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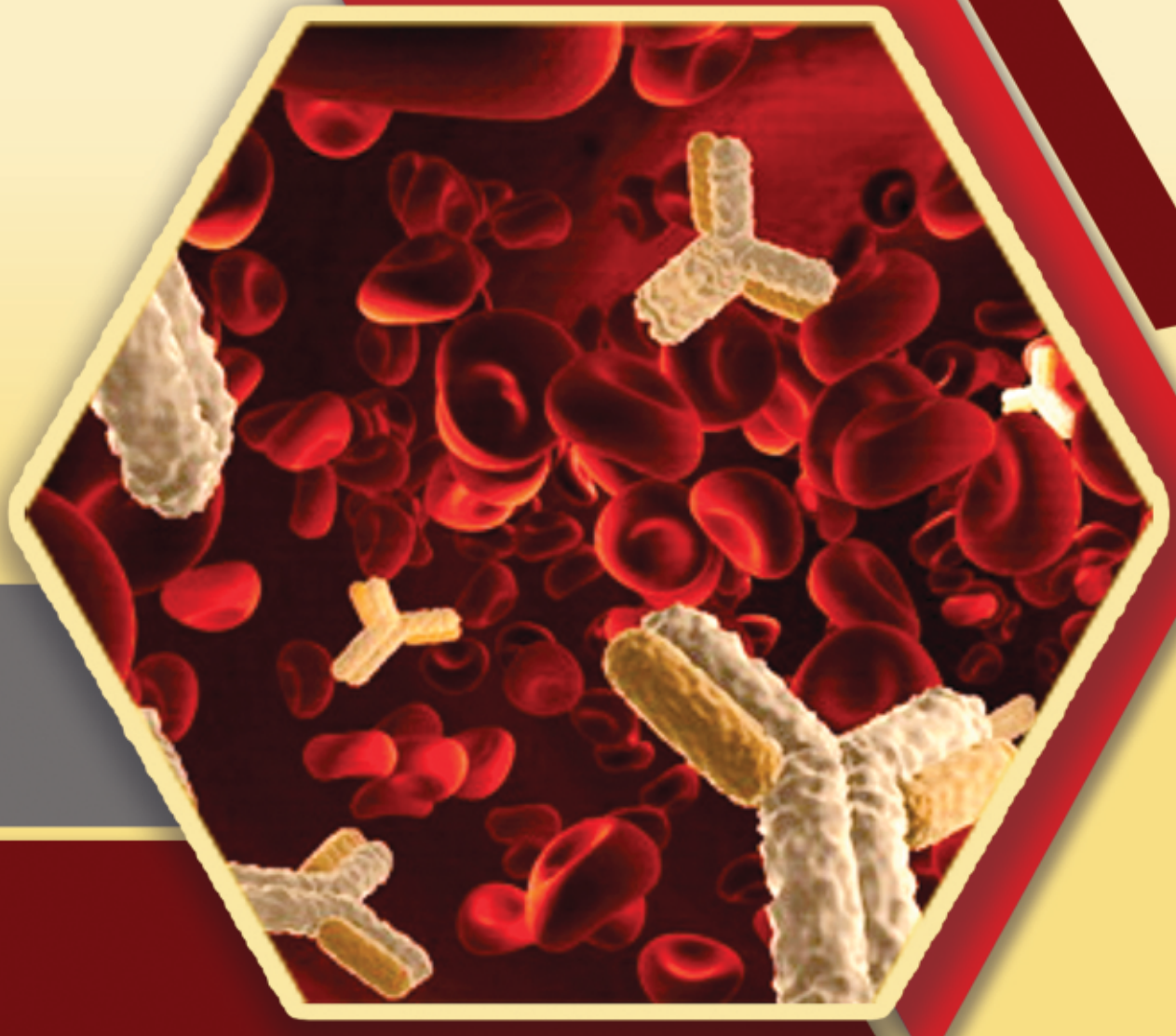

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# ICMR -National sero-surveillance to monitor the trend of SARS-CoV-2 infection transmission in India. Community-based surveillance was conducted in five containment zones in Mumbai 28-30 May 2020



# Autoimmune Lymphoproliferative Syndrome (ALPS)

**Priyanka Setia**

Apoptosis is critical for immune system homeostasis, as lymphocytes undergo massive expansion during an encounter with a pathogen and subsequently contract, leaving behind few memory cells. It also maintains immunological tolerance, by eliminating self-reactive T and B cells. The importance of this mechanism is illustrated by a human genetic defect in apoptosis machinery called autoimmune lymphoproliferative syndrome (ALPS) .

