Complete DiGeorge Anomaly in the Absence of Neonatal Hypocalcemia and Velofacial and Cardiac Defects

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ABSTRACT. We report an atypical case of complete DiGeorge (DG) anomaly that presented initially exclusively as severe combined immunodeficiency (SCID). The child had severe infections at diagnosis, in keeping with the SCID phenotype; however, normal lymphocyte counts and immunoglobulin levels were noted at admission, which delayed diagnosis. Importantly, the child presented without neonatal hypocalcemia or velofacial or cardiac abnormalities at the time of diagnosis, which masked underlying DG. This case outlines the difficulties in making the diagnosis of SCID in a timely manner and illustrates the variation in presentation of the 22q11.2 deletion syndrome. There should be a high index of suspicion for primary immunodeficiency among children with severe infections and, because management may vary, DG anomaly should be considered in the differential diagnosis of T−B+ natural killer+ SCID. Pediatrics 2005;116:457–460. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0371; primary immunodeficiency, stem cell transplant, thymic transplant, fluorescence in situ hybridization.

ABBREVIATIONS. DG, DiGeorge; PID, primary immunodeficiency; SCID, severe combined immunodeficiency; BMT, bone marrow transplantation; NK, natural killer.

Severe combined immunodeficiency (SCID) is life-threatening and usually presents in the first few months of life. Common manifestations include failure to thrive, recurrent thrush, and respiratory infections. The hallmark of SCID is absent or poorly functioning T lymphocytes. Although children with SCID often present with lymphopenia, normal or elevated lymphocyte counts are also seen. In addition, normal levels of serum immunoglobulins are often found.1,2 Therefore, normal lymphocyte counts or immunoglobulin levels should not exclude a diagnosis of primary immunodeficiency (PID) and, among children with recurrent infections, complete evaluation of the immune system, including T, B, and natural killer (NK) cell phenotyping, is required to ensure prompt diagnosis.

DiGeorge (DG) anomaly (OMIM 188400) is caused by developmental defects in the third pharyngeal pouch and fourth pharyngeal arch.3 This disorder is clinically heterogeneous and is characterized by cardiovascular defects and thymic, parathyroid, and craniofacial anomalies.4,5 Associated problems include esophageal reflux, laryngomalacia, and delay in speech acquisition. Phenotypes range from life-threatening heart defects or T cell immunodeficiency to mild craniofacial abnormalities and developmental delays. Approximately 80% of DG anomaly cases are caused by a chromosomal deletion generally referred to as del(22)(q11.2q11.2). In fact, 22q11.2 deletion syndrome6–12 is now used to describe a heterogeneous group of disorders including DG anomaly, velocardiofacial syndrome,13 and conotruncal anomaly face syndrome and is the most common chromosomal deletion syndrome among humans, occurring with an incidence of ~1 case per 3000 live births.8,11,12,14–16 Among patients with del(22), 90% have a virtually identical 3-megabase heterozygous deletion of 22q11.2 but show great clinical variability, which suggests the presence of additional genetic modifiers. Some patients have DG anomaly features in conjunction with the CHARGE association (association of coloboma, heart defect, agenesis of choanae, retardation of growth or development, genital hypoplasia, and ear anomalies or deafness)17 or in association with maternal diabetes mellitus18 and are more rarely 22q11.2 hemizygous. Others have DG anomaly features and are hemizygous for 10p13.19

In DG anomaly, the development of thymic tissue is affected; thymic defects occur for ~80% of patients, leading to varying degrees of cellular immunodeficiency.20 DG-SCID describes a small subset of children with clinical features of DG anomaly and severe T-cell immunodeficiency (1–2%) attributable to absent or highly hypoplastastic thymic tissue. This disorder is found often in conjunction with the CHARGE association, 22q11.2 hemizygosity (50–62% in 2 reports),21,22 or diabetic embryopathy. The profound T-cell immunodeficiency in DG-SCID is fatal without intervention within the first 2 years of life.9,23–26 Immune reconstitution is possible through infusion of peripheral mononuclear cells or bone marrow transplantation (BMT) from a genotypically HLA-identical donor or, more recently, through postnatal thymic tissue transplantation.22,27–29

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We report an unusual case of DG-SCID that presented exclusively as SCID, without neonatal hypocalcemia or velofacial or cardiac abnormalities, at the time of diagnosis. The child presented with a SCID phenotype, but normal lymphocyte counts and immunoglobulin levels were noted at the initial presentation, delaying diagnosis. This case clearly shows the variation in presentation of DG anomaly, and we outline difficulties in making the diagnosis of SCID in a timely manner.

