HYPER IgE SYNDROME

FOR PARTIAL FULFILLMENT OF B.Sc. BIOTECHNOLOGY

REVIEW

BY

SHASHANK SHEKHAR

T.Y. B.Sc.

UNDER THE GUIDANCE OF

Dr. RASHMI S. TUPE

BHARATI VIDYAPEETH DEEMED UNIVERSITY

RAJIV GANDHI INSTITUTE OF IT AND BIOTECHNOLOGY,

KATRAJ, PUNE-46

SUBMISSION YEAR: 2015-2016

BHARATI VIDYAPEETH UNIVERSITY
RAJIV GANDHI INSTITUTE OF IT & BIOTECHNOLOGY, Katraj, Pune-46

CERTIFICATE

23/03/16

This is to certify that **Mr. Shashank Shekhar** of **Third year, B.Sc Biotechnology** has satisfactorily completed the REVIEW REPORT for fulfillment of Bachelor Degree is Biotechnology as prescribed in the syllabus of **Rajiv Gandhi Institute of IT and Biotechnology, B.V.D.U, Pune, in the academic year 2015-2016.**

Candidate	Dr Rashmi S.Tupe	Dr. G.D. Sharma
	Review Guide	Principal

Acknowledgement

First of all, I want to acknowledge that the work would not be successful without the proper guidance of my guide Dr RASHMI TUPE ma'am. She has helped me in each and every step to let me conquer this part of my study. I also want to thanks Dr VIDYA ma'am, as she was a proper enlightenment for all of us students to do our review. The proper guidance of each of my friends was a way for me to do my work properly. I want to join hands for my parents, as they are the only one without whom I would have not been a part of this work. They are the god for me. And at last I want to thank the supreme god, who keep watching us every time. His blessings are all that I have needed.

Now coming over to the review I would like to describe some things which helped me in successful completion of my work. I would like to give a sincere thanks to NCBI. The research papers present in PubMed has given me courage and direction to complete my work. The reference provided in it is to the utmost extent which I needed for my work. The scientists and researchers has done a marvellous job in the findings of various topics of Hyper IgE syndrome. The fascinating work of everyone has done a great help to me. So once again I give a sincere thanks to everyone who reads this review, and put forward their views on it.

INDEX:-

B. Abstract:

Hyper IgE syndrome as the name suggests is an imbalance due to increase in the levels of IgE antibodies in the immune system.The various aspects are written to describe this syndrome. The review is based on various research aspects being done in the fields of clinical, genetical, physiological, immunological work, etc. The information provided is more or less fulfilled according to the given titles. The research fullfills the Hyper IgE syndrome effects and reasons on human population worldwide. The different prophyalaxis and treatment measures is satisfactorilly given. The units for different measurements are decided according to international parameters. The role of IgE is explained clearly in the following contents. The human body responses are visualized as the role of this antibody IgE. The receptors were also taken into consideration for the stimulus and responses at cellular and molecular level.

C. Keywords:

Hyper IgE, STAT 3, DOCK8, CD23, FcεRI, Th1 and Th17(T- helper), interlukins, calcium ionophore.

1. Introduction of Hyper IgE syndrome(HIES):

Hyper immunoglobulin-E syndrome (HIES) is a rare primary immunodeficiency disease, characterized by the classical triad of recurrent staphylococcal skin abscesses, pneumonia with pneumatocele formation, and elevated levels of serum IgE, usually over 2,000 IU/mL [1]. The immunoglobin IgE is abruptly increases due to several factors in immune system. IgE is responsible for allergic reaction caused by exposure to allergens such as dust mites, pollen, mold, animal dander, and peanuts. HIES is a group of primary immunodeficiencies with overlapping and distinct features most frequently caused by deficiency in STAT3 or DOCK8. Such deficiencies are believed to be the genetic cause of hyper IgE syndrome in patients who do not carry mutations in STAT3 or DOCK8 [2]. Free soluble IgE binds to Fcε RI on the surface of mast cells, basophils, and antigen-presenting dendritic cells. The binding of soluble CD23 to membrane-bound IgE and the complement receptor CD21 on B cells results in an increased production of IgE (Fig. 1).

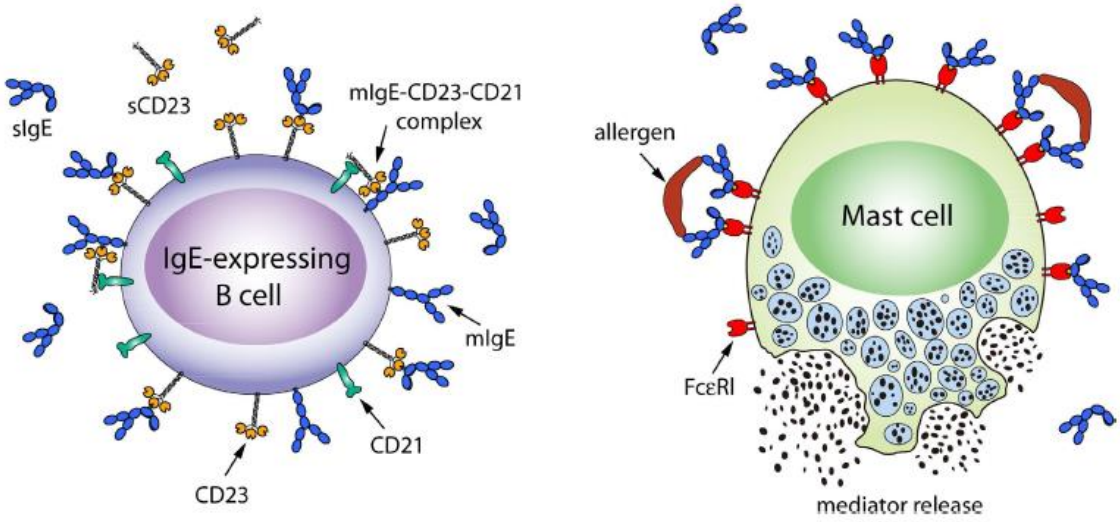

Fig 1. How IgE mediates an allergic reaction via interaction with its two receptors. (**Left**) Interactions of membrane-bound IgE (mIgE, blue) with CD23 (tangerine) on B-cells regulates soluble IgE (sIgE) production. (**Right**) Cross-linking of IgE bound to FcεRI (scarlet) on mast cells or basophils by allergens (brown) triggers the release of mediators, causing allergy.

Normally IgE is present in less than 0.003 % concentration in human body. As it is very less in the content present in the body, it doesn't cause much effect on the system. But if the traces increases to higher than normal levels, it could cause a severe effect. That is what explained in the context and topics given below. The IgE does not have sub classes, as it is almost negligible in the serum. Earlier it is produced in the liver, but after maturation, it is replaced by IgG antibodies.

2. Prevalence of Hyper IgE syndrome(HIES):

2.1. Prevalence of hyper IgE syndrome in Asia

The distribution of this disorder is prevalent among some parts of the world, for example Asia. In the Prediction of Allergies in Taiwanese children (PATCH) study, 1321 Asian children aged 5-18 in a population-based cohort, were evaluated for total and specific IgE by ImmunoCAP and Phadiatop Infant, respectively.

The male, atopy, allergic diseases, recent symptoms of upper respiratory infection, and lower FEV1/FVC, were associated with higher total IgE levels in univariate analyses.
As a result, Multivariate analysis revealed that atopy was the single most important determinant explaining 66.1% of the variability of total IgE levels in this population.

The area under the receiver-operator characteristic (ROC) curve of total IgE for diagnosing atopy, asthma, rhinitis, and eczema were 0.92, 0.72, 0.70, and 0.70, respectively. Altogether, the sensitivity, specificity, and positive and negative predictive values of total IgE at the optimal cutoff of 77.7 kU/L on the ROC curve for diagnosing atopy were 82.3%, 87.1%, 89.5%, and 78.6%, respectively.

As a result, the corresponding values using the upper 95% CI of total IgE (164.3 kU/L) in non-atopic children were 61.2%, 95.0%, 94.3%, and 64.6%, respectively; whereas a customary cutoff (100 kU/L) provided accuracy between that of the aforementioned two cutoffs. Total IgE at the cutoff of 77.7 kU/L provided modest sensitivity and specificity (49.0%-78.3%) for diagnosing allergic diseases, but had high negative predictive values (84.2%-97.9%).