ALPS is caused due to mutations in genes responsible for extrinsic apoptosis pathway i.e. FAS, FASLG, FADD, CASP8 and CASP10 (Figure1). Defective signalling leads to massive lymphadenopathy or splenomegaly, with chronic benign lymphoproliferation, autoimmune cytopenias and with increased risk of lymphomas. The pronounced lymphoproliferation is mainly attributed to the accumulation of double-negative T cells (DNTs) which is characterized by CD3+CD4-CD8-TCR+ cells and is considered as one of the major hallmarks of this disease. DNTs accounts for less than 2.5% of total T cells (or less than 1.5% of total lymphocytes). Other significant laboratory abnormalities observed in ALPS patients are elevated levels of serum or plasma soluble FASL (sFASL), VitaminB12, IL-10, IL-18 along with defective Fas-induced apoptosis assay .

The exact incidence and prevalence of ALPS is unknown since ALPS probably remain undiagnosed due to variable phenotypic expression and a constellation of symptoms that overlap with other monogenic disorders. These monogenic disorders that mimic ALPS are categorised as "ALPS-like disorders", which includes p110delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI or activated PI3K delta syndrome), lipopolysaccharide- responsive vesicle trafficking, beach and anchor containing (LRBA) deficiency with autoantibodies, regulatory T-cell defects, autoimmune infiltration, and enteropathy (LATAIE), cytotoxic T lymphocyte antigen 4 (CTLA4) haploinsufficiency with autoimmune infiltration (CHAI), Ras- associated leukoproliferative disease (RALD) caused due to somatic mutations in KRAS and NRAS, a gain-of-function mutation in signal transducer and activator of transcription 3 (STAT3-GOF) and protein kinase C delta (PRKCD) .

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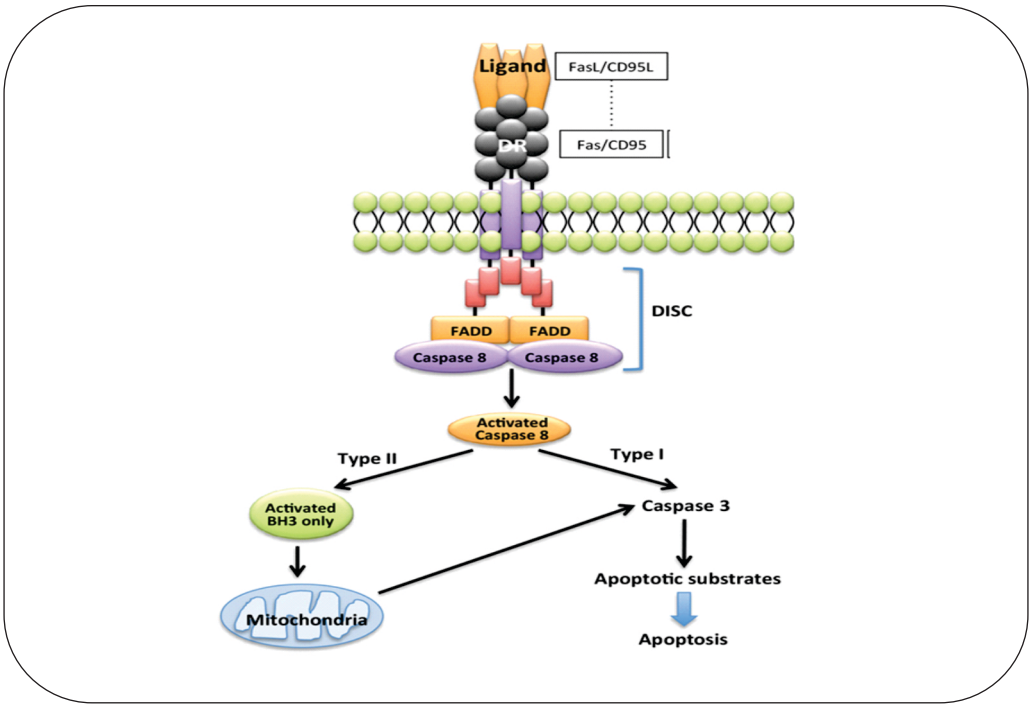



