

Primary combined immunodeficiency, growth retardation, and disturbed sexual development: A novel syndrome of congenital impairment of the cellular immune system and the endocrine system

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Primary immunodeficiencies depend on a variety of forms of impairment of the cellular or the humoral immune system. Only a small minority of immune disorders are associated with growth retardation.¹⁻⁵ Even more rare is the association of growth hormone deficiency with cellular or humoral immunodeficiency.¹⁻⁵ In this case report we present a novel syndrome of combined T-, B-, and natural killer (NK)-cell immunodeficiency in conjunction with a severe impairment of postnatal growth and sexual development.

CASE REPORT

A 25-year-old woman was transferred to our hospital with recurrent viral, fungal, and bacterial infections and refractory autoimmune hemolytic anemia. The patient had repeatedly had staphyloiderma and mucocutaneous infections with *Candida albicans* since the age of 4 months. Cystic fibrosis was ruled out as a possible cause.

Starting at the age of 9 months, a severe growth retardation became apparent. Up to her death at the age of 26, she remained childlike in stature (height: 135 cm, below the third percentile for age; body weight: 27 kg; body mass index: 14.8 kg/m²). She never showed any signs of puberty. Her facial appearance and her thinned, gray hair and markedly wrinkled skin were of senile appearance. X-ray examinations done at the age of 22 showed her skeletal age to be 12 years, with no signs of epiphyseal-diaphyseal fusion.

Measurement of endocrine hormones (Table I) revealed normal pituitary function for the adrenocorticotrophic, thyrotrophic, and lactotrophic axes. Gonadotropins and 17- β -estradiol were compatible with hypogonadotropic hypogonadism. Insulin-like growth factor 1 and insulin-like growth factor binding protein 3 were markedly lowered. Serum zinc levels were normal, as were iron and vitamin serum levels.

Investigations for known causes of primary and secondary immunodeficiencies were normal, including measurements of the intraerythrocytic enzymes adenosine deaminase and pyrovalnucleosidphosphorylase and evaluation of granulocyte function. Humoral

Abbreviation used

NK: Natural killer

and cellular immunodeficiency were documented from early childhood on. Vaccination against polio, pox, tetanus, and diphtheria was not followed by a specific humoral immune response. Intracutaneous testing of candidin, trichophytin, and varidase only showed a positive result for candidin at the age of 3 years. The reaction to tuberculin was negative despite BCG vaccination.

At the ages of 11 and 13 years, peripheral blood lymphocytes showed a normal proliferation to mitogens but a sharply reduced proliferation to antigens, including candidin. At the age of 25 years, a Multitest Merieux revealed complete anergy. Phenotypic analysis revealed normal total T cells but reduced CD4⁺ cells and CD56⁺ NK cells. CD20⁺ B cells were elevated despite the lack of specific antibody production in vivo. In addition, hypogammaglobulinemia with a marked defect in IgG₂₋₄ production was noted (Table II). There was a markedly reduced lymphocyte proliferation in response to purified protein derivative, and proliferation to mitogen stimulation was reduced to half the level of normal control subjects (Table III). There was no proliferation in response to candidin, cytomegalovirus, diphtheria, and tetanus antigens. NK cytotoxicity and antibody-dependent cytotoxicity were reduced by 50%.

Severe autoimmune hemolysis was treated by splenectomy at the age of 25 years. Despite an improvement in hemolytic parameters, the immunologic situation deteriorated further. Sixteen months later, the patient died of severe pneumonia and right heart failure.

DISCUSSION

This is the first case report describing a combined immunodeficiency syndrome with the involvement of NK cells, together with an alteration of somatotrophic, as well as gonadotrophic, pituitary function.

There have been previous reports describing forms of immunodeficiency in conjunction with growth retardation. In chronic mucocutaneous candidiasis growth retardation may be caused by severe dystrophy. These patients display a selective anergy to *Candida* antigens. In our patient there was an unselective and severe combined immunodeficiency. In addition, our patient showed a severely impaired pituitary function. A marked growth retardation was seen since the age of 9 months, as known to be typical for growth hormone deficiency. There are

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J Allergy Clin Immunol 1998;102:327-8.