3. Physiology role of IgE:

3.1.Role of immunoglobulin E and its high affinity receptor FcεRI

Immunoglobulin E (IgE) and its high affinity receptor (FcεRI) are well known functional in the allergic response. The allergic response can be of any type. The binding of IgE to FcεRI is of very high affinity ($KA \geq 1010M^{-1}$). This binding can be of high energy liberation bonding. Yet, it is reversible with a half life of greater than six days. IgE binding to mast cells or basophils led to the view that the binding of IgE is a passive or inert event and that the IgE-occupied FcεRI could be thought of as the “resting” receptor[Fig.1]. These researches suggest that monomeric human IgE can promote cellular responses, there remains considerable uncertainty on whether these effects occur in the absence of FcεRI aggregation.

The uncertainity of binding of IgE to its receptors is very less. Unless there is any other receptors are present with same configuration, the immunoglobulin will not bind to it. As a result, the affinity also changes accordingly with some other receptors this type of role of IgE is very common in the immunological system. Without the binding, it will not enhance the working of the antibody.

3.2.IgE and FcεRI; beyond allergic disease

As discussed above, IgE and FcεRI are related to each other more than just binding property. Increased levels of total IgE antibody (over normal circulating levels in blood) may not be

neccesary for such an inflammatory response. Experiments were carried out to study these features more. To test whether IgE contributes in autoimmune inflammation, an inflammatory response generally linked to Th1 and Th17 responses. It was confirmed that, helper T cells are also to be triggered by this immunoglobulin E. Autoreactive IgE functioned to amplify autoimmunity by FcεRI-dependent activation of basophils, which played a key role in plasma cell expansion and survival[Fig.2].

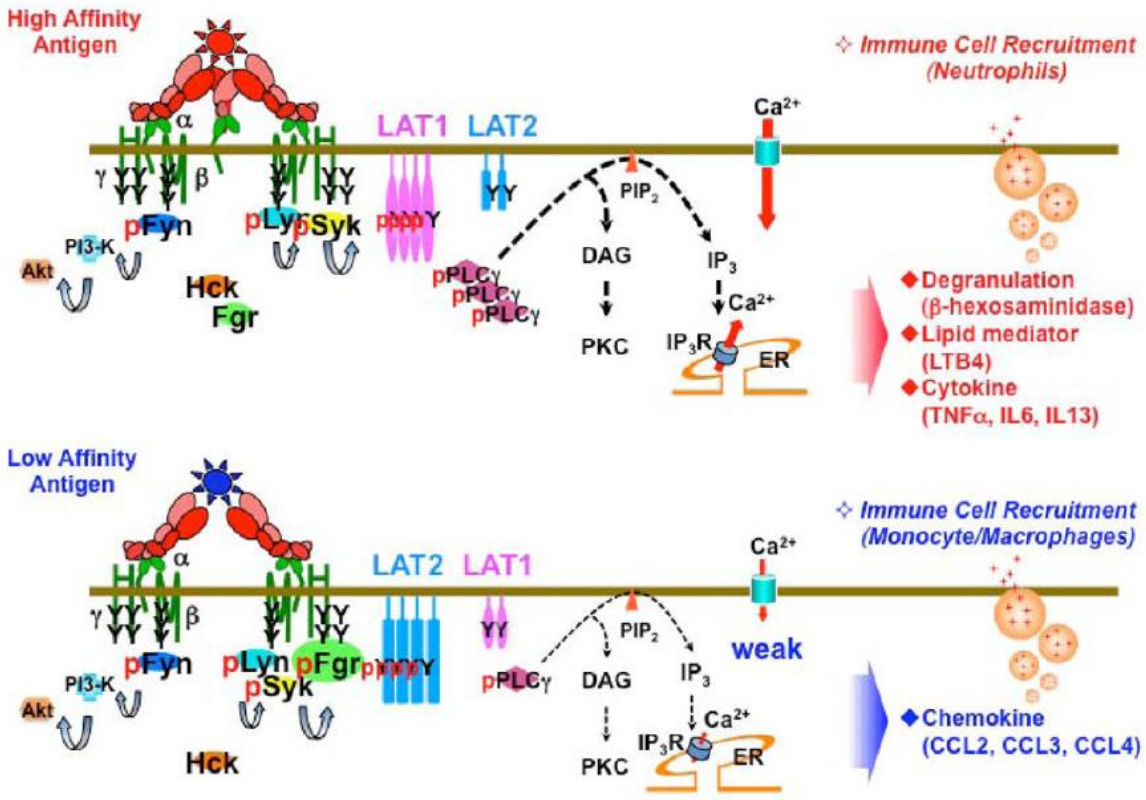

Fig 2. Schematic model of FcεRI signaling generated by high or low affinity antigen and IgE antibody interactions.

4. Gene information of Hyper IgE:

4.1.STAT3 and the Hyper-IgE syndrome

STAT3 are the genic composition responsible for IgE production. The STAT3 molecule binds to the interleukin (IL)-6 responsive element within the acute 0 phase response promoter. The STAT3 molecule plays a central role in signal transduction induced by multiple cytokines, including IL-6, IL-10, IL-11, IL-17, IL-21 and IL-22.

Therefore, STAT3 deficiency leads to upregulation of many Th1 cytokines, such as IFNγ and TNFα, and downregulation of pro-inflammatory and anti-inflammatory responses regulated by IL-6 and IL-10, respectively [17]. A remarkable decreased Th17 response is a hallmark of HIES, and indeed STAT3 mutations have been demonstrated to result in a failure of Th17 CD4 cell differentiation [18]. HIES patients have low numbers of antigen specific memory B cells, and since B cell immaturity has been linked to the preferential production of IgE in

mice, this may account for the elevated IgE in patients with HIES[19]. STAT3 is involved in regulating the activity of a number of matrix metalloproteases, which is supported by a clinical study involving 37 HIES patients demonstrating altered levels of some of these proteases compared with controls [20]. Overexpression or persistent activation of STAT3 has been reported in most human haematological malignancies and solid tumors [21].

4.2.Pathogenesis

The identification of *STAT3* mutations being the cause of AD-HIES has resulted in greater understanding of its role in both the immunologic and non-immunologic features of the disease, although there is much that is still not well understood. *STAT3* mutations result in failure of differentiation of Th 17 cells and subsequent failure of IL-17 secretion. This will lead to suppression of immune response. Also T cells will not be able to produce there own copy number. So there will be elevation in the number of IgE in the body fluids.

4.3.Treatment and Prophylaxis

For prophylaxis antibiotics against *Staphylococcus aureus*, such as sulfamethoxazole/ trimethoprim may be used [22]. In order to control eczema and skin abscesses anti-staphylococcal oral therapy combined with bleach baths and chlorhexidine washes are recommended [23]. Finally, bone marrow transplantation has been tried in a few HIES patients but with mixed results, hence leaving the role of bone marrow transplantation in HIES unclear [23].Two unrelated male children with sporadic *STAT3* mutations were transplanted for high grade non-Hodgkin's lymphoma. At 10 and 14 years following transplantation, both patients were reported to be well with continued resolution of both immunological and non-immunological features.

