Journal of Pediatric Endocrinology & Metabolism, 10, 425-428 (1997)

A Girl with Diabetes and Severe Combined Immunodeficiency from Adenosine Deaminase Deficiency

Gianpiero Stoppoloni†, Dario Iafusco, Bianca M. Amodeo, Eugenio De Felice, Roberto Toraldo, Corrado Betterle[3], Luigi D. Notarangelo[2], Giovanna Tosi[1], Roberto S. Accolla[1] and Francesco Prisco

Department of Pediatrics, Faculty of Medicine, Second University of Naples
[1] Institute of Immunology and Infectious Diseases, Faculty of Medicine, University of Verona
[2]Department of Paediatrics, Faculty of Medicine, University of Brescia,
[3]Institute of Semeiotica, Faculty of Medicine, University of Padua, Italy

ABSTRACT

We present a girl with severe combined immunodeficiency (SCID) from adenosine deaminase (ADA) deficiency who developed insulin dependent diabetes mellitus (IDDM). This combination of features has not been previously reported. Because HLA typing (DQbeta-57 Asp/Asp and DQalpha-52 Ser/Ser) showed no alleles usually associated with IDDM, and ICA were repeatedly negative even after treatment with PEG-ADA and gene transplant, hypotheses on the pathogenesis of diabetes mellitus in this patient are discussed.

KEYWORDS

insulin dependent diabetes mellitus, severe combined immunodeficiency, adenosine deaminase deficiency

INTRODUCTION

Hereditary adenosine deaminase (ADA) deficiency is a rare disease accounting for 20-30% of all cases of severe combined immunodeficiency (SCID) /1,2/. Large quantities of toxic metabolites, resulting from enzyme block, lead to nearly complete destruction of lymphocytes. Affected children usually die before 2 years of age.

Management of the disease has so far utilized bone marrow transplantation, administration of polyethylene glycol ADA (PEG-ADA), and gene therapy approaches /3-5/. Here we report new data on a patient, previously described /6/, affected by ADA deficiency and diabetes mellitus.

PATIENT REPORT

The patient is a girl born in March 1989. Family history is vague because she was adopted. A sibling died from respiratory disease at the age of 1 year. The patient suffered from recurrent respiratory tract infections, oral candidiasis and episodic diarrhea from the age of 6 months. Severe itching and eczema first appeared at the age of one year. Anti-gliadin antibodies (AGA) of the IgA isotype were present. Intestinal biopsy failed to show microscopic patterns compatible with celiac disease.

Diagnosis of SCID from ADA deficiency was made when the patient was 20 months old. The purine nucleotide phosphorylase (PNP) activity was normal (38.1 units/gHb), while complete absence of ADA activity was found both in erythrocytes and in lymphocytes. One month later strong hyperglycemia (800 mg/dl) and severe ketoacidosis (pH 7.17, BE -17) appeared. For this reason insulin treatment was started. At the present time the insulin regimen is

Reprint address:
Dr. Dario Iafusco
Dipartimento di Pediatria
Seconda Universita degli Studi
Via S. Andrea delle Dame n. 4
80138 Napoli
Italy

† Deceased

0.8 IU/kg/day, divided into three doses. Mean HbA_{1c} during the last year of treatment was 6.2 ± 0.5%.

Treatment with PEG-ADA (30 IU/kg/week) resulted in dramatic clinical and immunological improvement (Table 1) /6/. However, after two years of treatment a progressive worsening of the immunological status was noted. Thus, even in absence of anti PEG-ADA antibodies and of clinical signs of immunodeficiency, gene therapy was initiated in February 1993. For this purpose bone marrow cells and peripheral blood leukocytes infected with recombinant retrovirus containing the human ADA gene were transplanted into the patient. During gene therapy, antithyroglobulin and antimicrosomal antibodies were detected. (The details of the gene therapy are reported separately.)

Antibodies against mucosal epithelium of the stomach and against mumps virus, toxoplasma, rubeola and cytomegalovirus remained absent. ICA were repeatedly negative even after treatment with PEG-ADA and gene transplant. The patient was typed for HLA. The serological typing was A1, A26(10); B5, B40; DR14(w6), DR15 (2); DRw52d; DQ1. Further typing for HLA DQB1 and DQA1 loci, using new methods /7,8/ revealed: DQB1* 00531/ DQA1* 0101, DQB1* 0601/DQA1* 0103.