**CASE REPORT**

A 5-month-old male infant was admitted to our hospital with severe parainfluenza III virus bronchopneumonitis. He was born at 41 weeks, after an uneventful normal pregnancy. He had experienced recurrent thrush and more recently failure to thrive. There was no relevant family history, and there were 2 healthy siblings. On examination, the patient exhibited marked respiratory symptoms, with a respiratory rate of 70 breaths per minute, intercostal and abdominal indrawing, and bobbing of the head (evidence of marked respiratory distress). Growth failure, with height and weight below the 10th percentile, was also noted. The nasopharyngeal aspirate was exclusively positive for parainfluenza III virus. Chest radiographs showed marked pulmonary distention, with flattening of both diaphragms and diffuse bronchoalveolar infiltrates. There was no evidence of aspiration pneumonia. Biological screening showed normal absolute lymphocyte counts (9110 cells per mm³) and normal IgG (5.2 g/L), IgA (1.3 g/L), and IgM levels (0.7 g/L). Three weeks after admission, the patient's condition deteriorated rapidly and the immunology service was consulted. Lymphocyte phenotyping established the diagnosis of SCID with a T⁻ (150 cells per mm³), B⁺ (3850 cells per mm³), and NK⁻ (550 cells per mm³) phenotype and absent T cell proliferation in response to mitogens and anti-CD3 antibody (Fig 1). No obvious dysmorphic features were observed in a thorough physical examination, including no abnormal implantation of ears or micrognathia. The child had no history of gastroesophageal or nasopharyngeal reflux. His neurocognitive development was concordant with his age. Ionized calcium levels were normal. Nonmanipulated BMT from a HLA-matched sibling donor was performed without conditioning and resulted in T-cell engraftment and resolution of pulmonary infection within 2 weeks. On the basis of the T⁻ B⁺ NK⁺ lymphocyte phenotype and the absence of obvious facial, cardiac, and calcium abnormalities, the interleukin-7 receptor genotype was investigated and was found to be normal. CD3 subunits, which could have explained the molecular defect alternately, were not tested at that time.

One month after BMT, the child presented with generalized seizures secondary to hypocalcemia (ionized Ca²⁺ level of 0.84 mmol/L). Parathyroid hormone was undetectable (<30 pg/L). On the basis of the hypoparathyroidism and SCID, the possibility of DG anomaly was investigated. Cardiac ultrasound findings were normal. Chest computed tomographic scans revealed an aberrant right subclavian artery (an anatomic variation present in 1% of the population) and the absence of a thymus (Fig 2A). A fluorescence in situ hybridization study for deletions on chromosome 22q11.2, performed by the geneticist who is now monitoring the child jointly, the patient exhibited delayed speech acquisition and very subtle micrognathia. There were no additional features of DG anomaly, including no hearing defect and no vertebral, ocular, or renal abnormalities. The patient’s calcium level is controlled with vitamin D and calcium supplements. His neurocognitive development cannot be assessed fully at 2.5 years of age, especially in the presence of delayed speech acquisition, and needs to be reevaluated later in the child’s life.

