Unusual association of diseases/symptoms

Simultaneous onset of steroid resistant nephrotic syndrome and IDDM in two young children

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Summary

The cases are reported of two young children who developed insulin-dependent diabetes mellitus (IDDM) within 2 weeks of receiving a diagnosis of nephrotic syndrome. Neither patient responded to 8 weeks of daily prednisolone.

The first patient presented at 2 years and 9 months of age. Her renal biopsy showed mesangial proliferation. The second child presented with steroid resistant nephrotic syndrome at 18 months of age and developed IDDM 2 weeks later. He achieved partial remission with cyclosporine therapy. His initial renal biopsy at 3 years of age showed minimal change disease and follow-up renal biopsy at 5 years of age showed early diabetic glomerulosclerosis. Tests for NPHS2 and WT1 genetic mutations were negative in both patients.

To our knowledge this is the first report of steroid resistant nephrotic syndrome with almost simultaneous onset of IDDM in young children.

BACKGROUND

Insulin-dependent diabetes mellitus (IDDM) is associated with diabetic nephropathy which occurs in more than 50% of patients with childhood onset IDDM after approximately 12 years of disease.¹ Renal presentation of diabetic nephropathy is usually in the form of microalbuminuria and sometimes macroalbuminuria.^{1 2} Five years after the onset of IDDM in children, early changes in renal haemodynamics are detectable on Doppler sonography without any evidence of renal dysfunction; this suggests a preclinical phase of diabetic nephropathy.^{3 4}

The association between IDDM and steroid-sensitive nephrotic syndrome (SSNS) with minimal change glomerulopathies has been reported previously in several cases.^{5–9} However, simultaneous onset of steroid resistance nephrotic syndrome (SRNS) and IDDM has been reported in only one case in the literature and was of juvenile onset.⁸

The authors report the cases of two young children who developed SRNS and IDDM almost simultaneously.

CASE PRESENTATION

Case 1

A 3-year-old Saudi girl was diagnosed with SRNS at the age of 2 years and 9 months. She was described by the referring paediatrician as having nephrotic syndrome that developed into IDDM 2 weeks after commencing daily oral prednisolone to treat her nephrotic status. She did not respond to 8 weeks of oral prednisolone (60 mg/m²/day) and was therefore diagnosed with SRNS. She was referred to our institution 4 months after her initial presentation.

At presentation to us her weight was on the 90th centile, her height was on the 5th centile and she had normal blood pressure of 105/75 mm Hg. Her family history was negative for renal disorder, diabetes mellitus and consanguinity.

Case 2

A 5-year-old Saudi boy was diagnosed with SRNS at the age of 18 months. Similar to the first case, he was initially commenced on daily oral prednisolone (60 mg/m²/day). However, the referring paediatrician reported that 2 weeks after his initial presentation, he developed symptoms of IDDM with polyuria, polydipsia and weight loss. The diagnosis of diabetes mellitus was confirmed by a high blood glucose level of 20 mmol/l and 4+ glucose in urine.

The child's first renal biopsy was carried out at the referring institution at the age of 3 years and was compatible with minimal change disease (MCD). The patient received a 12-week course of oral cyclophosphamide and achieved incomplete remission.

He was referred to our institution at the age of 5 years as having SRNS. At presentation to us his weight was on the 25th centile, his height was on the 10th centile and he had normal blood pressure of 85/55 mm Hg. The family history was negative for renal disorder, diabetes mellitus and consanguinity.

INVESTIGATIONS

Case 1

Investigations for case 1 showed low serum albumin of 19 g/l, high blood glucose 19 mmol/l, normal serum creatinine 28 µmol/l, high urine protein 1000 mg/l (++) and normal complements: C3 0.77 g/l (0.75–1.65) and C4 0.19 g/l (0.2–0.6). The patient had negative screening for hepatitis B and hepatitis C. She had normal thyroid function tests, coeliac screen of tissue transglutaminase immunoglobulin A (IgA) 8 units (0–20), complete blood count (CBC), lipid profile, clotting profile and antibodies to glutamic acid decarboxylase (GADA); autoantibodies to islet cells insulin (IAA) and IA-2A protein were not investigated as this service is not available in our centre.

