

Immunodeficiency and other clinical immunology

Shwachman-Diamond syndrome associated with hypogammaglobulinemia and growth hormone deficiency

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Shwachman-Diamond syndrome is a rare congenital disorder of unknown etiology. Characteristic abnormalities of this disease include pancreatic insufficiency, skeletal anomalies, growth retardation, recurrent infections, and hematologic abnormalities. Significant morbidity and mortality in these patients result from respiratory infections, which are not well explained on the basis of neutrophil defects. We have had the opportunity to perform an in-depth clinical immunologic and endocrinologic evaluation of a patient with this syndrome with recurrent respiratory tract infections. She was found to have profound humoral immunologic defects, and serum thymulin was absent. In addition, endocrinologic evaluation for growth retardation revealed growth hormone deficiency. The patient responded to treatment with supplemental growth hormone and intravenous gammaglobulin with accelerated growth and cessation of infections. This case is unique in that it links growth hormone deficiency and hypogammaglobulinemia in a non-X-linked manner and may provide the basis for treatment of other patients with this rare syndrome. (J ALLERGY CLIN IMMUNOL 1995;96:247-50.)

Shwachman-Diamond syndrome, a rare congenital disorder, is characterized by pancreatic insufficiency, skeletal anomalies, growth retardation, recurrent infections, and hematologic abnormalities.¹ The most common hematologic abnormalities thus far described include variable degrees of neutropenia and monocyte and neutrophil chemotactic defects.^{2,3} Recurrent infections (typically respiratory tract infections) are responsible for significant morbidity and mortality in these patients but are not those usually seen with an isolated neutrophil defect. Variable dysgammaglobulinemias including IgG, IgA, and IgM deficiencies have been reported^{4,5} but have not been correlated with specific antibody responses. Slow growth in these patients has been attributed to

Abbreviation used
IL: Interleukin

nutritional deficits and recurrent illness. One case of Shwachman-Diamond syndrome has been reported in which growth hormone¹ was assayed and found to be significantly low. The patient, however, did not respond to treatment with growth hormone. Isolated growth hormone deficiency has also been reported to be associated with hypogammaglobulinemia inherited as an X-linked recessive disorder.⁶⁻¹⁰ We describe a female patient with Shwachman-Diamond syndrome associated with hypogammaglobulinemia, increased infections, and growth hormone deficiency. The patient experienced a significant increase in growth after treatment with growth hormone. The recurrent infections have been controlled by intravenous gammaglobulin therapy.

METHODS

Immunologic studies including determinations of immunoglobulins, total hemolytic complement, B- and

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TABLE I. Immunologic parameters: Humoral immunity

Parameter	Mo/yr	Mo/yr	Normal range
Immunoglobulins	10/91	6/92	
IgG	340 ↓	380 ↓	600 - 1575 mg/dl
IgA	< 1 ↓	7.5 ↓	23 - 137 mg/dl
IgM	71 ↓	40 ↓	74 - 228 mg/dl
IgE	—	4.96	2.6 - 135 mg/dl
Antibody (Ab) titers			
Diphtheria	0.024 ↓	0.051 ↓ *	0.1 - 10 IU/ml
Tetanus	0.02 ↓	0.01 ↓ *	0.1 - 10 IU/ml
Pneumococcus	0/12† ↓	0/12 ↓ *	> 200 ng Ab/ml
Isoagglutinins	—	anti-A < 1:2‡	> 1:4
T- and B-cell enumeration	12/91	6/92	
CD3	90% ↑	86% ↑	60 - 76%
CD4	59% ↑	58% ↑	37 - 56%
CD8	31% ↑	29% ↑	14 - 23%
CD11	92% ↑	90% ↑	66 - 83%
CD20	4% ↓	6% ↓	10 - 30%
CD56	5%	3%	2 - 9%
Thymulin and intracellular zinc	10/91	7/93	
Serum thymulin	< 1:4 ↓	< 1:4 ↓	> 1:32
Lymphocyte zinc	66.6	—	50.28 - 63.12 µg/10 ¹⁰ cells
Plasma zinc	112	—	99.3 - 126.5 µg/dl
Chemotaxis	12/91	6/92	
Stimulated	25 cells ↓	10 ↓	
Control	62 cells	62	
Nonstimulated	3 cells ↓	4	
Control	5 cells	4	

*After vaccination with diphtheria, tetanus, and pneumococcus.

†Number of serotypes.

‡Blood type B.

T-cell subsets, and neutrophil chemotaxis were performed as described previously.¹¹ Serum thymulin, plasma, and cellular zinc levels were performed as described earlier.¹² Serum interleukin (IL)-1 (Amersham Life Science, Arlington Heights, Ill.), IL-2 (T Cell Diagnostic, Cambridge, Mass.), and IL-6 (Endogen, Boston, Mass.) determinations were performed according to the manufacturers' instructions.

Thyroxine, triiodothyronine uptake, and thyroid-stimulating hormone values were determined with the Abbott IMx Ultrasensitive hTSH Reagent Pack (Abbott Diagnostics, Abbott Park, Ill.). T3RIA was measured by standard radioimmunoassay performed with a kit purchased from Kallestad Laboratories, Inc. (Chaska, Minn.). Serum cortisol was determined with a Diagnostic Products Corporation RIA kit (Diagnostic Products Corp. Los Angeles, Calif.). Serum growth hormone was determined according to a modification of the method of Root et al.¹³ insulin-like growth factor-1 and insulin-like growth factor binding protein-3 were measured by radioimmunoassay by Nichol's Institute (San Juan Capistrano, Calif.). GHBP was assayed by Nichol's Institute with a ligand immunofunction assay.

