

A 5-month-old boy with recurrent respiratory infections, failure to thrive, and borderline elevated sweat chloride levels

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ABSTRACT

Both severe combined immunodeficiency (SCID) and cystic fibrosis (CF) may present in infancy with a history of respiratory infections and failure to thrive. Elevated sweat chloride levels on multiple sweat tests is diagnostic of CF; transient elevation of sweat chloride has been reported in patients with hypogammaglobulinemia and antibody deficiency without CF. This article presents a case report of a 5-month-old boy with recurrent respiratory infections, failure to thrive, and two borderline elevated sweat test levels. Laboratory evaluation including testing for CF as well as immune deficiency was performed in this patient. Two borderline abnormal sweat chloride tests together with isolation of Pseudomonas from the airway caused clinicians initially to suspect CF; however, mutation in gene coding for the γ -chain of the IL-2 receptor and a negative CF genetic mutation analysis ultimately led to the final diagnosis of SCID. It is essential to make the diagnosis of SCID as early as possible because infants with SCID who do not undergo reconstitution of their immune system universally die in infancy because of infection. Early diagnosis and intervention can lead to an excellent prognosis in a previously fatal disease.

(Allergy Asthma Proc 27:285–288, 2006; doi: 10.2500/aap.2006.27.2847)

CASE PRESENTATION

Chief Complaint

Recurrent respiratory infections and poor weight gain.

History of Present Illness

A 5-month-old white male infant was admitted to the hospital for respiratory distress and hypoxia. He developed cough and wheeze at 4 months of age, which was treated with albuterol and budesonide with minimal response. He previously had respiratory syncytial virus–negative bronchiolitis with a nasal culture positive for parainfluenza virus type 2, and, beginning at 3 months of age, his weight declined from the 70th percentile to the 10th percentile.

Medical History

Medical history was significant for several episodes of otitis media, diarrhea, and a nonpruritic maculopapular erythematous rash across his abdomen. There was no known history of immunodeficiency, cystic fibrosis (CF), recurrent infections, or early childhood deaths on the father's side. Maternal family history was largely unknown because she was adopted at birth.

Physical Examination

The vital signs included a temperature of 39°C, heart rate of 130 beats/minute, and respiratory rate of 36/minute. His oxygen saturation was 95% on 1¼ L of oxygen *via* nasal cannula. His weight was 6.4 kg (10%). Tonsils were diminished in size with barely palpable lymphoid tissue. A prolonged expiratory phase with mild wheezes was present in all lung fields. His skin examination was notable for an erythematous maculopapular rash across his lower abdomen. The extremities had no signs of clubbing, cyanosis, or edema.

Initial Laboratory and Other Diagnostic Findings

A complete blood count obtained on admission was notable for a white blood cell count of 10,800 cells/ μ L (reference range, 4700–14,000 cells/ μ L) with a differential of 87% neutrophils, 2% bands, and 4% lymphocytes. A nasal pharyngeal wash again grew parainflu-

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Abstract presented at a meeting of the American College of Allergy, Asthma, and Immunology, Boston, Massachusetts, November 13, 2004

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Figure 1. Chest radiograph at time of admission shows moderate peribronchial thickening and absence of thymus.

enza type 2, and a deep throat culture grew *Pseudomonas aeruginosa*. Sweat chloride test revealed borderline elevated chloride on two occasions (54 and 50 mmol/L; normal, <40 mmol/L). His chest radiograph revealed moderate peribronchial thickening and hyperinflation, as well as a narrow superior mediastinum, suggesting an absent thymus (Fig. 1).

QUESTIONS

What Is the Differential Diagnosis?

In a young infant with recurrent respiratory infections and failure to thrive, CF, primary immunodeficiency, human immunodeficiency virus (HIV), metabolic disorders, and neurologic disorders should be considered. Patients with cell-mediated or combined immunodeficiency as well as HIV often present with opportunistic infections. Patients with metabolic disorders may present with failure to thrive because of malabsorption or difficulty processing foods. Neurologic disorders may manifest with hypotonia, which may lead to recurrent aspiration pneumonitis and recurrent respiratory infections. Patients who present with recurrent respiratory infections with wheezing may be treated initially for bronchospasm; however, the failure to thrive seen in this patient is not typical of asthma or transient wheezing of infancy.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Quantitative immunoglobulins resulted in an IgG of 75 mg/dL (reference range based on age, 228–635 mg/dL), IgA of <10 mg/dL (reference range, 27–72 mg/dL), and IgM of 13 mg/dL (reference range, 25–60 mg/dL). Silver stain from deep tracheal lavage revealed *Pneumocystis jiroveci*. Flow cytometry revealed a