*Figure 1: Components of the FAS mediated apoptosis pathway . Adapted from: Akiko Yamada et.al.*

**Clinical features:**

ALPS typically manifests in the first year of life, although with increasing awareness of the condition adults with autoimmune complications are now more frequently being diagnosed. The three most common clinical manifestations are listed as follows :

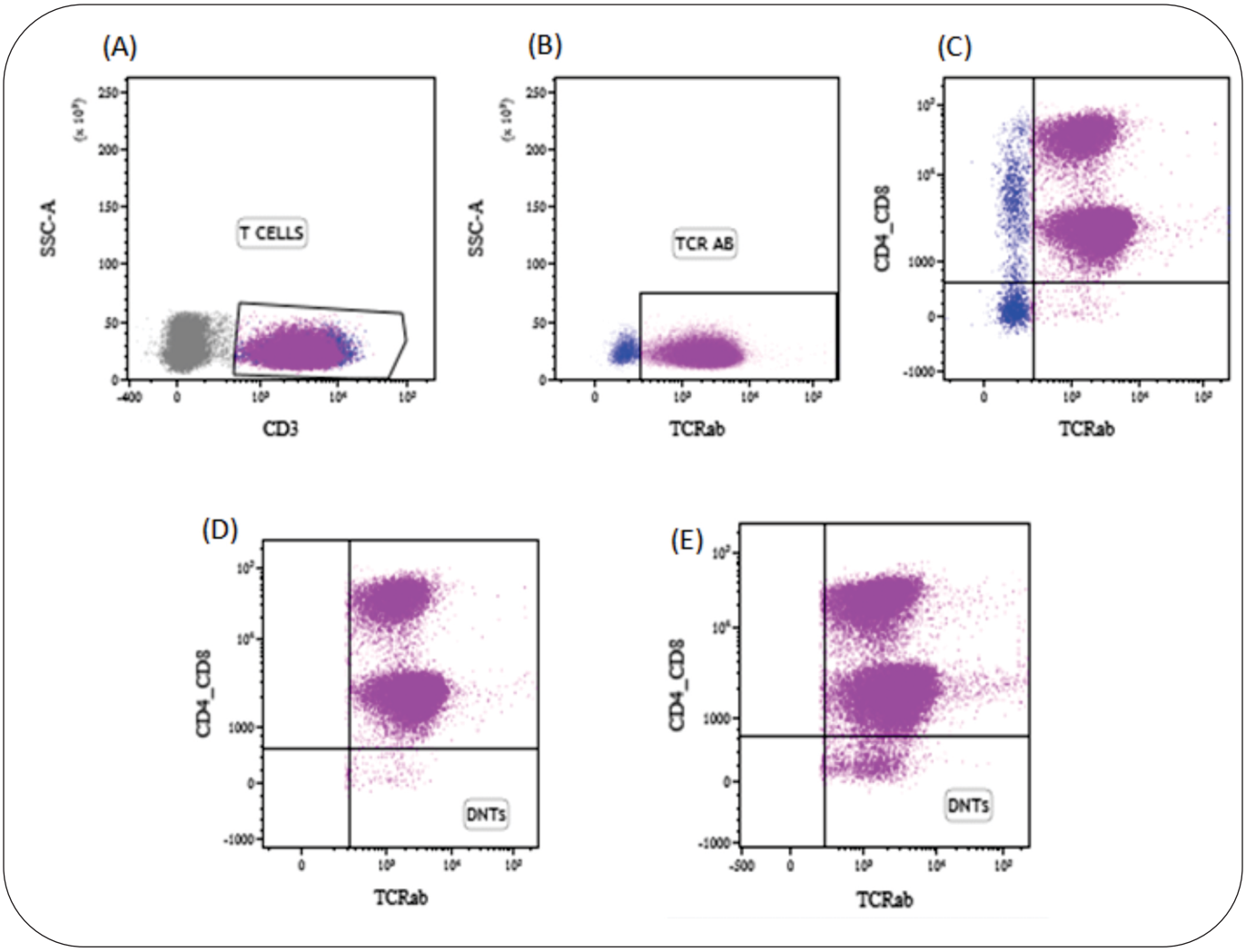
**1. Lymphoproliferation:** Lymphoproliferation is one of the most common clinical manifestation seen in patients with ALPS, which can manifest as lymphadenopathy, splenomegaly or hepatomegaly. To be diagnosed as ALPS, lymphoproliferation must be chronic (>6 months). If isolated lymphadenopathy is present, it must affect at least 2 distinct nodal groups. Neoplastic and infectious etiology must be ruled out. Splenomegaly is also seen in >85% of the patients. Splenectomy, originally performed to manage cytopenias, is now not recommended as it is associated with an increased risk of post-splenectomy pneumococcal sepsis.