5. Genetics of Hyper IgE:

5.1.Genetic Linkage of Hyper-IgE Syndrome to Chromosome 4

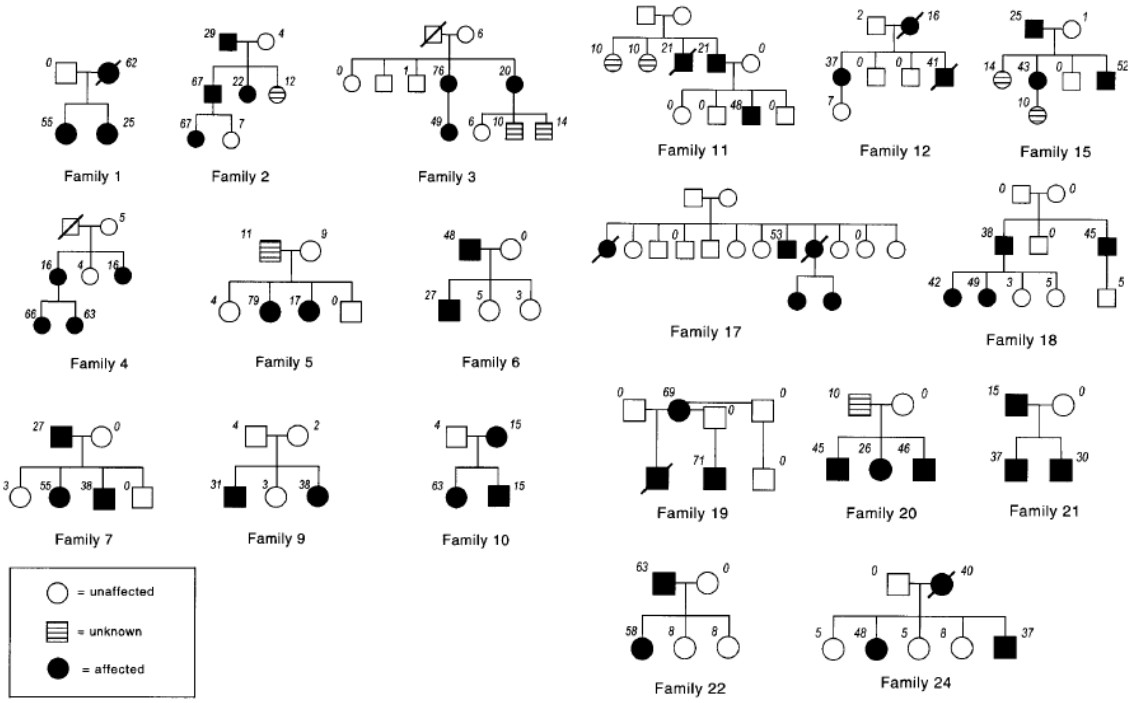

Fig 3. Pedigrees of multiplex HIES families. Numbers adjacent to pedigree symbols indicate HIES score (see table 2). Blackened symbols indicate a score of >15 (classification of "affected"); striped symbols indicate a score of 10–14 (classification of "unknown"); unblackened symbols indicate a score of 0–9 (classification of "unaffected"); and a slash indicates a deceased family member.

5.2. Maps and marker loci

The order of the polymorphic markers by comparing maps and marker loci from the following databases: Genemap'98 were studied at Whitehead Institute for Biomedical Research-MIT Center for Genome Research, and Research Genetics Inc. ILINK (it is a program for analysis of human genetic linkage) was used to establish the likely marker order in their data set.

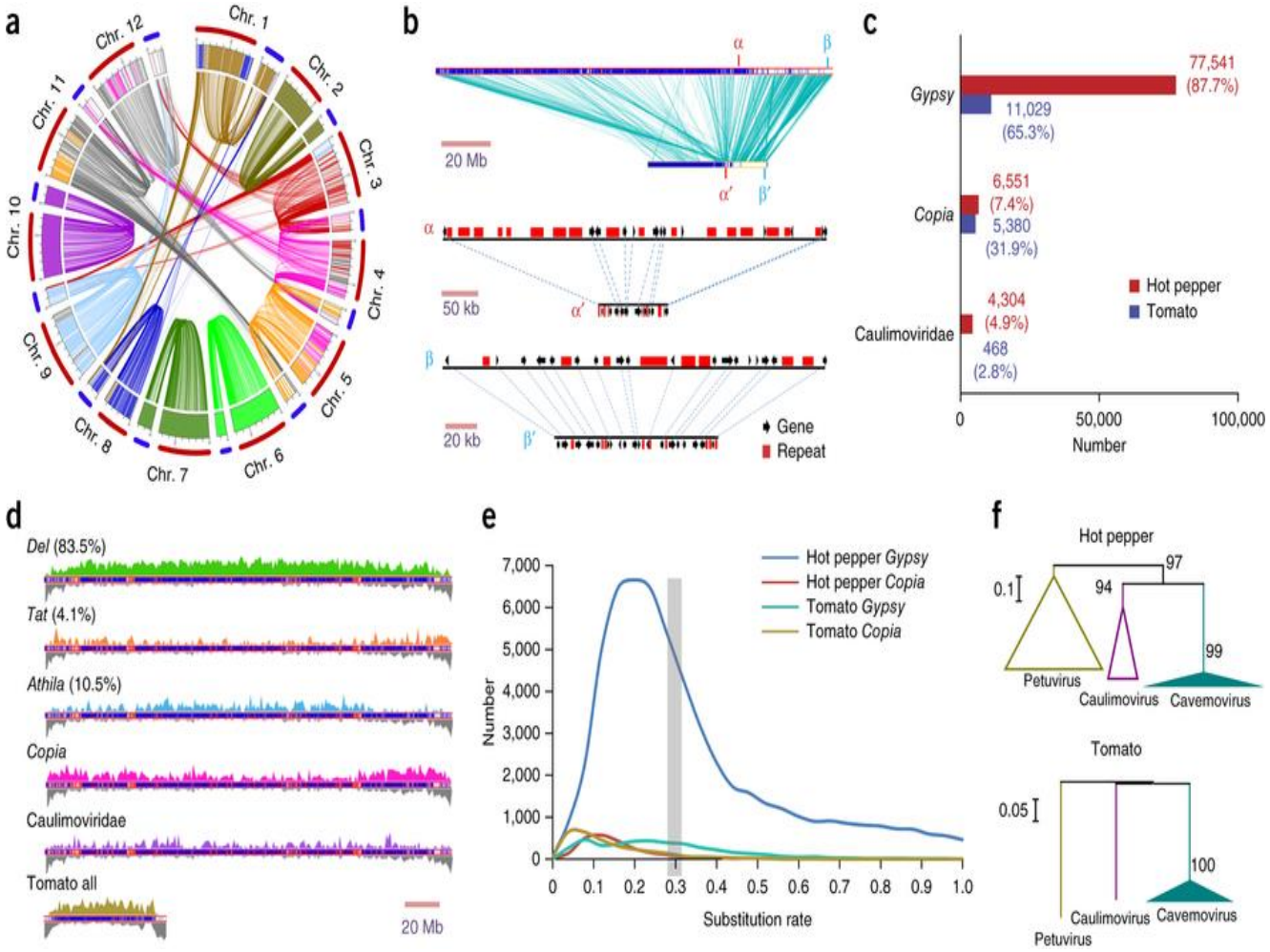

Fig 4. Results of genome sequence

5.3.Discussion

Analysis of known immunologic pathways has failed to elucidate the nature of the underlying defect in HIES. The observation of a cytogenetic anomaly, an interstitial deletion and marker-chromosome formation in chromosome 4q, in a sporadic HIES patient with mental retardation and autism prompted us to conduct a limited linkage study in this region of chromosome 4. Findings of HIES that are also common in the general population, such as recurrent upper respiratory infections, serum-IgE levels 500–1,000 IU/ml, or eczema, received fewer points. This scoring system was validated in newly enrolled NIH patients and in an independent HIES cohortin Germany.

5.4.Electronic-Database Information

Accession numbers and URLs for data in this article are as
Follows : Genemap'98, http://www.ncbi.nlm.nih.gov/genemap98 (for markers and loci) Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/Omim (for Job syndrome [MIM 147060] and hyper-IgE recurrent infection syndrome [MIM 243700]) Research Genetics Inc., http://www.resgen.com (for sex-averaged genetic map) Whitehead

Institute for Biomedical Research-MIT Center for Genome Research, http://www-genome.wi.mit.edu (for Whitehead-MIT genetic map)

6. Clinical manifestations & diversity of the Hyper IgE Syndromes(HIES):

6.1. Clinical manifestations:-

The Autosomal dominant- hyper IgE syndrome(AD-HIES) typically presents in the first few weeks of life with a newborn infants[3,4]. This white pus type rashes are often most pronounced on the face and scalp, in a pattern most consistent with neonatal acne or eosinophilic dermatitis. A characteristic facial appearance develops through childhood and adolescence, characterized by facial asymmetry, a broad fleshy nose and porous skin.Vascular abnormalities are common in HIES.

Clinical approach says that the symptoms depicted in AD-HIES are not common. But these type of symptoms are visibly so weird that it cannot be tolerated. Clinically, these are tested in labs and confirmed that the main cause of this is due to elevated increase in IgE immunoglobulin. So it needs to be visualized under proper care, so that it could not spread among the populations. Thus immunological and non immunological characteristics are depicted according to tests carried out [Table 1].

