Inborn errors of immunity*

Childhood and adult diseases. A description of ambulatory clinical immunology patients over six years of tracking

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Abstract

Introduction: inborn errors of immunity that present for the first time in adulthood are a recent topic of interest in internal medicine. First of all, this is a developing field within translational immunology, which internists should not overlook. Second, the number of adult patients with immunodeficiency symptoms seen by different medical services is increasing.

Design and method: in August 2015, a clinical immunology outpatient department was set up in the Hospital Universitario del Valle en Cali, Colombia. To describe the clinical experience with inborn errors of immunity in diagnosed adult patients, a cross-sectional study was conducted from 2015-2021.

Results: the ratio of males to females was 1.25:1, and all enrolled patients were over the age of 18. Antibody deficiency (40.7%) and common variable immunodeficiency were the most frequent categories and diagnoses, respectively. The patients' mean age at onset of symptoms was 24 years, with an average diagnostic delay of eight years.

Conclusion: understanding inborn errors of immunity (IEIs) is challenging and visionary for internists, entailing exploring new clinical areas and delving into clinical immunology. However, it is essential for achieving a more modern internal medicine. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3092).**

Keywords: *primary immunodeficiency, translational immunology, cross-sectional studies, antibody deficiency.*

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Introduction

Inborn errors of immunity (IEIs) are a diverse group of hereditary disorders that affect patients' innate and adaptive immune response (1). They were first described in 1952, and since then their incidence has increased, in contrast with the many limitations in information and clinical skills available for their diagnosis (2).

In its latest update in 2022, the Expert Committee of the International Union of Immunological Societies (IUIS) proposed 485 genetic defects as the cause of these diseases, with a marked increase in the rate of description of new IEIs from 1983 to 2022 (3).

However, since IEIs are considered orphan diseases and, therefore, rare, there are few epidemiological studies on this topic, especially in adults. An estimated 25-40% of all IEI diagnoses are made in adults, but the actual frequency of these diseases is thought to be underestimated (4).

Often, internists encounter patients with symptoms suggestive of systemic autoimmune diseases, as well as those who are more susceptible to drug-induced infections or have warning symptoms and abnormal laboratory results that indicate primary immunodeficiency (5). It is challenging to acquire information on IEIs, and there are few articles describing their characteristics in adults.

This cross-sectional, descriptive observational study collected data from the medical charts of patients over the age of 18 diagnosed with IEIs and seen as outpatients by the clinical immunology service, in order to describe their clinical and demographic differences. .

Materials and methods

A cross-sectional study was performed in the outpatient immunology service, collecting data from the electronic medical charts of adult patients diagnosed with any IEI from 2015-2021. The diagnosis was made using clinical and laboratory criteria according to the 2022 IUIS classification for dividing the various subgroups (3). A total convenience sample of 27 patients was selected using nonprobabilistic sampling, sequentially analyzing all available medical charts with a diagnosis of IEI in the hospital data system, from the most recent to the earliest year.

Statistical analysis

A descriptive statistical analysis was performed. Continuous variables were presented as averages and standard deviation or medians and interquartile range, depending on whether they met the assumption of normality. Categorical variables were divided into proportions and compared us-

ing the Chi-square or Fisher's exact test, as applicable. A level of statistical significance of $\alpha = 0.05$ was established a priori.

Pearson's correlation coefficient with its respective coefficient of determination was used for correlation between quantitative variables if at least one of the two variables met the assumption of normality. If this was not the case, Spearman's nonparametric correlation coefficient was used. The analyses were run on RStudio statistical software once they were imported from the Epi Info database.

Results

From July 2015 to September 2021, 484 patients were seen in the outpatient clinical immunology service at Hospital Universitario del Valle, 84 (17.35%) of whom had a confirmed IEI. Of these, 56 were under age 18 (67%) and 27 were over 18 (33%) (Figure 1).

Of the 27 adult patients with a confirmed IEI (Table 1), 51.85% debuted with a clinical phenotype of recurrent or severe infection, with the most common subtype, according to the 2022 IUIS classification, being antibody deficiency, with 11 patients (40.7%), and the most prevalent diagnosis being common variable immunodeficiency (CVID) (eight patients, 29.62%) (Table 2). Among patients classified as having dysgammaglobulinemia, 7 out of 11 (63.6%) debuted with an infection at the onset of symptoms, with pneumonia being the most common diagnosis (six patients).