**2. Autoimmunity:** The second most common clinical manifestation in patients with ALPS. Direct coombs positive autoimmune haemolytic anaemia (AIHA) is the most common autoimmune complication followed by immune-mediated thrombocytopenia (ITP) while autoimmune neutropenia is uncommon.

**3. Malignancy:** Patients with ALPS have an increased risk of malignancy. Most commonly patients develop lymphoma, but leukaemia and solid tumours have also been described. Increased risk of cancer has also been observed in unaffected family members (who may inherit the same mutation but fail to develop an overt ALPS phenotype).

**Laboratory Findings:**

**1. Double negative T cells:** Flow cytometry is important tools in diagnosing ALPS, since majority of patients have elevated DNTs (Figure 2). DNTs were earlier considered as the hallmark of ALPS, but the occasional elevation is also reported in other autoimmune diseases like Evan's syndrome, SLE etc. B220 (CD45R) is an isoform of CD45, which is uniquely expressed by DNTs in patients with FAS mutation , and hence can be used additionally to differentiate between DNTs of ALPS versus other non-specific elevation seen in other autoimmune diseases. Other immunological findings in ALPS




are expansion of CD3+ T cells, CD8+ T cells, CD3+ /HLA-DR+ T cells, CD8+ /CD57+ T cells, gamma delta T cell, total B cells, and CD5+ B cells.

*Figure 2: Gating strategy of DNTs using flow cytometry:* (A) Samples are analyzed by flow cytometry, using forward vs side scatter, lymphocytes are identified. SSC vs CD3 is used to gate T cells. (B) SSC vs TCRab is gated on total T cells. (C) Expression CD4 and CD8 are seen on total T cells vs TCRab (D) DNTs in healthy control =0.6% (E) Patient with ALPS, with elevated DNTs =5.2%.

**1. Biomarker evaluation:** The most reliable biomarkers associated with the diagnosis of ALPS are: sFASL, Vitamin B12, IL-10 and IL-18 . The combination of these markers along with elevated DNTs is a strong predictor for the presence of germline/somatic FAS mutation. DALD (Dianzani's autoimmune lymphoproliferative disease), a phenotypic variant of ALPS with no known molecular cause have DNTs that are not elevated. The only known biomarker which can distinguish ALPS and DALD is osteopontin (OPN) which is elevated in patients with DALD .

**2. Fas-mediated apoptosis:** Fas-mediated apoptosis assay is a critical assay that is used for the diagnosis of ALPS. Peripheral blood mononuclear cells (PBMCs) are incubated with agonistic anti-Fas antibody (APO-1-3) and rat anti-mouse IgG3. Using multiparametric flow cytometry, effector Th memory (TEM) subset is identified as CD3+ CD4+ CD45RA- CCR7- CD27- . The effector memory is considered as Fas- sensitive subset and taking advantage of this, the percentage of annexin V positive cells on TEM is calculated . The fold changes in the expression of annexin V compared to unstimulated control is used to evaluate Fas-induced apoptosis at different concentration of anti-FAS crosslinking antibody .