Renal biopsy was performed and submitted for light microscopy, immunofluorescence and electron microscopy studies. Under light microscopy the glomeruli showed diffuse expansion of mesangial matrix with normal mesangial cellularity and patent capillary lumina (figure 1A). There was no interstitial inflammation, fibrosis or tubular atrophy and blood vessels were unremarkable.

Immunofluorescence study showed (+1) IgM positivity in the mesangium and focal segmental distribution (figure 1B), but other antibodies and complements were negative.

Electron microscopic examination confirmed the increased mesangial matrix with rare nodules formation; the glomerular basement membrane demonstrated focal thickening and wrinkling. The epithelial foot processes were effaced, but there were no electron dense deposits (figure 1C).

The test for NPHS2 and WT1 genetic mutations was negative.

The family history was negative for renal disorder, diabetes mellitus and consanguinity.

Case 2

Investigations in case 2 showed mild low serum albumin of 30 g/l, high blood glucose 20 mmol/l, normal serum creatinine 36 µmol/l, significant proteinuria 600 mg/l (+) and normal complements: C3 1.30 g/l (0.75–1.65) and C4 0.22 g/l (0.2–0.6). The child had negative screening for hepatitis B and hepatitis C. Similar to the first case, he had normal thyroid function tests, CBC, lipid profile, clotting profile and coeliac screen of tissue transglutaminase IgA 21 units (0–20). As in the first case, we were unable to measure other immunological markers of IDDM, such as antibodies to GADA, IAA and IA-2A protein, as this service is not available in our centre.

Follow-up renal biopsy carried out at 5 years of age showed diffuse mesangial matrix increase with nodule formation on light and electron microscopy, findings compatible with early diabetic glomerular changes (figure 2A,B,C). There was no evidence of immune complex glomerulonephritis as shown by the negative immunofluorescence and absence of deposits on electron microscopy. These mild mesangial expansion changes were classified as class IIa.¹⁰

The test for NPHS2 and WT1 genetic mutations was negative.

The family history was negative for renal disorder, diabetes mellitus and consanguinity.

TREATMENT

Case 1

The patient was commenced on oral cyclophosphamide together with a tapering dose of oral prednisolone and ACE inhibitor. She achieved partial remission after 8 weeks of oral cyclophosphamide. At the end of the course her results revealed normal serum albumin 35 g/l (35–50 g/l) and 1+ proteinuria (300 mg/l). She was followed up for 1 year and continued to be in remission with no or minimal proteinuria (negative or trace).

Case 2

The patient was commenced on oral cyclosporine (5 mg/kg/day in two divided doses) together with a tapering dose of oral prednisolone on alternate days and ACE inhibitor. There was minimal improvement as his last results showed low serum albumin 37 g/l (35–45 g/l) and normal serum creatinine 40 µmol/l. His urine became negative to proteinuria as well as to microalbuminuria. He was followed up for 1 year and continued to be in remission.

Figure 1 Micrographs of the renal biopsy findings in case 1. (A) Light micrograph of a glomerulus showing mainly mesangial matrix expansion and segmental mild increase in mesangial cells (thick arrow) (periodic acid-Schiff stain). (B) A glomerulus showing positive immunofluorescence staining for immunoglobulin M in the mesangial area. (C) Electron micrograph demonstrating expansion of mesangial matrix (arrows) and thickened glomerular basement membrane.

Figure 2 Micrographs of the renal biopsy findings in case 2. (A) Light micrograph of a glomerulus exhibiting mild mesangial matrix expansion (arrow) (periodic acid-Schiff stain). (B) A glomerulus showing negative immunofluorescence staining. (C) Electron micrograph showing increased mesangial matrix with nodule formation (arrows).

OUTCOME AND FOLLOW-UP

Case 1

The diabetes mellitus was difficult to control as most of the time the patient had hyperglycaemia (>20 mmol/l), 4+ glycosuria, low serum C-peptide 0.023 nmol/l (0.37–1.47) and elevated haemoglobin (Hb) A1c 10–12% (normal 4–6%). She required a high insulin dose (around 1.3 IU/kg/day mix-tard). However, despite the poor control of her diabetes mellitus, she never experienced diabetic ketoacidosis.

Case 2

The diabetes mellitus was difficult to control as most of the time the patient had a high blood glucose level (>20 mmol/l), 4+ glycosuria, low serum C-peptide 0.109 nmol/l (0.37–1.47 nmol/l) and elevated HbA1c 10–12% (4–6%). He required a high insulin dose (around 1.4 IU/kg/day mix-tard). However, he never developed diabetic ketoacidosis.

