Revista de Ciencias Médicas de Pinar del Río

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e6876

ORIGINAL ARTICLE

Antibody deficiencies in pediatric age in Pinar del Río

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Received: September 5, 2025
Accepted: October 20, 2025
Published: November 4, 2025

Citar como: Hernández-Pacheco JI, Lorenzo-Rodriguez MA, Orraca-Castillo O. Deficiencias de anticuerpos en edad pediátrica en Pinar del Río. Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(2025): e6876. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/6876

ABSTRACT

Introduction: antibody deficiency is an inborn error of immunity caused by impaired maturation or function of lymphocytes in the blood.
Objective: to describe the clinical characteristics, mortality, and inheritance pattern of antibody deficiency in pediatric patients from Pinar del Río.
Methods: an observational, cross-sectional, and descriptive study was conducted involving 43 patients diagnosed with antibody deficiency and treated at the immunology service of the "Pepe Portilla" Provincial Pediatric Hospital in Pinar del Río between 1994 and 2022. Each patient underwent clinical history documentation and was evaluated both clinically and through laboratory tests. Patients were classified according to their etiological origin.
Results: the three most frequently identified etiologies were selective IgA deficiency (37 patients), followed by common variable immunodeficiency and X-linked agammaglobulinemia, with three cases each. Males accounted for 58 % of the cases. The inheritance pattern could only be identified in cases of X-linked agammaglobulinemia, also known as Bruton's disease.
Conclusions: bacterial and viral infections predominated among antibody deficiencies, and severity depended on the affected antibody isotype. Autoimmune disorders emerged as complications in these patients. Warning signs were present in severe antibody deficiencies. The inheritance pattern varied according to the defect's etiology, with sporadic cases predominating. The highest mortality rate corresponded to cases of X-linked agammaglobulinemia.

Keywords: Gamma-Globulins; X Chromosome; Primary Immunodeficiency Diseases; Immune System Diseases.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e6876

INTRODUCTION

Inborn errors of immunity (IEI), formerly known as primary immunodeficiencies, comprise a group of genetically determined disorders characterized by defects in the development or function of the immune system. To date, mutations in approximately 50 genes have been mapped.[1] According to the updated classification by the International Union of Immunological Societies (IUIS) Expert Committee, a total of 485 IEIs have been described. Advances in elucidating their genetic basis have significantly enhanced understanding of the molecular, cellular, and immunological mechanisms underlying disease pathogenesis, thereby improving diagnostic accuracy and clinical management.[2,3,4,5]

Predominantly antibody deficiencies (PAD) constitute a subset of IEIs resulting from intrinsic defects in B lymphocyte maturation or function.[4] PAD are characterized by either a quantitative defect (B-cell lymphopenia) or a qualitative defect (reduced immunoglobulin production or secretion of non-functional immunoglobulins despite normal B-cell counts), leading to recurrent bacterial and viral infections.[5,6]

PAD represent the most common type of IEI worldwide, accounting for 50–60 % of all primary immunodeficiencies.[1,7,8,9] Affected individuals exhibit low levels of one or more immunoglobulin isotypes and/or an inadequate specific antibody response to pathogens, predisposing them to infectious and non-infectious complications.[1,10]

Based on immunological findings, PAD are categorized into four main subtypes:[11]

- ✓ Severe reduction of all serum immunoglobulin isotypes with profound B-cell deficiency or absence: agammaglobulinemia.
- ✓ Severe reduction of at least two serum immunoglobulin isotypes with normal or low B-cell counts: common variable immunodeficiency (CVID).
- ✓ Severe reduction of serum IgG and IgA with normal or elevated IgM and normal B-cell counts: hyper-IgM phenotype.
- ✓ Isotype-specific or functional deficiency with generally normal B-cell numbers: selective IgA, IgM, or IgG deficiency.