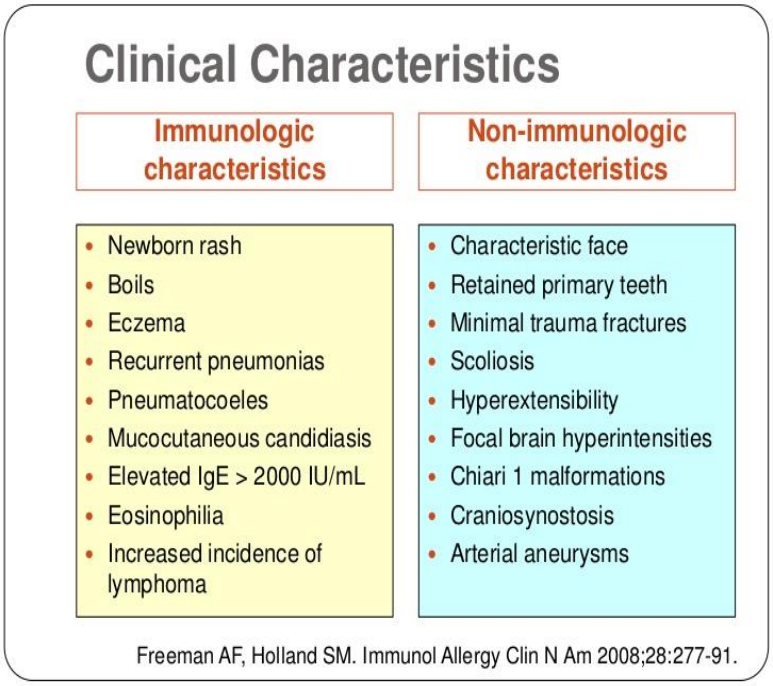

Table 1. clinical characteristics and symptoms of HIES

Esophageal dysfunction is poorly understood in adults with HIES. Other reported malignancies include leukemia, and cancers of the vulva, liver and lung. Poor wound healing, eosinophilia, osteoporosis, cardiomyopathy, lung and brain abnormalities are seen in these tissue-specific deletants.

6.2. Clinical manifestation diversity in primary immune deficiency

Preliminary diagnosis:-

The IgE was discoevered previously by the scientists. A system comprising both clinical and laboratory diagnostic criteria has been proposed by Grimbacher and colleagues and accepted by the National Institute of Health (NIH)[Table 2]. An analysis carried out indicates that the affected individual is probably a carrier of the hyper-IgE genotype, or that the presence of this genotype is not certain. The number of cases with infections, bone fractures and pulmonary disorders leading to the development of pneumatocele increases with age. The diagnostic approach proposed recently by Schimke and colleagues confirmed that the NIH scoring system accurately identifies patients with HIES.

So they are kept under proper care. The diagnosis are studied further for any more prophylaxis. And regularly the tests are conducted to diagnose any further results. So, clinical view is made clear for hyper IgE syndrome.

7. Immunology of HIES:

7.1.Immunologic and infectious disease manifestations

Autosomal dominant Hyper IgE syndrome (AD-HIES) is characterized by eczematoid rashes, skin abscesses, recurrent sinopulmonary infections, mucocutaneous candidiasis, and malignancies [7, 8, 9, 10, 11]. A biopsy may show eosinophilic infiltrate. Rashes may resolve or persist and are consistent with eczematoid dermatitis and, like eczema, appear to be *Staphylococcus aureus* driven. Antistaphylococcal therapy, along with topical antiseptics is part of the routine regimen and are typically quite effective in controlling the rash[12]. Secondary infections are very difficult to treat and are major causes of morbidity and mortality for these patients, due to recurrent exacerbations of infection and pulmonary hemorrhage [13]. AD-HIES is associated with an increased risk of malignancies—most notably non- Hodgkin's lymphoma (NHL), with the majority being of B cell origin and aggressive histology [14, 15]. Other reported malignancies have included Hodgkin's lymphoma, leukemia, and cancers of the vulva, liver, and lung [16].

7.2.Laboratory abnormalities:-

Laboratory abnormalities in HIES include eosinophilia and IgE usually elevated above 2,000 IU/ µL. The IgE level may decline over time and occasionally reaches normal levels in adulthood despite persistent symptoms. Serum IgG and IgM are usually normal, and serum IgA is normal or low; however, impaired specific antibody responses are seen in some with HIES.

7.3.Treatment

The mainstay of therapy for HIES revolves around proper skin care and prevention and aggressive treatment of infections. Since HIES patients may lack the classic signs and symptoms of infections, such as fevers, chills, or rigors, a careful history, physical exam. Some reports claim fewer infections in immune globulin recipients, and this is to be expected in selected cases. At this point it seems appropriate to test antibody responses and to consider replacement in those cases for which defects are demonstrated. The role of bone marrow transplantation (BMT) in HIES is unclear.

8. Expression of Interlukins:

8.1. Increased expression of interleukin-13 but not interleukin-4 in CD4+ cells from patients with the hyper-IgE syndrome:

The raised IgE levels have led researchers to study the synthesis of cytokines that regulate switching of immunoglobulin production towards IgE such as interleukin-4 (IL-4), IL-12 and interferon-g (IFN-g). Intracellular expression of IL-4 and IL-13 in mononuclear cells and CD4+ cells isolated from patients with HIES and healthy controls Cells were stained intracellularly with antibodies directed against IL-4 and IL-13 and analysed by flow cytometry before and after activation with PMA and calcium ionophore.

This study is the first to show that resting or activated CD4+ cells from patients with the HIES express higher levels of IL-13 compared to healthy controls. The levels of IL-4 expression were similar in the two groups, results that are in agreement with previous studies [24,25]. IL-4 expression was similar in both the mononuclear cell population as well as the CD4+ population with no differences between resting or activated cells.

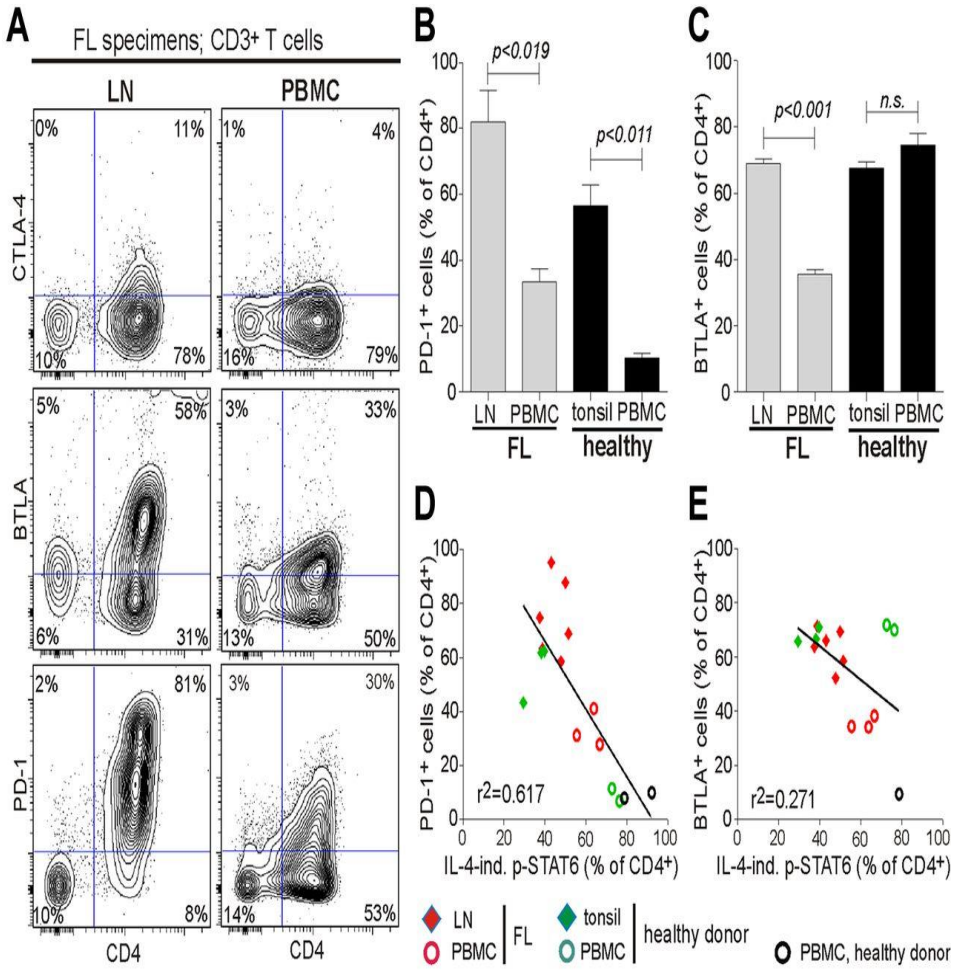

Fig 5. Differential expression of PD-1 in CD4+ FL TILs and autologous PBMC CD4+ T cells and negative association with IL-4–induced p-STAT6

9. Autosomal determination of HIES:

9.1.Autosomal dominant HIES

A hallmark of the syndrome is an increased concentration of immunoglobulin E in the serum, exceeding 2000 IU/µl, frequently higher than 5000. The severity of infectious complications in patients with hyper-IgE syndrome do not correlate with immunoglobulin E concentration in the serum. Immunological abnormalities do not explain the unique susceptibility to particular infections seen in HIES. This finding supports this hypothesis of the crucial role of the Th17-dependent responses in immunity to Candida.

