

Allergic comorbidities among inborn errors of immunity in children attended in a high-complexity center in Cali, Colombia

Comorbilidades alérgicas en pacientes pediátricos con errores innatos de la inmunidad atendidos en un centro de alta complejidad en Cali, Colombia

Jacobo Triviño-Arias,¹  Sofia Martínez-Betancur,¹  Oriana Arias-Valderrama,^{1,2}  Tania M. Guzmán,¹  Juan Pablo Díaz-Solórsano,¹  Diego Medina,³  Alexis Franco,³  Jaime Patiño,⁴  Paola Marsela Pérez,⁴  Harry Pachajoa,⁵  Manuela Olaya-Hernández,^{6*} 

¹Fundación Valle del Lili, Centro de Investigaciones Clínicas, Cali, Colombia

²Universidad Icesi, Facultad de Ciencias de la Salud, Cali, Colombia

³Fundación Valle del Lili, Departamento Materno Infantil; Servicio de Hemato-oncología Pediátrica, Trasplante de Medula Ósea, Cali, Colombia

⁴Fundación Valle del Lili, Departamento Materno Infantil; Servicio de Infectología Pediátrica, Cali, Colombia

⁵Fundación Valle del Lili, Departamento Materno Infantil; Servicio de Genética Clínica, Cali, Colombia

⁶Fundación Valle del Lili, Departamento Materno Infantil; Servicio de Alergología e inmunología, Cali, Colombia

Reception: 05/08/2025

Acceptance: 08/11/2025

Publication: 12/31/2025

*Correspondence: Manuela Olaya Hernández. vanessa.cabrera.gu@javerianacali.edu.co

Abstract

Objective: To describe the clinical characteristics of allergic diseases (AD) as comorbidities—distinct from primary atopic diseases (PAD)—in pediatric patients diagnosed with IEI.

Methods: An observational and retrospective study was made. We included pediatric population diagnosed with IEI and allergic comorbidity between 2013-2023. The diagnosis was done considering the criteria from the ESID and IUIS-2022. We performed a descriptive analysis of the variables (frequencies/percentages). For qualitative variables, we used OR to obtain the probability of occurrence of allergic sensitization among patients with AD and IEI. Every analysis was performed with the software R Studio version 3.2.2.

Results: There were 366 patients with diagnosis of IEI, 238 had concomitant AD. 59.6% were males. Mean age was 5 years. 84% had antibody-specific deficiencies, 8% combined immunodeficiencies associated to well-defined syndromes, 2.9% congenital defects in phagocytes, 2.5% combined-immunodeficiencies, 1.7% autoinflammatory diseases, and 0.8% defects in intrinsic and innate immunity. The distribution of the ADs was asthma 48.7%, rhinitis 18.9%, atopic-dermatitis 15.1%, food-allergy 8.4%, acute urticaria 5%, and chronic urticaria 3.8%.

Conclusion: Allergic diseases are increasingly recognized as key indicators for early IEI diagnosis. These conditions may coexist without representing PAD, emphasizing the need for comprehensive care. Recognizing this heterogeneity supports a multidisciplinary approach to improve early detection and management of IEI.

Keywords: Inborn errors of immunity; Allergic diseases; Sensitization; Hypersensitivity reactions.

Resumen

Objetivo: Describir las características clínicas de las enfermedades alérgicas (EA) como comorbilidades —distintas de las enfermedades atópicas primarias (EAP)— en pacientes pediátricos con diagnóstico de errores innatos de la inmunidad (IEI).

Métodos: Estudio observacional y retrospectivo, efectuado en una población pediátrica con diagnóstico de IEI y comorbilidad alérgica, atendidos entre 2013 y 2023. El diagnóstico se basó en los criterios de ESID y IUIS-2022. Se realizó un análisis descriptivo de variables (frecuencias/porcentajes). Para las variables cualitativas se utilizó razón de momios (OR), con la intención de estimar la probabilidad de sensibilización alérgica. Los análisis se realizaron con R Studio versión 3.2.2.

