

Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency

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Abstract

Severe Combined Immunodeficiency is the term applied to a group of rare genetic disorders characterised by defective or absent T and B cell functions. Patients usually present in first 6 months of life with respiratory/gastrointestinal tract infections and failure to thrive. Among the various types of severe combined immunodeficiency, enzyme deficiencies are relatively less common. We report the case of a 6 years old girl having severe combined immunodeficiency due to adenosine deaminase deficiency.

Keywords: Combined Immunodeficiency, T and B cell, Gastrointestinal tract infections, Adenosine deaminase.

Introduction

Severe Combined Immunodeficiency (SCID) group includes primary immunodeficiencies that lead to severe life

threatening infections and are usually fatal in infancy. SCID is rare with an incidence of about 1 in 40,000-100,000 live births.¹ Adenosine deaminase (ADA) deficiency is an inherited condition that accounts for about 12% of SCID variants.² Clinical onset may be delayed by 5-8 years in 10-15% of cases.³

Case Report

A 6 years old girl presented with repeated episodes of respiratory infections since the age of 2 years. Frequency of such attacks were variable. However, minimum two such episodes were noticed per month. There was no specific time of occurrence or any weather predilection. There was no history of loose motions, skin lesions, anorexia, weight loss, contact with patient suffering from Tuberculosis or family history of asthma or allergy. Response to antibiotics and bronchodilators was temporary at best. She received Anti-Tuberculosis treatment for 9 months in 2006. On

Table-1: Lymphocyte Subset Analyses (Peripheral Blood).

Parameters	Results Initial	Results After one month	Reference values of age group: (1-6 years)
TLC	5100/?1	4300/?1	6800-10,000/?1
Lymphocyte %	36%	18%	38-63%
Lymphocyte count	1836/?1	774/?1	2900-5100/?1
CD3+ T cells	91% (1671)	90% (696)	62-69% (1800-3000/?1)
CD3+CD4+ T cells	79% (1450)	80% (619)	30-40% (1000-1800/?1)
CD3+CD8+ T cells	21% (385)	12% (93)	25-32% (800-1500/?1)
CD19+ B cells	1% (18)	1% (7)	21-28% (700-1300/?1)
CD16+56+ NK cells	2% (36)	3% (23)	8-15% (200-600/?1)
CD4:CD8	3:7	6.2	1.0-1.6

Table-2: Adenosine Deaminase/Purine Nucleoside Phosphorylase levels.

	ADA (nmol/hr/mg)	PNP (nmol/hr/mg)	% dAXP
Results	2.2	1303	14.6
Ref values	18.5-46.5	2199-2565	0-4.0

examination, she was vitally stable with grade 1 clubbing. Examination of chest revealed vesicular breathing on right side of the chest. Bronchial breathing was appreciated over left middle part of chest. Rest of the systemic examination was unremarkable.

Investigations revealed complete blood counts (CBCs) within normal range with normal total and differential leukocyte counts. On chest x-ray, patchy shadowing and atelectasis were reported in right hilar region. CT chest revealed hyperventilated lungs and bronchiectasis with patchy consolidation/atelectasis. Serum immunoglobulin levels showed slightly raised Immunoglobulin E (IgE) levels while Immunoglobulin G (IgG) and Immunoglobulin A (IgA) levels were within the age specific reference range. DELTA F508 mutation was tested and found negative for cystic fibrosis. The patient was referred to Immunology Department of Armed Forces Institute of Pathology (AFIP), Rawalpindi for further evaluation and workup. Her Erythrocyte Sedimentation Rate (ESR) was 46 mm at 1st hour. The level of C reactive protein was raised at 12mg/l. Serum IgG and IgM were within the age specific reference range, while IgA was undetectable. The level of Serum IgE were raised to 95 IU/ml. Functional antibodies against Candida and E coli were positive. Anti aspergillus antibodies were negative. Anti Diphtheria and Anti Tetanus antibodies, before (0.12 IU/ml and 0.02 IU/ml respectively) and after the immunisation (0.42 IU/ml and 0.10 IU/ml respectively), showed adequate response. Nitroblue Tetrazolium (NBT) test results were within the reference range. Lymphocyte subset analysis of peripheral blood was performed and was repeated after one month. Both analyses revealed a decrease in percentage and absolute number of total lymphocytes. CD19+ B lymphocytes were virtually absent

from the peripheral blood with decrease in the absolute number of total CD3+ T and CD16 CD56+ NK cells.