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0091-6749/98 \$5.00 + 0 1/54/91759

TABLE I. Endocrinologic parameters

Parameter	Value	Units	Normal range
TSH	0.4 (n)	μU/mL	0.3-0.4
TT4	10.6 (n)	μg/100 mL	4.5-12.0
TT3	2 (n)	ng/mL	0.45-2.0
TBG	34.4 (+)	μg/mL	12.0-30.0
TT4/TBG (FT4-Index)	0.31 (n)	—	0.25-0.5
Prolactin	5.6 (n)	ng/mL	<2.5
LH	10.3 (n)	U/L	<15
FSH	6.2 (n)	U/L	<10
17-β-Estradiol	<5.0 (-)	pg/mL	>40*
STH (GH)	1.6 (n)	ng/mL	<20
IGF 1	28 (-)	ng/mL	178-344
IGF-BP3	1.7 (-)	mg/L	2.0-5.0
ACTH	23 (n)	pg/mL	<100
Cortisol	23.6 (n)	μg/100 mL	4.4-22.4
PTH	135 (+)	pg/mL	<60
Osteocalcin	2.5 (-)	ng/mL	4.0-12.0
Telopeptid ("cross links")	11.5 (+)	μg/L	1.8-5.0
25-OH-Vitamin D3	29.9 (n)	ng/mL	16-74

n, Normal; +, increased; -, decreased; TSH, thyroid-stimulating hormone; TBG, thyroxin-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; IGF, insulin-like growth factor; ACTH, adreno-corticotrophic hormone; PTH parathyroid hormone.

*Depends on cycle phase.

TABLE II. Lymphocyte phenotype analysis and immunoglobulins

Parameter	Cells (%)	Cells/μL	Normal range
CD2	83 (n)	2100 (n)	1300-2100
CD3	84 (n)	2100 (n)	1100-2100
CD4	24 (-)	600 (-)	700-1100
CD8	64 (+)	1600 (+)	500-900
TCR2	80 (n)	1980 (n)	1100-2100
T4/T8	0,38 (n)	—	1-1.5
CD16	8 (-)	210 (-)	250-400
CD56	12 (-)	360 (n)	250-400
CD20	22 (+)	540 (+)	0-100
sIgM	30 (+)	750 (+)	0-100
CD25	5 (n)	120 (n)	120-480
CD11a	88 (n)	2200 (n)	1400-2400
HLA I	100 (n)	2490 (n)	1600-2400
HLA-DR	43 (+)	1290 (+)	140-360
IgG1	8708 mg/L (n)	—	4900-11400
IgG2	344 mg/L (-)	—	1500-6400
IgG3	89 mg/L (-)	—	200-1100
IgG4	61 mg/L (-)	—	80-1400

n, Normal; +, increased; -, decreased.

some known forms of immune disorders associated with growth hormone deficiency; X-linked hypogammaglobulinemia with growth hormone deficiency is less severe and does not include a cellular immunodeficiency.¹

TABLE III. Lymphocyte and NK-cell stimulation data

Mitogen	Patient	Normal control subject
Lymphocyte stimulation		
Medium	287 cpm	706 cpm
Phytohemagglutinin	35,909 cpm (-)	118,554 cpm
Concavalin A	17,135 cpm (-)	107,021 cpm
Pokeweed	7725 cpm (-)	27,013 cpm
PPD	235 cpm (-)	2031 cpm
IL-2	641 cpm (-)	2486 cpm
NK-cell cytotoxicity		
Effector/target ratio (%)	60:1 (15) (-)	60:1 (31)
Effector/target ratio (%)	30:1 (13) (-)	30:1 (28) (-)
ADCC		
Effector/target ratio (%)	60:1 (20) (-)	60:1 (60)
Effector/target ratio (%)	30:1 (18) (-)	30:1 (58)

n, Normal; +, increased; -, decreased; ADCC, antibody-dependent cytotoxicity.

Another syndrome displaying similar clinical features is known to be caused by an increased chromosome fragility.² This was ruled out in our patient. A third syndrome reveals low levels of IgG but increased levels of IgM, a finding also not seen in our patient.³ In reports of premature aging and immunodeficiency, namely in Mulvihill-Smith syndrome, some findings paralleling our case are described. However, T-cell immunodeficiency is not seen in this syndrome.⁴

In children an association between idiopathic growth hormone deficiency and an impairment in thymic maturation was described.⁵ If the role of growth hormone in the development of immunocompetence can be confirmed, this may give a first lead to understanding the new syndrome described in this report.

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