

Early onset of diabetic nephropathy in a child with type 1 diabetes mellitus

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An 11-year-old prepubertal girl with a history of metabolically poorly controlled type 1 diabetes for six years was diagnosed with diabetic nephropathy based on persistent overt proteinuria, hypertension, and renal biopsy findings typical of diabetic nephropathy. This case illustrates that diabetic nephropathy can develop even before puberty when metabolic control of the disease is not sufficient.

Key words: diabetic nephropathy, type 1 diabetes mellitus, children.

Diabetic nephropathy (DN) is characterized by persistent proteinuria, decline in renal glomerular function, hypertension, and progression to end stage renal disease. It is an unusual finding in the pediatric age group, especially in the prepubertal period^{1,2}. Poor glycemic control and genetic factors are believed to be responsible for the development of DN^{3,4}. Here we present a prepubertal girl with six years of poorly controlled type 1 diabetes, who was diagnosed with DN.

Case Report

An 11-year-old girl with type 1 diabetes was admitted with diabetic ketoacidosis. She had been followed for her type 1 diabetes for six years in another hospital. Her history demonstrated poor control of the diabetes, such as recurrent diabetic ketoacidosis (DKA), hypoglycemic episodes, and frequent hospitalizations. There was no history of diabetes, any renal disease, or hypertension in her family. At the time of admission she was receiving two daily injections (mornings 15 units, evenings 12 units) of NPH insulin (one unit/kg). On her physical examination, her height and weight were below third percentile. Her blood pressure was 115/70 mmHg. No hepatomegaly and peripheral edema was detected. Her ophthalmologic and neurologic examinations were normal. Her sexual development was Tanner stage 1 and her bone age was of a 7-year-old female. She had never been evaluated for urinary

microalbumin or HbA1c levels. Her HbA1c level was found as 16.1% (reference range 3.5-6.9). Her blood glucose level was 471 mg/dl and urinary albumin was found as 308 µg/min. She recovered from DKA with appropriate management and with a new insulin regimen consisting of two daily injections of a mixture of regular and NPH insulins; a near-normal glycemia was established. On her follow-up monthly visits, her blood pressure was detected as higher than age- and sex-matched healthy children. Laboratory work-up showed the following: urinalysis; specific gravity 1015; 2+ protein; glucosuria; a few red blood cells in urine sediment. The urine protein (U_p) was 22 mg/dl, urine creatinine (U_{Cr}) 20 mg/dl, and U_p/U_{Cr} ratio 1.1 mg/mg. Serum electrolytes were normal; BUN 14 mg/dl, serum creatinine 1.0 mg/dl, calcium 8.7 mg/dl, phosphorus 5.6 mg/dl, total protein 6.7 mg/dl, serum albumin 3.0 g/dl, serum cholesterol 332 mg/dl (normal range 125-300 mg/dl), low density lipoprotein 223 mg/dl (normal range 80-150 mg/dl), high density lipoprotein 62 mg/dl (normal range 35-65 mg/dl), serum C_3 145 mg/dl, and serum C_4 28 mg/dl. Protein electrophoresis revealed: 51%; α_1 2.7%; α_2 13.7% β 14.1; γ 18.1%; Hb A_{1c} 16.4 mg/dl (reference range 3.5-6.9%); and creatinine clearance (C_{Cr}) calculated with the Schwartz formula 80 ml/min/1.73 m². Abdominal ultrasonography showed normal size of the liver and the kidneys were also

normal. Electromyography findings and thyroid function tests were within normal limits. One week later, the early morning U_p was 154 mg/dl and U_{Cr} 26.6 mg/dl, Daily protein excretion was 100/mg/m²/hour. Her blood pressure ranged between 100/60 and 140/100 mmHg.

A percutaneous renal biopsy was performed. On light microscopic examination, increased mesangial matrix and glomerular basement membrane thickening were seen in all glomeruli (Fig. 1). Also, mesangial matrix nodular formation was noted in a few glomeruli. Immunofluorescence microscopy showed linear staining for IgG in glomerular basement membranes. On electron microscopy, glomerular basement membrane thickening and increased mesangial matrix were found (Fig. 2). Upon establishing the diagnosis of diabetic nephropathy, an angiotensin-converting enzyme (ACE) inhibitor, captopril, was started. On her follow-up evaluations, a gradual decline in albumin excretion was observed. However, the level of albuminuria has remained in the macroalbuminuric range, despite the establishment of a near-normal glycemic control.

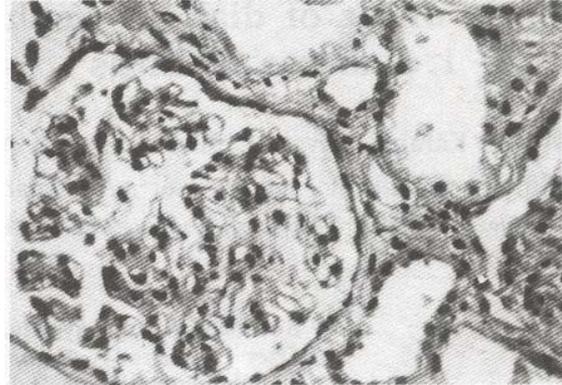


Fig. 1. Hematoxylin and eosin stain demonstrating increased mesangial matrix and glomerular basement membrane thickening (magnification x400).

