix expansion and mesangial cell proliferation were remarkable. The capillary walls were observed to have no bubbly appearance or spike formation. There was severe intimal thickening in the interlobular arteries and arteriolar hyalinosis (Fig. 2). Immunofluorescence microscopy showed granular deposition of IgA and C3 in the mesangial matrix (Fig. 3). According to these findings, the patient was diagnosed with IgA nephropathy and severe arteriosclerosis.

Clinical course

Her general condition did not change after the renal biopsy, and diet therapy and a statin medication were started. An angiotensin receptor blocker and anti-platelet agent were also prescribed. Tonsillectomy and three courses of steroid pulse therapy were performed. However, oral steroid therapy was not scheduled during or after steroid pulse therapy. The subsequent urinalysis showed improvement in the patient’s proteinuria and hematuria. Her proteinuria decreased from 5.7 to 2.2 g/gCr and hematuria from 3+ to 2+ two months after tonsillectomy and three courses of steroid pulse therapy. Additionally, the granular casts and red blood cell casts disappeared. Her creatinine levels have not changed.

Discussion

In this case, we highlight two important clinical issues. First, renal complications are rare in patients with PWS. To the best of our knowledge, this is the first report of an adult obese patient with PWS complicated by IgA nephropathy. Several renal complications, such as focal segmental
Figure 3. Immunofluorescent analyses for IgA and C3 are positive.

Table. Renal Complications in Patients with Prader-Willi Syndrome.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Kidney Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>16</td>
<td>Focal segmental glomerulosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>Membranoproliferative glomerulonephritis</td>
<td>3</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>Renal tubular acidosis</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>Mesangioproliferative glomerulonephritis</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>IgA nephropathy</td>
<td>This case</td>
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glomerulosclerosis (1), membranoproliferative glomerulonephritis (3), renal tubular acidosis (4), and mesangioproliferative glomerulonephritis (5), have been previously reported (Table). All of these reported cases may be negative with respect to causality in relationship with PWS. We speculate that our PWS patient developed IgA nephropathy in response to her upper respiratory infection. It is unclear whether there is a causal relationship between PWS and IgA nephropathy. However, it have been reported that adult PWS patients are susceptible to respiratory infections related to hypotonia (6). Although the pathogenesis of IgA nephropathy has not yet been fully elucidated, IgA nephropathy is generally assumed to be an immune complex disease in which a complex of antigen, complement and IgA antibodies in the blood is deposited into the renal glomeruli. A virus, such as Epstein-Barr (EB) virus, adenovirus, or herpesvirus, is reported to be one of the antigens forming the immune complex (7). These viruses generally cause upper respiratory infection, and some adult patients with PWS may be prone to developing IgA nephropathy in response to an upper respiratory infection.

Second, the renal biopsy revealed that intimal thickening of the interlobular arteries and arteriolar hyalinosis were severe in our patient in her 30s without the presence of atherosclerosis. While the etiology of intimal thickening of the interlobular arteries is not entirely clear, it is accelerated by hypertension. Intimal thickening in the interlobular arteries may cause abnormal transmission of the pulse wave into the small distal branches, leading to arteriolar hyalinosis (8). Arteriolar hyalinosis is more common in persons over 50 years of age without hypertension or diabetes (9). The development of arteriolar hyalinosis is associated with hypertension and diabetes. However, the present patient had no hypertension or diabetes and was 31 years of age. Although considered in the autopsies of persons who died from myocardial infarction, histological changes (such as arteriolar hyalinosis and arteriosclerosis of medium-sized arteries) are strongly associated with the renal function and proteinuria (10).