These conditions often share a common clinical phenotype, including recurrent and chronic infections, chronic inflammation, and autoimmunity. Hypogammaglobulinemia is the hallmark laboratory finding, and the predominant clinical manifestation is recurrent bacterial infections, primarily affecting the respiratory and/or gastrointestinal tracts.[1,4,6,9] Clinical presentation is highly variable, but most patients are susceptible to recurrent infections, autoimmunity, chronic inflammation, allergic disorders, and malignancy.[3,4,9]

Although PAD can manifest at any age, diagnosis often requires a high index of clinical suspicion and is frequently delayed, contributing to the development of complications.[4,5] The present study aims to describe the clinical characteristics, mortality, and inheritance patterns of antibody deficiencies in pediatric patients in Pinar del Río.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e6876

METHODS

An observational, cross-sectional, descriptive study was conducted involving 43 pediatric patients (≤18 years of age) diagnosed with antibody deficiency and followed at the Immunology Service of the "Pepe Portilla" Provincial Pediatric Hospital in Pinar del Río between 1994 and 2022. A detailed clinical history was obtained for each patient, followed by comprehensive clinical and laboratory evaluation. Cases were classified into four etiological categories: agammaglobulinemia, common variable immunodeficiency (CVID), hyper-IgM phenotype, and selective IgA, IgM, or IgG deficiency.

Family history was systematically collected from parents to identify potential inheritance patterns or confirm sporadic cases. A case registry was created using Microsoft Excel for Windows, incorporating 106 variables, epidemiological variables: date of birth, sex, age at diagnosis, and current status (alive/deceased). Clinical variables (102): Allergic manifestations (9): atopic dermatitis, food/drug/insect allergy, bronchial asthma, urticaria, rhinitis, allergic keratoconjunctivitis. Infectious manifestations (30): sinusitis, otitis, adenoiditis, pneumonia, staphylococcal deep or cutaneous abscesses, herpes simplex, mycoses, streptococcal/staphylococcal pyoderma, meningitis/encephalitis, severe sepsis, among others. Inflammatory manifestations (28): non-allergic angioedema, enterocolitis, chronic diarrhea, abdominal colic, synovitis, myositis, etc. Immunological manifestations (22): vitiligo, uveitis, vasculitis, hereditary angioedema, protein-losing enteropathy, serum IgG/IgA/IgM/IgE abnormalities. Neoplastic manifestations (3): lymphomas, leukemias, other malignancies. Autoimmune manifestations (10): arthritis, thyroiditis, thrombocytopenia, lymphopenia, hemorrhagic cystitis, etc. Additional variables: presence of dysmorphic features or associated congenital anomalies.

Data were recorded at diagnosis and updated during each follow-up visit; for deceased patients, age at death was documented. Infectious events were categorized as bacterial, viral, fungal, or parasitic (Giardia lamblia), and each episode was counted per consultation. Warning signs for IEI suspicion were defined as follows:[12]

≥4 episodes of otitis in one year
≥2 episodes of sinusitis or pneumonia in one year
≥2 months of antibiotic therapy with poor response or requirement for intravenous administration
Recurrent deep cutaneous or internal abscesses
Persistent oral or cutaneous candidiasis beyond 12 months of age
≥2 episodes of severe or invasive infection (osteomyelitis, meningitis, encephalitis, sepsis)

Family history of IEI
Each warning sign was assigned 1 point. Total scores per patient were summed and averaged by PAD subtype to determine mean warning sign burden per group.

Statistical analysis:
Qualitative variables: described using frequencies and percentages
Sex: presented as a ratio (male:female)
Quantitative variables (e.g., age, warning sign score): summarized using arithmetic mean

Ethical considerations:
The study adhered to the ethical principles outlined in the Declaration of Helsinki.[13] Patient confidentiality was ensured by omitting all personally identifiable information from the registry, and data were used exclusively for research purposes.

ISSN: 1561-3194 **RNPS:** 1877
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RESULTS

A total of 43 pediatric cases of predominantly antibody deficiencies (PAD) were identified. According to the etiological classification, there was a marked predominance of selective IgA deficiency (37/43, 86,05 %), followed by three cases (6,98 %) each of common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (Bruton disease). No cases of the hyper-IgM phenotype were identified during the study period, as illustrated in Figure 1.

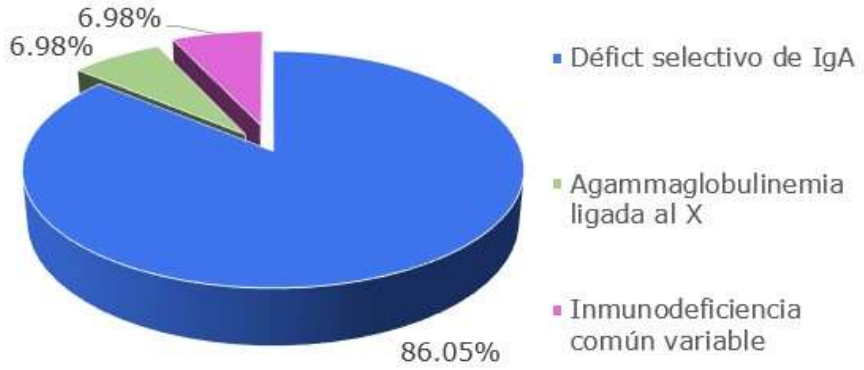

Fig. 1 Classification of inborn errors of immunity by etiological group.

