
Case report

Interleukin 7 receptor α -chain–mutation severe combined immunodeficiency without lymphopenia: correction with haploidentical T-cell–depleted bone marrow transplantation

Punita Ponda, MD*; Susan J. Schuval, MD*; Blanka Kaplan, MD*; Peter Logalbo, MD*; Joseph L. Roberts, MD†; and Vincent R. Bonagura, MD*

Background: Severe combined immunodeficiency (SCID) is a rare primary immunodeficiency characterized by abnormal lymphocyte development and lymphopenia. It often presents during the first year of life with recurrent, opportunistic infections, failure to thrive, and malabsorption.

Objective: To advocate newborn screening for SCID.

Methods: We reviewed the case histories of dizygotic twins with *Pneumocystis carinii* pneumonia (PCP) at the age of 6 months.

Results: Full-term fraternal twin girls were born to nonconsanguineous parents. Twin A developed recurrent oral candidiasis at 2 months, followed by pneumococcal bacteremia and PCP. At 5 months she had failure to thrive, but her absolute lymphocyte count was normal (5,887 cells/mm³). Subsequently, twin B presented with acute respiratory distress and was also diagnosed as having PCP; her absolute lymphocyte count was 5,852 cells/mm³. Flow cytometric analysis of peripheral blood lymphocytes from both girls demonstrated a T⁺B⁺NK⁺ phenotype consistent with interleukin 7 receptor α -chain–mutation SCID. Both girls received a haploidentical T-cell–depleted bone marrow transplant from their mother. In the interim, a homozygous point mutation in the interleukin 7 receptor α -chain gene was identified in twin B. Both parents were found to be carriers. Twin A died of chronic lung disease 8 months after transplantation; twin B is currently thriving.

Conclusions: Early diagnosis and treatment of SCID are associated with an increased rate of survival and improved long-term outcome. Some patients with SCID can present without lymphopenia. Thus, we advocate that more sensitive screening tests be considered for inclusion in the newborn screening program currently used in most states.

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INTRODUCTION

Severe combined immunodeficiency (SCID) is a rare primary immunodeficiency disease characterized by abnormal T-lymphocyte development and lymphopenia. It has an incidence of 1 in 80,000 live births, and patients with SCID usually experience severe infections, malabsorption, and failure to thrive during the first year of life.^{1,2}

Mutations in any of 10 known genes required for lymphocyte differentiation and maturation can result in SCID, including mutations in the interleukin 2 (IL-2) receptor common γ chain, IL-7 receptor α chain, CD3 δ chain, CD3 ϵ , CD45, janus kinase 3 (*JAK3*), recombina-
se activating gene 1

and 2, artemis, and adenosine deaminase deficiency.^{3,4} The specific mutation can be phenotypically differentiated based on the presence or absence of T, B, and natural killer (NK) cells in the peripheral blood.^{3,5}

Because early identification and treatment of SCID lead to improved survival, prompt diagnosis is critical.⁶ Although SCID characteristically presents with lymphopenia, some mutations of SCID may phenotypically have B and NK cells in sufficient numbers to lead to an absolute lymphocyte count in the reference range. Therefore, accurate identification of affected patients should not solely depend on the presence of lymphopenia. In this article, we describe 2 dizygotic twins initially seen with *Pneumocystis carinii* (*jiroveci*) pneumonia without associated lymphopenia. They were subsequently diagnosed as having SCID.

CASE REPORT

Two fraternal twin girls were born at 38 weeks' gestation to nonconsanguineous parents. The birth weight of twin A was

* Division of Allergy and Immunology, Department of Pediatrics, Schneider Children's Hospital, North Shore Long Island Jewish Health System, Great Neck, New York.

† Division of Allergy and Immunology, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina.

