

Purine Nucleoside Phosphorylate Deficiency Severe Combined Immunodeficiency in an Infant: Subtle Diagnostic Clues

Severe combined immunodeficiency (SCID) is one of the most severe forms of primary immunodeficiency disorders in children. We report additional findings in the patient of SCID reported earlier by Gupta, *et al.* [1]. This was a 7-month-old boy symptomatic since 3 months of age with recurrent pneumonia, failure to thrive, oral thrush and oral ulcers. There was a significant family history of death of two elder siblings during infancy due to repeated infections. The index child died in the hospital due to respiratory failure and acute respiratory distress syndrome. Investigations revealed severe lymphopenia. An autopsy performed revealed thymic dysplasia with marked lymphoid depletion in lymphoid organs and bone marrow consistent with the clinical diagnosis of SCID. He also had severe Respiratory syncytial virus pneumonia and Cytomegalovirus inclusions in the lungs and adrenals.

Genetic sequencing performed later identified a homozygous nonsense nucleotide substitution mutation in exon 3 of the *PNP* gene (PNP c.244C>T; p. Q82X). This variation has previously been reported in Human Gene Mutation Database and is consistent with Purine nucleoside phosphorylate (PNP) deficiency SCID.

PNP deficiency is very rare form of SCID, and constitutes approximately 1-2% of all combined immunodeficiency [2]. Patients with SCID usually develop disseminated BCG infection following BCG vaccination [3]. The index patient did not develop a disseminated BCG infection following vaccination at birth, which was conspicuously unusual for common forms of SCID. This query was also highlighted in discussion of the reported case [1].

PNP deficiency is widely recognized as a T cell immune-defect. However, there are certain peculiarities which distinguish it from other forms of SCID and need to be highlighted. First, T lymphocyte cell function can be normal at birth in children with PNP deficiency with a gradual waning of function with advancing age. This is probably due to gradual accumulation of toxic metabolites of purine metabolism. Second, T cell function tends to fluctuate in some patients. Due to these reasons patients with PNP deficiency may not develop disseminated BCG

infection following vaccination [4,5]. Importantly, children with PNP deficiency also usually have decreased serum and urine uric acid levels unlike other forms of SCID [4]. In the index patient, lymphocyte subset analysis by flow cytometry revealed CD3- 45.7%; CD19-1.6%; and CD16-21.7%. However, there was profound lymphopenia at the time of diagnosis. There is often a marked lymphopenia with low T cells and CD19+ B cells numbers are typically normal in PNP deficiency. However, a few patients can have low or absent B cells also [4]. Neurologic problem has been seen in patients with PNP deficiency independent of infections. These manifestations include developmental delay and behavior problems, spastic weakness, microcephaly, ataxia and tremor. Index patient had severe microcephaly. However, developmental assessment could not be performed as child was symptomatic since 3 months of age with significant illness. Serum uric acid was not estimated in this child, which could have provided an important clue to the underlying cause of this disease. To conclude, PNP deficiency should be suspected in children presenting with a predominant T cell defect along with features of neurologic dysfunction. It is also imperative to perform repeated immunological investigations in children with suspected PNP deficiency since fluctuations in T cell number and function has been reported frequently in this form of SCID.

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