9.2.Invasive fungal disease in autosomal-dominant hyper-IgE Syndrome

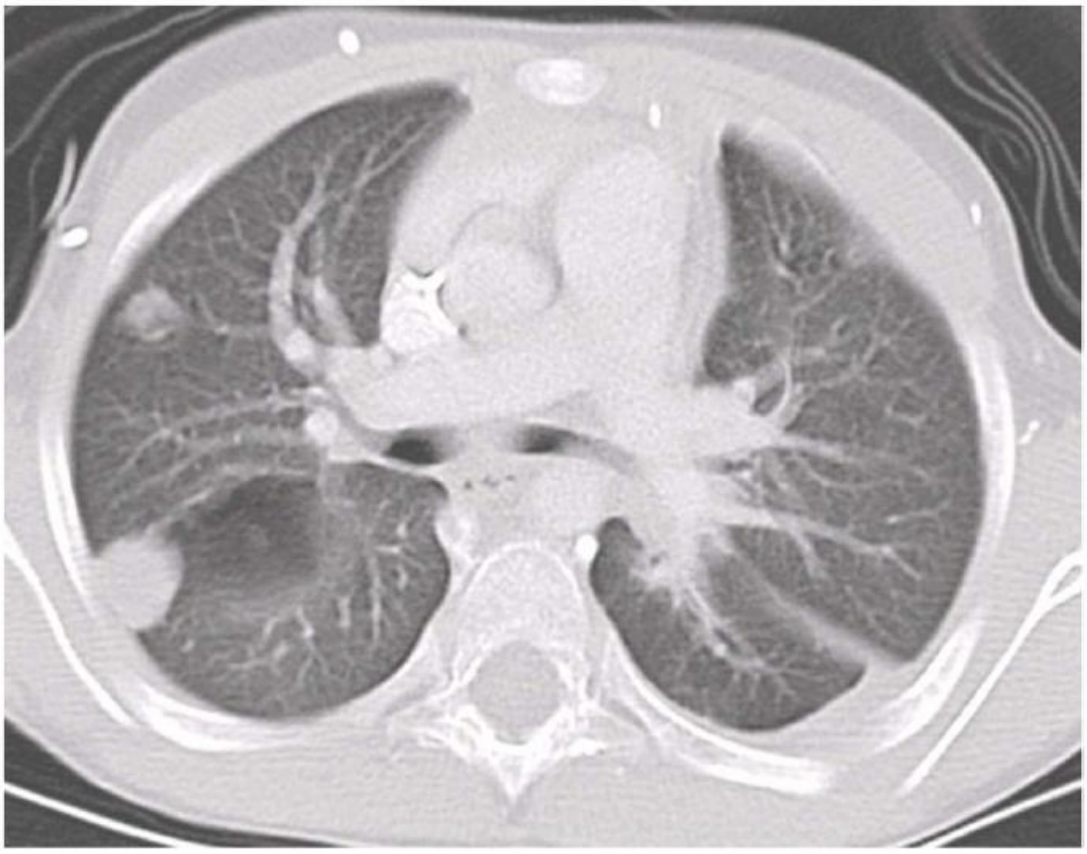

Fig 6. CT of invasive fungal pneumonia in AD-HIES.

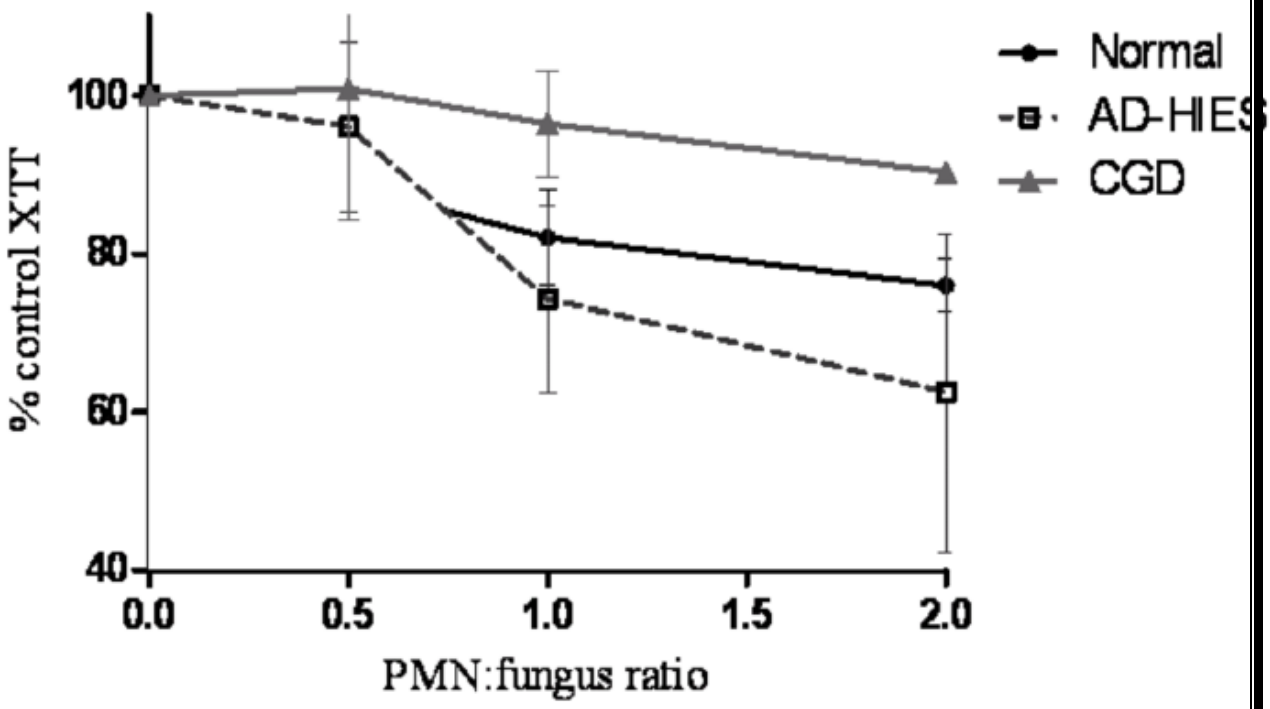

Fig 7. Growth inhibition of *A. fumigatus* hyphae by neutrophils from AD-HIES patients compared to normal donors and chronic granulomatous disease (CGD) patients

9.3.Autosomal Recessive Hyper IgE syndrome

These individuals lack the somatic features, such as the characteristic facies, scoliosis and the failure of baby teeth to exfoliate. Eosinophilia and elevated serum IgE are the most consistent laboratory findings, and may be more dramatic than in AD-HIES. Autoimmune cytopenias may occur. Other immunologic studies, such as lymphocyte phenotyping, do not have characteristic findings.

10.Gene expression of peripheral blood cells in HIES:

10.1. Distinct gene expression patterns of peripheral blood cells in hyper–IgE syndrome

To investigate the pathophysiology and candidate genes involved in this disease, we performed microarray analysis of unstimulated peripheral CD4+ T cells and CD14+ cells, as well as peripheral blood mononuclear cells (PBMNC) stimulated with *Staphylococcus aureus* isolated from HIES patients and healthy controls. 38 genes showed over 2-fold differences between the HIES patients and healthy controls in purified CD14+ cells, although only small differences in the gene expression profiles were observed between the two groups in purified CD4 + T cells. Microarray analysis using an AceGene Human Oligo Chip 30K that contains approximately 30 000 genes. Each gene expression level of CD4+ T cells and CD14+ cells from the patients or controls was determined by comparison with that from the standard sample.

