intravenous antibiotics and catheter drainage remain the mainstays of treatment of neonatal empyema, VATS can be safely considered as a primary treatment modality to promote earlier recovery and shorten antibiotic therapy.

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**REFERENCES**


**Varied Clinical Manifestations of LRBA Deficiency (Immune Dysregulation Disorder)**

Inborn errors of immunity or Primary immune deficiencies (PIDs) are a heterogeneous group of disorders affecting several components of immune system, and the number of genetically defined PIDs is currently estimated to be more than 400 [1].

LRBA (LPS-responsive beige-like anchor protein) is a cytosolic protein which participates in polarized vesicle trafficking and turnover of CTLA4 (cytotoxic T-lymphocyte-associated protein 4) receptor in regulatory T (Treg) cells [2]. LRBA deficiency is an autosomal recessive disorder caused by biallelic mutations in the LRBA gene leading to immune dysregulation. The clinical spectrum has now been extended to include autoimmune lymphoproliferative syndrome (ALPS), cytopenia and lymphoproliferation [3]. Although initially categorized under common variable immunodeficiency (CVID), the International Union of Immunological Societies Expert Committee of Inborn Errors of Immunity has now classified LRBA deficiency under Diseases of immune dysregulation - Regulatory T cell defects [4]. In clinical practice immunodeficiency is always entertained in any recurrent infections but seldom in children presenting with autoimmunity and malignancy.

We present a series of three children with LRBA deficiency treated at tertiary care centres in Southern India. This case series is to make people aware of its presence in our community and its varied presentations.

**Case 1:** An 18-month-old male, born to consanguineous parents was evaluated for prolonged fever, respiratory distress, severe anemia, and thrombocytopenia for 4 months. He was undernourished, had generalized lymphadenopathy and hepatosplenomegaly. Blood picture was suggestive of hemolytic anemia and thrombocytopenia. Direct Coombs test was strongly positive and immunoglobulin profile was normal. Flowcytometry showed elevated double negative T cells consistent with ALPS. Imaging of lungs showed diffuse bilateral ground glass opacities consistent with interstitial lung disease. The child was treated with intravenous immunoglobulins and prednisolone with partial response. In view of inadequate response, PID was suspected and clinical exome sequencing done. It showed a homozygous two base pair deletion in exon 29 of the LRBA gene (chr4:151752970-151752971delAG; Depth:75x) resulting in a frameshift and premature truncation of the protein at codon 1576 (p.Ser1576Ter;ENST00000357115) – pathogenic. He was started on immunomodulators – sirolimus, hydroxychloroquine and fortnightly abatacept (10 doses in total). His transfusion requirements decreased along with regression of liver and spleen size. The child is awaiting a hemopoietic stem cell transplant (HSCT).

**Case 2:** A 5-year old male, born to consanguineous parents, was evaluated for chronic diarrhea since 7 months of age. His elder sibling had similar illness and had died at 3 years of age. Infectious causes for diarrhea were ruled out. Gut biopsy was suggestive of autoimmune enteropathy. He responded partially to steroids with intermittent flare up of enteropathy and hence, started on azathioprine. The child presented to us with abdominal distension, dys电解trolytemia and features of hyperperistalsis. Immunoglobulin profile was normal, while lymphocyte subset analysis showed reduced CD19+ B-lymphocytes. Clinical exome sequencing showed a homozygous missense variation in exon 6 of the LRBA gene (chr4:151837793T-C; Depth: 54x) resulting in substitution of Glycine for Aspartic Acid at codon 248 (p.Asp248Gly; ENST00000357115.3 – pathogenic; and another homozygous missense variation in exon 30 (chr4:151749420C-G; c.5083G>C; p.Val1695Leu) – of uncertain significance. The same mutations were detected in heterozygous state in his parents and elder sibling. The child underwent matched sibling HSCT successfully. Enteropathy resolved post-transplantation.

**Case 3:** A 5-year old girl, born to consanguineous parents, was...
evaluated for chronic diarrhea and failure to thrive since 3 months of age. She had a history of neonatal hepatitis at 2 months and infective spondylodiscitis at 11 months of age. Colonoscopic biopsy was suggestive of autoimmune enteropathy. Basic immunological workup including immunoglobulins and lymphocyte subsets were normal. Clinical exome sequencing showed a homozygous termination mutation in exon 4 of \textit{LRBA} gene (c.544C>T; p.Arg182Ter) – (likely pathogenic). The child is awaiting HSCT.

This is likely the first reported case series of LRBA protein deficiency from our country. Our cohort of children presented with autoimmune enteropathy or cytopenia rather than severe infections. Since there was inadequate response to first line immunosuppression, clinical exome sequencing was done which confirmed the diagnosis. The mutation reported in patient 1, and one of the mutations in patient 2 (Val1695Leu) have been found to be novel on literature search. The other mutation in patient 2 and patient 3 have been previously reported [5,6].

There is no standard therapeutic approach to LRBA deficiency yet. Glucocorticoids and Sirolimus have been used historically. Recently, Abatacept, a CTLA4-fusion protein, has been introduced as a promising agent [7], which is used as a bridging option pending HSCT. HSCT appears to be an effective therapeutic option. Tesch, et al. [8] reported an overall survival 70.8% among 24 patients that underwent HSCT. Higher disease burden, longer duration before HSCT, and lung involvement were associated with poor outcome. A recent systematic review [9] of 109 cases of \textit{LRBA} deficiency autoimmune (82%), enteropathy (63%), splenomegaly (57%) and pneumonia (49%) as the most common clinical manifestations.

LRBA defects should be suspected in any child presenting with autoimmune manifestations of unusual severity, multisystem involvement, with presence of consanguinity, sibing death or unresponsiveness to first line immune suppressants. Early diagnosis and HSCT could be life-saving.

**REFERENCES**