0021-7557/03/79-06/557
Jornal de Pediatria

CASE REPORT

Simultaneous onset of steroid-sensitive nephrotic syndrome and type 1 diabetes

Eduardo A. Rego Filho,[1] Solange F.R. Mello,[2] André M. Omuro,[3] José O.C. Loli[4]

Abstract

Objective: We describe the case of a boy with steroid-sensitive nephrotic syndrome coexisting with type-1 diabetes mellitus.

Description: Nephrotic syndrome was diagnosed in a boy (age 3 years and 11 months) with generalized edema. Marked weight loss (23 to 16 kg), polyuria, polydipsia and weakness were observed after three weeks of treatment with prednisone 2 mg/kg/day. Diabetic ketoacidosis was confirmed by laboratory tests: hyperglycemia (glucose 657 mg/dl), glycosuria without proteinuria, acidosis and ketonuria. Therapy with insulin and prednisone was started. He was then maintained on a daily dose of NPH insulin. At age 4 years and 1 month a new episode of ketoacidosis without proteinuria occurred in association with a viral infection of the upper airways. At age 4 years and 4 months nephrotic syndrome relapsed, but the child responded well to steroid therapy. There was another relapse three months later, when prednisone treatment was interrupted. This led to the introduction of cyclophosphamide, with good results. Since then, the patient (now 5 years and 6 months old) has been taking insulin daily and nephrotic syndrome has not relapsed. Plasma levels of C3 and C4 and renal function are normal. Hematuria is occasionally present. Anti-GAD antibodies (glutamic decarboxilase) are normal and anti-islet cell antibodies are positive. HLA antigens: A2; B44; B52; DR4; DR8; DR53.

Comments: The simultaneous occurrence of steroid-sensitive nephrotic syndrome and type-1 diabetes mellitus is rare.

J Pediatr (Rio J). 2003;79(6):557-60: *Type-1 diabetes mellitus, nephrotic syndrome, steroid-sensitive, HLA antigens.*

1. Professor, Department of Pediatrics and Pediatric Surgery, Centro de Ciências da Saúde, Universidade Estadual de Londrina, Londrina, PR, Brazil.
2. Associate professor, Department of Pediatrics and Pediatric Surgery, Centro de Ciências da Saúde, Universidade Estadual de Londrina, Londrina, PR, Brazil.
3. Pediatrician, Hospital Regional João de Freitas e Casa de Saúde Santa Rita, Arapongas, PR, Brazil.
4. Endocrinologist and metabologist.

Manuscript received Oct 28 2002, accepted for publication Jun 11 2003.

Introduction

Diabetes mellitus is a metabolic syndrome characterized by an absolute or a relative deficiency in insulin production or activity. Its current classification into diabetes mellitus type 1 or insulin dependant (IDDM) and type 2 or non-insulin dependent NIDDM) follows the recommendations of the World Health Organization.[1] Among children and adolescents, the most common type is IDDM with an incidence in our country of 7.4 cases/ 100,000 inhabitants per year.[2]

Nephrotic syndrome (NS) is characterized by edema, significant proteinuria, hypoalbuminemia and, often, hyperlipemia. In pediatrics the most common form is idiopathic or primary and the majority of these cases are associated with minimal change glomerulopathy.[3] There is a correlation between NS due to minimal change glomerulopathy and a favorable response to corticoid therapy and patients that respond to this treatment rarely suffer from other histological syndromes than minimal change glomerulopathy.[4] Sensitivity to corticoids has become synonymous with good prognosis and a histological profile of minimal glomerulopathies.[4] In the United States, among children and adolescents under 16, the incidence of this syndrome varies from two to nine new cases per 100,000 inhabitants per year.

The simultaneous and random occurrence of the two conditions, NS from minimal change glomerulopathies and type I diabetes mellitus, in the same patient is extremely rare.[5]

The objective of this article is to describe the case of a preschool male who presented, with an interval of three weeks, corticoid-sensitive NS and diabetic ketoacidosis. The description is justified by the rarity of the combination and the opportunity it provides of commenting on diagnostic conduct and the therapeutic difficulties related to the interference of one entity with the other.