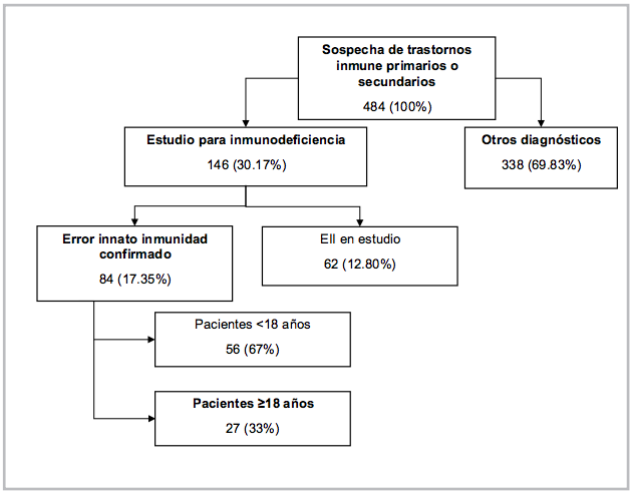

Figure 1. *Flow chart of the total patients. The experience of the sub-specialty clinical immunology service.*

Table 1. *Clinical and laboratory characteristics of patients with confirmed IEIs.*

	PI diagnostic group								
Variable	**I**	**III**	**IV**	**VI**	**VII**	**VIII**	**IX**	**X**	**General**
N. n (%)	1 (3.70)	11 (40.70)	1 (3.70)	2 (7.41)	6 (22.20)	4 (14.80)	1 (3.70)	1 (3.70)	27 (100)
Sex. n (%)	n=1	n=11	n=1	n=2	n=6	n=4	n=1	n=1	n=27
0=Male	1 (100)	7 (63.60)	1 (100)	1 (50.00)	3 (50.00)	1 (25.00)	1 (100)	0	15 (55.60)
1=Female	0	4 (36.40)	0	1 (50.00)	3 (50.00)	3 (75.00)	0	1 (100)	12 (44.40)
Age at symptom onset. Mean (sd)	n=1	n=9	n=0	n=2	n=6	n=4	n=1	n=1	n=24
	8	27.33 (15.09)	-	17.50 (16.00-19.00)	24.33 (13.40)	20.25 (7.13)	10	26	24 (10.00-27.25)
Age at final diagnosis. Median (IQR)	n=1	n=10	n=1	n=2	n=6	n=4	n=1	n=1	n=26
	19	32 (28.00-38.75)	24	27 (22.00-29.50)	43.50 (29.00-52.00)	24 (21.00-30.75)	32	52	31.50 (24.00-43.75)
Time elapsed between id and fd. Median (IQR)	n=1	n=11	n=1	n=2	n=6	n=4	n=1	n=1	n=27
	11	3 (1.00-9.00)	24	9.50 (3.00-16.00)	12 (7.75-18.50)	5 (1.75-10.75)	22	26	8 (2.50-19.50)
Eosinophils. Median (IQR)	n=1	n=7	n=1	n=2	n=2	n=2	n=1	n=0	n=16
	40	70 (64.00-277.50)	30	15 (10.00-20.00)	738 (176.00-1019)	235 (207.50-262.50)	20	-	70 (29.25-207.50)
Neutrophils. Mean (sd)	n=1	n=10	n=1	n=2	n=2	n=2	n=1	n=1	n=20
	3,060	5,316 (3,292.57)	6,770	2,460 (730.00-4,550.00)	4,825 (2,600.00-7,050.00)	10,025 (8,900.00-11,150.00)	910	7910	5,321.50 (3,350)
Platelets. Mean (sd)	n=1	n=10	n=1	n=2	n=2	n=2	n=1	n=1	n=20
	162	259 (117.77)	147	299.50 (242.00-357.00)	383 (352.00-414.00)	453 (441-465)	15	566	287.55 (145.53)
Hemoglobin. Median (IQR)	n=1	n=10	n=1	n=2	n=2	n=2	n=1	n=1	n=20
	8	13 (11.25-14.75)	17	22,475 (10-44,939)	12 (11-13)	22,582 (14-45,150)	9	12	13 (11-15)
Mean corpuscular volume. Median (IQR)	n=1	n=9	n=1	n=2	n=1	n=2	n=1	n=1	n=18
	73	82 (80-85)	78	83.50 (82-85)	83	89.10 (84.00-94.20)	120	87	83 (80.00-85.75)