Resultados: Se registraron 366 pacientes con IEI y de estos 238 manifestaron EA concomitante (59.6% hombres; edad media: 5 años). Los tipos de IEI más frecuentes fueron las deficiencias específicas de anticuerpos (84%), seguidas por inmunodeficiencias combinadas asociadas a síndromes (8%), defectos congénitos de fagocitos (2.9%), inmunodeficiencias combinadas (2.5%), enfermedades autoinflammatorias (1.7%) y defectos de inmunidad innata (0.8%). Las EA incluyeron asma (48.7%), rinitis (18.9%), dermatitis atópica (15.1%), alergia alimentaria (8.4%), urticaria aguda (5%) y urticaria crónica (3.8%).

Conclusión: Las EA son un signo de alerta cada vez más reconocido para la detección temprana de IEI. Su coexistencia, sin ser necesariamente EAP, destaca la necesidad de un abordaje integral y multidisciplinario.

Palabras clave: Errores innatos de la inmunidad; Enfermedades alérgicas; Sensibilización; Reacciones de hipersensibilidad.

INTRODUCTION

Inborn Errors of Immunity (IEI), previously known as primary immunodeficiencies,¹ is a heterogeneous group of hereditary disorders caused by defects in the development or function of the immune system.¹ They can affect any person, independent of age or sex, being more prevalent during childhood, with a predominance of 5:1 for males.² The prevalence of IEI can vary between countries.³ Yet, it is estimated that around 70% of patients with IEI are not diagnosed,⁴ especially in countries with low global development indexes, as a result of limited awareness about these diseases, delay in diagnosis, comorbidities that may go unrecognized and be underreported.³

Clinical presentations of IEI are variable, including severe or atypical infections, autoimmune diseases, malignant tumors, autoinflammatory states, and allergies.⁴ Even severe atopic conditions, especially those unresponsive to conventional treatments, could serve as an alarming sign to raise suspicion for an underlying IEI.⁵

Hypersensitivity reactions, including allergic conditions such as atopic dermatitis, allergic rhinitis, asthma, and food allergy are exaggerated immune responses against specific allergens.⁶ They can present in people with diagnosed IEI and can affect both the quality of life of both patients and caregivers. Furthermore, their development is thought to be the result of an altered balance within the immune system of its effector and regulatory cells.⁷

The objective of this study is to describe the clinical characteristics of a pediatric population with IEI and allergic disease as comorbidities that are not primary atopic disorders, seen in a high-complexity tertiary care center in Cali, Colombia, between 2013 and 2023.

METHODS

We conducted an observational study using clinical records. Patients included were under 18 years of age, with a diagnosis of IEI with allergic comorbidities treated between 2013 and 2023 in a high-complexity hospital located in southwestern Colombia.

Information was obtained through institutional records of patients under 18 years old who were diagnosed with any of the following ICD-10 codes: D80-D89, added to the infectious diseases and pediatric immunology records. The diagnosis of IEI was established considering the clinical and laboratory criteria from the European Society for Immunodeficiencies (ESID). The definitions of immunodeficiencies for each disease were based on the diagnostic criteria from ESID, and patients were grouped according to the ten categories described in the IUIS classification. For more details on the criteria, please consult the corresponding references.⁸

Variables

We collected demographic variables, clinical manifestations, immunoglobulin levels, sensitization tests, and history

of allergic diseases. IEI were classified according to the International Union of Immunological Societies' (IUIS) 2022 Expert Committee for Primary Immunodeficiencies for subgroup immune typification.⁹

Setting

Fundación Valle del Lili is a teaching hospital located in southwestern Colombia, it is a reference center for the region for IEI, and it is the only hospital in the region that is suited to perform multidisciplinary treatment by an immunology, pediatric infectious diseases, clinical genetics, and hematology group, with a clinic exclusively set to attend IEI and, if it is necessary perform bone marrow transplants.