So, Six up-regulated and 4 down-regulated genes in HIES showed over 2-fold differences compared with controls in CD4+ T cells [Fig.6] while 33 up-regulated and 5 down-regulated genes in HIES showed over 2-fold differences compared with controls in CD14+ Cells. The expression levels of major Th1- or Th2-related genes in CD4+ T cells and CD14+ cells did not show more than 2-fold differences between HIES patients and controls.

Gene name	Synonyms	Gene bank	Fold increase of gene expression* HIES	Control	Fold difference** HIES/Control
HIES > Control					
Ubinuclein 1	UBN1	AF108460	3·5	1/1·4	4·9 (5·0, 4·9)
Rho guanine nucleotide exchange factor (GEF) 1	ARHGEF1	Y09160	2·7	1/1·7	4·7 (2·7, 8·3)
Hydroxymethylbilane synthase	HMBS	X04808	3·4	1/1·3	4·3 (1·4, 13)
Bromodomain containing 3	BRD3	D26362	2·5	1/1·6	4·0 (3·7, 4·4)
Incyte EST			2·9	1/1·3	3·9 (2·8, 5·2)
KIAA0582 protein	KIAA0582	AK000856	1·3	1/3·0	3·8 (3·4, 4·2)
A kinase (PRKA) anchor protein (yotiao) 9	AKAP9	NM_005751	2·1	1/1·8	3·7 (4·6, 2·9)
Haloacid dehalogenase-like hydrolase domain	HDHD1A	M86934	2·6	1/1·4	3·7 (1·3, 11)
KIAA0555 gene product		AL137976	5·1	1·4	3·7 (2·3, 5·8)
Ral GEF with PH domain and SH3 binding motif 2	RALGPS2	AK001106	1·6	1/2·2	3·6 (3·2, 3·9)
Tripartite motif-containing 2	TRIM2	AB011089	1·5	1/2·4	3·5 (2·6, 4·7)
Serine (or cysteine) proteinase inhibitor, member 1	SERPINI1	NM_005025	2·1	1/1·6	3·5 (7·9, 1·5)
Cysteine conjugate-beta lyase; cytoplasmic	CCBL1	X82224	1·4	1/2·4	3·4 (3·3, 3·5)
Homeo box A7	HOXA7	AJ005814	3·2	1·0	3·3 (3·7, 3·0)
Scaffold attachment factor B2	SAFB2	D50928	3·3	1·0	3·3 (4·5, 2·4)
5′-nucleotidase, ecto (CD73)	NT5E	X55740	1·4	1/2·3	3·3 (3·7, 2·9)
Mad4 homolog		AL040187	1·4	1/2·3	3·3 (3·3, 3·3)
Aldo-keto reductase family 1, member C1	AKR1C1	M86609	5·8	1·8	3·3 (2·5, 4·3)
Hypothetical protein FLJ13213	FLJ13213	AK000867	2·6	1/1·3	3·3 (4·5, 2·4)
Human FLI1 gene for ERGB transcription fuctor		AB012624	2·0	1/1·6	3·3 (3·1, 3·4)
Myosin XVB, pseudogene	MYO15B	AK026339	1·3	1/2·5	3·2 (3·3, 3·2)
Adducin 2 (beta)	ADD2	S81079	1·6	1/2·0	3·2 (2·5, 4·2)
Zinc finger protein 236	ZNF236	AF085244	1·7	1/1·9	3·2 (4·1, 2·5)
Yippee-like 1 (Drosophila)	YPEL1	AW006162	3·1	1·0	3·2 (2·0, 5·1)
Incyte EST			1·1	1/3·0	3·2 (3·3, 3·0)
NIMA (never in mitosis gene a)-related kinase 1	NEK1	AL050385	3·3	1·1	3·1 (5·0, 2·0)
Protocadherin 9	PCDH9	AF169692	1·7	1/1·8	3·1 (4·2, 2·3)
Poly (ADP-ribose) polymerase family, member 2	ADPRTL2	AK001980	2·1	1/1·4	3·0 (3·2, 2·8)
Calcium/calmodulin-dependent protein kinase (CaM kinase) II delta	CAMK2D	AF071569	1·5	1/2·0	3·0 (1·7, 5·3)
HIES < Control					
Solute carrier organic anion transporter family, member 1A2	SLCO1A2	U21943	1·8	24	1/14 (1/29, 1/6·7)
Normal mucosa of oesophagus specific 1	NMES1	AK026298	4·6	37	1/8·1 (1/10, 1/6·3)
Syndecan 2	SDC2	J04621	4·1	23	1/5·6 (1/12, 1/2·7)
Interleukin 17	IL17	U32659	1/1·3	4·1	1/5·5 (1/8·0,1/3·7)
TBC1 domain family, member 15	TBC1D15	AK022147	1/2·0	2·2	1/4·5 (1/6·9, 1/2·9)
Syndecan 4 (amphiglycan, ryudocan)	SDC4	D13292	1·0	4·6	1/4·4 (1/5·2, 1/3·7)
Recombining binding protein suppressor of hairless (Drosophila)	RBPSUH	AW968632	1/2·3	1·7	1/4·0 (1/4·8, 1/3·3)
Humour necrosis factor, alpha-induced protein 6	TNFAIP6	M31165	5·5	22	1/3·9 (1/3·0, 1/5·2)
Hypothetical protein FLJ10199	FLJ10199	AI216532	1·0	3·8	1/3·9 (1/6·2, 1/2·4)
Small inducible cytokine subfamily B (Cys-X-Cys), member 11	CXCL11	AF030514	1·5	5·6	1/3·8 (1/2·7, 1/5·4)
Cathepsin L	CTSL	AI041851	5·5	21	1/3·8 (1/7·7, 1/1·9)
Enhancer of rudimentary homolog (Drosophila)	ERH	U66871	1/1·9	1·9	1/3·6 (1/3·0, 1/4·3)
Tryptophanyl-tRNA synthetase	WARS	X59892	1/1·7	2·1	1/3·6 (1/3·8, 1/3·4)
Epithelial membrane protein 1	EMP1	Y07909	1·2	4·4	1/3·6 (1/5·6, 1/2·3)
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13 kDa	NDUFA5	U53468	1/3·7	1/1·1	1/3·4 (1/4·1, 1/2·9)
Hect domain and RLD 5	HERC5	AB027289	7·5	25	1/3·3 (1/1·2, 1/8·7)
Feline leukaemia virus subgroup C cellular receptor	FLVCR	AK001419	1/2·8	1·2	1/3·3 (1/5·2, 1/2·0)
FK506 binding protein 5	FKBP5	U42031	1/2·3	1·3	1/3·1 (1/4·5, 1/2·2)
Deleted in lymphocytic leukaemia, 2	DLEU2	AW978447	1/2·8	1·1	1/3·1 (1/2·1, 1/4·6)
Cathepsin L2	CTSL2	AB001928	4·2	13	1/3·0 (1/5·7, 1/1·6)
Methionine adenosyltransferase II, alpha	MAT2A	F07456	1/2·4	1·3	1/3·0 (1/1·8, 1/5·1)
v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian)	MAF	AF055376	1·0	2·9	1/3·0 (1/3·7, 1/2·5)

Fig 8. Microarray analysis of purified CD14+ cells between HIES and healthy controls.

11. Bone related problems :

11.1. Bone Density and Fractures in Autosomal Dominant Hyper IgE Syndrome

11.1.1. Study:-

This was done to understand the bone related study of increase in IgE in the population. So many of the individuals were selected for this study which were demonstrated for HIES.

We recorded minimal trauma fractures, bone marrow density (BMD) and bone metabolic markers for 56 individuals with AD-HIES not receiving bisphosphonates or parathyroid hormone therapy. Patients were diagnosed clinically and by *STAT3* mutational analysis.

11.1.2. Demographics-

Results were obtained after the tests were conducted . The 56 AD-HIES patients not on osteoporosis therapy included 33 adults, ages 21–50 years and 23 children, aged 6–18 years. DNA genotyping was available for all but one deceased adult with an HIES score of 89.