**When n=1, only the value obtained by the patient for this characteristic is presented. When n=2, the mean (minimum-maximum) is expressed. The highlighted cells are those in which n=1 or n=2; that is, the presented statistic is different. The "n"s in red type are those for which there was missing data.*

*continuation....***Table 1.** *Clinical and laboratory characteristics of patients with confirmed IEIs.*

PI diagnostic group									
Variable	**I**	**III**	**IV**	**VI**	**VII**	**VIII**	**IX**	**X**	**General**
Immunoglobulin A. Median (IQR)	n=1	n=10	n=1	n=2	n=2	n=1	n=0	n=1	n=18
	88	5.50 (5.00-54.25)	40	89 (75-103)	398 (387-409)	269	-	639	70.50 (5.25-357.50)
Immunoglobulin G. Mean (sd)	n=1	n=9	n=1	n=2	n=2	n=1	n=0	n=1	n=17
	1769	712.11 (728.10)	593	940 (720-1,160)	1,990 (1,705-2,276)	920	-	927	969.35 (705.73)
Immunoglobulin M. Mean (sd)	n=1	n=8	n=1	n=2	n=2	n=1	n=0	n=1	n=16
	112	67.62 (78.19)	25	100.50 (43-158)	73.50 (70-77)	93	-	84	75.19 (60.80)
Immunoglobulin E. Median (IQR)	n=1	n=8	n=1	n=2	n=2	n=2	n=0	n=1	n=17
	206	12.50 (7.25-30.75)	0	22,562 (15-45,108)	891 (101-1,681)	51.20 (32-70.40)	-	2	25 (9-101)
NK cells. Mean (sd)	n=1	n=4	n=0	n=1	n=0	n=0	n=0	n=0	n=6
	125	175 (113.29)	-	294	-	-	-	-	186.50 (104.28)
CD19. Median (IQR)	n=1	n=6	n=0	n=0	n=0	n=0	n=0	n=0	n=7
	96	226 (39.50-318.00)	-	-	-	-	-	-	140 (5-316)
CD3. Mean (sd)	n=0	n=7	n=1	n=2	n=0	n=0	n=0	n=1	n=11
	-	1706.14 (942.78)	1,301	1,222 (281-2,163)	-	-	-	1,298	1,544.18 (872.63)
CD4. Mean (sd)	n=1	n=8	n=1	n=1	n=0	n=0	n=0	n=1	n=12
	71	944.37 (696.78)	328	113	-	-	-	904	747.58 (658.46)
CD8. Mean (sd)	n=1	n=7	n=1	n=2	n=0	n=0	n=0	n=1	n=12
	165	952 (682.56)	883	629.50 (393.80)	-	-	-	299	772.50 (611.39)
Leukocytes. Mean (sd)	n=1	n=10	n=1	n=2	n=2	n=2	n=1	n=1	n=20
	4,130	8,905 (3,927.92)	8,870	4,344 (1,557-7,130)	9,325 (9,300-9,350)	13,590 (11,290-15,890)	5,100	10,790	8,622.85 (3,907.31)
Lymphocytes. Mean (sd)	n=1	n=10	n=1	n=2	n=2	n=2	n=1	n=1	n=20
	440	2,399.80 (1201.81)	1,220	1,305 (930-1,680)	3,765 (1,330-6,200)	2,385 (1,400-3,370)	3,160	90	2,190.90 (1,512.71)
Hematocrit. Mean (sd)	n=1	n=9	n=1	n=2	n=2	n=2	n=1	n=1	n=19
	24	38.38 (5.56)	54	36.40 (32.00-40.80)	39 (34-44)	41.05 (39.10-43.00)	28	37	37.96 (7.16)
MCH. Median (IQR)	n=1	n=9	n=1	n=2	n=1	n=2	n=1	n=1	n=18
	23	26 (24-28)	24	22,521 (29-33,766)	26	22,598 (27-45,168)	42	27	27 (24.25-30.50)
Mortality. n (%)	n=1	n=11	n=1	n=2	n=6	n=4	n=1	n=1	n=27
Yes	0	2 (18.20)	0	0	0	0	0	0	2 (7.41)
No	1 (100)	9 (81.80)	1 (100)	2 (100)	6 (100)	4 (100)	1 (100)	1 (100)	25 (92.60)
Clinical phenotype. n (%)	n=1	**n=11**	**n=1**	**n=2**	**n=6**	**n=4**	**n=1**	**n=1**	n=27
Infection	1 (100)	9 (81.80)	1 (100)	2 (100)	0	0	0	1 (100)	14 (51.90)
Dermatological	0	0	0	0	6 (100)	4 (100)	0	0	9 (37)
Hematological	0	2 (18.20)	0	0	0	0	1 (100)	0	3 (11.10)
Hospital stay. n (%)	n=1	n=8	n=1	n=2	n=5	n=4	n=1	n=1	n=23
0	1 (100)	5 (62.50)	1 (100)	2 (100)	4 (80)	4 (100)	1 (100)	1 (100)	19 (82.60)
6	0	2 (25)	0	0	0	0	0	0	2 (8.70)
62	0	1 (12.50)	0	0	0	0	0	0	1 (4.35)
730	0	0	0	0	1 (20)	0	0	0	1 (4.35)