Both DQB1 alleles contained an Asp residue in position 57 of the DQ beta chain. Both DQA1 alleles contained a Ser residue in position 52 of the DQ alpha chain. The above DQB1 and DQA1 alleles are strongly associated with resistance to IDDM /7,8/.

DISCUSSION

The difficulty in this patient is to establish the pathogenesis of IDDM. Type I diabetes is an autoimmune disease frequently associated with other autoimmune conditions /9/, but the severe immunodeficiency in our patient makes it difficult to ascertain whether diabetes is of autoimmune origin.

The number of peripheral blood T-lymphocytes in our patient was markedly lower than normal. On the other hand the number of B-lymphocytes was normal, but their function was compromised. This can be seen by the high levels of non-specific and low levels of specific immunoglobulins (anti A and anti B isohemagglutinins, anti-polio, anti-diphtheria and anti-tetanus antibodies) despite the O Rh positive blood group of the patient and vaccinations against poliomyelitis, diphtheria and tetanus she had received. A non-specific production of immunoglobulins may explain the AGA IgA found at diagnosis with normal intestinal biopsy. AGA IgA disappeared after treatment for immunodeficiency.

If we hypothesise that the IDDM in our patient is of autoimmune origin, then lack of ICA may be due to scant production of specific immunoglobulins. The fact that ICA negativity persisted even after treatment with PEG-ADA and gene transplant seems to exclude immunologic memory to beta-cells, although 20-30% of patients with type I diabetes mellitus fail to exhibit ICA /10/.

At diagnosis the patient presented with low levels of CD8+ and CD3+ and a high percentage of activated T-cells (CD3+ DR+, CD3+ CD25+). The latter finding has not previously been reported in ADA deficiency. The reason for low levels of CD8+ is unknown. Unbalanced equilibrium between CD4 and CD8 positive cells may favor humoral versus cell-mediated response and predispose to a higher frequency of autoantibodies. A low CD8+ count has been reported in a 12 year-old girl with partial ADA deficiency and Hashimoto's thyroiditis /11/.

Another finding compatible with the autoimmune origin of diabetes in our patient is the similarity with diabetes mellitus in BB rats. These animals present severe immune deficiency, low CD3+ and CD8+ lymphocyte count, autoreactive T clones coupled with thymic and bone marrow anomalies, hypereosinophilia and eosinophile infiltrates in the pancreatic islets even before the onset of diabetes /12/. In thymocytes from immunodeficient diabetic BB rats, there has been a recent demonstration of a deficiency of purine nucleoside phosphorylase activity, an enzyme along the same ADA metabolic pathway /13/.

Regarding the possibility of a non-autoimmune pathogenesis, it should be remembered that pathologic changes in non-lymphatic organs have been reported in patients with ADA derangement /14,15/, although direct damage of beta cells from low levels of ADA has not been reported.

A non-autoimmune pathogenesis of diabetes mellitus in our patient may be postulated on the basis of the HLA-DQ genotype strongly associated

TABLE 1

	Time from the beginning of therapy			
	Basal	2 mo	17 mo	Normal values
Lymphocytes /µl	707	1638	2728	1200 - 7800
Eosinophils /µl	4040	189		180 -360
Lymphocyte subpopulations (%)				
CD3	44.6	59.0	80	69.1 ± 14.4
CD4	37.0	51.3	56	43.4 ± 8.8
CD8	2.1	14.6	17	23.8 ± 7.7
CD19	17.0	7.0	8	6.8 ± 3.5
CD20	1.1	8.8		6.0 ± 3.0
DR	43.0	12.0		12.0 ± 5
CD25	38.0	11.4		4.0 ± 0.6
Serum immunoglobulins (mg/dl)				
IgG	1680	1200		462 - 1710
IgA	127	116		27 - 273
IgM	194	110		62 - 257
IgE	4500	1581		< 29,5
Isohaemagglutinins				
Anti A	1:2	1:2		1:8 - 1:512
Anti B	1:2	1:16		1:8 - 1:512
ICA	neg	neg	neg	
Anti - thyreoglobulin	neg	neg	pos	
Anti - microsomes	neg	neg	pos	

with resistance to, rather than susceptibility to, IDDM /16/, and because of the absence of ICA even after recovery from immune deficit. Moreover, the data from linkage between MODY, as expressed in the RW pedigree, and the polymorphic locus associated with the ADA gene on chromosome 20 /17,18/ makes it more difficult to interpret the pathogenesis of diabetes in this patient.