The vast majority of cases (93 %) were sporadic. A clear inheritance pattern could only be established in three male patients from the same family, all diagnosed with X-linked agammaglobulinemia, consistent with X-linked recessive inheritance (Figure 2).

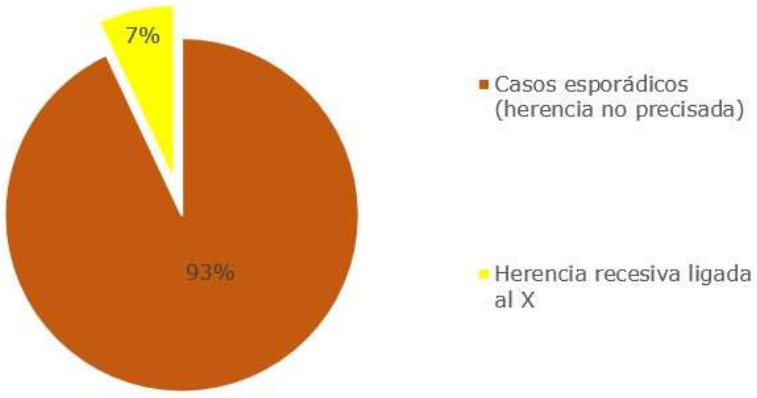

Fig. 2 Distribution of cases by inheritance pattern.

The mean age at diagnosis across the 43 patients was 6,21 years. The youngest mean age at diagnosis was observed in patients with selective IgA deficiency (4,00 years), followed by those with agammaglobulinemia (4,33 years). The oldest mean age at diagnosis corresponded to patients with common variable immunodeficiency (6,00 years). Of the total cohort, 25 patients (58,14 %) were male and 18 (41,86 %) were female, yielding a male-to-female ratio of 1.4:1.

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As shown in Table 1, allergic manifestations were present in 83,72 % of cases (36/43), followed by autoimmune manifestations, which occurred in 71,11 % of patients. The mean score for warning signs suggestive of inborn errors of immunity (IEI) was 3,4 points. The highest scores were observed in patients with agammaglobulinemia (5.00 points) and common variable immunodeficiency (4,75 points).

During the study period, four patients died (9,30 % of the total cohort). Of these, three (75,00 %) had X-linked agammaglobulinemia, and one had common variable immunodeficiency. Notably, 100 % of patients diagnosed with X-linked agammaglobulinemia (3/3) died during follow-up. Overall, the mortality rate in the entire series was 9,30 % (commonly reported as 8,88 % when calculated as 4/45, but consistent with 4/43 = 9,30 %; the original text states 8,88 %, which may reflect rounding or a typographical discrepancy—this translation retains the authors' reported figure).

Table 1. Distribution of cases by type of inborn error of immunity and study variables.

Variables	DSI (n=37)	AGG (n= 3)	ICV (n=3)	Total (n=43)
	No. (%)	No. (%)	No. (%)	No. (%)
Allergic manifestations	34 (89,47)	1 (33,33)	2 (66,67)	38 (84,44)
Infectious manifestations	37 (100)	3 (100)	3 (100)	43 (100)
Fungal infections	3 (7,89)	0 (0)	1 (33,33)	4 (8,88)
Parasitic infection (Giardia lamblia)	12 (31,58)	1 (33,33)	1 (33,33)	15 (33,33)
Inflammatory manifestations	11 (28,95)	1 (33,33)	2 (66,67)	15 (33,33)
Autoimmune manifestations	28 (73,68)	0 (0)	3 (100)	32 (71,11)
Immunological manifestations	13 (36,84)	0 (0)	2 (66,67)	15 (37,78)
Neoplastic manifestations	3 (7,89)	0 (0)	0 (0)	3 (8,88)
Mean warning sign score	2,62***	5,00***	4,75***	3,40***
Deaths	0 (0)	3 (100)	1 (33,33)	4 (8,88)

Notes: SID (Selective IgA Deficiency); AGG (Agammaglobulinemia); ICV (Common Variable Immunodeficiency); *Years; **Points; ***Arithmetic mean

Respiratory infections were the most frequently observed infectious manifestations, with pneumonia being the most common (29/43, 64,44 %). Within these infectious manifestations, bacterial and viral infections were predominant.