Statistical analysis

We performed a descriptive analysis of the variables that were presented as frequencies and percentages. For qualitative variables, we used the odds ratio (OR) to obtain the probability of occurrence of allergic sensitization among patients with allergic disease and IEI. Every analysis was performed with the software R Studio version 3.2.2.

RESULTS

In the time frame, there were 366 patients that came to the hospital with diagnoses of IEI, of which 238 had allergic comorbidities. Forty-two (59.6%) were males. Of the 238 patients, 200 (84%) had antibody specific deficiencies, followed by 19 (8%) with combined immunodeficiencies associated to well-defined syndromes, seven (2.9%) had congenital defects in number or function of phagocytes, six (2.5%) had combined immunodeficiencies, four (1.7%) had autoinflammatory diseases, and 2 (0.8%) had defects in intrinsic and innate immunity. The mean age was 5 years (IQR 2-9), the distribution of the age at diagnosis of allergic diseases by IUIS group indicates that most diagnoses occur before the age of twenty. **Figure 1**

The distribution of the 238 patients with allergic disease included 116 (48.7%) cases of Difficult-to-treat asthma, 45 (18.9%) rhinitis, 35 (15.1%) atopic dermatitis with clinical assessment tool from mild to severe without improvement to treatment, 20 (8.4%) food allergy, 12 (5%) acute urticaria, and 9 (3.8%) chronic urticaria. A single patient could present more than one allergic disease simultaneously. Allergic diseases were classified according to the IEI found on the International Union of Immunological Societies (IUIS) classification.⁹ [Table 1] The median total IgE value was 58 UI/mL (IQR 18-243).

Fifty-three (22.2%) patients had allergic sensitization, predominantly to pneumoallergens, with 47 (88%) to dust mites, and 1 (0.4%) to pollen and dog epithelium, respectively. Regarding sensitization to food allergens, only two patients (0.8%) had a positive test: one to tuna and one to shrimp. The sensitization found in different patients with allergic diseases who had IEI according to the IUIS classification is described in Table 2.¹⁰