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Table 1. T-Cell Enumeration and Immunoglobulin Levels at Various Ages in the Study Twins*

	Twin A			Twin B		Reference range, 6–15 mo
	6.5 mo	7 mo	11 mo†	7 mo	15 mo†	
Total leukocyte (WBC) count, x1,000/ μ L	9.8	5.1	5.9	14.1	8.2	6.0–17.0
Absolute lymphocyte count, cells/mm ³	5,887	2,193	1,200	5,852	2,540	4,000–13,500
CD3 ⁺ , cells/mm ³	20	6	1	9	829	1,600–6,700
CD4 ⁺ , cells/mm ³	10	0	0	0	427	1,000–5,100
CD8 ⁺ , cells/mm ³	3	1	0	0	374	400–2,200
CD15 ⁺ /56 ⁺ (NK cells), cells/mm ³	NA	386	274	316	882	300–700
CD19 (B cells), cells/mm ³	NA	4,874	933	6,901	1,248	600–2,700
IgG, mg/dL	270	218 (217–904)‡	1,230 (294–1,069)‡	217 (217–904)‡	757 (345–1,213)‡	NA
IgA, mg/dL	16	11 (11–90)‡	27 (16–84)‡	7 (11–90)‡	33 (16–84)‡	NA
IgM, mg/dL	22	42 (34–126)‡	NA	70 (34–126)‡	203 (43–173)‡	NA
IgE, IU/dL	<2	NA	NA	NA	NA	NA

Abbreviations: NA, not available; NK, natural killer; WBC, white blood cell.

* Gower WA. Immunology. In: Roberston J, Shilkofski N, ed. *The Harriet Lane Handbook*. 17th ed. Philadelphia, PA: Mosby; 2005:370–371.

† Posttransplantation values with replacement intravenous immunoglobulin.

‡ Age-specific reference ranges are included in parenthesis.

2.56 kg (5th–10th percentile) and of twin B was 2.75 kg (10th percentile); both girls were discharged from the hospital uneventfully and had a normal neonatal course. Both twins remained between 5% and 25% for weight and between 50% and 75% for height until the age of 4 months.

However, starting at the age of 2 months, twin A developed recurrent oral candidiasis, and at 5 months of age she had pneumococcal bacteremia. At 6 months of age, she was admitted to the hospital with respiratory distress and was diagnosed as having *P carinii* (*jiroveci*) by histopathologic analysis from bronchial alveolar lavage. She was treated with intravenous trimethoprim-sulfamethoxazole and methylprednisolone sodium succinate and was transferred to Schneider Children's Hospital of the North Shore Long Island Jewish Health System on worsening of respiratory symptoms.

Physical examination at the age of 6 months revealed a weight of 5.2 kg (<5th percentile), diffuse oral candidiasis, respiratory distress (respiratory rate, 64 breaths/min), supraclavicular retractions, and bilateral rhonchi. The infant required endotracheal intubation and mechanical ventilation. Results of direct fluorescent antibody testing and viral culture of tracheal washings were positive for parainfluenza 3, and 2 courses of ribavirin were given.

Results of human immunodeficiency virus testing via enzyme-linked immunosorbent assay and polymerase chain reaction were negative. At 5 months of age, her absolute lymphocyte count was normal for her age (Table 1). However, T and B lymphocyte enumeration at 6 months of age showed an absolute T-lymphocyte count of 20 cells/mm³ (Table 1). Repeated laboratory values and immunoglobulin levels are also listed in Table 1; the patient was given intravenous immunoglobulin.

Although twin B was reported to be thriving, she presented at the age of 6 months with a weight of 6.05 kg (<5th percentile), oral candidiasis, and respiratory distress. *P cari-*

nii (*jiroveci*) pneumonia was subsequently confirmed by means of histopathologic analysis. Her absolute lymphocyte count was normal for her age, with an absolute T-cell count of 9/mm³ and normal or high B and NK cell counts (Table 1); she also received intravenous immunoglobulin for a low IgG level (Table 1). Both twins had poor lymphocyte proliferative responses to mitogens (concanavalin A, phytohemagglutinin, and pokeweed).

Both twins' lymphocyte phenotypes were consistent with T-B⁺NK⁺ SCID, most likely due to an IL-7 receptor α mutation.³ Both infants underwent maternal haploidentical T-cell-depleted bone marrow transplantation (BMT) at 7 months of age. No preparatory chemotherapy was given. Five months after transplantation, twin B had signs of partial donor T-cell engraftment with 18% T lymphocytes, but twin A had no evidence of engraftment. Twin A developed chronic lung disease requiring supplemental oxygen and did not clear parainfluenza virus; she died at the age of 16 months (8 months after BMT) of chronic lung disease. Twin B is thriving more than 21 months after transplantation. She has 15% donor engraftment, with an absolute lymphocyte count of 3,037 cells/mm³, an absolute CD3⁺ cell count of 805 cells/mm³, and normal T-cell function (normal lymphocyte mitogen responses to concanavalin A, phytohemagglutinin, and pokeweed). She continues to require replacement intravenous immunoglobulin.

