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Two cases of severe combined immunodeficiency caused by adenosine deaminase deficiency with a new mutation and a novel missense mutation in DCLRE1C

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Abstract:
Severe combined immunodeficiency (SCID)is a potentially fatal primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. There are at least 13 different genetic defects that can cause SCID. SCIDIs the most serious primary or congenital human immunodeficiency disorder. Adenosine deaminase (ADA) deficiency is among the most common causes of severe combined immunodeficiency and is autosomal recessively inherited through mutations in the ADA gene, characterized by dysfunction of the T, B, and natural killer (NK) cells (T-B-NK-SCID)
Mutations in the gene for Artemis (DCLRE1C) cause a rare form of autosomal recessive radiosensitive SCID, which results in a T-B-NK+ phenotype.
General presentation occurs in infancy with lymphopenia, failure to thrive, diarrhea, candidiasis, and Pneumocystis jiroveci pneumonia. In Artemis deficiencyPatients with an Omenn syndrome phenotype have also been described. Even with supportive therapies, patients with SCID will not survive without aHematopoietic stem cell transplantation (HSCT). Patients transplanted before 3 months of age have a greater survival while patients who are transplanted later and have suffered end organ damage from infections have a much lower success rate. Overall, patients with T-B-SCID have less successful HSCT outcomes than patients with T-B+ SCID.

Introduction:
SCID is a rare, potentially fatal syndrome of diverse genetic causes in which there is combined absence of T-lymphocyte and B-lymphocyte function (and in many cases also natural killer, or NK, lymphocyte function) and considered to be the most serious of the primary immunodeficiencies. The different genetic causes of SCID vary with respect to laboratory findings and patterns of inheritance.
There are about 13 genes that implicated in SCID which increase the susceptibility to very serious infections. Luckily, effective treatments, such as stem cell transplantation, exist that can cure the disorder. All types of primary immunodeficiencies, not just SCID, stand to benefit from early diagnosis so early identification of SCID can make possible life-saving intervention before infections occur.[1, 2]
In this report I will discuss adenosine deaminase deficiency with a new mutation that cause severe combined immunodeficiency and atypical severe combined immunodeficiency (SCID) associated with a novel missense mutation in DCLRE1C.
Adenosine deaminase (ADA) deficiency is among the most common causes of severe combined immunodeficiency and is autosomal recessively inherited through mutations in the ADA gene, characterized by dysfunction of the T, B, and natural killer (NK) cells (T-B-NK-SCID) and severe lymphopenia. [1,3]
Artemis (DCLRE1C) deficiencyis arare form of autosomal recessive radiosensitive SCID, which results in a T-B-NK+ phenotype.[1, 4]

Discussion:

- **Case presentation:**
A 3-month-old girl was referred for recurrent fever, pneumonia, diarrhea, chronic dermatitis, failure to thrive, and motor retardation. The patient was the daughter of consanguineous parents and had a female sibling who had died due to recurrent infections. She suffered from oral thrush and a diffuse brownish colored macular rash on the trunk. Chest auscultation revealed bilateral crackles at the lower zones. Chest X-ray indicated the absence of thymus shadow; a Para cardiac infiltration and an inferolateral squaring scapulae were demonstrated.
Laboratory tests revealed mild anemia with profound lymphocytopenia, and hypogammaglobulinemia. A lymphocyte subgroup analysis revealed a severe combined immunodeficiency. Adenosine deaminase (ADA) activity was absent. The total deoxyadenosine nucleotides (dAXP) in the erythrocytes were markedly elevated, confirming the diagnosis of ADA deficiency. The patient was found to be homozygous for a point mutationc.478þ3G>C, which causes an IVS5 splicing

mutation (IVS5þ3G>C).Her mother, father, and sister were carriers of this mutation, and her brother was wild-type (no mutation), this is a novel mutation.

About the treatment she cannot do steam cell transplantation as all of her family members were mismatched, but they started enzyme replacement therapy this cause marked increase in ADA and decrease in dAXP.

In areas where there are consanguineous marriages the percentage of SCID is increased due to the genetic susceptibility.