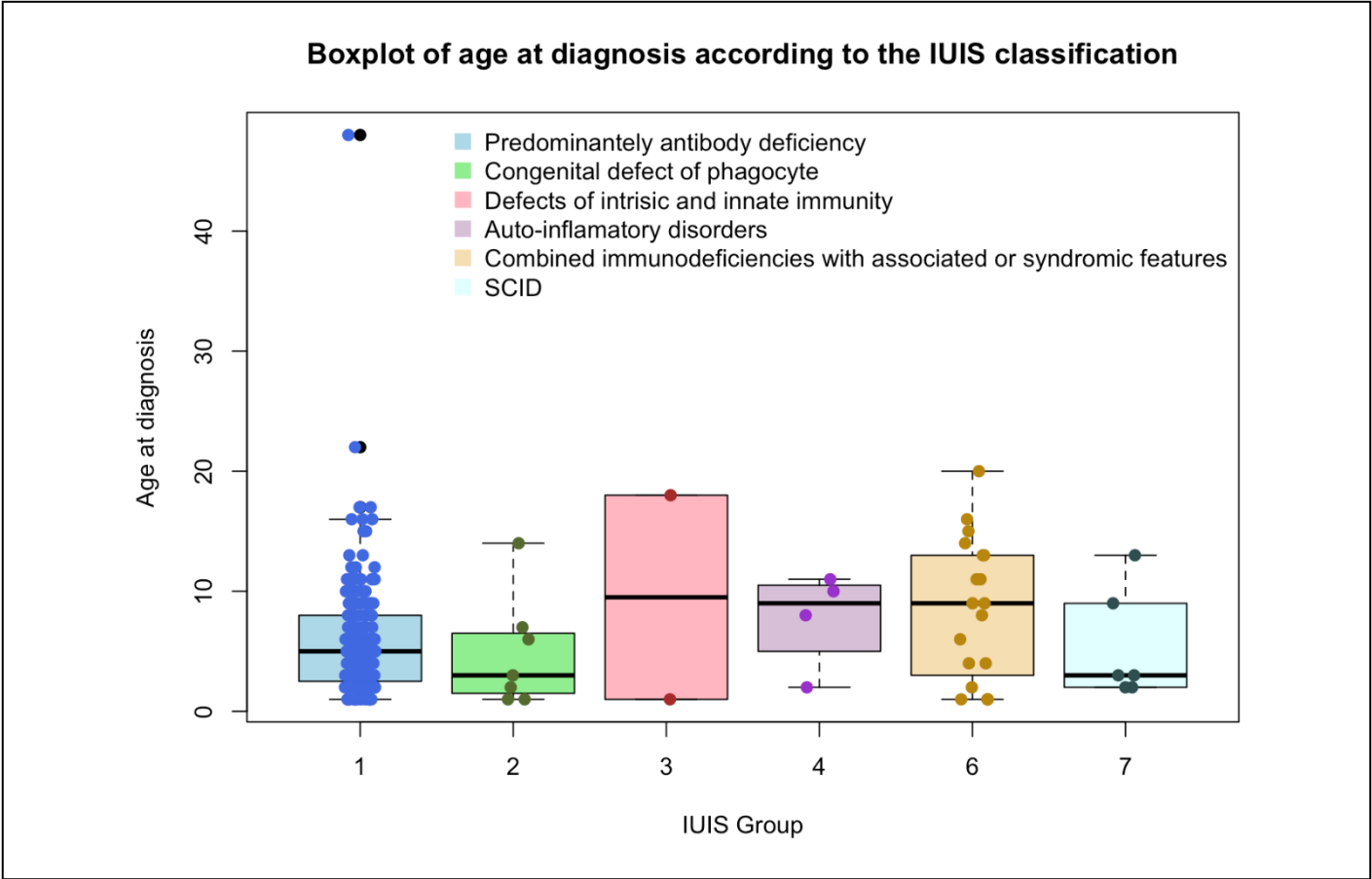


Figure 1. Age at diagnosis according to the IUIS classification.

Table 1. Allergic disease in patients with IEI according to the IUIS classification.

Patients with Allergic Disease according to the IUIS						
Variables	Antibody deficit, N = 200 [†]	Phagocytes defect, N = 7 [†]	Inborn Error of Immunity, N = 2 [†]	Auto-inflammatory disease, N = 4 [†]	IEI with impairment of humoral and cellular immunity, N = 19 [†]	Combined IEI, N = 6 [†]
Asthma	106 (53%)	1 (14%)	0 (0%)	3 (75%)	4 (21%)	2 (33%)
Acute Urticaria	8 (6.6%)	1 (17%)	0 (0%)	0 (0%)	2 (25%)	1 (17%)
Chronic Urticaria	7 (3.5%)	2 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Atopic Dermatitis	27 (14%)	2 (29%)	0 (0%)	2 (50%)	2 (11%)	2 (33%)
Food allergy	14 (7.0%)	1 (14%)	1 (50%)	1 (25%)	1 (11%)	2 (33%)
Allergic Rhinitis	42 (35%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	2 (33%)

Data are presented as number of patients (n) and percentage (%).

Table 2. Allergic sensitization according to the IUIS group.

Allergic sensitization according to the IUIS group						
Variable	Antibody deficit, N = 200 ¹	Phagocytes defect, N = 7 ¹	Defects in intrinsic and innate Immunity, N = 2 ¹	Auto-inflammatory disease, N = 4 ¹	Immunodeficiencies affecting cellular and humoral immunity, N = 19 ¹	CID with associated or syndromic feature N = 6 ¹
Pneumoallergens						
Mites	44 (22%)	0 (0%)	1 (50%)	0 (0%)	4 (21%)	0 (0%)
Polen	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)
Dog	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Food						
Shrimp	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tuna	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Peanuts	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No data	3 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are presented as number of patients (n) and percentage (%).

The risk of having sensitization to pneumoallergens or food among patients with any manifestation of allergic disease and a IEI is 70% higher than in those that do not have any allergic disease (OR 1.71, 95% CI 1.26-2.28).