REFERENCES

1. Kredich NM, Hershfield MS. Immunodeficiency diseases caused by adenosine deaminase deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic Basis of Inherited Diseases. New York: McGray Hill, 1989; 1045-1075.
2. Hirschhorn R. Inherited enzyme deficiencies and immunodeficiency: Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) deficiencies. Clin Immunol Immunopathol 1986; 40: 157-165.
3. Fisher A, Landais P, Friedrich W, Morgan G, Gerritsen B, Fasth A, et al. European experience of bone marrow transplantation for severe combined immunodeficiency. Lancet 1990; II: 850-854.
4. Hershfield MS, Buckley RH, Greenberg ML, Melton AL, Schiff R, Hatem C, et al. Treatment of adenosine deaminase deficiency with polyethylene glycol modified adenosine deaminase (PEG-ADA). N Engl J Med 1987; 316: 589-596.
5. Ferrari G, Rossini S, Giavazzi R, Maggioni D, Nobili N, Soldati M, et al. An in vivo model of somatic cell gene therapy for human severe combined immunodeficiency. Science 1991; 251: 1363-1366.
6. Notarangelo LD, Stoppoloni G, Toraldo R, Mazzolari E, Coletta A, Airò P, Bordignon C, Ugazio AG. Insulin dependent diabetes mellitus and severe atopic dermatitis in a child with adenosine deaminase deficiency. Eur J Pediatr 1992; 151: 811-814.
7. Tosi G, Brunelli S, Mantero G, Magalini AR, Soffiati M, Pinelli L, Tridente G, Accolla R. The complex interplay of the DQB1 and DGA1 loci in the generation of the susceptible and protective phenotype for insulin dependent diabetes mellitus. Molec Immunol 1994; 31: 429-437.
8. Tosi G, Pinelli L, Facchin A, Accolla RS. Assessment of the DQB1 - DQA1 complete genotype allows best prediction for IDDM. Diabetes Care 1994; 17: 1047.
9. ISPAD Workshop on IDDM and Associated Autoimmune Disorders (Facts and Questions). J Pediatr Endocrinol Metab 1996; 9 (Suppl. 1): 73-144.
10. Bruining, GJ, Molenarr J, Tuk CW, Lindeman J, Bruining HA, Marner B. Clinical time course and characteristics of islet cell cytoplasmic antibodies in childhood diabetes. Diabetologia 1984; 16: 24-29.
11. Geffner ME, Stiehm ER, Stephure D, Cowan MJ. Probable autoimmune thyroid disease and combined immunodeficiency disease. Am J Dis Child 1986; 140: 1194-1196.
12. Maruta K, Treichel U, Kolb Bachofen V, Kolb H. Prospective analysis of eosinophilia in spontaneously diabetic BB rats: correlation with islet inflammation but not with diabetes development. Diabetes Res 1989; 11: 173-176.
13. Wu G, Marliss EB. Deficiency of purine nucleoside phosphorylase activity in thymocytes from the immunodeficient diabetic BB rat. Clin Exp Immunol 1991; 86: 260-265.
14. Ratech H, Greco MA, Gallo G, Rimoin DI, Kamino H, Hirschorn R. Pathological findings in adenosine deaminase deficient severe combined immunodeficiency. I. Kidney, adrenal and chondro osseous tissue alterations. Am J Pathol 1985; 120: 157-168.
15. Ratech H, Horshorn R, Greco MA. Pathological findings in adenosine deaminase deficient severe combined immunodeficiency. II. Thymus, spleen, lymphonode and gastrointestinal tract lymphoid tissue alterations. Am J Pathol 1989; 135: 1145-1156.
16. Accola R, Tosi G. Insulin dependent diabetes mellitus: A multistep autoimmune disease with multigene dependence. J Immunol Res 1992; 4: 147-151.
17. Bowen DW, Gravius TC, Akots G, Fajans SS. Identification of genetic markers flanking the locus for maturity onset diabetes of the young on human chromosome 20. Diabetes 1992; 41: 88-92.
18. Rothschild CB, Akots G, Hayworth R, Pettinati MJ, Rao PN, Wood P, Stolz FM, Hansmann I, Serino K, Keith TP, Fajans SS, Bowen DW. A genetic map of chromosome 20: multiple highly polymorphic microsatellite and RFLP markers linked to maturity onset diabetes of the young (MODY) locus. Am J Hum Genet 1993; 52: 110-123.