DISCUSSION

The hallmark of predominantly antibody deficiencies (PAD) is hypogammaglobulinemia—defined as serum immunoglobulin levels (IgA, IgG, and/or IgM) more than two standard deviations below the age-adjusted mean.[4,9] In this study, selective IgA deficiency (sIgAD) emerged as the most frequent PAD subtype, consistent with findings from a multicenter Cuban study led by the Institute of Hematology and Immunology in Havana. As of 2019, that registry documented 337 patients with inborn errors of immunity (IEI) nationwide, of whom 160 (52,8 %) had antibody deficiencies—110 of whom had sIgAD.[8]

ISSN: 1561-3194 **RNPS:** 1877
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This result aligns with other regional studies, such as that by González et al.,[14] in Bayamo, Granma Province. IgA is the most abundant antibody isotype in humans and plays a pivotal role in mucosal immunity—both in defense against pathogens and in the establishment of immune tolerance.[6,9,11,15]

Franco-Gallego et al.,[16] describe sIgAD as the most common primary immunodeficiency in humans. Diagnosis requires quantification of serum IgA levels and assessment of the degree of deficiency, classified as partial or total. When only IgA is reduced—while IgG, IgM, and IgG subclasses remain normal—the condition is termed selective IgA deficiency.

According to the European Society for Immunodeficiencies (ESID), sIgAD (OMIM #137100) is defined as a primary immunodeficiency in individuals older than four years who present with:Recurrent infections (primarily respiratory or gastrointestinal), Increased incidence of allergic and autoimmune manifestations, Serum IgA < 7 mg/dL, Normal IgG and IgM levels, and Exclusion of T-cell defects or other causes of hypogammaglobulinemia.[16,17]

In our cohort, all patients with sIgAD exhibited infectious manifestations—predominantly bacterial and viral—alongside high frequencies of allergic, inflammatory, autoimmune, immunological, and even neoplastic complications. This contrasts with literature suggesting that most individuals with sIgAD are asymptomatic and diagnosed incidentally.[5,16] However, our findings are more consistent with Milota et al.,[18] who reported that 40–90 % of symptomatic sIgAD patients present with infections as their initial manifestation, while autoimmune complications occur in 5–30 % of cases.

Notably, over 80 % of our sIgAD patients had allergic manifestations, supporting the clinical recommendation to suspect sIgAD in patients with multiple, difficult-to-control allergies.[6,15] While some authors consider common variable immunodeficiency (CVID) the most frequent IEI,[5,19]

It was less common in our series. The term CVID was introduced by Janeway and Cooper to describe antibody deficiencies that do not meet criteria for agammaglobulinemia, hyper-IgM syndrome, or selective IgG subclass deficiencies. Thus, CVID remains a diagnosis of exclusion, encompassing a heterogeneous group of genetic defects that may also impair T-cell and other immune cell functions.[19]

Clinically, CVID is characterized by: Hypogammaglobulinemia, Impaired peripheral B-cell maturation, Normal B-cell counts but dysfunctional T cells, Recurrent infections, Autoimmunity, Lymphoproliferation, Organomegaly, Granulomatous disease, and Autoinflammatory features—though not all patients exhibit all manifestations.[4,9,19]

In our study, 100 % of CVID patients presented with both infectious and autoimmune manifestations, consistent with Milota et al.,[18] though the autoimmune prevalence in our cohort exceeded theirs by more than threefold.