DISCUSSION

The understanding of primary immunodeficiencies, now known as IEI, has progressed considerably, revealing a heterogeneous set of conditions with diverse clinical manifestations.^{1,2} Ranging from potentially deadly presentations that arise in childhood to less severe presentations that are diagnosed well into adulthood. These diseases can fundamentally impair essential immunological pathways, increasing susceptibility to recurrent or chronic infections. Initially, the diagnostic suspicion turns around pediatric patients with recurrent and atypical infections. Nonetheless, it is now recognized that a significant number of patients can manifest with a different clinical picture, such as growth delay, autoinflammatory or autoimmune diseases, or even severe atopic conditions, which in turn represents an even bigger clinical and diagnostic challenge.^{1,2}

Every day, it is more understood that common allergic symptoms might indicate an underlying immunologic alteration. It is important to consider that not all patients exhibit severe clinical presentations; as a matter of fact, many of them are admitted with mild manifestations, but refractory to conventional treatment. These conditions highlight the

complexity of immune system and the need for an integral approach for the identification and management of IEI in current medical practice.^{2,7}

We performed an analysis of a group of 238 patients diagnosed with IEI associated with type 2 inflammation. It is noteworthy to highlight that our cohort had a larger number of antibody-specific defects, similar to what is reported in recent literature.^{11,12}

We observed a considerably high incidence of allergic diseases among patients with IEI during the evaluated period, adding up to 238 cases, representing 65% of the included population. One patient could have more than one allergic disease. This disclosure is in line with Oggershok et al., who in a study of 12 patients diagnosed with common variable immunodeficiency, described that 85% had asthma as a standout allergic manifestation.¹³ In a study by El-Sayed ZA et al., the median frequency of allergic diseases in patients diagnosed with IEI was found to be 16.3% (IQR).¹⁴

Nonetheless, this result contrasts significantly with data gathered by the ESID registry. According to this registry, only around 9% of the 16.486 registered patients with immunodeficiencies presented "immune dysregulation", a term that encompasses not only allergic diseases but also conditions such as autoimmunity. It could be inferred that the role of allergies could be even less in this context.¹¹ This point of view is confirmed by Edwards et al., who examined a group

of 127 patients diagnosed with IgA deficiency and found that only 13% of them had allergies or asthma.¹⁵

In our study, patients with IEI had asthma in 116 (48%), rhinitis in 45 (18.9%), atopic dermatitis in 35 (15.1%), and urticaria in 21 (8.8%), as described in [Table 1]. This finding can be compared with the report by El-Sayed ZA et al., who described the distribution of allergic diseases in patients with IEI, the total observed frequencies were bronchial asthma in 35% of patients, atopic dermatitis in 30%, rhinitis in 20%, and food allergy in 5%; the same study revealed a 10.6% incidence of anaphylaxis among the patients assessed, that we didn't found in our group.¹⁴

These findings differ from what is reported by C.M. Davis¹⁶ who described a higher prevalence of atopic dermatitis, followed by food allergy, rhinitis, and in a smaller proportion, asthma. The difference in our results could be determined by the origin of our patients, as most of them are referred to by pediatric pulmonology specialists. Twenty-two percent of our patients with IEI and allergic disease showed allergic sensitization, with a considerable predisposition to pneumoallergens, mainly dust mites, which are common in our tropical environment [Table 2]. This contrasts with the study published by El-Sayed ZA et al, where, despite conducting a significant characterization of patients with allergic diseases and IEI, they did not investigate allergic sensitization in all these patients.¹⁴

Furthermore, it is important to note that some patients did not present severe atopic conditions (We know as severe atopic presentation a SCORAD over 40 points), on the contrary, they conformed to a challenging population in terms of management which further motivated extension studies to run out cystic fibrosis and IEI.