The disease is characterized by severe lymphopenia with low numbers of T, B, and NK cells. Although eosinophilia is a typical feature of Omenn syndrome, eosinophilia accompanied by absolute lymphopenia has also been reported, as in the present case

ADA-SCID patients suffer from recurrent infections, a failure to thrive, and neurologic manifestations. Extensive dermatitis, and persistent diarrhea can also develop. The cause of these manifestations not fully understood whether the metabolic effects of ADA deficiency or secondary as a result of immunodeficiency cause them.

Patients may also have prominent metaphyseal changes that are reversible by enzyme replacement therapy.

There are about 70 different types of mutation implicated in ADA deficiency, in this case homozygous for a 5' splice site mutation in IVS5.

The only curable treatment is hematopoietic stem cell transplantation, and the enzyme replacement therapy is only temporary solution.[3]

- **Case presentation**:

A 5-year-old boy presenting with cytomegalovirus (CMV) pneumonia and long-term viral gastroenteritis. The patient was the son of consanguineous parents and first presented at 3 months postpartum with upper respiratory tract infection and intermittent diarrhea, where the symptoms recurred in bouts during the following 5 years. He was evaluated for coeliac disease, inflammatory bowel disease and food allergies without a definite diagnosis. The boy had normal psychomotor development, and there was no failure to thrive, despite the recurrent symptoms.

At the time of evaluation, the patient had developed a febrile illness with cough and worsened diarrhea. Chest CT showed bilateral ground glass opacities, and PCR detected 43 000 copies/mL of CMV in bronchoalveolar lavage. Peripheral T-cell numbers were diminished, and the proportion of double-negative T cells (CD3+CD4−CD8−) was elevated with at 20% of the peripheral T-cell population.The peripheral B-cell population was reduced and showed a decreased level of naïve B cells (IgD+ CD27−) and an increased proportion of switched memory B cells (IgD−, CD27+).

The patient has a novel homozygous missense mutation in DCLRE1C. The mutation(c.272G>T, p. G91V) localized to the β-lactamase domain of Artemis, which is essential for its enzymatic activity.The patient's parents were both heterozygous carriers.

The patient mutations in DCLRE1C give rise to an Artemis protein that is unable to fully assist in V(D)J recombination and thus lead to an impaired T-cell receptor (TCR) diversity, resulting clinically in atypical SCID. Assessing the impact of novel mutations in DCLREC1C on radiosensitivity is clinically important, asincreased radiosensitivity will affect a patient response to alkylating chemotherapy, which is often used in the conditioning regiment of allogeneic hematopoietic stem cell transplantation (HCT). The patient's fibroblasts showed a marked increase in radiosensitivity compared to fibroblasts from a healthy donor, indicating compromised DNA repair. The difference in fibroblast survival was most pronounced with lower doses of radiation. There are no significant differences at a higher radiation dose, possibly due to the insensitivity of the method.

The patient's CMV pneumonia responded to treatment with ganciclovir. A decision was made to perform HCT based on the clinical picture with progressive immunodeficiency and inability to control latent CMV in conjunction with immunologic findings indicating atypical radiosensitive SCID. Due to the lack of HLA-matched donors, an in vitro TCR alpha/ beta-positive T-cell depleted peripheral

blood stem cell graft from the patient's haploidentical father was used.The patient had an uneventful post-HCT course and is now in good clinical condition beyond the 2-year follow-up. [4,5]

Conclusion:

To sum up SCID is fatal syndrome of diverse genetic causes in which there is combined absence of T-lymphocyte and B-lymphocyte function. The second most common cause of SCID is ADA deficiency, 15% of the cases; it's an autosomal recessive trait. It has a very low total lymphocyte count of all, T, B and NK; also leads to neurological problems, which are not fully curable by HCT unlike the syndrome itself.Whereas Artemis (DCLRE1C) deficiency is arare form of autosomal recessive radiosensitive SCID, which results in a T-B-NK+ phenotype. In consanguineous marriages the percentage of SCID is increased due to the genetic susceptibility.Overall HCT is the only curable treatment, if there's no matched donor enzymatic replacement therapy is a temporary solution to improve the symptoms.

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