DISCUSSION

The authors report the cases of two young children with almost simultaneous onset of SRNS and IDDM in early childhood. This could not be explained by diabetic microangiopathy as it usually takes several years to develop.^{1 2} Furthermore, both children initially presented with nephrotic syndrome and 2 weeks after commencing prednisolone, they were diagnosed with diabetes mellitus. There have been reports in adults of rare cases of glomerulopathies that are not diabetic nephropathies in the early phases of IDDM but rather immune complex glomerulonephritis such as IgA nephropathy and C1q nephropathy, which are often associated with significant proteinuria and

nephrotic syndrome resistant to immune-suppressor treatment.^{11 12} However, renal biopsies in our cases did not show immune complex glomerulonephritis.

There are several reports in the literature of SSNS coexisting with IDDM in children,^{5–9} but in none of the reports was treatment influenced by renal biopsy results which all showed MCD.^{5–9} However, daily steroid tapering was suggested in preference to alternate day steroids to allow better glycaemic control. Therefore, the indications for renal biopsy in nephrotic children with and without IDDM were suggested to be similar.¹³

Similarly, SSNS with MCD was reported in a patient with type 2 diabetes mellitus.¹⁴ It was accompanied by mild worsening of renal function. Steroid treatment induced complete remission of the nephrotic syndrome and recovery to normal renal function. The reported patient experienced two relapses, but was sensitive to steroid¹⁴ and eventually achieved persistent remission after a course of chlorambucil.

Interestingly, in a report of two young women who developed nephrotic syndrome within 2 weeks of presenting with IDDM, neither received steroids; in one of them the oedema resolved spontaneously while the other required diuretics.¹⁵ One of these patients had a renal biopsy which showed changes consistent with MCD on electron microscopy but no evidence of diabetic glomerulosclerosis.

The occurrence of MCD causing SSNS is rarely seen in IDDM patients presenting with nephrotic syndrome. Furthermore, in a search for an explanation of the coexistence of MCD in IDDM patients, the pathogenesis was linked to the shared human leucocyte antigen (HLA) typing in both IDDM and renal disease.^{5 6 16} In our cases we did not test

for HLA typing, however, our patients were negative for the genetic mutations underlying SRNS (podocin NPHS2 and WT1). The coexistence of the two diseases may be due to chance but could perhaps be caused by as yet undiscovered underlying genetic predisposing factors.

Our patients' pathology initially showed MCD but both had SRNS. It is generally accepted that SRNS is usually caused by non-MCD and is mostly due to focal segmental glomerulosclerosis (FSGS).¹⁷ In our cases the diagnosis of FSGS was not made on the first biopsies and so could have been missed or not present at all. The follow-up biopsy in the second case demonstrated more prominent glomerular changes which were consistent with class IIa diabetic nephropathy according to the 2010 classification of diabetic nephropathy of the Research Committee of the Renal Pathology Society.¹⁰

It is important to distinguish changes arising from diabetic nephropathy from other primary glomerular diseases developing on top of diabetic nephropathy in situations such as the second biopsy of case 2 where the changes were similar to early features of FSGS. It could not be distinguished at this stage whether the glomerular sclerotic lesions were caused by idiopathic FSGS or diabetic nephropathy.¹⁸

In another case series, a patient with juvenile onset IDDM presented with SRNS and associated mild diabetic glomerulosclerosis, and later developed Grave's disease.⁸ The association between IDDM and thyroid disease could be explained by an immunomediated underlying disease. Both of our cases had normal thyroid function tests. However, they did not have long duration of follow-up.

The observed poor control of diabetes mellitus in our two patients could be attributed to corticosteroid therapy. In both patients steroid treatment was accompanied by hyperglycaemia and glycosuria but not academia or ketonuria. However, the diagnosis of IDDM was confirmed as the diabetes did not resolve after tapering prednisolone therapy.