The clinical presentation of allergic diseases and their conventional diagnostic methods tend to show eosinophilia and increased serum immunoglobulin E (IgE) levels.⁹ Smith K. et al. Using the United States Immunodeficiency Network, assessed the prevalence of alterations in IgE levels and eosinophils in patients with monogenic IEI before the initiation of treatment; they found that around one in five patients showed this, which they considered indicated allergic conditions.¹² This contrast with our findings with low to normal IgE, this difference could be attributed that we describe patients with IEI and allergic disease as comorbidities that are not primary atopic disorders.

The clinical presentation of IEI is highly variable, especially when it is associated with allergic diseases. It could be dependent on the type of genetic alteration and its association with the allergic disease.¹⁷ It is imperative to determine allergic sensitization in these patients to prescribe lifestyle modifications, including environmental precautions, and specific drug management.

Limitations

The findings, while significant, are derived from a single tertiary care center in southwestern Colombia. This geographic and institutional specificity might limit the generalizability of the results to broader populations or different healthcare settings. Furthermore, the fact that the setting

was a high-complexity, tertiary referral center, can introduce a selection bias favoring more severe or complex cases and possibly skewing the prevalence and association strength between IEI and allergic diseases. Another limitation of our study was that we did not analyze whether the allergic disease presented by the patients was the initial clinical manifestation of IEI. Consequently, the patients included in our analysis were those who were refractory to initial treatment.

As per limitations regarding the methodology, the observational nature of our study supposes an inherent limitation in inferring causality. Moreover, the reliance on clinical records and ICD-10 coding might introduce diagnostic variability that cannot be accounted for. Lastly, the combination of the setting and methodology might have led to the underrepresentation of certain subtypes of IEI.

CONCLUSION

The heterogeneity of the clinical presentation in IEI represents a significant challenge for clinicians in terms of diagnosis and management. This study provides a valuable contribution by highlighting the importance of being aware and suspicious of patients with allergic diseases, as it can be the first indication of an underlying IEI.

Allergic disease is increasingly recognized as an important warning sign for the early suspicion and diagnosis of IEI. Our study aimed to demonstrate how these two conditions can coexist without necessarily involving a primary atopic disorder, thereby allowing for comprehensive management of these patients.

Furthermore, this study provides a solid foundation for implementing more efficient diagnostic and management strategies for patients with IEI. Acknowledging the diverse clinical presentations and utilizing available diagnostic tools, we advocate for a more integrated, personalized, and multidisciplinary approach to managing immunologic disorders. Allergists must be adept at expanding diagnostic studies to facilitate the early detection of immunodeficiencies. Identifying and assessing these conditions at early stages is crucial for timely management and treatment, ultimately improving clinical outcomes and patients' quality of life.

DECLARATIONS

Conflict of interest

The authors declare not to have any conflict of interest.

Fundings

This study was funded by Fundacion Valle del Lili.

Ethics responsibilities

The study was carried out in adherence to ethical standards, the Regulation of the General Health Law on Health Research, and the Declaration of Helsinki.

Human and animal rights and informed

Consent This article does not contain any studies with human, or animal subjects performed by any of the authors.

Key References

1. Tangye SG, Al-Herz W, Aziz Bousfiha, Cunningham-Rundles C, Jose, Franco L, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. <https://doi.org/10.1007/s10875-022-01289-3>
2. Raje N, Dinakar C. Overview of Immunodeficiency Disorders. *Immunol Allergy Clin North Am* [Internet]. 2015; 35 (4): 599. /pmc/articles/PMC4600970/
3. Amaya-Urbe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. Primary immunodeficiency and autoimmunity: A comprehensive review. *J Autoimmun*. 2019; 99: 52-72. <https://pubmed.ncbi.nlm.nih.gov/30795880/>
4. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies - principles of care. *Front Immunol*. 2014; 5 (DEC). <https://pubmed.ncbi.nlm.nih.gov/25566243/>
5. Inborn errors of immunity (primary immunodeficiencies): Classification. 2024. <https://medilib.ir/uptodate/show/117758>

Permissions

All figures and tables are original.

