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Infantile cystinosis and insulin-dependent diabetes mellitus

A. Ammenti, A. Grossi, and S. Bernasconi

Istituto di Clinica Pediatrica, Università degli Studi, Via Gramsci n. 14, I-43100 Parma, Italy

Abstract. A 13-month-old infant was admitted to our Institution because of difficult metabolic control of diabetes mellitus. Clinical and laboratory findings revealed that the child was affected by both insulin-dependent diabetes mellitus and nephropathic cystinosis.

Treatment with indomethacin was associated with growth improvement at an early stage of renal insufficiency, but not in more advanced renal failure.

Key words: Diabetes mellitus – Cystinosis – Indomethacin

Introduction

In cystinosis involvement of multiple tissues and organs, related to intracellular deposition of cystine crystals, is well recognized [8]; among endocrine glands, the thyroid is most often affected, leading to hypothyroidism in some cases [4, 6]. Insulin-dependent diabetes mellitus (IDDM) has been described in two cystinotic children, in whom diabetes appeared after renal transplantation, at the ages of 10 and 14 years [3].

We report on a child with infantile cystinosis who first presented with diabetes mellitus.

Case report

M.C. is a boy who presented at the age of 13 months with polydipsia, polyuria and progressive anorexia. Diabetes mellitus was diagnosed on the basis of hyperglycaemia and glycosuria, and insulin therapy was started. A few weeks later metabolic control became difficult, and the child was transferred to our Department. On admission, physical examination revealed a pale, fair-haired, profoundly dehydrated child; body weight was 9.5 kg (10°–25° percentile), lenght 68 cm (< 3rd percentile), body temperature 38.5°C and pulse 150 b/min. The abdomen was distended, liver and spleen palpable 4 cm under the costal margin. Chemical investigation of the blood revealed: ESR 44/88; blood sugar 1.7 g/l; Na 135, K 1.7 mEq/l; Ca 7.9, P 4.0 mg/dl; creatinine 0.8 mg/dl; Hb 8.7 g/l, Ht 26.2%; pH 7.30, HCO_3^- 14.7 mEq/l, B.E. – 9.8. There was marked glycosuria (20 g/l) and slight proteinuria.

Offprint requests to: S. Bernasconi

Abbreviation: IDDM = insulin-dependent diabetes mellitus

Shortly after admission blood sugar levels rose to 3.7 g/l. Insulin therapy, together with i.v. infusion of fluids, potassium and bicarbonate was started, a satisfactory control of glycaemia being achieved within a few days. However, acidosis worsened and polyuria persisted unchanged (2–4 l/day), unresponsive to vasopressin (maximal urinary osmolarity after 1-deamino-8-D-arginine-vasopressin: 319 mOsm/l). Craniotabes was noted and the body temperature showed multiple sudden increases to 39°C. Serum Ca and P progressively decreased to 5.5 and 1.0 mg/dl respectively, while alcaline phosphatase increased from 282 to 1500 IU/l in the presence of normal GFR and calcium excretion. In addition, generalized hyperaminoaciduria and proteinuria of the mixed type (55 mg/m^2 per h) were present. A better control of acidosis was obtained with a sodium bicarbonate dose of 120 mmol/day, which was later discontinued for a few days, showing a distal acidification defect (urinary pH 8.15, H^+ O, NH_4^+ 20.5 mEq/day; plasma pH 7.28, HCO_3^- 12 mEq/l). Cystinosis was suspected, and confirmed by the finding of a leucocyte cystine content of 4.04 μmol/g protein and later of a fibroblast cystine level of 5.85 μmol/g protein (normal values < 0.2). HLA typing showed the following pattern: A_1 A_2 B_8 B_{W51} B_{W4} B_{W6}. Insulin therapy was discontinued on two occasions, but each time glycaemia rapidly rose over 5 g/l. Later, determination of HbA_{1c} (8.3 mg/dl) also confirmed IDDM. In the following months the child was treated with insulin (7–8 U/day), vitamin D (10000 U/day), sodium bicarbonate (tapered to 40 mEq/day) and a 1300 KCal diet, with satisfactory control of glycaemia (values ranging between 0.8 and 2.4 g/l). Acidosis persisted and no improvement in rachitic signs was observed; iPTH was 2.08 ng/ml (normal values < 0.9). Only with a further increase of bicarbonates to 100 mEq/day was a constant control of acidosis obtained. A 1 year follow-up revealed that the velocity of height increase had been 2.9 cm/year and creatinine clearance had dropped from 130 to 70 ml/min per 1.73 m^2. At that time therapy with $1–25(OH)_2$ cholecalciferol (0.25 μg/day) and indomethacin (2 mg/kg per day) was started. In the following year the velocity of height increase improved (7.1 cm/year), as did rachitic signs and calcaemia; iPTH decreased to 0.98 ng/ml and alkaline phosphatase to 663 U/l. Polyuria and GFR did not decrease during this period. Indomethacin therapy was then interrupted in order to evaluate further growth without this medication: the velocity of height increase first fell to 3.4 cm/year, and has remained constant around 5 cm/year in the last 18 months, without being favourably influenced by a second indomethacin treatment period, performed when creatinine

clearance was 46 ml/min per 1.73 m^2 and thyroid function still normal.