11.2. Bone marrow density(BMD):-

Due to Hyper IgE, at least one BMD measure, 79 % of subjects had either osteopenia or osteoporosis. Then, Spine BMD determination in 23 children found that 12 had normal, 9 had osteopenic and 2 had osteoporotic BMD Z-scores in the ppopulation. Out of the 32 adults with available studies, 10 had normal, 13 had osteopenic, and 9 had osteoporotic BMD T-scores. Forty (71 %) of the 56 patients had experienced minimal trauma fractures, ranging from one to 18 or more fractures altogether.

12. Pulmonary infections:

12.1. Pulmonary Nontuberculous Mycobacterial(NTM) Infections in Hyper-IgE Syndrome:-

Of the 62 HIES patients followed, 32 (51%) had at least one specimen submitted for AFB testing [17 females, 15 males, ages 2 – 56 (31±14 years) at the time of culture with an HIES clinical score of 52 to 100 (79±12)]. *STAT3* mutation was found in 30 of 32 patients with AFB testing.

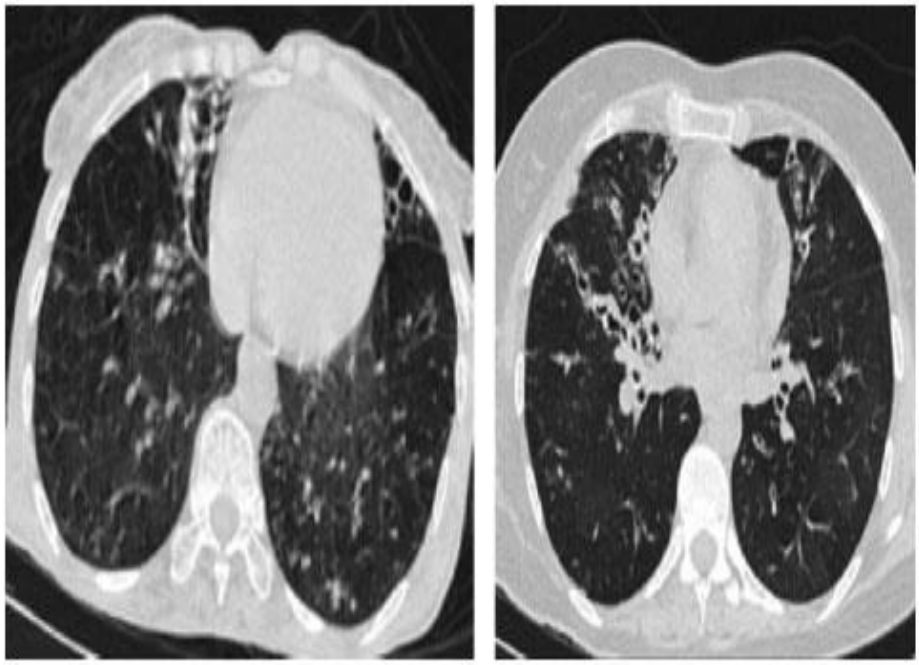

Fig. 5 – Middle and lower lobes bronchiectasis.

Fig 9. Radiographic manifestations of NTM in HIES

13.Helminth infection:

13.1. The IgE response is a physiological immune response to helminth infection

Most other inflammatory/infectious conditions, allergy, and helminths induce strongly Th2-skewed responses associated with cytokines such as IL-4, IL-5, and IL-13, with mastocytosis, eosinophilia, and antibody class-switching to produce IgE[27].Helminths actively moderate the inflammatory Th2 response of the host, inducing regulatory T and B cells, alternatively activated macrophages and production of immunoregulatory cytokines. Most of the evidence relating IgE to anti-helminth immunity comes from epidemiological data.

The global increase in allergy especially in urban areas [29] has led researchers to propose a modified hygiene hypothesis in which the decline in helminth infections is associated with an increase in allergic diseases.

13.2. Helminths and malaria co infections are associated with elevated serum IgE

197 malaria patients and 216 malaria free apparently healthy controls were included. It is very difficult to have a normal range of IgE even at a population level, a range of values of IgE levels was defined enabling the analysis of the frequency of normal, moderate and high IgE levels in each group of patients. Normal values were adjusted because the groups had a wide range of different total serum IgE level. Serum IgE values between N and 1.5 N were considered as low, between 1.5 N and 2 N as moderate IgE levels and above 2 N as the highest levels. A remarkably elevated total serum IgE level in malaria patients irrespective of helminth coinfection was observed.

14.Treatment of Hyper IgE syndrome:

Treatment of the diseases caused by hyper IgE various factors. This will include the process in which the levels of IgE will have to be normal. It means if the levels are higher, then it should be brought to normal, then only further treatments will be carried out.

Because IgE is a key mediator in allergic reactions, one way to treat IgE-mediated allergic diseases is to target both membrane-bound and soluble IgE2[29]. Such an approach is advantageous as it is independent of allergens.

14.1.Mechanisms of allergen-specific immunotherapy

Allergen-specific immunotherapy (allergen-SIT) is a potentially curative treatment approach in allergic diseases. It has been used for almost 100 years as a desensitizing therapy. The induction of peripheral T cell tolerance and promotion of the formation of regulatory T-cells are key mechanisms in allergen-SIT.

14.2. Acupuncture for Symptom Management in Patients with Hyper-IgE (Job's) Syndrome

Out Of the 8 patients with HIES, 4 were male and 4 were female; 7 were white and 1 was Asian. Seven (7) patients had the STAT3 genetic mutation. They were reported with numerous symptoms associated with dermatitis and infections, as well as skeletal and connective-tissue abnormalities. There is no cure for HIES at the present time. The multiple manifestations of the disease result in complicated physical and mental symptoms, and death often occurs in the second and third decades of life, usually due to pulmonary disease[26]. Acupuncture can be a useful therapy to reduce symptom severity, improve patients life expectancy. The safety of acupuncture was monitored in this case series and no serious adverse events occurred, including no acupuncture-associated infections.

14.3. Therapy of AD-HIES

Therapy of HIES remains largely supportive, but will likely be refined greatly in the next several years as the pathogenesis of HIES is delineated and animal models created. Intravenous immunologlobulin (IVIG) may decrease the number of infections for some individuals, and is the most frequent immunomodulator used [5,6].

14.4. Successful engraftment of donor marrow following allogeneic hematopoietic cell transplantation in autosomal recessive Hyper IgE syndrome due to DOCK8 deficiency

A child with homozygous partial deletion of the dedicator of cytokinesis (*DOCK)8* gene showed characteristic clinical findings of autosomal recessive hyper-IgE syndrome and full donor chimerism early after matched sibling bone marrow transplantation. The results suggest that HCT may be a viable option to treat DOCK8 deficiency. Unfortunately, the demise of the patient precluded further follow up of immune function and clinical status.

This study demonstrated that acupuncture is a useful and safe therapy for symptom management in patients with HIES. Further research is needed to better understand the mechanisms of action.

15.Case study:

15.1. Brain Abscess and Keratoacanthoma Suggestive of Hyper IgE Syndrome

Case Report:-

Patient is an 8-year-old boy whose disease started with an unusual skin manifestation and extraordinary findings were seen during the course of treatment. At 6 months old he developed generalized red, nontender nodules, and at 2 yrs, he developed a painless, cold abscess in the medial axis of his thigh. During the same year, another skin biopsy was taken which was in favor of keratoacanthoma (Figure 12), and it also showed wart infection.

After completing 8 years of age, patient was febrile for another 2 weeks so we employed broader spectrum antibiotics and IV-IG. After a week passed with no improvement in his condition, a magnetic resonance imaging (MRI) of brain was performed which showed expansion of existing abscess to contralateral frontal lobe (left side) (Figure 11); hence full evacuation of the contents and wall of abscess was done.