CD3/CD4 count of 0% (0 cells/mm³), CD3/CD8 count of 0% (0 cells/mm³), CD16/56 count of 1% (5 cells/mm³), and CD19 count of 99% (540 cells/mm³) of all lymphocytes (T⁺B⁺NK⁺ phenotype). Lymphocyte stimulation tests showed a markedly diminished response by the patient to the mitogens phytohemagglutinin, concanavalin A (con A), and pokeweed mitogen with normal values in a control subject.

Treatment and Clinical Course

Based on the findings on sweat chloride test and the presence of *Pseudomonas* in the airway, treatment was started initially for probable CF-associated pneumonia with inhaled dornase α and i.v. cefepime. Despite this therapy, the patient developed severe respiratory distress. On further consideration, the physicians managing the case felt that the findings of lymphopenia, hypogammaglobulinemia, diminished lymphocyte proliferation, and evidence of opportunistic infection supported the diagnosis of severe combined immunodeficiency (SCID) rather than CF.^{1,2} The apparent absence of a thymic shadow on chest radiograph and decreased lymphoid tissue on examination are additional findings typical of SCID. With this diagnosis, further cardiac, metabolic, and infectious workup including ELISA or DNA polymerase chain reaction for HIV was deferred. His gene mutation analysis for CF was negative.

The patient was placed in reverse isolation and received i.v. immunoglobulin (IVIG) as well as broad-spectrum antibiotic therapy. The persistent rash across his abdomen was initially thought to be a manifestation of graft-versus-host disease, which may occur as a result of the transfer of maternal T-cells across the placental barrier; however, skin and liver biopsy revealed no evidence of graft-versus-host disease.³ The patient subsequently underwent a T-cell-depleted haploidentical maternal bone marrow stem cell transplantation after which he was maintained on IVIG and monthly pentamidine prophylaxis. The diagnosis of X-linked SCID was later confirmed when mutation analysis sent to the Immunologic Genetics Section of the National Institutes of Health revealed a mutation in exon 3 of the gene coding for the γ -chain of the IL-2 receptor. The patient's mother was found to be a carrier of this mutation. At 9 months posttransplant, analysis revealed reconstitution of the patient's lymphocytes including a B-cell line with 100% female (donor) cells. As the patient's immunoglobulin levels normalized, IVIG and prophylactic antibiotics were discontinued at 1 year posttransplant. This patient continues to thrive at this time without significant infections.

DISCUSSION

Both SCID and CF may present in infancy with a history of recurrent respiratory infections and failure to

Table 1 Comparison of SCID and CF

	SCID	CF
Incidence	1:100,000	1:3200
Inheritance pattern	X-linked or AR	AR
Age of presentation	Early infancy	Early infancy to adulthood
Presenting symptoms	Respiratory infections, failure to thrive, diarrhea, and rash	Respiratory infections, failure to thrive, and diarrhea
Specific pathogens	Viruses, <i>Pneumocystis jiroveci</i> , and <i>Candida</i> , parasites	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , and <i>Burkholderia cepacia</i>
Confirmatory laboratory findings	Lymphopenia, hypogammaglobulinemia, decreased lymphocyte proliferation to mitogens and antigens, and presence of known mutations associated with different types of SCID	Abnormal sweat chloride test, presence of two mutated alleles for CFTR gene, and measurement of nasal PD
Management	IVIG, reverse isolation, <i>Pneumocystis</i> prophylaxis, and stem cell transplant	Respiratory therapy, pancreatic enzyme supplements, and lung transplant

Source: Refs. 2, 3, 7, and 8.