Discussion

Diabetic nephropathy is a clinical condition characterized by persistent proteinuria, decline in glomerular function, hypertension, and progression to end-stage renal disease. Among the complications of type 1 diabetes, nephropathy is the major life-threatening one⁵. Our patient was unusual in that a persistent overt proteinuria was documented in the prepubertal age with no

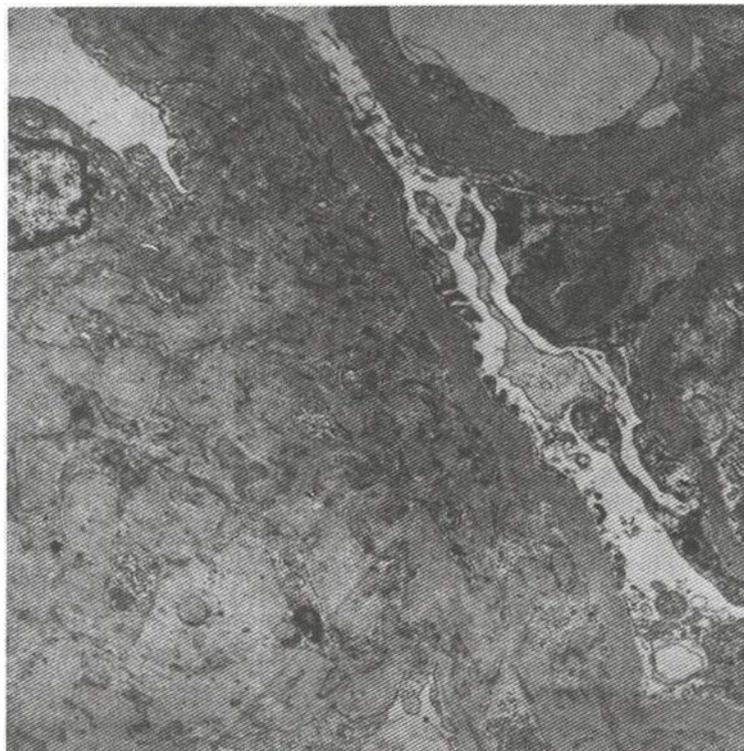


Fig. 2. Gross thickening of the glomerular basement membrane and increased mesangial matrix demonstrated on electron microscopy (magnification x8800).

family history of DN or hypertension, or personal history of any renal disease.

There are only a few reports of diabetic children who develop DN in the prepubertal period^{1,2}. Francis et al.¹ reported a DN case in a 12-year-old Asian girl with a four-year history of poorly controlled type 1 diabetes without a family history of DN. DeClue et al.² reported a prepubertal child with less than five years' duration of diabetes with a family history of DN. In our case, the child was in the prepubertal period with six years' duration of diabetes and she had characteristic clinical features of DN. She had significant growth retardation, proteinuria, hyperlipidemia and hypertension. In the literature, poor glycemic control, hypertension, genetic factors, hyperlipidemia and duration of the disease have been found to be associated with an increased risk for diabetic nephropathy^{2,3}. Advanced glycation products (AGPs) are shown to be important pathogenetic factors, causing renal damage by increasing the production of mesangial cell transforming factor β and platelet derived growth factor AGPs increase the synthesis of basement membrane, collagen and mesangial matrix, and enhance vascular permeability⁶. Poor control of diabetes, such as recurrent diabetic ketoacidosis, hypoglycemic episodes and frequent hospitalizations, is the likely explanation for DN in our case. It is reported that tight glycemic control has an impressive effect in both delaying the onset and slowing the progression of long-term diabetic complications, such as nephropathy, retinopathy and neuropathy⁷. Our patient had very poor glycemic control because of inappropriate insulin regimen. Renal biopsy findings of our patient revealed mesangial matrix expansion, thickening in the basement membrane and linear deposition of IgG.

The patient was in stage IV diabetic nephropathy with the presence of proteinuria, hypertension and hyperlipidemia. Similar to our patient, it has been shown that hypertension in diabetic patients accompanies, rather than precedes, the onset of the nephropathy⁷. Hyperlipidemia typically develops once microalbuminuria has occurred. There are variable increases in low-density lipoprotein cholesterol and lipoproteins in these patients⁸. Proteinuria is the hallmark of diabetic nephropathy. But it could also be the result of the diabetic nephropathy or superimposed glomerulopathy⁹. Furthermore, the onset of

proteinuria is associated not only with renal morbidity and mortality but also with an increased risk of other diabetes complications⁵. Our patient had no retinopathy and had normal electromyographic findings. Several investigators have reported a variety of chronic glomerulonephritis and minimal change disease in children with type 1 diabetes^{9,10}. Therefore, the differential diagnosis should be based on the biochemical parameters and renal biopsy findings. Our patient's complement levels were within normal limits and renal biopsy findings were consistent with DN. Enlarged glomeruli, thickened glomerular and tubular basal membranes with mostly IgG and albumin deposits and mesangial hypercellularity are always seen when significant proteinuria is detected in DN.

It has been demonstrated that ACE inhibitors delay the progression of the diabetic nephropathy by normalizing glomerular capillary pressure independent of their antihypertensive effect¹¹. After starting captopril, an angiotensin converting enzyme inhibitor, the patient's proteinuria gradually decreased and her blood pressure normalized with the metabolic control of hyperglycemia.

In conclusion, the appearances of proteinuria and hypertension during the prepubertal period suggest that metabolic control of diabetes seems to be an important factor of diabetic nephropathy. Careful blood pressure screening is strongly recommended because blood pressure is often raised in microalbuminuric patients⁵.

Screening for microalbuminuria should be done regularly in pediatric patients for preventing diabetic nephropathy.

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