Results of the second analysis showed deterioration in the lymphocyte count as compared to the first one, which provided the first clue to possible ADA deficiency. Because of limitations of diagnostic modalities in Pakistan, blood specimen of patient was sent to Duke University Medical Center, North Carolina, where ADA (adenosine deaminase), PNP (purine nucleoside phosphorylase), dAXP (total deoxyadenosine nucleotide) and %dAXP (dAXP/AXP+dAXP) levels were tested.

Results were interpreted as deficient ADA activity with normal PNP activity; dAXP (total deoxyadenosine nucleotide) was elevated. She was found to be homozygous for a missense mutation (R156H in exon 5; a delayed onset phenotype of ADA deficient SCID). The whole data was consistent with Late Onset/Partial ADA-Deficient Severe Combined Immunodeficiency. The patient responded reasonably well to antimicrobial and antifungal therapy. Disease prognosis was explained to parents with counseling regarding possible benefits of ADA replacement therapy. Gene replacement therapy was explored but not offered to this patient as it is indicated for patients with complete ADA deficiency. Bone marrow transplant from HLA identical donor was also discussed and possible hazards of bone marrow transplant such as infections, graft versus host disease and lack of engraftment were told. The family, due to stable state of the patient, decided not to go for this option at present.

Discussion

Deficiency of ADA is an autosomal recessive genetic disorder.⁴ It accounts for about 10-15% of all cases of SCID. ADA deficiency may present in infancy, childhood, adolescence or adulthood. Age of onset and severity is related to some 29 known genotypes associated with the disorder.^{5,6}

Clinical features are due to the lack of enzyme ADA, encoded by a gene on chromosome 20 (20q13.11). Accumulation of adenosine and deoxyadenosine follows and confers a toxic effect on immature lymphocytes, particularly

thymocytes, which thus fail to mature. The deficiency causes a build up of toxic metabolites in all cells, but this build up is specifically detrimental to developing T cells and B cells. Most of the body cells have effective means of removing these metabolic byproducts and remain unaffected by ADA deficiency. However, T lymphocytes are unable to do so in the absence of ADA.² Thus, T cells bear the brunt and affected individuals tend to have a small, underdeveloped thymus.⁷ Consequently, the immune system is severely compromised or completely lacking. Instead of having a normal life span of a few months, T cells of individuals with ADA deficiency live only for a few days.²

Most cases (about 85%) of ADA deficiency show severe depression of T and B lymphocyte counts in their peripheral blood and are thus typical cases of SCID. Infection and growth failure are usually accompanied by skeletal and neurological problems (hearing disorders, blindness, dystonia etc.).³ Late onset ADA deficiency is characterised by lymphocytopenia of gradual onset. Autoimmune disorders like refractory thrombocytopenic purpura may be evident. Red blood cells show only mild to moderately increased levels of dAXP as compared to those in the early onset type.²

Individuals with SCID are unable to mount an effective immune response to any infection. Therefore, exposures to organisms that normal, healthy individuals easily overcome become deadly infections in SCID patients. Prior to present-day treatments, most ADA-deficient SCID victims died of infections before reaching the age of two years. Although SCID is usually diagnosed in the first year of life, approximately one-fifth of ADA-deficient patients have delayed onset SCID, which is only diagnosed later in childhood, as was observed in our patient. There are few cases of ADA deficiency diagnosed in adulthood.⁸

The treatment of choice for ADA deficiency is bone marrow transplantation from a matched sibling donor. Unfortunately, only 20-30% of patients with ADA deficiency have a matched sibling donor. Alternate treatment involves injecting the patient with Polyethylene Glycol-Coated Bovine ADA (PEG-ADA) derived from cows. The latest treatment for ADA deficiency is gene therapy. It provides patients with their own T cells into which a normal copy of the human ADA gene has been inserted. ADA deficiency was the first disease to be treated with human gene therapy.⁸ On September 14, 1990, Dr. W. French Anderson performed first such procedure on a four year old girl, Ashanti de Silva, at the National Institutes of Health, Bethesda, Maryland, USA.⁹ Subsequent research is focused on developing a permanent cure for ADA deficiency using gene therapy. Unlike T cells

which only live for a few months, stem cells live throughout the patient's life. If the defective gene is replaced in the stem cells, the patient has a lifetime supply of ADA without requiring further treatment. More than 30 SCID patients have achieved life-saving immune reconstitution lasting for up to 10 years after successful gene therapy.¹⁰

Conclusions

ADA deficiency is a rare type of immunodeficiency and its diagnosis is critically dependent upon a high degree of suspicion and close coordination between the clinician and immunological laboratory services. Correct and early diagnosis assumes greater importance in this disorder as the modern research has revolutionised the clinical management of the condition, making it treatable, even curable in many cases.

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