AR = autosomal recessive; CFTR = CF transmembrane conductance regulator; PD = potential difference.

thrive. CF is the most common genetic disease occurring in white populations with an incidence of ~1 in 3000 births; SCID is a rare condition estimated to occur in 1 in 100,000 births.⁴⁻⁷ Patients with SCID but not CF are typically lymphopenic with diminished lymphocyte proliferative responses (Table 1).²

CF is defined by the presence of at least one phenotypic feature or a history of CF in a sibling or a positive newborn screening test plus evidence of CF transmembrane conductance regulator gene dysfunction through (1) elevated sweat chloride concentrations, (2) identification of two mutations on genetic mutation analysis, or (3) *in vivo* demonstration of nasal potential difference.^{7,8} Abnormal or borderline sweat tests should be repeated before the diagnosis of CF is established. Borderline sweat tests in the range of 40–60 mmol/L occur in 4–5% of all tests; repeat testing often results in clearly normal or abnor-

mally elevated sweat chloride levels.⁷ CF is ultimately diagnosed in 0.1–1% of cases with borderline or normal sweat chloride values.⁷ Apart from CF, malnutrition, psychosocial failure to thrive, adrenal insufficiency, celiac disease, and hypothyroidism have been associated with elevated sweat chloride.⁸⁻¹⁰ Hypogammaglobulinemia and antibody deficiency also have been reported in patients with transiently elevated sweat chloride levels.⁸⁻¹⁰ Our patient had two borderline sweat tests; his diagnosis of SCID was determined before a third repeat sweat test.

Matthews *et al.* found that 22% of children with CF <10 years of age had low serum IgG concentrations but normal specific antibody response to tetanus antigen.¹¹ Additional studies of immune function are necessary to determine if the patient with hypogammaglobulinemia and an elevated sweat chloride actually has immune dysfunction.¹¹⁻¹³

Table 2 Characteristics of different types of SCID

	Frequency	Inheritance Pattern	Genetic Mutation	Lymphocyte Phenotype
X-linked SCID	45%	X-linked	Chromosome Xq13.1	T ⁺ B ⁺ NK ⁻
Adenosine deaminase deficiency	16%	AR	Chromosome 20q13	T ⁺ B ⁻ NK ⁻
IL-7 receptor α deficiency	10%	AR	Chromosome 5p13	T ⁺ B ⁺ NK ⁺
Janus kinase 3 deficiency	6%	AR	Chromosome 19p13.1	T ⁺ B ⁺ NK ⁻
RAG1/RAG2 deficiency	3%	AR	Chromosome 11p13	T ⁺ B ⁻ NK ⁺
Artemis gene mutation	?	AR	Chromosome 10p13	T ⁺ B ⁻ NK ⁺
CD45 deficiency	?	AR	Chromosome 1q31-32	T ⁺ B ⁻ NK [±]

Source: Refs. 2 and 3.

AR = autosomal recessive; T = T lymphocyte; B = B lymphocyte; NK = natural killer; IL = interleukin; RAG = recombination-activating genes; CD = cluster of differentiation.

The term SCID refers to a group of disorders that result from varied genetic mutations. The X-linked form of SCID, which results from a mutation in the gene encoding the γ -chain of the IL-2 receptor, accounts for 45% of all cases of SCID.² An autosomal recessive inherited form of SCID is caused by the Janus Kinase 3 (Jak 3) gene mutation and results in a similar lymphocyte phenotype— $T^-B^+NK^-$.² Other forms of SCID result in different lymphocyte phenotypes as displayed in Table 2.²

When confronted with a child suspected of having SCID, it is essential to make the diagnosis as early as possible; SCID has been referred to as a “pediatric emergency.”¹⁴ The treatment of SCID is immune reconstitution *via* human leukocyte antigen (HLA) identical or T-cell depleted HLA haploidentical bone marrow, and patients with SCID do not require pretransplant chemoablative therapy.^{2,15} Pretransplant care should include assessing the patient’s humoral and cell-mediated response, placing the patient in reverse isolation, administering antibiotic prophylaxis and IVIG, and transfusing with cytomegalovirus (CMV)-negative, irradiated blood products, if necessary.² Children with SCID who undergo bone marrow transplant before the age of 3.5 months have a survival rate of 97%.¹⁵

Final Diagnosis

X-linked SCID was the final diagnosis.

CONCLUSIONS

This case emphasizes the importance of suspecting primary immune deficiency in patients with recurrent respiratory infections and failure to thrive. The finding of two borderline abnormal sweat chloride tests together with isolation of *Pseudomonas* from the airway caused clinicians initially to suspect CF; however, subsequent laboratory findings led to the final diagnosis of

SCID. Early diagnosis and intervention can lead to an excellent prognosis in an otherwise fatal disease.

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