

Novel *RAG2* Mutation in a Patient with T– B– Severe Combined Immunodeficiency and Disseminated BCG Disease

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■ Abstract

T–B–NK+ severe combined immunodeficiency (SCID) is an autosomal recessive disease that is caused mainly by a defect in the recombination activating genes (RAG). Patients with SCID usually experience life-threatening opportunistic infections in early infancy and complications after vaccination with bacille Calmette-Guérin (BCG).

We report a patient of consanguineous parents who was referred to our center with subaxillary lymphadenitis and respiratory distress. Laboratory studies confirmed the diagnosis of T–B–NK+ SCID and molecular studies revealed homozygous mutations in the *RAG2* gene. The patient died despite administration of antituberculosis drugs, antibiotics, and intravenous immunoglobulin.

Inoculation of live vaccines such as BCG should be postponed in families with a positive history of SCID until screening tests rule out this condition.

Key words: BCG. Mutation. *RAG2*. Severe combined immunodeficiency. Vaccine.

■ Resumen

Comunicamos el caso de un paciente con padres consanguíneos que fue referido a nuestro centro con una linfadenitis subaxilar y distrés respiratorio. Los análisis de laboratorio confirmaron el diagnóstico de T–B–NK+ IDCG y los estudios moleculares revelaron mutaciones en homocigosis del gen *RAG2*. El paciente murió a pesar de la administración de fármacos antituberculosos, antibióticos, e inmunoglobulina intravenosa.

La inoculación de vacunas vivas como BCG debería posponerse en familias con una historia positiva IDGC hasta que las pruebas de detección puedan descartar esta condición.

Palabras clave: BCG. Mutación. *RAG2*. Inmunodeficiencia combinada grave. Vacuna.

Introduction

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency disease, and is characterized by impaired B-cell function and complete absence of T-cell-mediated immunity in most cases. SCID is

a heterogeneous disease that can be subclassified according to the peripheral blood lymphocyte immunophenotype and genetic etiology [1,2].

One subgroup of SCID patients lack circulating T cells and B cells, but have normal natural killer (NK) cells [3]. T–B–NK+ SCID (OMIM-601457) is an autosomal recessive

disease, which is most commonly caused by a defect within recombination-activating genes (*RAG1*, OMIM*179615; *RAG2*, OMIM*179616) [1]. Regardless of SCID type and the underlying genetic defect, affected patients usually present severe and life-threatening opportunistic infections in early infancy [4]. Numerous SCID patients have experienced complications after vaccination with bacille Calmette-Guérin (BCG); in some cases, these include disseminated BCG disease and may even lead to death [5,6].

We report the case of a patient with T-B-NK+ SCID who died due to disseminated BCG disease.

Case Description

The patient was a 6-month-old boy, the second child of a family with a Turkish ethnic background. The parents were consanguineous and the first child of the family died of disseminated BCG at 7 months (Figure).

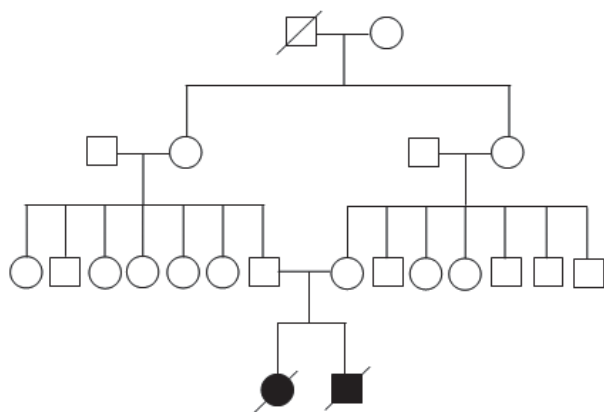


Figure. Pedigree showing 4 generations, with healthy individuals (open shapes), affected patients (filled shapes), and deceased individuals (shapes with slashes). Boxes indicate males; circles, females.

The first child, the patient's sister, had a history of recurrent oral candidiasis and had been referred to Tabriz Children's Hospital in northwestern Iran with fistulated subaxillary lymphadenitis, multifocal osteolytic lesions, and respiratory distress. Culture of pleural effusion was positive for bacille Calmette-Guérin. Further evaluation revealed T-B-NK+ SCID, based on the following values: severe decreased serum immunoglobulin (Ig) G, IgM, and IgA levels; white blood cells, 5200/mm³; lymphocytes, 27%; CD19, 0%; CD3, 11%; CD4, 8%; CD8, 3%; CD16, 35%. The patient died despite administration of antituberculosis drugs, antibiotics, and intravenous immunoglobulin. The family was advised to undergo further evaluation and prenatal screening, and to avoid live vaccines with future children.

Two years later, their new infant was shown to have a similar phenotype to that of the first child. However, despite recommendations, the child was vaccinated with BCG at birth. Subaxillary lymphadenitis, oral candidiasis, respiratory

distress, and hepatomegaly were detected. Further evaluation of the patient indicated T-B-NK+ SCID (IgG, 418 mg/dL; IgM, 54 mg/dL; IgA, 95 mg/dL; white blood cells, 3200/mm³; lymphocytes, 49%; CD19, 2%; CD3, 10%; CD4, 6%; CD8, 12%; CD56, 93%). A DNA sample was extracted for molecular studies. Treatment with antituberculosis drugs, intravenous immunoglobulin, and antibiotics was started. However, the patient did not respond to treatment and died.

In an attempt to find the molecular defect of SCID in this family, the *RAG1* and *RAG2* genes were sequenced. The homozygous mutations C1782A (S194X) and T1784G (Y195D) were detected in the *RAG2* gene. Both parents were heterozygous for the *RAG2* mutations and polymorphisms.

Discussion

Vaccination with BCG is used in many countries for prophylaxis against tuberculosis, especially in children. Although this vaccine is generally considered safe, it can cause complications in patients with underlying immunodeficiency diseases, such as SCID, and can lead to disseminated BCG disease and death [5,6]. Disseminated BCG disease is one of the most common causes of death in patients with primary immunodeficiency disease, particularly SCID [7].

Although the underlying genetic defect of SCID has not always been reported, our patient had a novel mutation within the *RAG2* gene, although all patients with SCID are susceptible to early-onset life-threatening opportunistic infections [4,5].

The report of 2 patients with SCID who died due to disseminated BCG disease should alert not only pediatricians, but medical personnel in general. Taking an exact family history before vaccination is strongly recommended, as families with low socioeconomic status may not provide information if not asked.

Furthermore, BCG vaccination should be postponed for a few months in suspected families, at least in regions with a high incidence of SCID (eg, northwestern Iran) [7,8]. Although the first dose of vaccine is generally recommended at birth in many regions, live vaccines should be prohibited in patients with underlying immunodeficiency, particularly SCID, and their families [9,10].

Consanguineous mating and a family history of early deaths due to recurrent infections in siblings should also alert to underlying immunodeficiency diseases. In areas with a high rate of consanguinity, genetic counseling and public education programs should be provided [11].

Patients with SCID seem to be more susceptible to infections by *Mycobacterium* species and to BCG vaccine. Inoculation of live vaccines should be postponed in suspected cases until appropriate screening rules out a diagnosis of SCID.

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