The prognosis of obese PWS patients is poor due to cardiovascular disease, choking, and infection associated with obesity (2). Conversely, the incidence of diabetes mellitus in adult PWS patients is low, and the prevalence of cerebrovascular accidents in non-obese PWS patients is also low (11). Thus far, there has been no published study showing histological evidence of arteriosclerosis in patients with PWS. Despite the young age of the present patient, vascular remodeling of the interlobular arteries and arterioles was observed, which is typically determined to indicate arteriosclerosis in the renal biopsy. It is unclear whether obese PWS patients potential have severe arteriosclerosis if they have no hypertension, diabetes, or smoking history. Our patient’s other arteries, such as the carotid artery and the arteries of her lower extremities, showed no obstruction or remodeling on ultrasonography. However, we speculate that remodeling of the arteries may progress rapidly, and arteriosclerosis may be promoted when some type of load, e.g., glomerulonephritis such as IgA nephropathy, is applied to the vessels and organs in PWS patients.

Intimal thickening of the interlobular arteries plays an important role in glomerular sclerosis in IgA nephropathy patients with mild proteinuria (12). Patients with hypertension show more severe intimal thickening of the interlobular arteries than those without hypertension (12). Although the possibility of coincidental development of PWS, IgA nephropathy and intimal thickening of the interlobular arteries cannot be completely excluded, we believe that PWS may be a risk factor for vascular remodeling. Apart from that, PWS patients have hypogonadotrophic hypogonadism and estrogen secretion insufficiency. Such combined factors as
PWS, obesity, IgA nephropathy, and estrogen secretion insufficiency may be associated with intimal thickening of the interlobular arteries and arteriolar hyalinosis.

In the present case, we decided to prescribe steroid pulse therapy and perform tonsillectomy for her IgA nephropathy treatment. Maintenance therapy of oral steroid was not performed. Steroid therapy may be considered to be a risk of arteriosclerosis and CVD events. However, Walker reported that oral steroid administration at a dose of less than 7.5 mg/day did not increase the risk of CVD events and all cause of death (13). Asanuma et al. reported that the activity of systemic lupus erythematosus increased the risk of arteriosclerosis and CVD events more than steroid oral administration (14). Proteinuria is an independent risk factor of CVD in CKD patients (15). The reduction of proteinuria is associated with a good prognosis, such as decreases in all cause death and renal function in IgA nephropathy patients (16). In the present case, the reduction of proteinuria may contribute to the significant improvement of arteriosclerotic progress and CVD events. Therefore, we decided to prescribe steroid pulse therapy and perfume tonsillectomy because the glomeruli, except collapsing glomeruli in IgA nephropathy, demonstrated active inflammation, such as cellular crescents. In order to suppress the arteriosclerosis progress and CVD events, an angiotensin receptor blocker and anti-platelet agent were started in addition to the statin. Steroid therapy should be carefully discussed in severe arteriosclerosis cases, including the present case. Although the patient’s urinalysis improved after tonsillectomy and steroid pulse therapy, we also should carefully observe her clinical course.

The lower intelligence quotient (IQ) in PWS patients confers on them a higher hazard ratio for death (17). The reason may be their inability to ask for help regarding their condition and its associated manifestations. The present patient could not speak meaningfully. It is necessary to conduct thorough medical examinations, including urinalyses, in adult obese patients with PWS and a low IQ, because they may have cardiovascular disease caused by arteriosclerosis. Careful attention is required to monitor the present patient for the possible future occurrence of cardiovascular events, especially since she has a combination of obesity and chronic kidney disease in addition to PWS, as it is difficult for her to seek help for her symptoms. We speculate that the ABI, PWV, and fundus image could be useful non-invasive tools to detect arteriosclerosis in the early phase, especially in young patients.

In conclusion, we reported the case of a 31-year-old woman with PWS complicated by IgA nephropathy. The renal biopsy revealed severe intimal thickening of the interlobular arteries, which is considered to be an atherosclerotic change. Because PWS patients with low IQ cannot recognize their own symptoms, risk reduction and the early detection of cardiovascular disease and chronic kidney disease are required via medical examinations, including urinalyses. The causal relationship between PWS and renal complications is unknown because the number of reports is small. The future accumulation of cases is necessary.

The authors state that they have no Conflict of Interest (COI).

References