Case history

V.P.D. born on 30 April 1997 in Arapongas in the state of Paraná, white, male. Onset aged three years and 11 months with edema progressing to anasarca in two weeks. The mother reported a weight gain of three kilograms.

Personal history was not significant. Family history: mother and uncle are albino, two family members - aunt and cousin on the mother's side - have been diagnosed with steroid-sensitive NS and a third degree cousin on the father's side has been diagnosed with type 1 diabetes mellitus.

On physical examination presented normal blood pressure with generalized edema. Weight was 23 kg and height 107 cm.

Initial laboratory examinations revealed: hypoalbuminemia at 1.4 g/dl and proteinuria at 529 mg/day or 28 mg/h/m^2 (significant proteinuria is above 40 mg/h/m^2).

On diagnosis of NS, treatment was begun with prednisone at a dosage of 2 mg/kg/day. After three weeks of daily treatment significant weight loss was observed (weight at 16.8 kg) along with polyuria, polydipsia and apathy. Further examinations revealed hyperglycemia at 687 mg/dl, acidemia, ketonuria and glycosuria without proteinuria. With the diabetic ketoacidosis diagnosis, insulin therapy was started in association with corticoid therapy. After the acidemia had been compensated for, the patient was maintained on daily doses of insulin NPH (20 UI a day in two doses). At four years and one month he presented a fresh episode of ketoacidosis associated with upper airway infection. On this occasion there was no proteinuria and he received prednisone at a dosage of 5 mg/day, which was suspended soon afterwards. At four years and four months he presented a fresh complex of generalized edema with significant proteinuria (4.3 and 4.6 g/day) and corticoid therapy was resumed (40 mg/day) with good clinical and laboratory responses. Three months later, during the corticoid withdrawal phase, he presented a fresh episode of decompensation with edema and significant proteinuria (4.7 g/day).

In August 2001, at four years and eight months, he was started on treatment with cyclophosphamide and prednisone on alternate days for 10 weeks with normalization of the proteinuria. By the date that data was collated, he had presented two relapses of the nephrotic syndrome and had received three cycles of immunosuppressor treatment, the first two with corticoid in isolation and the third with cyclophosphamide associated with prednisone on alternate days. In September 2002 he was still in remission.

During the period when data was collected, August 2002, at five years and eight months the patient was receiving insulin in varying doses depending on glycemia controls.

Renal biopsy has not been performed. During the two ketoacidosis episodes, maximum observed hyperglycemia was 678 mg/dl in December 2000 and 371 mg/dl in January 2001, both associated with severe acidemia.

The complementary examinations performed during the period of observation can be found in Table 1.

Discussion

Nephrotic syndrome associated with IDDM angiopathy occurs in 35 to 45% of patients after 10 or more years evolution. Its histological features are well defined, it does not respond to therapy with immunosuppressors and is associated with varying degrees of chronic renal failure, arterial hypertension and retinopathy.[6] Some authors have described rare cases of glomerulopathies that are not diabetic nephropathies in early phases of IDDM. They were thus described as immune complex glomerulonephritis by IgA and by C1q, often associated with significant proteinuria and NS resistant to immunosuppressor treatment.[7-9]

The prevalence of NS from minimal glomerulopathies is highly variable. In the USA there is an observed prevalence of 15.7 cases/100,000 children with a peak incidence among preschool children. The majority of patients are less than 6 years old at the onset of the syndrome. In the same country, the prevalence of IDDM is approximately 190/100,000 children with a peak incidence between 5 and 7 years and is 12 times more common than steroid-sensitive NS. Based on

Table 1 - Complementary examinations performed during the period of observation

Variable	Result	Reference value
C3	119 mg/dl	70 to 176 mg/dl
C4	30 mg/dl	15 to 45 mg/dl
Anti-GAD antibodies (glutamic decarboxilase)	0.40 U/ml	< 1.0 U/ml
Anti-islet cell antibodies	8.1 U/ml	< 0.50 U/ml
HLA antigens class I and II	A2; B44, B52; DR4, DR8, DR53	
Urea and plasma creatinine	Several findings, all of them were normal	
Hematuria	One initial episode	

this data from the USA, the chance of steroid-sensitive NS and IDDM occurring simultaneously in the same patient is estimated at one case in every 3,300,000 inhabitants at risk.