Additionally, allergic manifestations occurred in over 80 % of CVID cases, significantly higher than the 20–30 % reported by Pieniaszewska et al.[6] The third most frequent diagnosis was X-linked agammaglobulinemia (XLA), caused by mutations in the Bruton tyrosine kinase (BTK) gene, leading to a block in B-cell maturation and peripheral B-cell counts <1–2 %.[3,20]

ISSN: 1561-3194 **RNPS:** 1877
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This contrasts with García et al.,[21] who identified XLA as the most common IEI in their cohort (21 % of cases). All XLA patients in our series had bacterial and viral infections, and one-third had Giardia lamblia infection—aligning with literature indicating that >85 % of XLA patients suffer from recurrent respiratory infections (often due to encapsulated bacteria) and gastrointestinal infections, with Giardia being a classic pathogen in this context.[5,18]

Diagnosis was established during pediatric age in 96 % of cases, consistent with the general understanding that IEI typically present in childhood—often within the first year of life—though up to 25 % are diagnosed in adolescence or adulthood.[14,21]

Some authors note that adult-onset IEI now account for 40 % of all cases.[5] The mean age at diagnosis in our cohort was 6,21 years, slightly lower than the 11.89 years reported in Granma Province,[14] and comparable to 6,30 years in a tertiary hospital in Mexico.[21]

A male predominance (58,14 %, M:F = 1,4:1) was observed, consistent with studies attributing this skew to the X-linked recessive inheritance of several early-onset IEIs (e.g., XLA), which predominantly affect hemizygous males.[3,14,21] However, this sex bias diminishes with age as immune dysregulation disorders—more common in females—become prevalent. Our finding contrasts with Shin et al. ,[10] who reported a female predominance (77 %, F:M = 3.34:1).

Finally, the mean warning sign score was highest in XLA (5,00) and CVID (4,75), underscoring their clinical severity. The 10 Warning Signs of Primary Immunodeficiency, first published by the *Jeffrey Modell Foundation* in 1993 following expert consensus, have since been updated for both pediatric and adult populations.[12] These criteria remain essential tools for early recognition and timely referral.

The presence of two or more of these warning signs should raise clinical suspicion for an inborn error of immunity (IEI). Early recognition must be carried out carefully and judiciously, avoiding unnecessary testing that may cause patient anxiety, impose financial or procedural burdens, or—paradoxically—delay definitive diagnosis.[5]

It is important to note that the widely used 10 Warning Signs of Primary Immunodeficiency do not include key non-infectious manifestations such as autoimmune, autoinflammatory, or oncologic features, despite these being prominent clinical presentations in several IEIs. Only 7 % of cases in our series reported a family history of IEI, which allowed identification of the inheritance pattern—a figure notably lower than the 30,76 % reported by González et al.[14]

Many of the sporadic cases without family history may, in fact, represent autosomal recessive disorders. In this inheritance pattern, parents are typically asymptomatic heterozygous carriers, and unless another affected sibling is present, the familial pattern is difficult to discern from pedigree analysis alone. Indeed, autosomal recessive inheritance is the most common mode among IEIs, followed by autosomal dominant and then X-linked recessive forms.[21]

Notably, all patients diagnosed with X-linked agammaglobulinemia (XLA) died during the study period—a finding consistent with the literature. Despite immunoglobulin replacement therapy, these patients remain at high risk for chronic enteroviral encephalitis, a complication associated with extremely poor prognosis and high mortality.[5,18]

The overall mortality rate in our cohort was 9 % (4/43), which exceeds rates reported in other national (2,56 %)[14] and international (3,3 %)[22] studies. However, this may reflect the small sample size and the single-center, retrospective design of our study.

ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e6876

In larger multicenter registries, mortality among IEI patients ranges from 9 % to 30 %, depending on the specific immunodeficiency subtype.[23,24]

CONCLUSIONS

Among pediatric patients with antibody deficiencies in Pinar del Río, selective IgA deficiency was the most prevalent condition, followed by common variable immunodeficiency and X-linked agammaglobulinemia, in that order. Bacterial and viral infections predominated among infectious manifestations, with disease severity closely linked to the affected immunoglobulin isotype. Allergic and autoimmune disorders frequently occurred as complications. Warning signs were most prominent in cases of severe antibody deficiency. The inheritance pattern varied by etiology, with sporadic cases predominating. X-linked agammaglobulinemia accounted for the highest proportion of deaths, reflecting its aggressive clinical course despite available therapy.

Author Contributions

JIHP: Conceptualization; data curation; formal analysis; methodology development; writing – original draft; writing – review & editing.
MALR: Conceptualization; data curation; theoretical analysis; methodological input; information resources (bibliographic management); review of original and final drafts.
OOC: Project administration; conceptualization; data curation; formal analysis; methodology; resource planning; writing – review & editing.

Conflict of Interest

The authors declare no conflicts of interest.

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