**Limitation:** This assay is useful only in identifying patients with FAS or sFAS mutations. Apoptosis assay was earlier used as a diagnostic tool to identify ALPS patients, however, due to technical difficulties and variability this assay is no longer used for routine diagnosis.

**Histopathological findings:**

**1. Bone marrow findings:** Bone marrow lymphocytosis is seen in around 70% of the patients. DNTs by immunohistochemistry can be used to distinguish DNT lymphoid infiltrates from neoplastic lymphoid infiltrates .

**2. Lymph node biopsy:** Typical findings in ALPS include follicular hyperplasia, often with focal progressive transformation of germinal centres, paracortical expansion with a mixed infiltrate containing DNT cells, and polyclonal plasmacytosis.

**Molecular spectrum of ALPS:**

FAS is the most common gene responsible for ALPS, nearly 70% of the reported patients harbors germline heterozygous mutation, inherited in an autosomal dominant manner . FAS is a member of the tumor necrosis factor receptor superfamily (TNFRSF) which comprises of the death receptor, which is responsible for inducing apoptosis . FAS gene is located on chromosome 10q24.1 spanning 9 exons. Exon one to five encodes for the extracellular region which acts as the binding site for the cognate ligand, FASLG and receptor trimerization. Exon six encodes for the transmembrane domain, whereas exons seven to nine encodes for the intracellular region of the gene . The death domain is encoded by exon nine, which is critical for apoptosis signalling.

The mutations are widely spread across the entire gene, intracellular death domain mutations demonstrate high clinical penetrance since the mutations exert a dominant-negative effect on the

apoptosis pathway . However, extracellular mutations are associated with haploinsufficiency, since they induce less severe disruption of FAS induced apoptosis signalling which can be rescued by invitro FAS overexpression .

FAS is also associated with somatic mutations, which accounts for nearly15-20% of the cases. The mutations reside only in the DNT compartment and hence sorting of these cells is important to detect the mutations. These patients present clinically like ALPS-FAS, with elevated biomarkers as well but can be missed by routine sequencing methods .

Mutations in FASLG/CASP8/CASP10 and FADD are extremely rare and accounts for less than 10% of ALPS cases. Most of these patients present clinically like ALPS but due to the paucity of data, it is difficult to understand the exact clinical phenotype.

**Treatment and Management**

The treatment key of ALPS depends on patients clinical manifestations and disease complications. The first line of treatment usually involves treating underlying haematological disease, which is by using intravenous immunoglobulins or corticosteroids. The second line treatment can be using immunomodulatory drugs like mycophenolate mofetil (MMF) or rapamycin, they are of better choice since they induce complete response in patients with refractory cytopenias .

**NIIH experience**

A total of 161 patients were referred for ALPS workup in the last four years. Out of which, 50 patients presented with lymphadenopathy, splenomegaly or hepatosplenomegaly with or without autoimmune cytopenias. Molecular diagnosis was available for (25/50) using NGS and these patients were categorized as ALPS (n=7) and ALPS like disorders (n=13), no variant was identified in 3 patients and 2 patients had the mutation in genes not categorized as an inborn error of immunity.

Patients categorized as ALPS had mutations in FASLG (n=3), FAS (n=1), FADD (n=1), CASP8 (n=1), CASP10 (n=1). The median age of presentation was 6.5 months. Female predominance was seen (71%). Parental consanguinity was noted in 4 patients.

Lymphadenopathy and splenomegaly were seen in nearly 85% of the patients. AIHA was the most common autoimmune manifestation seen in 83% of the patients. Absolute lymphocyte count (ALC) was elevated in 57%, and within normal range for 43% of the patients. The percentage of DNTs ranged from 0.6-41% of total T cells, B220+ DNTs were observed in 40% of the patients. Immunoglobulin levels were available for 6 patients, 33% of the patients had hypergammaglobulinemia and nearly 66% had normal Ig levels. Biomarker evaluation was done for 5 patients, sFasl levels were low (<10pg/ml) in 40% of the patients, elevated (>200pg/ml) in 40% and within normal range for 20% of the patients. Vitamin B12 levels were elevated in 20% of the patients.