The first reported cases of this coincidence date from the start of the 1960s, with publications by McCrory in 1960 and Robinson in 1961.[10,11] Urizar added three more cases with histological features indicative of minimal change glomerulopathy, calling attention to the rarity of this occurring by chance and suggests the possibility that there may be metabolic defects in the basement membrane of the vessels that are common to both entities and which may be the pathogenic basis for both conditions, a supposition that is as yet unproven.[5]

The family history of this patient is particularly positive. He has a cousin on the father's side with difficult to control IDDM and on the mother's side a cousin and an aunt with steroid-sensitive nephrotic syndrome who are progressing well. The aunt's syndrome had onset at five years of age in 1987 and she has been in remission since 1988 while the cousin presents frequent relapses. The family-based pattern of IDDM and Steroid-sensitive NS occurrence, observed in association in the case described is well known in the scientific community. The albino mother and uncle are a new feature not found in bibliographical citations.

Studies of the HLA (human leukocyte antigen) of patients with IDDM have often encountered the antigen DR4 and in patients with NS the antigen DR7. Peces observed an association between DR4 and DR7 in patients with both conditions and speculates on the possibility of a similar etiopathogenesis influenced by genetic predisposition.[12,13] In our patient antigen assay revealed DR4.

Some of the clinical and epidemiological features common to both conditions can be found in Table 2.

What might the influence of one entity over the other be in terms of patient progress? Both entities and their respective treatments provoke, with frequency, profound systemic changes with abnormalities in protein, carbohydrate and lipid metabolism and reduced immune system competence.

Diabetic microangiopathy progresses during the initial phases with an increased rate of glomerular filtration (hyperfiltration). This situation is partially ameliorated by rigorous glycemia control, but protein loss may intensify

Table 2 - Clinical and epidemiological features of IDDM and NS

	IDDM	NS
Age of the highest incidence	5 to 7 years; puberty	2 to 6 years
Sex (M:F)	1:1	3:2
Family characteristics	Positive	Positive
Prevalence	190/100,000 1/526	15.7/100,000 1/6,000
Pathogeny with immunological base	Positive	Positive
HLA	DR4	DR7

during periods of increased basement membrane permeability as occurs during the uncompensated phase of Steroid-sensitive NS. This syndrome, in general, has a favorable prognosis. Cases that are resistant to steroids, with frequent relapses and immunosuppressor dependence, are generally given prolonged corticoid therapy. Glycemia control and stabilization of insulin and its fractions becomes more difficult in these cases. Goldman, in order to attenuate the influence of alternate day corticoid therapy on the metabolism of carbohydrates, is in favor of the withdrawal of corticoids with smaller, daily doses.[14] Both entities are accompanied by dyslipidemia which ought to be more conspicuous in a patient with IDDM associated with NS due to minimal change glomerulopathy.

In our case, after the second relapse in eight months, we decided to treat with cyclophosphamide with the objective stabilizing the development of the NS. The response was favorable and the patient has not had a relapse for 13 months.

Renal biopsy was not performed on our patient. This conduct is defended by Goldman.[14] The indication for this examination for NS with or without IDDM is the same and it should be reserved for cases where progress and therapeutic response are unfavorable.[14]

Based on the information presented above, the following diagnoses were fixed upon:

1.– Primary nephrotic syndrome with 21 months' course, sensitive to steroids and cyclophosphamide, without hematuria or arterial hypertension and with renal function intact. Has been off immunosuppressors for 12 months.

The first quantitative proteinuria assay did not return a significant result in our patient (529 mg/day or 28 mg/kg/m^2). This fact may be explained by incorrect urine collection, with a proportion of the urine lost, or it may have been a proteinuria variation as has been observed in patients known to have NS. It does not invalidate the diagnosis since during later phases the patient presented proteinuria compatible with diagnostic criteria.