CASE REPORT

The patient, a 5-year-old girl, was diagnosed at 4 months of age with Shwachman-Diamond syndrome. She was first seen with perinatal diarrhea, recurrent pneumonia, and neutropenia. A detailed evaluation revealed pancreatic insufficiency without evidence of cystic fibrosis. At 6 months of age, the patient was started on a regimen of pancreatic enzyme replacement, which normalized the stool pattern. The patient received her full complement of infant immunizations. There was no family history of recurrent infections or early infant deaths. Because of persistent infections including pneumonia, sinusitis, and otitis media, despite continuous use of prophylactic antibiotics, at age 3 she was referred to our service for immunologic evaluation. During her evaluation, she was noted to have severe growth retardation (4.2 cm/yr). She was then referred to the endocrinology department.

RESULTS

Table I presents the results of the immunologic analyses. IgG, IgA, IgM, isoagglutinins, and spe-

cific postvaccination antibody titers to both protein and polysaccharide antigens were reduced. Serum thymulin levels were persistently depressed. Neutrophil chemotaxis was reduced. The remaining immunologic studies showed that lymphocyte and plasma zinc levels; lymphocyte proliferative responses to both mitogens and antigens; serum levels of IL-1, IL-2, and IL-6; and levels of total hemolytic complement were normal. B-cell subsets were moderately decreased, whereas T-cell subsets were mildly elevated.

Thyroid function test results and cortisol response to hypoglycemia were normal. Peak growth hormone level after insulin-arginine was 4.1 ng/ml (normal >10 ng/ml), serum insulin-like growth factor-1 was less than 16 ng/ml (normal, 17 to 248 ng/ml), and insulin-like growth factor binding protein-3 was 0.5 mg/L (normal, 0.9 to 4.1 mg/L). All values were subnormal. Growth hormone binding protein level was 69 pmol/L (normal, 65 to 393 pmol/L), which is at the lower limit of normal. Magnetic resonance imaging of the brain revealed a small mass of high-signal intensity, interpreted to represent an ectopic posterior pituitary, a finding suggestive of hypopituitarism. Bone age was 1½ years behind chronologic age. Her karyotype was 46 XX. The patient responded to treatment with subcutaneous growth hormone with an accelerated growth rate of 16.4 cm in the first 12 months of therapy. Her infections were controlled with intravenous gammaglobulin therapy and continuation of prophylactic antibiotics.

DISCUSSION

In this report we describe a 5-year-old female patient with Shwachman-Diamond syndrome who exhibited panhypogammaglobulinemia with deficient specific antibody responses and depressed secretion of growth hormone. The patient has responded to therapy with intravenous gammaglobulin and subcutaneous growth hormone with a cessation of infections and markedly accelerated growth. We believe that growth hormone supplementation has been the primary stimulus for growth because the patient had been aggressively treated with antibiotics for her recurrent infections, although it is impossible to completely rule out a combined effect of both treatments. In light of our findings and a prior report¹ of growth hormone deficiency in a patient with Shwachman-Diamond syndrome, endocrinopathy should be considered in patients with this disorder.

The patient was found to have a profound deficiency of humoral immunity characterized by

panhypogammaglobulinemia, an absence of isohe-magglutinins, deficient specific antibody responses to both protein and polysaccharide antigens, and depression of B-lymphocyte numbers. Prior immunologic studies of patients with this disease have demonstrated variable dysgammaglobulinemias,^{4,5} but in-depth evaluation of antibody function and vaccination responses have not previously been performed. It is therefore possible that patients with this disease may have more profound defects in humoral immunity than previously suspected. Such defects may be attributable to functional rather than quantitative antibody deficiencies. Defects in neutrophil chemotactic function were also demonstrated, as previously described.¹⁻³ Other indices of cell-mediated immune function were within normal limits except for a low thymulin level. Zinc deficiency, which could contribute to a broad-based alteration of this patient's immune status and growth retardation,¹⁴ was not found. The significance of the patient's low thymulin level is unclear in light of the patient's otherwise apparently normal T-cell-mediated immune functions. However, this abnormality may indicate a subtle dysregulation of her T-cell-mediated immune mechanism. Animal data have linked growth hormone deficiency with insufficient thymulin secretion.¹⁵ Treatment of dogs with supplemental bovine growth hormone was reported to result in significant elevations in serum thymulin.¹⁶ Repeat thymulin levels were performed 6 months after growth hormone treatment was started and were unchanged, making a direct association between thymulin and growth hormone levels unlikely in our patient.

Our report extends the definition of the spectrum of immunologic and endocrinologic abnormalities associated with this rare disorder. This case is unique in that it links growth hormone deficiency and hypogammaglobulinemia in a non-X-linked manner. An association between growth hormone deficiency and hypogammaglobulinemia has been previously noted, but only as an X-linked recessive disorder.⁶ In light of documented endocrine immune interactions, it remains possible that a single as yet unknown defect could explain the phenotypic presentation of patients with Shwachman-Diamond syndrome. Detailed endocrinologic and immunologic evaluation of other patients with this disorder will be necessary to determine whether the several abnormalities and the responses to therapy that were observed in this patient occur regularly, frequently, or infrequently in other patients with this syndrome. Further study

of the association of growth hormone deficiency, hypogammaglobulinemia, and depressed thymulin levels in this patient and others with similar abnormalities may help us to better understand the complex interactions between the neuroendocrine and immune systems, both of which were disturbed in this patient.

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