

Severe combined immunodeficiency in an infant with multiple congenital abnormalities

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Subjects with severe combined immunodeficiency (SCID) exhibit profound deficiencies of T- and B-cell functions and early fatality in the absence of immune reconstitution, such as bone marrow transplantation. The genetic and molecular bases of SCID include mutations in genes encoding recombinase-activating gene-1 and -2, adenosine deaminase (ADA), Janus kinase 3 (Jak3), ζ -associated protein-70, and the IL-2 γ -chain. In other SCID syndromes, the molecular bases remain unknown.^{1,2}

CASE REPORT

A full-term male (birth weight, 6 lb 3 oz) was born to a 30-year-old first-time mother with gestational diabetes. Family history was negative for skeletal abnormalities or immune dysfunction, and there was no consanguinity between the parents. The infant had multiple musculoskeletal abnormalities, preaxial polydactyly, syndactyly, scoliosis, butterfly vertebrae of the lower thoracic spine (T8-T12), fused ribs (T9-T10), abdominal muscle hypoplasia, and laryngomalacia. Rib cage and vertebral anomalies and respiratory distress necessitated mechanical ventilation. Prenatal amniotic α -fetoprotein and results of chromosomal analyses were normal. Chromosomal breakage and results of fragility analyses were negative. Hypocalcemia, absent parathyroid hormone, and elevated alkaline phosphatase (1446 U/L; normal range, 24 to 146 U/L) indicated hypoparathyroidism. Hepatic enzyme levels were elevated to 3 times the normal level since birth, and the initial α -fetoprotein level was 427,000 ng/mL at 1 month, which persisted for 3 months and decreased to 1660 ng/mL (normal adult range, 0 to 13.4 ng/mL) at the age of 102 days. A parenteral nutritional supplement was given at 3 weeks of age for a total of 5 weeks, with no significant changes in hepatic enzyme level. Metabolic work-up was negative. The results of liver biopsy were consistent with early cirrhosis. No thymic tissue was observed by chest computed tomography scan. An echocardiogram revealed no cardiac abnormality. Recurrent infections included central line sepsis and pneumonia caused by *Enterobacter cloacae*, *Candida albicans*, and *Pseudomonas aeruginosa*. Despite intensive antibiotic and supportive treatment, at 200 days the patient died of overwhelming sepsis.

Abbreviations used

ADA: Adenosine deaminase
IDM: Infant of diabetic mother
Jak3: Janus kinase 3
SCID: Severe combined immunodeficiency

Immunologic evaluations revealed low total lymphocytes, low T cells, and elevated B cells (Table I). IgG (101 mg/dL; normal range, 172 to 1069 mg/dL), IgA (undetectable), and IgM (63 mg/dL; normal range, 17 to 149 mg/dL); ADA, purine nucleoside phosphorylase, and thymulin levels were normal. The level of antibodies to diphtheria was 0.041 IU/mL (normal level, >0.01 IU/mL), and the level of antibodies to tetanus was 0.1 IU/mL (normal level, >0.1 IU/mL) after 3 doses of vaccine. Jak3 protein was analyzed by using polyclonal antibodies (C-20, N-15, and H-20; Santa Cruz Biotechnology, Santa Cruz, Calif) and SupraSignal ULTRA (Pierce, Rockford, Ill). EBV-transformed B cells were measured by immunofluorescence with anti- γ -chain mAb (TUGh4; Pharmingen, San Diego, Calif), and sequencing analysis of coding and splice regions of IL-2R γ -chain gene in both patient and mother were normal. Cytogenetic analysis of peripheral blood failed because of nonproliferation after mitogen treatment. On the EBV-transformed cell line, a high-resolution Giemsa-banded karyotype and fluorescence in situ hybridization were performed. The karyotype was normal male, 46XY, with no deletion of either allele at the chromosome 22q11.2 DiGeorge locus (TUPLE1 probe from Vysis, Downer's Grove, Ill)³ and also no deletion at the chromosome 11p13-p14 region associated with a minority of cases of DiGeorge and velocardiofacial syndrome.⁴ The latter region was probed with YAC10p1 and YAC10p47 (kindly provided by Peter Scambler, Institute of Child Health, London, UK).⁴

DISCUSSION

This patient demonstrated abnormalities in immunologic function, including decreased T cells, increased B cells, and low antibodies to specific antigens. Human subjects with T-B⁺SCID most often have defects either in the common γ -chain, which is found in the receptor complexes for IL-2, IL-4, IL-7, IL-9, and IL-15, or in Jak3, the intracellular signaling kinase, which is phosphorylated in response to interaction with the common γ -chain.¹ However, this patient had normal cell surface expression of γ -chain and normal DNA sequence of the x-linked gene, ruling out a γ -chain defect. The normal Jak3 expression with his cells also argues against a Jak3 defect. The results of ADA and purine nucleoside phosphorylase analyses were normal. Cellular and immuno-

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TABLE I. Lymphocyte immunophenotype results

	Lymphocytes/ μ L (%)			Normal age-matched level
	Day 109	Day 112	Day 175	
Total lymphocytes	1785 (21.8), L	1950 (30), L	3192 (42.3), L	3610-8840 (45-79)
CD3 ⁺ cells	37 (2), L	39 (2), L	225 (7), L	2248-6450 (45-79)
CD4 ⁺ cells	NA (<1), L	NA (<1), L	129 (4), L	1690-4600 (36-61)
CD8 ⁺ cells	NA (<1), L	NA (<1), L	64 (14), L	720-2490 (16-34)
CD20 ⁺ cells	1705 (92), H	1775 (91), H	2700 (84), H	500-1500 (19-31)
CD56 ⁺ cells	193 (6)	137 (7)	111 (6)	110-550 (1-5)

NA, Not able to calculate; L, low; H, high.

logic defects did not fit with reticular dysgenesis, MHC class II deficiencies, ζ -associated protein-70 deficiency, or other known causes of SCID.²

Multiple musculoskeletal, urologic, and metabolic abnormalities are known to occur in infants of diabetic mothers, and one such infant has been reported to have DiGeorge syndrome, as well as renal agenesis.⁵ Interestingly, our patient did manifest hypoparathyroidism, a frequent abnormality in the DiGeorge and velocardiofacial syndromes, which may also include characteristic facial dysmorphisms, cardiac abnormalities, and heterozygous deletions of either chromosome 22q11.2 (90% of subjects) or the border between chromosomes 10p13 and 10p14.⁴ However, cytogenetic investigations failed to detect deletions at either locus to support this diagnosis in our patient.

The World Health Organization Scientific Group has listed more than 40 primary immunodeficiency diseases, including syndromes with combined skeletal and immunologic abnormalities.² However, this patient represents a

unique syndrome in which multiple congenital abnormalities and T-B⁺SCID have occurred together in an infant of a diabetic mother.

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