Ethics approval statement

Ethical approval was waived by the Institutional Review Board (Comité de Ética en Investigación Biomédica), Protocol number 2023-217. Approval No. 026

REFERENCES

1. Tangye SG, Al-Herz W, Aziz Bousfiha, Cunningham-Rundles C, Jose, Franco L, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. <https://doi.org/10.1007/s10875-022-01289-3>
2. Raje N, Dinakar C. Overview of Immunodeficiency Disorders. *Immunol Allergy Clin North Am* [Internet]. 2015; 35 (4): 599. /pmc/articles/PMC4600970/
3. Amaya-Urbe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. Primary immunodeficiency and autoimmunity: A comprehensive review. *J Autoimmun*. 2019; 99: 52-72. <https://pubmed.ncbi.nlm.nih.gov/30795880/>
4. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, et al. Primary immune deficiencies - principles of care. *Front Immunol*. 2014; 5 (DEC). <https://pubmed.ncbi.nlm.nih.gov/25566243/>
5. Inborn errors of immunity (primary immunodeficiencies): Classification. 2024. <https://medilib.ir/uptodate/show/117758>
6. Leonardi L, Rivalta B, Cancrini C, Chiappini E, et al. Update in Primary Immunodeficiencies. *Acta Biomed*. 2020; 91 (11-S): 1-6. <https://pubmed.ncbi.nlm.nih.gov/33004780/>
7. Chan SK, Gelfand EW. Primary Immunodeficiency Masquerading as Allergic Disease. *Immunol Allergy Clin North Am* 2015; 35 (4): 767-78. <https://pubmed.ncbi.nlm.nih.gov/26454318/>
8. ESID - European Society for Immunodeficiencies. 2024. <https://esid.org/>
9. Castagnoli R, Lougaris V, Giardino G, Volpi S, et al. Inborn errors of immunity with atopic phenotypes: A practical guide for allergists. *World Allergy Organ J*. 2021; 14 (2). <https://pubmed.ncbi.nlm.nih.gov/33717395/>
10. Bousfiha A, Moundir A, Tangye SG, Picard C, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. *J Clin Immunol* 2022; 42 (7): 1508-20. <https://pubmed.ncbi.nlm.nih.gov/36198931/>
11. Thalhammer J, Kindle G, Nieters A, Rusch S, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. *J Allergy Clin Immunol* 2021; 148 (5): 1332-1341.e5. <https://pubmed.ncbi.nlm.nih.gov/33895260/>
12. Smith KL, Dai D, Modi BP, Sara R, et al. Inborn Errors of Immunity Associated With Type 2 Inflammation in the USIDNET Registry. *Front Immunol* 2022; 13. <https://pubmed.ncbi.nlm.nih.gov/35273610/>
13. Ogershok PR, Hogan MB, Welch JE, Corder WT, et al. Spectrum of illness in pediatric common variable immunodeficiency. *Ann Allergy Asthma Immunol* 2006; 97 (5): 653-6. <https://pubmed.ncbi.nlm.nih.gov/17165275/>
14. El-Sayed ZA, El-Ghoneimy DH, Ortega-Martell JA, Radwan N, et al. Allergic manifestations of inborn errors of immunity and their impact on the diagnosis: A worldwide study. *World Allergy Org J* 2022; 15 (6): 100657.
15. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: Clinical correlates and responses to pneumococcal vaccine. *Clinical Immunology* 2004; 111 (1): 93-7. <https://pubmed.ncbi.nlm.nih.gov/15093556/>
16. Chin A, Balasubramanyam S, Davis CM. Very Elevated IgE, Atopy, and Severe Infection: A Genomics-Based Diagnostic Approach to a Spectrum of Diseases. *Case Reports Immunol* 2021; 2021.
17. Vaseghi-Shanjani M, Smith KL, Sara RJ, Modi BP, et al. Inborn errors of immunity manifesting as atopic disorders. *J Allergy Clin Immunol* 2021; 148 (5): 1130-9. <https://pubmed.ncbi.nlm.nih.gov/34428518/>