Discussion

In cystinosis, cystine crystals accumulate in many organs. Functional impairement of endocrine glands, however, is rare. In 1977 Lucky et al. [6] reported on autopsy findings of four children with cystinosis, aged 2–10 years: abundant cystine crystals were present in the stroma of all endocrine glands, but no deposition of crystals was found in epithelial cells in glands other than the thyroid; correspondingly, hypothyroidism was the only endocrine abnormality detected.

In 1980 Broyer et al. reported on two children with cystinosis in whom diabetes mellitus appeared after renal transplantation, at the ages of 10 and 14 years, and speculated that diabetes mellitus may be a late manifestation of the disease [3].

Polyuria, polydipsia, acidosis and glycosuria in children with nephropathic cystinosis may often create problems in differential diagnosis with IDDM. In our case, the child presented with the usual first overt signs of cystinosis, i.e. polyuria and polydipsia, at the age of 13 months. However, IDDM was already present at that time, and only when polyuria and acidosis did not improve, in parallel with a good control of glycaemia, was cystinosis suspected. Whether in this case diabetes mellitus is a consequence of cystinosis or the two diseases are independent of each other is debatable. Considering that the child is carrying a genetic risk factor for IDDM, i.e. HLA Locus B_8, we tend to believe that the two diseases are independent of each other.

Beneficial effects on polyuria, serum electrolytes and hormone levels have been achieved by treating children suffering from nephropathic cystinosis with indomethacin, 2.5–3 mg/kg [5, 7]. Reports on growth during indomethacin therapy are controversial: a definite enhancement was described in one case [1], but no effect was demonstrated in other children [5]. We treated our patient with indomethacin, 2 mg/kg, during two different periods: the first time we observed a definite improvement in growth velocity that was not maintained when indomethacin was stopped; the second time, approximately 2 years later, however, there was no positive influence on growth. Creatinine clearance was 70 ml/min per 1.73 m^2 during the first treatment period, and had dropped to 46 ml/min per 1.73 m^2 at the beginning of the second period.

Taking account of the beneficial effects of indomethacin on nephropathic cystinosis reported in the literature, and of the enhancement of growth observed in our patient during the first period, we believe that the use of this drug should be considered, particularly during the early stages of the disease, before advanced renal failure becomes by itself a cause of poor growth [2].

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References

1. Bétend B, David L, Vincent M, Hermier M, François R (1979) Successful indomethacin treatment in two pediatric patients with severe tubulopathies. Helv Paediatr Acta 34:339–357
2. Broyer M (1978) La croissance chez l'enfant en insuffisance rénale chronique. Arch Franç Pédiatr 35:225–231
3. Broyer M, Guillot M, Gubler MC, Habib R (1980) La cystinose infantile, réevaluation des symptômes précoces et tardifs. Act Néphr Hop Neck 127–141
4. Chan AM, Lynch MJB, Baily JD, Ezrin C, Fraser D (1978) Hypothyroidism in cystinosis. Am J Med 48:678–682
5. Haycock GB, Al-Dahhan J, Mak RHK, Chantler C (1982) Effect of indomethacin on clinical progress and renal function in cystinosis. Arch Dis Child 57:934–938
6. Lucky AW, Howley PM, Megyesi K, Spielberg SP, Shulman JD (1977) Endocrine studies in cystinosis: compensated primary hypothyroidism. J Pediatr 91:204–210
7. Proesmans W, Snoeck L, Kyele Akumola Sina J, Van Aerde J, Eeckels R (1981) Inhibitors of prostaglandin synthetase as a therapy for cystinosis. Int J Ped Nephrol 2:130 (Abstract)
8. Schneider JA, Schulman JD, Seegmiller JE (1978) Cystinosis and the Fanconi Syndrome. In: Stanbury JB, Wyngaarden JB, Fredrickson DS (ed) The metabolic basis of inherited disease. McGraw-Hill, New York, pp 1660–1682

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