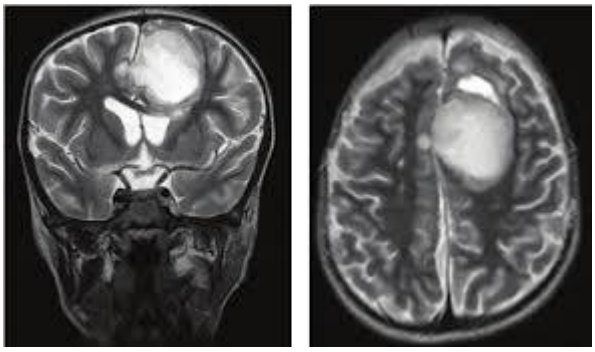

Fig 10. Brain MRI showing expansion of aspirated brain abscess to contralateral frontal lobe:-

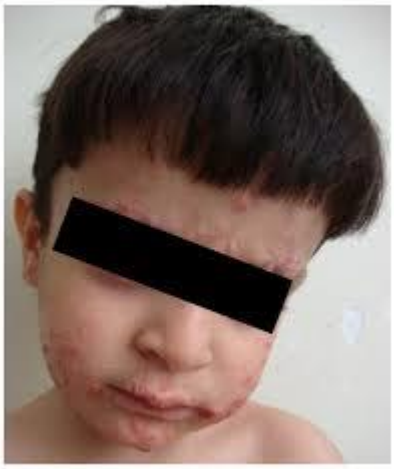

Fig 11. Skin manifestations of keratoacanthoma in hyper IgE syndrome (4 years old).

Table 2.

Assessment by NIH scoring system with clinical and laboratory tests [28].

Clinical and laboratory finding	Results	points
Highest serum IgE level (IU/mL)	1001-2000	8
Skin abscesses	1-2	2
Pneumonia (episodes over lifetime)	None	0
Parenchymal lung anomalies	Absent	0
Retained primary teeth	>3	8
Scoliosis, maximum curvature	15◦–20◦	4
Fractures with minor trauma	None	0
Highest eosinophil count (cells/□L)	>800	6
Characteristic face	Midely Present	2
Midline anomaly	Absent	0
Newborn rash	Absent	0
Eczema (worst stage)	Mild	1
Upper respiratory infections per year	1-2	0
Candidiasis	Fingernails	2
Other serious infections	Severe	4
Fatal infection	Absent	4
Hyperextensibility	Absent	0
Lymphoma	Absent	0
Increased nasal width	<1 SD	0
High palate	Absent	0
Young-age correction	>5 years	0
TOTAL		41

16. Conclusion:

Hyper IgE syndrome(HIES) is a combination of various diseases. The onset of disease is from age group of 5-18 years. The symptoms included in it is not enough to reveal the syndrome. This happens because the symptoms are very common, which includes other diseases also. HIES is caused by various factors. First of all, there is a mutation in STAT3 protein, which is a major factor in transfer of cytokines. Secondly, the Hypo secretion of T helper cells, also causes increase in levels of IgE.

The symptoms are inflammation in lymph nodes, swelling, rashes. If left untreated, it may lead to bone disorders, lungs disease, etc. There are no proper prophylaxis of hyper IgE. As the symptoms are unpredictable so one cannot decide the accurate remedy for the syndrome. But, once diagnosed properly, the treatment can be effective. The treatment is not specific for Hper IgE. The symptoms can be reduced by certain treatments like acupuncture, lumbar puncture, bone marrow transplant etc. These treatment can reduce the disease only, it cannot make the patient disease free. The life expectancy can be prolonged by the treatments.

Hyper IgE can be a opportunistic study in research of certain immune cells. By knowing the fact of this immunoglobulin, many factors related with IgE can be studied. The study of Hyper IgE can also be helpful in diagnosis of certain factors which are still unknown

17. Reference:

[1]. S. Farmand and M. Sundin, Hyper-IgE syndromes: recent advances in pathogenesis, diagnostics and clinical care, Current Opinion in Hematology, vol. 22, no. 1, pp. 12–22, 2015.

[2]. A. Sassi, S. Lazaroski, G.Wu et al., Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity

[3]. Chamlin SL, McCalmont TH, Cunningham BB, Esterly NB, Lai CH, Mallory SB, Mancini AJ, Tamburro J, Frieden IJ. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr 2002;141:572–575. [PubMed: 12378200]

[4]. Eberting CL, Davis J, Puck JM, Holland SM. Dermatitis and the newborn rash of hyper-IgE syndrome. Arch Dermatol 2004;140:1119–1125. [PubMed: 15381553]

[5]. Kimata H. High dose intravenous gammaglobulin treatment for hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1995;95:771–774. [PubMed: 7897163]

[6]. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol 1998;81:153–158. [PubMed: 9723561]

[7]. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. N Engl J Med. 1999; 340:692–702. [PubMed: 10053178]

[8]. Buckley RH. The hyper-IgE syndrome. Clin Rev Allergy Immunol. 2001; 20:139–154. [PubMed:11269224]

[9]. Gharib AM, Pettigrew RI, Elagha A, et al. Coronary abnormalities in hyper-IgE recurrent infection syndrome: depiction at coronary MDCT angiography. Am J Roentgenol. 2009; 193:W478–W481. [PubMed: 19933621]

[10]. Gorin LJ, Jeha SC, Sullivan MP, et al. Burkitt's lymphoma developing in a 7-year-old boy with hyper-IgE syndrome. J Allergy Clin Immunol. 1989; 83:5–10. [PubMed: 2783597]

[11]. Leonard GD, Posadas E, Herrmann PC, et al. Non-Hodgkin's lymphoma in Job's syndrome: a case report and literature review. Leuk Lymphoma. 2004; 45:2521–2525. [PubMed: 15621772]

[12]. Huang JT, Abrams M, Tlougan B, et al. Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. Pediatrics. 2009; 123:e808–e814. [PubMed: 19403473]

[13]. Freeman AF, Kleiner DE, Nadiminti H, et al. Causes of death in hyper-IgE syndrome. J Allergy Clin Immunol. 2007; 119:1234–1240. [PubMed: 17335882]

[14]. Oztop I, Demirkan B, Tarhan O, Kayahan H, et al. The development of pulmonary adenocarcinoma in a patient with Job's syndrome, a rare immunodeficiency condition. Tumori. 2004; 90:132–135. [PubMed: 15143986]

[15]. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 2007; 357:1608- 19; PMID:17881745; http://dx.doi.org/10.1056/ NEJMoa073687.

[16]. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 2008; 452:773-6; PMID:18337720; http://dx.doi.org/10.1038/nature06764.

[17]. Wesemann DR, Magee JM, Boboila C, Calado DP, Gallagher MP, Portuguese AJ, et al. Immature B cells preferentially switch to IgE with increased direct Sμ to Sε recombination. J Exp Med 2011; 208:2733- 46; PMID:22143888; http://dx.doi.org/10.1084/ jem.20111155.

[18]. Sekhsaria V, Dodd LE, Hsu AP, Heimall JR, Freeman AF, Ding L, et al. Plasma metalloproteinase levels are dysregulated in signal transducer and activator of transcription 3 mutated hyper-IgE syndrome. J Allergy Clin Immunol 2011; 128:1124-7; PMID:21872914; http://dx.doi.org/10.1016/j.jaci.2011.07.046.

[19]. Debnath B, Xu S, Neamati N. Small molecule inhibitors of signal transducer and activator of transcription 3 (Stat3) protein. J Med Chem 2012; 55:6645- 68; PMID:22650325; http://dx.doi.org/10.1021/ jm300207s.

[20]. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev 2009; 228:273- 87; PMID:19290934; http://dx.doi.org/10.1111/ j.1600 065X.2008.00754.x.

[21]. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. Ann N Y Acad Sci 2012; 1250:25- 32; PMID:22268731; http://dx.doi.org/10.1111/ j.1749 6632.2011.06387.x.

[22]. King CL, Gallin JI, Malech HL et al. Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon gamma. Proc Natl Acad Sci USA 1989; 86:10085–9.

[23]. Vercelli D, Jabara HH, Cunningham-Rundles C et al. Regulation of immunoglobulin (Ig) E synthesis in the hyper-IgE syndrome. J Clin Invest 1990; 85:1666–71.

[24]. Freeman AF, Kleiner DE, Nadiminti H, et al. Causes of death in hyper-IgE syndrome. J Allergy Clin Immunol 2007;119: 1234–1240.

[25]. AllenJE,MaizelsRM.Diversityanddialogueinimmunitytohelminths. Nat RevImmunol (2011) 11:375–88.doi:10.1038/nri2992

[26]. A. P. Hsu, J. Davis, J. M. Puck, S. M. Holland, and A. F. Freeman, Autosomal dominant hyper IgE syndrome, in GeneReviews, University of Washington, Seattle, Wash, USA, 2012, http://www.ncbi.nlm.nih.gov/books/NBK25507/

[27]. Chang, T. W. et al. Monoclonal antibodies specific for human IgE-producing B cells: a potential therapeutic for IgE-mediated allergic diseases. Bio/technology 8**,** 122–126 (1990).