Patients categorized as ALPS-like disorders had mutations in LRBA (n=4), PIK3CD (n=2), PRKCD (n=1), SH2D1A (n=1), STXBP2 (n=1), FoxP3 (n=1), Tet2 (n=1), STAT1-GOF (n=1) and JAK1-GOF (n=1).The

median age of presentation was 2 years. Male predominance was seen (77%). Lymphadenopathy and splenomegaly was noted in 84% of the patients. AIHA was the most common autoimmune manifestation seen in nearly 90% of the cases. DNTs % varied from 2.5- 8.6% of total T cells.

Immunological evaluation for these patients showed that 45% of the cases had ALC within normal ranges, lymphopenia in 38% and lymphocytosis in 7% of the cases.

Low B and T memory cells were seen in 46% of the cases. Immunoglobulin levels were within normal ranges for nearly 77% of the patients, hypogammaglobulinemia and hypergammaglobulinemia was noted in 15% and 7% of the cases respectively. sFasl level was elevated in 23% of the patients with mutation in SH2D1A, STXBP2 and Tet2.

**Conclusion:**

To summarize, ALPS is an extremely rare disorder, the diagnostic criteria published in 2010 is still widely used to categorize these patients. However, other monogenic disorders categorized as ALPS-like disorders may also fulfill this criteria and can be easily misdiagnosed. Therefore, for definitive diagnosis ,elevated DNTs along with elevated serum sFASL levels is a positive predictor for mutations in FAS related pathway ' . Our findings suggests that elevated DNTs is not a hallmark of ALPS rather they are also elevated in patients with ALPS-like disorders and in other autoimmune conditions like Evan's and SLE. Therefore, upfront evaluating B220 expression on DNTs along with enumerating memory subsets of T and B cells helped us in categorizing patients into ALPS and ALPS-like disorders. Since the spectrum of ALPS is expanding, NGS is a rapid tool to identify mutations , which is important to understand the genotype phenotype correlation and for better management of the disease.

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# ऑटोइम्यून लिम्फोप्रोलीफ़ेरेटिव सिंड्रोम (ALPS) : प्रतिरक्षा तंत्र संबंधी एक दुर्लभ परंतु निदानसम रोग

श्री सोमप्रकाश धनगर

एपोप्टोसिस हमारे शरीर के प्रतिरक्षा तंत्र की एक मुख्य प्रक्रिया है, जो कि हमारे शरीर में पैदा होने वाली स्व- प्रतिक्रियाशाली कोशिकाओं जैसे टी एवं बी सेल्स को शरीर से बाहर निकाल कर हमारे प्रतिरक्षा तंत्र की सहनशीलता को बढ़ाती है। साथ ही प्रतिरक्षा तंत्र और शरीर की प्रकिया के मध्य साम्य व्यवस्था बनाए रखती हैं। हमारे प्रतिरक्षा तंत्र की साम्य व्यवस्था में गड़बड़ी होने पर जो रोग उत्पन्न होते हैं, उनमें से एक मुख्य रोग है: आल्पस (ALPS)। आल्पस हमारे प्रतिरक्षा तंत्र संबंधी बीमारी है, जो कि कोशिका में उपस्थित एपोप्टोसिस पाथ-वे से संबंधित जीनो (ऍफ़ ए एस एल जी, ऍफ़ ए डी, सीएएसपी 8 एवं सीएएसपी 10) में उत्परिवर्तन के कारण पैदा होती है। जिसके कारण लंबे समय से लिंफोसाइट का बड़ा हुआ रहना, तिल्ली का बढ़ना, ऑटोइम्यून कोशिकाओं में कमी आदि लक्षण मरीजों में दिखाई देते हैं। जो आगे चलकर एक गंभीर बीमारी लिंफोमा (एक प्रकार का रक्त कैंसर) को भी जन्म दे सकते है। हालांकि इस रोग की आवृत्ति भारतीयों में कम पाई गई हैं। जिसका मुख्य कारण इसके विभिन्न लक्षण हो सकते हैं, जिसके कारण मरीजों में इसका निदान आसानी से नहीं हो पाता है।