**When n=1, only the value obtained by the patient for this characteristic is presented. When n=2, the mean (minimum-maximum) is expressed. The highlighted cells are those in which n=1 or n=2; that is, the presented statistic is different. The "n"s in red type are those for which there was missing data.*

Table 2. *Diagnoses by subgroups in adult patients with IEIs.*

Group 1	Combined immunodeficiency due to IL-7 mutation	1
Group 2	None	0
Group 3	Common variable immunodeficiency	8
	Selective IgA deficiency	2
Group 4	X-linked lymphoproliferative syndrome	1
Group 5	None	0
Group 6	WHIM syndrome	1
	Inborn immune deficiency	2
Group 7	Autoinflammatory syndrome	1
	DITRA	1
Group 8	Hereditary angioedema type 1	7
	Nonclassified hereditary angioedema	1
Group 9	Bone marrow failure syndrome	1
Group 10	Susceptibility to mycobacteria	1

Table 3. *Classification of IEIs by subgroups, disaggregated by sex.*

	Sex			
PI diagnosis	**Male**	**Female**	**Total (%)**	**P values**
I	1 (100)	0	1 (3.70)	
III	7 (63.60)	4 (36.40)	11 (40.70)	0.71
IV	1 (100)	0	1 (3.70)	
VI	1 (50)	1 (50)	2 (7.41)	
VII	3 (50)	3 (50)	6 (22.20)	
VIII	1 (25)	3 (75)	4 (14.80)	
IX	1 (100)	0	1 (3.70)	
X	0	1 (100)	1 (3.70)	

Table 4. *Frequency of Jeffrey Modell warning signs for primary immunodeficiencies in the evaluated cohort.*

Jeffrey Modell Foundation – Warning Signs	**n (%)**
0 - None	12 (32.43)
1 - ≥2 new ear infections in 1 year	1 (2.7)
2 - ≥2 new sinus infections in 1 year, without allergies	6 (16.22)
3 - 1 pneumonia per year for >1 year	4 (10.81)
4 - Chronic diarrhea with weight loss	0 (0)
5 - Recurrent viral infections (colds, herpes, warts, condyloma)	1 (2.7)
6 - Recurrent need for intravenous antibiotics to treat infections	7 (18.92)
7 - Recurrent deep skin or internal organ abscesses	1 (2.7)
8 - Persistent candidiasis or other fungal infections of the skin or other sites	1 (2.7)
9 - Infection with tuberculosis-like bacteria which are normally harmless	2 (5.41)
10 - Family history of primary immunodeficiencies	2 (5.41)

Various clinical and laboratory characteristics were evaluated (Table 1). A total of 27 patients with IEIs were enrolled, including 15 males (55.55%) and 12 females (44.44%), with no significant gender difference in the diagnostic subgroups (Table 3). Initially, the clinic focused mostly on adults, although children were also seen. This focus led to a higher proportion of adults being evaluated compared to what is reported in the literature, in order to mainly address IEIs in adults.

The patients examined in the clinic mainly consulted due to recurrent infections, a severe infection, an infection caused by opportunistic pathogens, autoinflammatory symptoms and abnormal laboratory results, especially on the complete blood count. However, it is important to highlight that 32.43% of the patients referred by the Colombian healthcare system did not have Jeffrey Modell warning signs of primary immunodeficiency as the reason for referral (Table 4).