2.– Type I diabetes mellitus with 21 months' course and under treatment with insulin.Certain facts observed in relation to our patient together with information contained in the scientific literature permit emphasis to be given to the following:

The association between IDDM and steroid-sensitive NS or NS with minimal glomerulopathies is very rare. Nephropathies that occur during the initial phases of IDDM are different to NS with minimal glomerulopathies, possess specific characteristics and are easily differentiated from the former.

Diabetic glomerulosclerosis with significant proteinuria occurs after a number of years of evolution and is generally associated with retinopathy, arterial hypertension and impaired renal function.

Therapy with corticosteroids is occasionally accompanied by hyperglycemia and glycosuria that may cause difficulties in making a diagnosis of diabetes mellitus. We should emphasize that in these cases acidemia and ketonuria are not observed. Treatment with glucocorticoids, on the other hand, may make an insipient case of diabetes become patent or make glycemic control difficult.

These entities have a definite familial character.

The conduct of these cases requires understanding and monitoring of possible interference between the two conditions with synergic effects that might modify the patient's prognosis.

References

1. Calliari LEP, Dib AS, Chacra AR. Diagnóstico e prevenção do Diabetes Mellitus. In: Monte O, Longui CA, Calliari LEP. Endocrinologia para Pediatra. 2nd ed. São Paulo: Atheneu; 1998. p. 75-81.
2. Ferreira SR, Franco LJ, Vivolo MA, Negrato CA, Simoes AC, Ventureli CR. Population-based incidence of IDDM in the state of São Paulo, Brazil. Diabetes Care. 1993;16:701-4.
3. Bergstein JM. Síndrome Nefrótica. In: Behrman RE, Kliegman RM, Jenson HB. Tratado de Pediatria. 16th ed. Rio de Janeiro: Guanabara Koogan; 2002. p. 1568-72.
4. Barratt TM, Clark G. Minimal change nephrotic syndrome and focal segmental glomerulosclerosis. In: Barratt TM, Avner ED, Harmon W, editors. Pediatric Nephrology. 3rd ed. Baltimore: Lippincott, Williams & Wilkins; 1994. p. 767-87.
5. Urizar RE, Schwartz A, Top F Jr., Vernier RL. The nephrotic syndrome in children with diabetes mellitus of recent onset. N Engl J Med. 1969;281:173-81.
6. Dib AS. Complicações crônicas do diabetes mellitus. In: Monte O, Longui CA, Calliari LEP. Endocrinologia para Pediatra. 2nd ed. São Paulo: Atheneu; 1998. p. 88-97.
7. Aziz S, Cohen A, Winer R, Llach F, Massry S. Diabetes mellitus with immune complex glomerulonephritis. Nephron. 1979;23:32-7.
8. Kasinath BS, Mujais SK, Spargo BH, Katz AI. Non-diabetic renal disease in patients with diabetes mellitus. Am J Med. 1983;75:613-17.
9. Cavallo T, Pinto JA, Rajaraman S. Immune complex disease complicating diabetes glomerulosclerosis. Am J Nephrol. 1984;4:347-54.
10. McCrory WW, Najjar S, Read CH, Vernier L. Observation on the nature of the nephrotic syndrome occurring in young diabetes. Am J Dis Child. 1960;100:764.
11. Robinson GC, McConnell D. Simultaneous onset of diabetes mellitus and nephrotic syndrome. Can Med Assoc J. 1961;85:80-1.
12. Peces R, Riera JR, Larrea CL, Alvarez A. Steroid-responsive relapsing nephrotic syndrome associated with early diabetic glomerulopathy in a child. Nephron. 1987;46:78-82.
13. Bouissou F, Meissner I, Konrad M, Sommer E, Mytilineos J, Ohayon E, et al. Clinical implications from studies of HLA antigens in idiopathic nephritic syndrome in children. Clin Nephrol. 1995;44:279-83.
14. Goldman M, Hebert D, Geary DF. Management of steroid-sensitive nephrotic syndrome in children with type I diabetes. Pediatr Nephrol. 2002;17:351-4.

Corresponding author:
Eduardo de A. Rego Filho
Rua Antonio Morais, 120
CEP 86039-610 - Londrina, PR, Brazil
Tel./Fax: +55 (43) 3339.4251
E-mail:alrego@sercomtel.com.br