**आल्पस के लक्षण:**

आल्पस के लक्षण बाल्यावस्था में ही दिखाई पड़ने लगते हैं। हालांकि आमजन में जागरूकता एवं तकनिकी विकास के कारण अब इस रोग के विभिन्न प्रकारो का निदान युवा अवस्था में भी संभव हो पा रहा हैं।

**आल्पस के तीन मख्यु लक्षण है:-**

1. **लिंफोसाइट कोशिकाओं का बढ़ना:** लिंफोसाइट कोशिकाओं का बढ़ना इस रोग का मुख्य लक्षण है, जिसके कारण लिम्फएडिनोपैथी, तिल्ली (Spleen) का बढ़ना, लीवर का बढ़ना आदि होता है। आल्पस के निदान के लिए लिंफोसाइटोसिस का इतिहास 6 महीने से ज्यादा का होना चाहिए। हालांकि इसके निदान हेतु लिंफोसाइटोसिस के साथ-साथ, लिंफोसाइट बढ़ने के अन्य कारण जैसे कैंसर और संक्रमण आदि की भी जांच करना आवश्यक होता है।

2. **ऑटोइम्यूनिटी:** यह आल्पस का दूसरा मुख्य लक्षण है, जो की रोगियों में देखने को मिलता है। इसके साथ डायरेक्ट कुम्ब्स टेस्ट की सकारात्मकता, ऑटो इम्यून हिमोलिटिक एनीमिया एवं आई टी पी भी इन रोगियों में देखने को मिलती है।

3. **कैंसर:** इन मरीजों में कैंसर होने का खतरा बड़ जाता है, ज्यादातर आल्पस के मरीजों में लिंफोमा नामक कैंसर रोग देखने को मिलता है, हालांकि गठान रूपी कैंसर भी इन मरीजों में होने की सम्भावना रहती है।

**फ्लो साइटोमेट्री प्रयोगशाला संबंधी जांचें**

1. **डबल नेगेटिव टी -सेल्स का पाया जाना:** डबल नेगेटिव टी -सेल्स के स्तर की जांच की मदद से आल्पस का निदान किया जा सकता है। साथ ही इसकी मदद से अन्य बीमारियों में विभेदन भी किया जा सकता है।

2. **बायोमार्कर मल्यूांकन :** आल्पस के निदान से संबंधित मुख्य बायो-मार्कर ऍफ़ ए एस एल, विटामिन B12 , आई एल 10 और आई एल 18 है। इन तीनो बायो मार्करों के साथ डी एन टी एस को मिलाकर आल्पस का निदान आसानी से किया जा सकता है। इसी तरह एक अन्य बायो मार्कर ओस्टियोपोंटिन भी डालड (DALD) एवं आल्पस में विभेदन करने में उपयोगी होता है।

3. **ऍफ़ ए एस मीडिएटेड एपोप्टोसिस जाँच:** ऍफ़ ए एस मीडिएटेड एपोप्टोसिस जाँच एक ऐसी जांच है, जो कि आल्पस के निदान में उपयोगी पाई गई है। हालांकि यह विधि ऍफ़ ए एस एवं एस ऍफ़ ए एस जीनो में उत्परिवर्तन के कारण हुए रोगो के निदान एवं विभेदन में काम आती थी। किन्तु तकनीकी अनियमितता के कारण यह विधि अब उपयोग में नहीं लाई जाती है।

**उत्तक विकृति विज्ञान संबंधी जांचें**

- **अस्थि मज्जा जांच:** आल्पस के 70% मरीजों में लिंफोसाइटोसिस देखने को मिलती है। इम्यूनोहिस्टोकेमेस्ट्री के माध्यम से जांच करने पर डबल नेगेटिव टी सेल्स और नियोप्लास्टिक वृद्धि भी देखी जा सकती है।