As mentioned earlier, diabetic microangiopathy was unlikely in our cases at presentation, although diabetes causes mostly glomerular disease. IDDM is associated with progressive increase in urinary albumin excretion to a nephrotic range proteinuria over 5–12 years, followed by hypertension and a decline in glomerular filtration rate (GFR) after a mean duration of 17 years of diabetes in patients at risk. The pathological lesions of diffuse glomerular sclerosis or nodular intercapillary glomerular sclerosis are typically seen in biopsies from patients with advanced diabetic nephropathy. There is a close correlation between the expansion of the glomerular mesangium and the declining filtration surface area, as well as the declining GFR in affected patients.¹⁹ Inadequate glycaemic control during the first 5 years of diabetes seems to accelerate time to occurrence, whereas a young age at diabetes onset seems to prolong the time to the development of microvascular complications.¹ Therefore, the occurrence of nephrotic syndrome at presentation in both patients could not be explained by IDDM. However, in the second case the presence of proteinuria could have accelerated the appearance of early diabetic changes which was controlled by the immune suppression and ACE inhibitor used for the nephrotic status.

Learning points

- The authors report two cases of almost simultaneous incidence of steroid resistance nephrotic syndrome and insulin-dependent diabetes mellitus in two young children.
- To our knowledge this is the first report of such concurrence in young children.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. *Diabetes Care* 2004;**27**:955–62.
2. Svensson M, Sundkvist G, Arnqvist HJ, et al. Signs of nephropathy may occur early in young adults with diabetes despite modern diabetes management: results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS). *Diabetes Care* 2003;**26**:2903–9.
3. Pelliccia P, Savino A, Cecamore C, et al. Early changes in renal hemodynamics in children with diabetes: Doppler sonographic findings. *J Clin Ultrasound* 2008;**36**:335–40.
4. Raes A, Donckerwolcke R, Craen M, et al. Renal hemodynamic changes and renal functional reserve in children with type I diabetes mellitus. *Pediatr Nephrol* 2007;**22**:1903–9.
5. Agras PI, Kinik ST, Cengiz N, et al. Type 1 diabetes mellitus associated with nephrotic syndrome. *J Pediatr Endocrinol Metab* 2006;**19**:1045–8.
6. Peces R, Riera JR, López Larrea C, et al. Steroid-responsive relapsing nephrotic syndrome associated with early diabetic glomerulopathy in a child. *Nephron* 1987;**46**:78–82.
7. Urizar RE, Schwartz A, Top F Jr, et al. The nephrotic syndrome in children with diabetes mellitus of recent onset. *N Engl J Med* 1969;**281**:173–81.
8. Gilboa N, Durante D, McIntosh RM, et al. Etiologic variability of nephropathy in juvenile diabetes mellitus. *Arch Pathol Lab Med* 1979;**103**:479–82.
9. Rego Filho EA, Mello SF, Omuro AM, et al. Simultaneous onset of steroid-sensitive nephrotic syndrome and type 1 diabetes. *J Pediatr (Rio J)* 2003;**79**:557–60.
10. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 2010;**21**:556–63.
11. Aziz S, Cohen AH, Winer RL, et al. Diabetes mellitus with immune complex glomerulonephritis. *Nephron* 1979;**23**:32–7.
12. Cavallo T, Pinto JA, Rajaraman S. Immune complex disease complicating diabetic glomerulosclerosis. *Am J Nephrol* 1984;**4**:347–54.
13. Goldman M, Hébert D, Geary DF. Management of steroid-sensitive nephrotic syndrome in children with type 1 diabetes. *Pediatr Nephrol* 2002;**17**:351–4.
14. García Donaire JA, Manzanera MI, Valentín MO, et al. Relapsing nephrotic syndrome in a diabetic patient with minimal change. *Nefrología* 2004;**24**:179–82.
15. Dornan TL, Jenkins S, Cotton RE, et al. The nephrotic syndrome at presentation of insulin-dependent diabetes mellitus: cause or coincidence? *Diabet Med* 1988;**5**:387–90.
16. Kagiya S, Tsuruta H, Tominaga M, et al. Minimal-change nephrotic syndrome and acute renal failure in a patient with aged onset insulin-dependent diabetes mellitus and autoimmune thyroiditis. *Am J Nephrol* 1999;**19**:369–72.
17. Gulati S, Sengupta D, Sharma RK, et al. Steroid resistant nephrotic syndrome: role of histopathology. *Indian Pediatr* 2006;**43**:55–60.
18. Alsaad KO, Herzenberg AM. Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update. *J Clin Pathol* 2007;**60**:18–26.
19. Mauer SM. Structural-functional correlations of diabetic nephropathy. *Kidney Int* 1994;**45**:612–22.

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