The median age at the onset of symptoms was 24 years (IQR, 10-27.25 years), and the median age at diagnosis was 31.5 years (IQR, 24-43.75 years), with an eight-year delay between the onset of symptoms and definitive diagnosis (IQR, 2.5-19.5 years).

As far as hospital stay, 82.6% did not require hospitalization, with the longest stay being 730 cumulative days for one patient. Mortality was evaluated during the six years of follow up, and two patients died due to severe respiratory infections related to the IEI (Table 1).

Discussion

This study reports six years of experience in classifying IEIs at Hospital Universitario del Valle, Cali, Colombia. During this period, 484 patients were evaluated, of whom 27 adults were diagnosed with IEI. Since this was a retrospective study using the laboratory tests allowed by the healthcare system, it was extremely difficult to determine the underlying cause of the recurrent infections in some cases (6).

It is always important to differentiate between primary immunodeficiencies and secondary causes (like steroid treatment, HIV infection, leukemia, lymphoma, nephrotic syndrome or malabsorption syndrome) (3, 7). Therefore, these patients benefit from a comprehensive evaluation, which was an advantage of our service, as the patients were seen by an internal medicine specialist who was also an immunologist.

Regarding the different classification subgroups, we found that the most common subgroup according to the 2022 IUIS classification was antibody deficiency (37.03%), followed by complement deficiencies (29.62%), which is consistent with the international literature (3). The 2020 LASID international registry of IEIs found a predominant antibody deficiency with 53.2% (8).

The presented data are similar to previous reports in Latin America (8) and Europe (9). However, there is a lack

of information in Colombia regarding the different IEIs. At a regional level, the Primary Immunodeficiencies Group at Universidad de Antioquia phenotypically evaluated 98 cases of immunodeficiency from 1994-2002 in one of its reports. They found that most cases had a predominant antibody deficiency (40.8%), followed by combined deficiencies (21.5%) and immunodeficiency syndromes associated with phagocyte dysfunction (15.3%) (10).

The most frequent diagnosis was CVID, followed by hereditary angioedema type 1, which were among the most prevalent phenotypes. Most congenital diseases with a genetic component manifest during childhood. Diseases related to antibody deficiency are an important exception, with CVID being the most common IEI. The median age for the onset of symptoms in CVID is 24 years, with an average diagnostic delay of four years. Early diagnosis of primary immunodeficiencies (PIs) is critical to prevent the morbidity and mortality associated with these diseases (7).

The results indicated that 51.85% of the patients had experienced at least one serious infection prior to being diagnosed with an IEI. These results are similar to those found in Boton et al.'s cohort, in which 61.5% of the patients had severe respiratory infections with serious secondary manifestations (11). These findings coincide with the Jeffrey Modell Foundation warning signs, which suggest the need for a high suspicion of IEI and, therefore, complementary studies (12).

Among the initial diagnoses, two patients (7.4%) had signs of immune dysregulation, which entailed a diagnostic challenge. Therefore, clinicians should keep in mind that autoimmune cytopenia (anemia, thrombocytopenia), granulomatous inflammation or inflammatory bowel disease may account for up to 20% of the initial manifestations in patients with IEIs (7).

The patients' symptoms began at an average age of 24 years; however, the delay from the onset of symptoms to diagnosis was eight years. In Latin America, an estimated 60% of patients with IEIs are not diagnosed until adulthood, despite showing signs suggestive of the diagnosis, such as recurrent infections like sinusitis, bronchitis and pneumonias (13, 14). The presence of an outpatient immunology clinic may be beneficial, as it allows education and awareness raising, which increases the probability of early IEI diagnosis and reduces the number of hospitalizations.

Patients with IEI have a higher risk of dying due to the various complications associated with their disease. In our study, there was a 7.4% mortality rate during a six-year follow up, which is consistent with other reports (15). It is important to keep in mind that mortality may vary depending on the type of IEI diagnosed, which reflects the heterogeneity of these diseases and highlights the need to perform an appropriate phenotype-genotype assessment for their treatment (12, 16).

Conclusion

Understanding IEIs is both challenging and visionary for internists. It is challenging because it entails delving into new clinical areas, and visionary because it implies a deeper understanding of clinical immunology, immune dysregulation and new treatment strategies. However, it is essential to focus on this area to achieve a modern internal medicine.

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