**DISCUSSION**

Although lymphopenia is common in SCID, infants presenting with persistent infections and failure to thrive may have normal lymphocyte counts and immunoglobulin levels, delaying the diagnosis of PID. We report an unusual case of DG anomaly presenting exclusively as T⁻ B⁺ NK⁺ SCID. In the past decade, many molecular and genetic defects causing SCID have been identified. Defects that have been defined genetically for this subset of SCID are

![Fig 1. Lymphocyte subsets before and after BMT.](http://pediatrics.aappublications.org/Downloaded from)
interleukin-7 receptor α deficiency, which was excluded for our patient, CD3 subunit deficiencies, and DG anomaly (reviewed in refs 1, 2, and 33). Hypocalcemia and facial or cardiac defects are the hallmarks of DG-SCID, and del(22)(q11.2q11.2) is present in cases reported to date. For our patient, hypocalcemia was evident only at 7 months of age. Latent hypoparathyroidism in DG anomaly has been described and diagnosed even among adults during evaluation of refractory hypocalcemia.34,35 Cardiac defects may be absent in DG-SCID; however, severe hypoparathyroidism and dysmorphic facies have been associated frequently, allowing early diagnosis.36 In another specialized center that treats children with SCID routinely (Hôpital Necker, Paris, France), one other child with SCID and isolated labial cleft had del(22)(q11.2q11.2) and a similarly delayed diagnosis (Alain Fischer, MD, PhD, oral communication, 2004). However, only 50% of children with DG-SCID have del(22)(q11.2q11.2)21,22 and can thus be diagnosed on the basis of this genetic characteristic. In all other DG-SCID cases in which such a deletion is not present, diagnosis is possible only when all of the other molecular diagnoses of T−B−NK− SCID are known and excluded or when we gain better knowledge of the exact mechanisms underlying the DG-SCID phenotype.

Several avenues of treatment have been used to treat the life-threatening immunodeficiency associated with DG-SCID. Transplantation of fetal thymus has been used historically and resulted in immune reconstitution in a few cases.37–39 Genotypically HLA-identical BMT has also been used successfully in a few cases.27,28,40 This treatment resulted in restoration of T-cell function, most likely through adoptive transfer of postthymic donor T cells, as was the case for our patient. Two different groups postulated that only postthymic lymphocytes, and not stem cells, were responsible for immune reconstitution after successful BMT. On the basis of this hypothesis, they performed peripheral blood mononuclear cell transplantation from a HLA-identical sibling. This procedure was followed by partial T-cell engraftment and immune reconstitution through adoptive transfer of mature T cells among patients.29,36 It is very likely that children with DG-SCID cannot form new thymic immigrants from infused stem cells because they have little residual, functional, thymic tissue. Transplantation of postnatal thymic tissue is a more recent therapeutic approach and is yielding very promising results.21,22,25,41 In fact, only after this procedure did episomal circular DNA excision products of T-cell receptor gene rearrangement analysis among recipients show evidence of new thymopoiesis. In SCID-DG cases with no genotypically HLA-identical donor, this is the obvious treatment. These

Fig 2. A shows serial axial slices from chest computed tomographic scans performed after BMT, showing the absence of thymus in the anterior mediastinum and the presence of an aberrant right subclavian artery arising from the aortic cleft behind the tracheal carina (arrows). B shows fluorescence in situ hybridization analysis of a metaphase preparation from a fibroblast culture, showing 46,XY,del(22)(q11.2q11.2)(TUPLE1,D22S553,D22S609,D22S942–). The target probe shows heterozygous deletion of DG region loci on one chromosome 22 (in red). The control probe hybridizes to both chromosomes 22 (in green).
CONCLUSIONS

There should be a high index of suspicion for PID among children with severe infections, and this diagnosis is not to be excluded on the basis of normal lymphocyte counts or immunoglobulin levels. We recommend strongly performing lymphocyte phenotyping and stimulation tests to ensure diagnosis of PID. Chromosome 22 deletions are underdiagnosed among patients with cardiac abnormalities, and screening with fluorescence in situ hybridization for chromosome 22 deletion, a widely accessible diagnostic tool in specialized centers, is increasingly part of the evaluation of congenital cardiac disorders. Patients with T-B+NK+ SCID may have the molecular defect of DG anomaly even in the absence of neonatal hypocalcemia or obvious cardiac or facial defects. Screening for chromosome 22 deletions among patients with T-B+NK+ SCID should be routine. In the absence of this chromosomal deletion, enlisting the help of a geneticist and an endocrinologist can prove useful for diagnosis. Ensuring a correct molecular diagnosis has a profound impact on genetic counseling and, most importantly, on treatment and therapeutic options for affected children.

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