



# Immune Dysregulation Disorder: CHAI Syndrome

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## I. BACKGROUND:

Autoimmune lymphoproliferative syndrome due to CTLA-4 Haploinsufficiency is a rare Autosomal Dominant disorder of children and adolescents, with a prevalence of < 1,000,000.

Human CTLA4 haploinsufficiency causes dysregulation of FoxP3(+) regulatory T (Treg) cells, hyperactivation of effector T cells, and lymphocytic infiltration of target organs.[1]

Patients also exhibited progressive loss of circulating B cells which results in Hypogammaglobulinemia, associated with an increase of predominantly autoreactive CD21(lo) B cells and accumulation of B cells in non-lymphoid organs. Also characterized by enteropathies, recurrent respiratory infections, autoimmune haemolytic anaemia and cytopenias.[2,3]

## II. CASE REPORT:

A 15-year-old presented with chief complaints of redness of both left and right eyes since 1 week.

At the age of 3, the patient presented with unexplained bruises, suggestive of ITP & had relapses every year till the age of 5.

Then encountered an episode of ITP at the ages of 10,11, 13 and two episodes at the age of 12 respectively. A month later had difficulty breathing and Infiltration of lungs was seen on Chest X-ray, which was suggestive of Pneumonia. After 5 months, presented with complaints of fatigue and

upon laboratory investigations it was suggestive of an episode of Haemolytic anaemia.

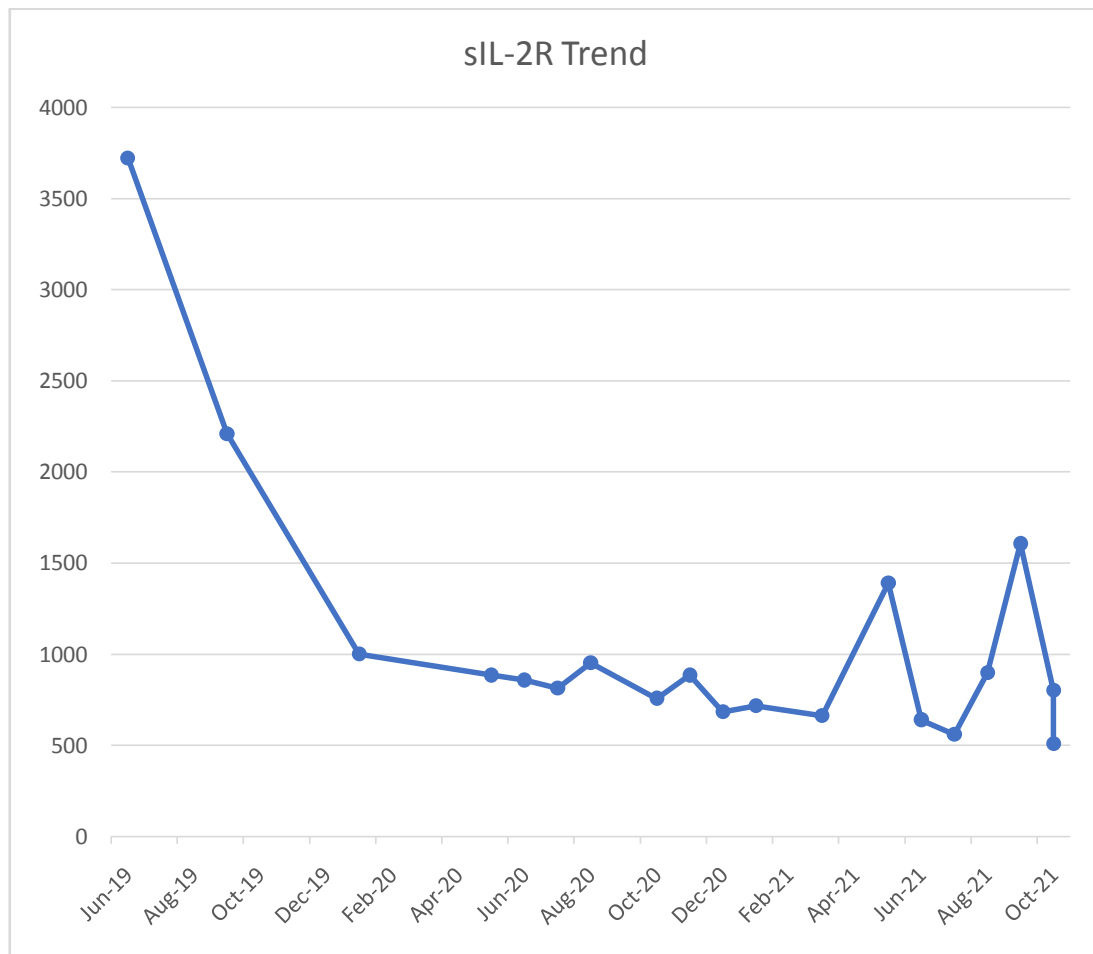
At the age of 14, had an episode of Pneumonia and Haemolytic anaemia.