- **लिंफनोड बायोप्सी:** जब लिंफनोड के टुकड़े की जांच की जाती है, तो इसमें आल्पस के रोगियों में फॉलिकुलर हाइपरप्लेजीया, जोकि फोकल प्रोग्रेसिव ट्रांसफॉर्मेशन अवस्था में होता है, दिखाई देता है। जिसमें डबल नेगेटिव टी सेल्स और पॉलीक्लोनल प्लाज्मासाइटोसिस भी दिखाई देती है।

**आल्पस में उपस्थित अनुवांशिक दोष:**

आल्पस के लगभग 70% मरीजों में ऍफ़ ए एस जीन में उत्परिवर्तन पाया जाता है। इस जीन के उत्परिवर्तन का अनुवांशिक स्थानांतरण ऑटोसोमल प्रभावी तरीके से होना पाया गया है। यह जीन डेथ रिसेप्टर के लिए इनकोड करता है, जोकि एपोप्टोसिस शुरू करने में लिए उत्तरदायी होता है। यह जीन क्रोमोजोम 10 के q24.1 स्थान पर उपस्थित होता है। और 9 एक्सॉन (सुचना सहित भाग) से मिलकर बना होता है। इसका 9 वां एक्सॉन ही एपोप्टोसिस सिगनलिंग के लिए महत्वपूर्ण होता है। अधिकांश मरीजों में ऍफ़ ए एस जीन उत्परिवर्तन जर्म लाइन प्रकार के होते हैं। इसके अलावा 15 से 20% मरीजों में कायिक (सोमेटिक) प्रकार के उत्परिवर्तन भी पाए जाते हैं। जो कि आल्पस समान बीमारी उत्पन्न करते हैं। इन उत्परिवर्तनों को पहचानने के लिए हाई सेंसटिविटी सीक्वेंसिंग तकनीक का उपयोग किया जाता है। इसके अलावा 15% आल्पस के मरीजों में कुछ अन्य जीन जैसे ऍफ़

ए एस एल जी, ऍफ़ ए डी, सीएएसपी 8 एवं सीएएसपी 10 आदि में उत्परिवर्तन देखने को मिलते हैं, हालांकि इनकी आवृत्ति कम होती है। यह मरीज, लक्षणों में आल्पस के मरीजों जैसे ही दिखाई देते हैं। परंतु पयार्प्त जानकारी के अभाव में इन मरीजों में चिकित्सकीय लक्षणों को समझना थोड़ा कठिन होता है।

**उपचार एवं प्रबंधन:** आल्पस के मरीजों का इलाज उनके लक्षणों एवं बीमारी की गंभीरता के आधार पर किया जाता है। प्राथमिक उपचार के तौर पर रक्त संबंधी रोगों को ठीक करने के लिए एंटीबॉडी एवं कॉर्टिकोस्टेरॉइड दिया जाता है। इसके अलावा कुछ प्रतिरक्षा तंत्र को मॉडुलेट करने वाली औषधियां जैसे एम् एम् ऍफ़ और रापामायसीन भी दी जाती है।

राष्ट्रीय रुधिर प्रतिरक्षा विज्ञान संस्थान में वर्ष 2008 से आल्पस के निदान हेतु कार्य किया जाता है। प्रतिवर्ष इस संस्थान में आल्पस के सस्पेक्टेड मरीजों को निदान हेतु रेफर किया जाता है। संस्थान में इस रोग के निदान हेतु कई महत्वपूर्ण जांचे जैसे एल एस एस ए, डीएनटी, एंटीबाडी लेवल, बायो मार्कर (ऍफ़ ए एस एल, विटामिन B12 , आई एल 10 और आई एल 18) आदि भी की जाती है। इसके अलावा इसके मुख्य अनुवांशिक कारक जीनो में उत्परिवर्तन संबंधित जांच भी की जाती है। जिससे प्राप्त सूचना रोग के लक्षणों एवं उत्परिवर्तन में संबंध स्थापित करने में सहायक होती है।

Dr. Shrimati Shetty, Scientist F, Farwell on 30th June, 2021

**ICMR -National sero-surveillance to monitor the SARS-CoV-2 infection transmission in containment zones in Mumbai**




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