To confirm the clinical diagnosis, genetic analysis for the IL-7 receptor α -chain mutation was performed at Duke University Medical Center. Twin B was found to be homozygous for a G662T missense mutation in exon 5 of the IL-7 receptor α -chain gene (chromosome 5p13). The 662G→T sequence abnormality is predicted to lead to the amino substitution S221I, which is thought to be important for proper receptor folding and ligand binding.⁷ Both parents were found to be heterozygous for the same mutation.

DISCUSSION

Pluripotent hematopoietic stem cells give rise to all white blood cell, red blood cell, and platelet precursors. Several cytokines expressed by thymic epithelial cells, including IL-7, promote T-lymphocyte differentiation and stimulation.⁸ Interleukin 7 is also involved in progenitor B, precursor B, and NK cell proliferation but is not critical for their proliferation or survival.^{9,10}

Interleukin 7 signals through a *JAK3*-coupled cellular receptor that contains the IL-7 receptor α chain and the common γ chain.^{5,11,12} Although IL-7-deficiency SCID in humans, to our knowledge, has not been described, a defect in the IL-7 receptor leads to the total absence of T lymphocytes and phenotypic deficiency in cellular and humoral immunity.³ The latter is likely a result of absent or defective T-lymphocyte help for B-cell maturation. If uncorrected, the lack of cellular immunity leads to profound failure to thrive and a predisposition for opportunistic infections, often leading to a fatal outcome. The therapy of choice is BMT. Often, the best option is transplantation with T-cell-depleted haploidentical hematopoietic stem cells originating from a family member.³ Overall, long-term survival after stem cell transplantation is 71% to 81%.^{3,13} However, stem cell transplantation in the first 4 weeks of life is associated with improved survival (up to 95%).⁶

These 2 infants were diagnosed as having SCID after presenting with opportunistic infections. It is possible that delayed diagnosis may have contributed to the poor outcome of twin A, and poor weight gain or recurrent infections should have prompted earlier intervention in these patients. A newborn screening program would identify these patients at the optimal time for BMT. The Centers for Disease Control and Prevention¹⁴ found that SCID meets many of the criteria needed for effective screening. Newborn screening may also be cost-effective compared with the sequelae of opportunistic infections and complications of administration of live viral vaccines to immunodeficient patients.¹⁵

A newborn screening program using complete blood cell counts with a manual differential might identify cases of SCID with lymphopenia, but patients with IL-7 receptor α -chain deficiency who are not leukopenic at birth would be missed. Of the known SCID mutations, IL-7 receptor α -chain deficiency is the third most common and results in a T⁺B⁺NK⁺ phenotype with a mean lymphocyte count of 2,000 cells/mm³ on presentation.³ Similarly, patients who have other mutations, including *JAK3*, and common γ -chain-deficiency SCID with a T⁺B⁺NK⁺ phenotype may present with high numbers of B cells and without absolute lymphopenia. Therefore, T-cell lymphopenia may be a more sensitive and specific marker for SCID because up to 45% of patients with SCID have absolute lymphocyte counts greater than 1,000 cells/mm³.¹⁶ However, newborns with Omenn syndrome (T⁺B⁺NK⁺ SCID) who have oligoclonal T cells and newborns with maternal T-cell engraftment in sufficient num-

bers may still be missed when screening for absolute or T-cell lymphopenia.

A recent method using T-cell receptor excision circles (TRECs) after isolation of DNA from dried blood spots on filter paper has shown more promise. Normal T-lymphocyte maturation requires recombination by cutting and splicing of T-cell antigen receptor genes. As a by-product, episomal TRECs are formed. One type of episomal TREC is produced late in maturation in 70% of newly matured T cells. Polymerase chain reaction identification of these TRECs provides an estimate of the amount of recently formed T cells in the peripheral blood. Healthy newborns are expected to have TRECs equal to 10% of their T lymphocytes. Newborns with T⁺ SCID are expected to have undetectable TRECs. Thus, this could be an effective future tool for newborn screening programs.¹⁷

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- Requests for reprints should be addressed to:*
Punita Ponda, MD
Division of Allergy and Immunology
Department of Pediatrics
Schneider Children's Hospital
North Shore Long Island Jewish Health System
865 Northern Blvd
Suite 101
Great Neck, NY 11021
E-mail: punitaponda@hotmail.com
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