He was born out of non-consanguineous marriage at term, with no complications during Antenatal, Natal and Postnatal periods. He is immunized up to date. He has a sibling who is 20 years old, who does not have similar complaints and has an uneventful history.

The patient is also known to have Seasonal Asthma and is Allergic to Penicillin.

He has been under Azithromycin for treatment of Pneumonia, Prednisone for the episodes of ITP which was given for a course of 10 days and started off with 40 mg/day and slowly tapered; it was also given for a course of 3 months for treatment of Haemolytic anaemia and was started off with 60-80 mg/day and slowly tapered to 5 mg/day along with Iron supplements.

The patient has been given 4 doses of and is currently under Abatacept IV infusion of 10 mg/kg. Upon general examination the patient was conscious, coherent and co-operative, moderately built and moderately nourished. His vitals were normal and there were no signs of pallor, cyanosis, bruises or petechiae and no difficulty in breathing. Investigations revealed Soluble IL2R (Normal 100-500 u/ml): 3333 u/ml before undergoing treatment with Abatacept and has drastically reduced to 885 u/ml after 4 doses of Abatacept, and slightly elevated ESR and C-reactive protein levels.



Normal levels of Soluble IL-6R and no significant findings seen on Peripheral smear, Complete Blood picture, Bone Marrow and Lung biopsy, Chest X-ray, and Lung function test. Genetic testing revealed that Arginine is replaced by Tryptophan at the Codon 70 of Exon 2, of the CTLA-4 protein, which indicates a Heterozygous point mutation; suggestive of CHAI Syndrome.

### III. DISCUSSION:

This is a case of Autoimmune lymphoproliferative syndrome due to CTLA-4 Haploinsufficiency which has come into light recently.

CTLA-4 is an important T-cell Inhibitory receptor which is expressed on Treg cells and is expressed on conventional T-cells only after its activation. It regulates the immune responses by negative feedback/signaling. CD28 is a T-cell costimulatory molecule, which is a homolog to CTLA-4. Both CD28 and CTLA-4 competitively bind to CD80 and CD86 present on the surface of antigen presenting cells, whereas the latter has higher affinity and avidity.[4]

Most of the CTLA-4 is stored in recycling endosomes, which go to the cell surface following T-cell activation, allowing for control over the T-cell response.[5]

In CHAI patients due to Haploinsufficiency of CTLA-4 gene it predisposes to severe infiltrative T lymphoproliferative disease, which leads to varying diseases among patients. Thus, CTLA-4 performs vital quantitative regulation of T lymphocyte expansion.[4,6,7]

The treatment options for patients with CHAI syndrome are Abatacept IV infusion for maintenance of the disease, specific treatment for the presenting diseases (pneumonia, haemolytic anaemia, ITP etc), supportive therapy and Hematopoietic stem cell transplantation (HSCT)[4], (although it's effective, has increased mortality risk). Early detection by gene mapping can help the patient take precautions. Gene therapy is under trial.



#### IV. CONCLUSION:

Since it is a severe T lymphoproliferative disease there are no specific set of characteristic features for its diagnosis clinically and other diseases have to be ruled out prior to its diagnosis as genetic testing is not feasible at all times. This patient presented with ITP, Pneumonia, Haemolytic anaemia and Uveitis.

As it is an autosomal disorder, children born out of a consanguineous marriage are at more risk of developing the disease. Hence, genetic counseling to the parents of consanguineous marriage might prevent conceiving of such babies and also to help in raising the child. Since this disease is not associated with any Developmental or Intellectual disabilities, the child can lead a normal life considering they are undergoing proper treatment leading to slowing of the progression of the disease.

Since this a new disease that's coming into light recently, it is important for early recognition and diagnosis of this disease.

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