A FAMILY OF ADENOSINE DEAMINASE DEFICIENCY WITH SEVERE COMBINED IMMUNODEFICIENCY

Shigeru TSUCHIYA, Kuniaki NARISAWA, Tasuke KONNO, and Keiya TADA

Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan

Summary Adenosine deaminase (ADA) activities in erythrocytes from 10 relatives including parents of a patient with ADA deficiency and severe combined immunodeficiency (SCID) were reported. His parents, maternal uncle and grandmother showed ADA activity in their erythrocytes below the half level of the mean value of controls. These results suggested the autosomal recessive inheritance pattern of ADA deficiency, confirming other reports.

INTRODUCTION

The adenosine deaminase (ADA) deficiency associated with severe combined immunodeficiency (SCID) is a disease inherited in an autosomal recessive form (Giblett *et al.*, 1975). All parents of the ADA deficient reported had ADA levels of erythrocytes significantly lower than controls and were assumed to be heterozygotes. The affected patients are homozygous for allele and have a "silent" gene (ADAo) (Chen *et al.*, 1974).

Recently, we had a patient with ADA deficiency and SCID, the first case in Japan. Estimation of ADA activities of erythrocytes from 10 relatives of the patients revealed an autosomal recessive inheritance of the disease.

CASE REPORT

The patient was the product of a gravida 2, para 2 mother. The parents were nonconsanguineous. Two sisters were died of pneumonia at a year of age. One of them had hypogammaglobulinemia and hypoplasia of thymus and lymphoid organs shown by autopsy. The patient was admitted to Yamagata University Hospital with severe pulmonary candidiasis at the age of 15 months, and suspected to have ADA deficiency disease. He was referred to our ward one month later for further examination and treatment including bone marrow transplantation. Marked lymphocytopenia, agammaglobulinemia, negative skin tests against candida, SK/SD and DNCB, and markedly decreased lymphocyte proliferative responses to phytohemagglutinin, pokeweed mitogen and concanavalin A were noticed (Yokoyama

Table 1. Clinical and immunological data of the patient with ADA deficiency.

Peripheral blood picture		Lymphocyte surface markers	
WBC	5,000/mm ³	Membrane immunoglobulin bearing cells not detected	
Neutro.	62.5%	Rosette forming cells	
Mono.	14.5%	E	47% (117/mm ³)
Eosino.	18.0%	EAC ^{hu}	53% (113/mm ³)
Lymph.	5.5%	Lymphocyte proliferative responses (stimulation index)	
Serum protein		PHA	3.3 (controls 310)
Total protein	5.8 g/dl	PWM	5.0 (controls 106)
Alb.	71.3%	Con A	6.6 (controls 228)
α_1 -glob.	5.4%	Skin tests for delayed-type hypersensitivity	
α_2 -glob.	13.9%	Candida	negative
β -glob.	8.6%	SK/SD	negative
γ -glob.	0.5%	DNCB	negative
Serum immunoglobulin			
IgG	128 mg/dl		
IgA	0		
IgM	0		
IgE	<25 I.U.		

et al., submitted for publication) (Table 1). Enzyme replacement therapy with fresh irradiated erythrocytes with normal ADA activities was tried resulting in a partial improvement of immunological impairment of the patient (Tsuchiya *et al.*, 1979). However, he was died of *Pneumocystis carinii* pneumonia and bacteremia of *Pseudomonas aeruginosa* at the age of 19 months. No HLA-matched donor for bone marrow transplantation was found.

MATERIALS AND METHODS

Blood specimens were collected in heparinized syringes. After removal of plasma and leukocytes, the erythrocytes were washed 3 times with saline, and then lyzed by freezing and thawing in dry ice-acetone. The cell lysates were centrifuged at 3,000 rpm for 20 min, and the supernatants were applied for enzyme assay. ADA activity in the erythrocyte lysates was measured by linked enzyme assay using 0.3 μ mole adenosine (Wako, Tokyo) as substrate, endogenous nucleoside phosphorylase and exogenous 10 μ l of xanthine oxidase (Boehringer, Mannheim, 10 mg/ml) (Hopkinson *et al.*, 1969). Increased uric acid was measured at 293 nm in a UVIDEC-405X recording spectrophotometer (Japan Spectroscopic Co., Ltd., Tokyo).

RESULTS AND DISCUSSION

Figure 1 showed the ADA activities of erythrocytes in the patient and his rela-

Fig. 1. ADA of erythrocytes in patient, relatives and controls.

tives, and in controls. ADA activities in 16 control subjects ranged from 47.7 to 109.7 nmoles/mg Hb/hr with the mean value of 69.6 ± 16.6 nmoles/mgHb/hr. ADA activity in the patient's erythrocytes was not detectable by the method used. Among the 10 family members extending 3 generations examined, the parents, maternal uncle and grandmother had ADA activity below the half level of the mean of controls and assumed to be heterozygotes. ADA activities in erythrocytes of other 6 relatives were within normal range. Pedigree of the family of the patient shown in Fig. 2 suggested clearly an autosomal recessive inheritance pattern of ADA deficiency disease. Nucleoside phosphorylase activities in all these specimens examined were within normal range (2.61 ± 0.31 μ moles/mg Hb/hr).

Two sisters of the patient were died of pneumonia at a year of age, respectively. They were noticed to have lymphocytopenia and hypogammaglobulinemia. Autopsy findings of the 2nd sister revealed that the thymus and systemic lymphatic tissues were extremely hypoplastic, suggesting primary immunodeficiency. These

Fig. 2. Pedigree of family with ADA deficiency.

clinical and autopsy findings, in addition to the family study might suggest the sisters had ADA deficiency and SCID although ADA was not determined.

In Japan, another case of ADA deficiency disease has been found (personal communication). But the frequency in the general population of the "silent" gene (ADAO) has not been determined. Screening for ADA deficiency disease is now in progress (Ito *et al.*, 1977), but no ADA-deficient patient has been found yet in a mass screening test in Japan.

REFERENCES

- Chen, S.-H., Scott, C. R. and Giblett, E. R. 1974. Adenosine deaminase: Demonstration of a "silent" gene associated with combined immunodeficiency disease. *Am. J. Human Genet.* **26**: 103-107.
- Giblett, E. R., Scott, C. R., and Chen, S.-H. 1975. Adenosine deaminase: Genetic aspects. *In*: Combined Immunodeficiency Disease and Adenosine Deaminase Deficiency: A Molecular Defect. H. J. Meuwissen, R. J. Pickering, B. Pollara, and I. H. Porter, eds., Academic Press, New York, pp. 103-110.
- Hopkinson, D. A., Cook, P. J. L., and Harris, H. 1969. Further data on the adenosine deaminase (ADA) polymorphism and a report of a new phenotype. *Ann. Human Genet.* **32**: 361-367.
- Ito, K., Sakura, N., Usui, T., and Uchino, H. 1977. Screening for primary immunodeficiencies associated with purine nucleoside phosphorylase deficiency or adenosine deaminase deficiency. *J. Lab. Clin. Med.* **90**: 844-848.
- Tsuchiya, S., Arai, N., Kudo, M., Konno, T., Tada, K., and Yokoyama, S. 1979. Effect of adenosine deaminase replacement therapy on a child of adenosine deaminase deficiency with severe combined immunodeficiency disease. *Tohoku J. Exp. Med.* **128** (3), in press.